A REVIEW OF MEDICAL LITERATURE ON RELATIONSHIPS OF VARIOUS DEGENERATIVE DISEASES TO DIET AND ACTIVITY

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PREFACE

Not many people know that Nathan Pritikin's studies of the medical literature in the area of the relationship of diet to degenerative diseases culminated in the early '70's in the writing of three comprehensive technical volumes covering the many pathologies he believed were due to the high-fat Western diet. Never before published, these dissertations--herein printed as Parts I, II, and III corresponding to the original three volumes--provided the fundamental source material for the educational lectures he presented to thousands of lay people and medical professionals who attended his residential centers and health seminars, as well as for his popular books.

These writings are part of his remarkable legacy. Together, they provide a view of the manner in which he selected many hundreds of studies from the medical literature, and with unusual insight and meticulous scholarship wove them together to build a stunning thesis: that the high-fat, high-in-cholesterol, high-in-simple carbohydrates Western diet is responsible for a myriad of degenerative conditions which are separate manifestations of the same basic malady. Pritikin liked to make an analogy with poisoning by a substance like arsenic, but, in this case, he said, we were being poisoned by substances in our everyday diet which in excess acted like toxins. In different individuals, or even in the same individual, the degenerative conditions produced could be atherosclerosis and coronary heart disease, hypertension, adult-onset diabetes, certain cancers, and conditions like gall bladder disease, gout, glaucoma, and osteoarthritis.

In the decade and a half since Nathan Pritikin perused the medical literature searching for answers to the riddle of the Western degenerative diseases, many additional important studies have corroborated his basic conclusions, and his point of view has won wide acceptance.

This small private printing places Nathan's writings in the hands of a few libraries and individuals. It is dedicated with gratitude to Dr. R. James Barnard, Director of Research for the Nathan Pritikin Research Foundation, for his valued contributions in the design and supervision of research studies, and especially for his assistance in the preparation and presentation of the resultant data for publication in scientific journals.

Ilene Pritikin
Santa Barbara, California
October, 1988

INTRODUCTION

The civilized world is confronted with a giant paradox: as the benefits of modern technology and advanced medicine become more readily available to the inhabitants of the developed nations, life expectancy drops. To no avail are the immense hospital complexes, the increasing number of care centers, the sophisticated and expensive diagnostic equipment, the huge and costly research programs designed to develop drug cures and ferret out the causes of the disease fatalities which cut down so many before they have lived their promised three score and ten years--even in the very prime of their lives. The various degenerative diseases--atherosclerosis, including coronary heart disease, hypertension, diabetes, cancer, glaucoma, and arthritis--proceed relentlessly to claim many millions of victims. If not fatal, these diseases may be severely crippling, but millions suffer quick unsuspected deaths, and millions more suffer slow agony, uncertainty, and equally untimely deaths.

Man throughout his history has endured the specter of unnatural death. Disease--often achieving plague proportions--earthquake, flood, wars--all have taken their terrible toll. While most of these calamities were beyond his ability as an individual to prevent, man was rarely rendered completely passive by them. He was typically acutely aware of these catastrophic events at the time of their occurrence and responded with what he considered appropriate measures. During the plague he fled from the cities or wore amulets to ward off the threat of death. In the face of imminent disasters, whatever their source, he sought more fervently than ever the aid of supernatural powers. These actions, though perhaps futile, were nevertheless positive attempts to counteract the dangers he perceived.

Today, one of the degenerative diseases--atherosclerosis--has been designated by the World Health Organization as "the greatest epidemic mankind has faced"--an epidemic which flourishes in all of the major industrialized nations of the world and is no respecter of race, sex, or age. In the United States alone, over 800,000 deaths each year are caused by cardiovascular disease, an outcome of atherosclerosis. 165,000 of these deaths occur in individuals under 65 years of age, and indications from death-rate trends are that deaths in this age group will continue to rise. Similar conditions are found in the major industrialized nations of the world.

Does this widespread epidemic elicit a great response--any cry of fear, any impassioned pleas for help--mortal or divine--as has occurred at times of catastrophe in the past?... There is hardly a ripple of concern among the general populace! Hardly an awareness that we are in the midst of anything particularly unusual! People have to die of something and these deaths seem so natural. In many cases, denouement by death is a blessing, releasing the individual from debilitating effects due to the progression of the disease state. And when the deaths occur unexpectedly (the fatal heart attacks most often take place when the individual is asleep)--what better way to go!

Much of the incredibly passive acceptance of this epidemic of death stems from the attitudes of both medical practitioners

and the general populace that the symptoms and consequences of atherosclerosis, as well as other degenerative diseases, are normal unavoidable parts of the aging process and that their greater prevalence today is due to the lengthening of the average life-span resulting from advances in modern medicine. Although this fatalistic view has been overturned by data from important investigations proceeding since World War II, it remains widely entrenched among professionals and lay individuals alike.

So universal is the view that the degenerative diseases are unavoidable concomitants of aging that aging in Western cultures is considered synonymous with the onset of degenerative diseases. A distinguished professor of gerontology has stated: "The first goal of most gerontologists is not extension of the human life span to 120 years but rather to reduce the suffering and misery attendant to the terminal years of the present life span. This objective means eradicating the heart attacks, strokes, and other catastrophic events associated with degenerative vascular disease, as well as diabetes, cancer, and the mental deterioration of the aged--to mention the most common problems."(1)

In the absence of accepted definitive views concerning the etiology of the common degenerative diseases, speculation abounds. While most believe that the degenerative diseases are mainly natural consequences of aging and the processes involved are unpreventable, heredity is also considered an important cause of many conditions, such as heart disease and diabetes, and again, the prevailing attitude is that the consequences must be accepted fatalistically. Stress and negative emotions associated with the tensions of modern life or strained family relationships are also regarded as major predisposing factors. In arthritic diseases, there is much discussion about the role of autoimmune etiologies. And so on.

Adherents to the views that the degenerative diseases are due to factors largely outside our control so far as prevention is concerned look to drugs and surgery as the primary resources for therapy. The failure of this approach is reflected in the growing degenerative disease epidemic and the mortality rates for these diseases.

Solutions have been provided by modern medicine for many of the health problems that historically have plagued mankind. These include most of the infectious diseases, maternal and infant mortality in childbirth, surgical repairs necessitated by injuries or congenital defects, etc.; but the cause and cure for the modern-day scourge of degenerative diseases remain largely a mystery to most--laypersons and professionals alike.

The theme of this book is that the degenerative diseases are not the consequences of aging. Rather they are an unnatural condition created by man's "civilized" nutritional customs developed over many hundreds of years. A large and convincing body of scientific evidence, the subject of the chapters that follow, points in this direction. The weight of this evidence indicates that the common degenerative diseases are largely due to nutritional factors, and do not require explanation in terms of such concepts as heredity, inevitability with aging, stress, etc. While presently acknowledged by only a small segment of the

medical profession, recognition of the validity of the evidence upon which this viewpoint rests is gaining momentum.

This evidence demonstrates that the cure for many of the degenerative diseases also has a nutritional basis: as the offending dietary factors are removed from the food regimen, the symptoms of many of the degenerative diseases regress, often completely. These offending dietary substances are found characteristically in the food intake of people of the more advanced nations, but are generally absent from the diet of primitive peoples or the peoples of less developed countries, being usually associated with rich foods or refined food products.

Neither physical nor mental impairment is inevitable with aging. True aging need only bring a gentle loss of function over the life-span of the individual. The length of this span is unknown, but studies of certain population groups cited in these chapters point to an active life of at least a century as ordinary. The evidence indicates that decreased mental and physical agility--thought to be part of the aging process--in reality are merely functional losses produced by the degenerative diseases. Because of the crippling degenerative diseases--arthritis, gout, etc.--aging has been associated with lameness, stiffness of joints, and forced inactivity. With freedom from disease, activity is not limited to the young. Seventy-five year olds are running marathon races--26 miles of continuous running. Even 90-year olds run as a routine; the sports publications regularly list 80-90 year olds in running contests.

Osteoporosis, the "porous bones" of the aged, is a result of the forced inactivity of older people brought on by degenerative diseases. With activity, bones strengthen and become dense.

Due to the destructive effect of arthritis on the sliding surfaces of the joints, knees, hips, etc., it was thought that cartilage is subject to "wear and tear", and once it wears out, function ends. It is now known(2) that this is not true. Cartilage maintains its elasticity indefinitely, and lasts as long as there is circulation to support its needs. Elderly people, if freed from the forced inactivity brought about by degenerative diseases, could achieve an activity level greater than that of many youngsters.

Degenerative diseases also produce senility by preventing sufficient circulation to the brain. Experiments reversing senility by breathing oxygen have been achieved in test groups.(3)

The same program that prevents degenerative diseases permits a maximum level of oxygen in the blood and tissues of the body. This protects continuously against insufficient circulation in the brain and entire body. Senility is prevented, and functions, such as sight, hearing, and the other senses, perform at high efficiency.

It is now being realized that the seeds of degenerative disease are planted in children, with unnatural nutritional practices daily poisoning their bodies. By the time they are young adults, their bodies are damaged and are well on the way to loss of function. For example, the problem of atherosclerotic deaths in the young is very real. At the 5th annual meeting of

the Association of European Pediatric Cardiologists held in Rome recently, a topic discussed concerned 44 children--under the age of two--in whom blockage of major vessels to the heart had produced extensive damage, as revealed by post-mortem examination. The arterial damage in these children was no different from the common findings of atherosclerosis in adults: the linings of their young arteries showed all the typical damage associated with this disease.

Without studying the evidence, the postulation linking diet and the scourge of degenerative disease may seem farfetched, until one reflects upon some basic biological facts. All animals, man included, have a diet that emerged from the long-term experience of the species in nature over many thousands of years. Now, man no longer eats food his body was designed to eat, but has created a synthetic diet--the penalty for which is to endure the adverse effects of short-term experience. The more man's diet departs from foods to which he is biologically suited, the more the adverse effects.

The significance of this may be appreciated somewhat by comparing the intake of such synthetic diets with the intake of individual drugs, the ill effects of which are sometimes not discovered even after years of widespread usage. Foods which man is not biologically adapted to consume--for whatever reason--act as "food drugs", producing countless undesirable side effects in the body, some clinically observable, others too subtle to detect.

What was man designed by nature to eat? While it is possible to learn about the natural diet of man's relatives, the primates, by observing them in nature, only little information about man's natural diet can be gained directly. We can, perhaps, make some tentative conclusions by deduction. We note, for instance, that the diet of primitive peoples must be closer to a natural diet than is the diet of more civilized peoples--being less processed and closer to the grown state, and also because this diet confers freedom from degenerative diseases. But there are more direct ways, too, to attempt to reconstruct an approximation of man's natural diet. Studies of the reactions of the body enzymes and organs to various foods as well as other types of biochemical tests could aid us in this quest.

Until man's natural diet becomes known to us, we can only grope at what seems to be an optimal diet, avoiding what trial-and-error experience teaches us to be harmful. In this manner, utilizing many hundreds of ingeniously designed laboratory and clinical investigations with human and animal subjects, as well as carefully conducted field observations of dozens of populations consuming diverse diets, it has been possible to single out with certainty those factors in diet responsible for the growing epidemic of degenerative diseases, as the studies reported in the pages to follow will demonstrate.

These volumes are an attempt to bring to the reader, lay and professional, some of the impressive data amassed by many of the important studies which have tied the common degenerative diseases to factors present in our modern diet. In bringing together and analyzing these studies, certain conclusions grew apparent. One major conclusion is the interrelatedness of many

of the degenerative diseases, which tend now to be regarded as discrete pathological entities. (Let it be noted that many clinicians have observed the presence of many--and even of all!--of the degenerative diseases in various states in the same individual.)

The evidence indicates that they do indeed have common causes: the excessive intake of fat and cholesterol over long periods of time, as well as the habitual consumption of simple carbohydrate foods. The sustained elevated blood lipids--bloodfats and cholesterol--so created provide the underlying conditions for many of the degenerative conditions, as will be developed in detail in the chapters that follow.

The common origin of many of the degenerative diseases, in addition to the common therapy to which they respond (i.e., withdrawal of the offending dietary substances and replacement by other suitable foods), has led us to view these ailments as really being one disease, manifesting diverse symptoms. This concept will be dealt with throughout these writings.

Another major conclusion from a careful study of the mountain of impressive evidence on the subject concerns the failure of present forms of therapy used for the degenerative diseases. This failure arises from the neglect of the root cause: the nature of the patient's diet. If one were sick from arsenic poisoning, the crux of proper treatment would be stop ingesting arsenic. So long as the patient continued to ingest arsenic, the condition could be expected to worsen, regardless of the therapy employed.

The "arsenic" which we ingest in our diet--day after day, meal after meal--comes in the form of fats, cholesterol, and simple carbohydrates. While the body can use and tolerate these substances to a point, in excess they behave as toxins with the capacity for producing many different kinds of symptoms as they are ingested over long periods of time. The circumstances that lead to the development of particular degenerative diseases are discussed in the chapters that follow.

The ill effects of our daily dose of "arsenic" are compounded by our generally sedentary lifestyle, which enables the degenerative diseases to progress even faster. The mechanisms by which this occurs are the subject of the chapter entitled "Exercise".

Can valid insights be drawn second-hand by one who merely surveys the research of others? That this can be done--at times with brilliant and revelationary results--is beautifully illustrated by the work of two eminent biologists, Watson and Crick, who collected and analyzed data from work entirely done by other investigators, then developed their revolutionary interpretation of the structure of DNA, which gave birth to molecular biology. There was no first-hand observation or research involved.

We have collected some of the important data concerning the causes of the degenerative diseases, but little interpretation is required. All the facts necessary to substantiate the concepts linking high fat, high cholesterol, and simple carbohydrates in the diet to the degenerative diseases are there and have been demonstrated. Why have they not been acclaimed and implemented?

Here we would need to enter into the realm of conjecture: the author prefers to leave such philosophical riddles to others.

The message of this book is this: one need not fall prey to the degenerative diseases. Coronary heart disease, angina, diabetes, arthritis, glaucoma, hypertension, gout, and some cancers are entirely avoidable. There is a price to pay for health, however: this is a return to simpler foods and a more active existence. If you are not prepared to pay this price, the reading of this book will not benefit you; if you are, the evidence assembled in the chapters of this book will convince you that you will be rewarded for your investment with the good health and long life which nature intended for you. Each degenerative disease is discussed in detail; the facts and studies presented will support the concept that a simple nutritional and activity program is all that is required to eliminate virtually all of the modern plagues of degenerative diseases.

Aging research has attracted scientists worldwide and many approaches are under investigation at the present time. The nutritional approach, as supported by the data presented in these chapters, must be given serious attention because it offers an immediate solution to problems of aging in our culture.

Nathan Pritikin
Santa Barbara, California
1973

REFERENCES

1. Blumenthal, H. T. Letters to the Editor. Sat. Rev. p. 19, Dec. 1970.

2. Sokoloff, L. Elasticity of Aging Cartilage. Fed. Proc. 25: 1089-95, 1966.

3. Arehart, J. L. Retaining Memory in Older People. Sci. News 101: 188, 1972.

PART I

ATHEROSCLEROSIS
ANGINA PECTORIS
HYPERTENSION

ATHEROSCLEROSIS (PLAQUE DISEASE)

The origins of atherosclerosis have become manifest through the systematic observation of populations and laboratory and clinical research dating over the past three decades, indicating incontrovertibly a causal relationship with diets high in fats and cholesterol.

Atherosclerosis and its now-established relationship to "rich" diets have a long history: the appearance of plaque-filled arteries has even been demonstrated by pathologists in mummies exhumed from the Egyptian tombs. The mummies, being the remains of members of the Egyptian ruling classes, perhaps reflect the consumption of a privileged (i.e., "richer") diet. Plaque-filled, partially calcified vessels were found by the pathologists even in individuals who were still relatively young, the damage appearing very much like what is observed in modern victims of this disease.(1)

The cause of this age-old killer lay shrouded in mystery over the millennia. Even in our time "hardening of the arteries" is regarded as an inevitable form of physical deterioration, a natural though poorly understood process of aging. Not until World War II, when large populations were deprived of their standard diets due to austerity programs caused by the scarcity and inaccessibility of many foodstuffs ordinarily regularly consumed, was there any appreciable insight into the etiology of the disease.

I. THE UNDERLYING CAUSES BECOME KNOWN

Lessons from World War II provide earliest clues as to dietary origins of atherosclerosis.

A review of this evidence begins with the earliest diet trial, known by its code name as "World War II: European Theatre." "Designed" by the forces of history, this first large-scale experience with a low-fat, low-cholesterol diet lasted for five years and involved upwards of 50,000,000 people. Initial intake was 40-50% of total calories from fat and cholesterol in quantities averaging 600 mg. per day. During the five-year "experimental" period, cholesterol intake was dropped to less than 300 mg. per day and fat calories to below 25% of total calories. Coronary heart disease reached a plateau during the first year of the diet, then dropped to its lowest value in the five-year period, with an approximate 30% reduction in coronary heart deaths. At the end of the five-year period, fat and cholesterol intake returned to and rapidly exceeded pre-diet levels.

A summary of the death rates for circulatory deaths in a number of European countries for the period 1939 to 1947 is of interest,[2] especially in comparison with data from the U.S. which did not undergo the severe wartime rationing of fats and cholesterol-bearing foods. Whereas the mortality rate in the European countries in the table shows a substantial drop in the war years, there was no comparable drop for the mortality rate in the U.S. during this period.

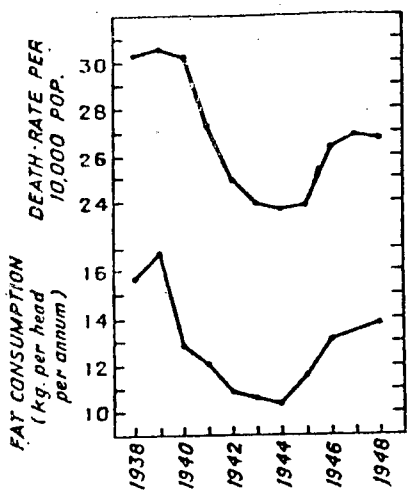
Mortality (in Percentage) from Circulatory Diseases during 1939-1947

Deaths for 1939 = 100%

	1939	1942	1944	1946-7
Finland	100	55		72
Norway	100	70	50	74
France	100	80(est.)		100(est.)
Sweden*	100	80		110
U.S.	100	116		133

*Moderate rationing during war (not a belligerent)

The graph below depicts an especially significant study which correlates the drop in mortality rate due to atherosclerosis with a drop in the consumption of dairy fats and cholesterol in Norway, telling evidence of the relationship between the two.



Mortality in Norway from circulatory diseases corrected for age; consumption of fats in form of butter, milk, cheese and eggs. (Malmros)

In 1946, a U.S. physician, impressed with the wartime data indicating a correlation between lowered fat and cholesterol intake and decline in circulatory deaths, decided to make a study[3] among his own patients. One hundred subjects with proven cases of coronary infarctions were involved. Fifty of the subjects were kept on their standard diet; the other fifty were placed on the experimental low-fat, low-cholesterol diet, as shown below.

	50 CONTROL	50 ON EXPERIMENTAL DIET
Calories per day (Est.)	1,500-2,000	1,500-1,800
Protein "	90 gms.	90-120 gms.
Fats "	100 gms.*	20-30 gms.**
Cholesterol "	800 mg.	50-100 mg.

*50% total calories **15% total calories

The 100 patients were followed until all of the controls had died. The table below summarizes the results.

	LOW-FAT, LOW-CHOLESTEROL SERUM VALUES Mg.%			% SURVIVING	
	Total Lipids	Cholesterol	Triglycerides	Control	Exper
Start	840	312	236	100%	100%
End of 3 yrs.	571	220	120	70	86
End of 8 yrs.	571	220	120	24	56
End of 12 yrs.	571	220	120	0	38

Lipid values for the control group are not shown, since no substantial changes occurred in these subjects. The survival rates substantiate the advantages of the low-fat, low-cholesterol diet. Even though the cholesterol and triglyceride levels only reached a low of 220 mg. and 120 mg., respectively, 38% of the 50 subjects on this diet survived, whereas all of the 50 controls died.

In a later study, a group of 280 patients[4] went on a low-fat, low-cholesterol diet for four years. One hundred fifty-five of them followed a diet of 20-25% of total calories in fat and a maximum of 200 mg. daily of cholesterol. The control group of 125 was on the standard U.S. diet with a fat intake of 40-50% of total calories in fat and a cholesterol intake of 500-1,000 mg. daily. All 280 patients had had a previous myocardial infarction, so that this study was similar to the previous one. At the end of the four-year diet period, the control group had suffered four times as many new coronary infarcts and four times as many deaths as had the low-fat diet group.

The interest in searching out a possible correlation between cardiovascular incidents and diet continued to grow in the United States, resulting in the organization of a number of large group studies designed to isolate the risk factors responsible. We now turn our attention to these studies and to the important conclusions at which they arrived.

New population studies determine relative role of possible disease factors.

Elevated cholesterol and triglyceride levels emerge as most significant factor among groups with high disease incidence.

Studies establishing role of cholesterol as major risk factor.

One of the earliest of these large group studies began in 1947 in Minnesota[5] under the direction of Ancel Keys, involving as subjects 281 apparently healthy business and professional men. Several parameters were noted in annual examinations over a period of many years--blood pressure, ECG, skin folds and blood tests, values for which were recorded together with histories and complaints.

Certain patterns became evident in the first 15 years of the study: the only statistically significant variables were the systolic blood pressure and the serum cholesterol, with cholesterol being the most significant. The higher the cholesterol, the greater the death rate.

During these years, other independent studies under different investigators were confirming the findings of the Keys group. The results of the various studies are summarized in the table below:

GROUP	NUMBER OF YEARS	NUMBER OF PEOPLE	NEW CHD CASES CHOL < 200	NEW CHD CASES CHOL > 200	INITIAL AGE GROUP
Minnesota	15	281	100%	560%	45-55
Framingham	8	1537	100%	750%	30-49
Framingham	8	590	100%	300%	50-59
Albany	6	1661	100%	300%	39-55

In the Minnesota study, if the number of new coronary heart disease cases for those with cholesterol levels under 200 mg. are represented as 100%, for those with levels from 200-219 mg., new cases are 117%; from 220-239 mg., new cases are 250%; from 240-259 mg., new cases are 400%; and from 260+ mg., new cases are 560%. The risk was shown to be proportional to the cholesterol level. Relative weight had the least significance and cholesterol level was not significantly related to any of the other variables. In the 20-year follow-up study,[6] cholesterol level still ranked as the major predictive factor out of 20 characteristics tested.

The Framingham study, cited in the table, was one of the most important of these investigations so far as number of participants and period of observation are concerned. Begun in 1948, the project examined 5,209 men and women aged 29 to 62 years at two-year intervals. All of these subjects were initially free of coronary heart disease or vascular disease. As disease symptoms appeared, certain correlations became evident based on their statistical occurrence. Twelve years after the study started,[7] cholesterol level continued to be the principal predictor of coronary heart disease: a cholesterol level of 260+ mg. in the 30-49 year age group produced 400% more cardiovascular events than did a cholesterol level of 220 mg. or lower. (This compares with the eight-year incidence of 300% more cardiovascular events.) Cholesterol levels were also found to be significantly related to strokes in this same age group. Men and women were equally affected when cholesterol level and percentage of cardiovascular events were correlated, although women had a lower incidence of coronary heart disease in the same age group.

Findings from international investigations coincided in important respects with the national studies, such as the Minnesota

and Framingham tests. A very ambitious program involving 18 population groups in 7 countries was begun in 1956, largely planned and implemented by Ancel Keys,[8] in which 12,770 men aged 40-59 years were examined, questioned and followed in great detail, with the aim of isolating coronary heart disease risk factors. Extraordinary efforts were taken to assure the use of test procedures that would guarantee the reliability of the final data. Clinicians were briefed on the use of standardized forms to be employed in all of the test countries for the recording of the examinations; uniform procedures were utilized including a 12-lead ECG and a 3-minute exercise tolerance test; and much of the data classification, including ECGs and some of the blood analyses, such as cholesterol levels, was done at a coordinating center at the University of Minnesota, in order to ensure identical conditions. Keys personally visited the various test areas over the years to be certain of the coordination of methods and reporting procedures.

An important new dimension was added to this study. This was the determination of the food intake of the participants. Special dietary survey teams carefully analyzed everything eaten by a random sampling of subjects in each of the groups studied. The analysis was conducted over several 7-day periods at different seasons of the year, so as to arrive at a more accurate average of total nutrients and their distribution into the various food groups. In performing the food analyses, duplicate meals of foods to be consumed were prepared, weighed, then chemically analyzed. While it would have seemed simpler to have resorted to tables of food compositions for these determinations, this was ruled out because of concern that discrepancies might arise due to differences in actual compositions of foods grown in different localities.

This excellently designed study yielded important data confirming and enlarging upon earlier investigations:

1. The incidence rate of coronary heart disease was directly related to cholesterol level;
2. Relative body weight or body fatness were not related to coronary heart disease;

3. Cholesterol levels and coronary heart disease rate were not related to protein intake.

Average cholesterol levels were directly and proportionately related to intake of saturated fat--to be expected since foods with cholesterol normally contain principally saturated fats. Striking differences in coronary heart disease death rates in various parts of the world were established. Finland, for example, was found to have an 800% higher coronary heart disease death rate than Japan, corresponding to the fact that the percentage of men with a cholesterol level over 260 mg. was shown to be 700% higher in Finland.

In another interesting study comparing diet to coronary heart disease, nearly 3,000 Benedictine and Trappist monks from 30 monasteries were observed for a six-year period beginning in 1958.[9] Benedictines eat a typical American high-fat diet, while Trappists eat a comparatively low-fat diet with little animal matter. During the test period, the Benedictines developed about 350% more coronary heart disease than did the Trappist monks, while total lipids and cholesterol levels were also found to be higher in the Benedictine group.

In a three-year Scandinavian study involving 7,000 40- to 50-year old male industrial workers,[10] relationships between cholesterol level and weight to coronary heart disease and stroke were found to be similar to those in studies in the United States. In the 28 cases of stroke, cholesterol levels were higher than in non-cases; 24 new cases of atherosclerosis were found to be related to cholesterol levels; and those with cholesterol levels of 325+ mg. had 400% greater incidence of coronary heart disease than those with 200 mg. or less. No significant relationship was found between body weight and either stroke or atherosclerosis.

Studies establishing role of triglycerides as another major risk factor

The role of triglycerides as an independent risk factor became evident in the early 1960's. In a study in the San Francisco area, 3,182 men aged 39-59 years were followed for

4-1/2 years.[11] Significant risk factors were found to be both cholesterol and triglyceride levels. Data from this study are summarized below:

Study	CHD Rate/1000	Cholesterol Level Mg.	Triglyceride Level Mg.
Choles. only	4.4	< 220	
	17.5	> 259	
Triglycer. only	5.2		< 100
	14.9		> 176
Choles. and Triglycr.	20.8	> 259	> 176

A cholesterol level of 259+ mg. was found to produce a 400% greater incidence of coronary heart disease than a level under 200 mg. A triglyceride level of 176+ mg. produced a 300% greater incidence of coronary heart disease than a level under 100 mg. The lipid risks were cumulative, since a cholesterol level of 250+ mg. and a triglyceride level of 176+ mg. produced the maximum risk factor, almost 500% more than the lowest values.

The role of triglycerides as an independent risk factor was confirmed by a Swedish study,[12] in which 3,168 men were followed for nine years. Cholesterol and triglyceride levels were found to be significantly related to coronary heart disease. In fact, triglycerides were found to be as great a risk as cholesterol. The following table summarizes the data:

Cholesterol (mg./100 ml.)	< 280	> 280	< 280
Triglyceride (m mole/1.)	< 1.80	< 1.80	> 1.80
CHD rate/1000	10.2	20.4	36.9

With a triglyceride level under 1.80, a cholesterol level above 280 mg. caused a 200% greater incidence of coronary heart disease than was produced by levels under 280 mg. With a cholesterol level under 280 mg., a triglyceride level of 1.80+

produced 360% the incidence of coronary heart disease found below 1.80. There was no risk factor shown for weight in this study, in accordance with findings of the various other studies.

Direct confirmation linking diet and high coronary heart disease incidence

Comparison death-rate studies for coronary heart disease in different countries have been criticized because of lack of uniformity of diagnostic and pathological techniques in determining cause of death. This can introduce problems in ascertaining the role of dietary fat in deaths due to coronary heart disease in areas where various types of food is consumed. Any such basis for criticism was met by IAP--the International Atherosclerosis Project.(13)

IAP coordinated the gathering of autopsy material and data from 15 cities in 14 nations, involving 22,509 autopsies of persons aged 10-69 years of age who died during 1960-65. To determine the amount of arterial damage in these individuals, the aorta and coronary and cerebral arteries were trimmed, numbered and prepared according to a standardized procedure, then sealed in plastic bags. Evaluations of intimal damage on a 1-20 scale were made at grading centers by pathologists three of four times yearly, in order to assess the amount of intimal surface covered with plaques.

The results of this comparative quantitative determination of intimal damage in the arteries and correlation with the related data were as follows:

1. Intimal damage was proportional to coronary heart disease;
2. Both diabetes and high blood pressure worsened the damage;
3. Weight, obesity, or skinfold measurements had no correlation to plaques on the intima;
4. Cholesterol level was statistically significant in relation to plaque coverage of intima;
5. Saturated fat intake was statistically significant in relation to plaque coverage of intima;

6. There was no relationship between hard- and soft-water areas and coronary heart disease and plaque coverage of intima;
7. Populations with high intake of saturated fat and high cholesterol level had the greatest amount of surface area damage by plaques.

It is difficult to overrate the importance of this work. No longer can it be said that there are populations immune to coronary heart disease, or that race makes a difference, nor can other rationalizations be offered to discount the environmental cause of coronary heart disease. This study unequivocally establishes the link between diet and coronary heart disease.

The investigations we have cited implicate diet as a major risk factor in coronary heart disease. Besides diet, other risk factors have been well established--high blood pressure, diabetes, and hyperglycemia. The common factor behind all these risk factors--elevated cholesterol level--was demonstrated in an important study in which 13,148 men were given frequent health examinations in a period from 1950 to 1964. Analysis of the data from this 14-year period disclosed that cholesterol level was the significant factor in all these disorders.(14)

Observations of native populations with low disease incidence

Populations on low-fat, low-cholesterol diets have consistently low disease rates

If cholesterol level and fat intake seem to be high risk factors, one could hypothesize that populations with low cholesterol and fat intake should have a low coronary heart disease rate. Populations consuming such diets have been studied and the data are of interest.

Bantus of central and southern Africa have not yet entered the stream of civilization sufficiently to change their age-old life patterns. Their food intake limits fat to 10% of total calories compared to 40+% in the U.S. diet. Daily cholesterol intake is probably under 100 mg. This is reflected in their blood levels.

In healthy Bantu schoolchildren, lipids are very low: triglycerides average 48 mg., cholesterol levels are from 90-120 mg., and fasting glucose is so low at 43 mg., that it would be considered hypoglycemic in American children.

The incidence of coronary heart disease among the Bantu is almost zero. At the Knana Nune Hospital, which has 300 beds for Africans, the autopsy rate is high, but no deaths from coronary heart disease were found over a 5-year period (1948-53). During this same period, in the European wing of 40 beds, 23 deaths were attributed to coronary heart disease.[17] In autopsies performed at the hospital on 42 Africans and 22 Europeans who had died suddenly for any reason, only one African had extensive atheroma, while 35 lacked even a plaque or trace of damage. By contrast, all 22 Europeans had extensive damage, even a youth of 15.

Natives of New Guinea eat little protein, probably 30-40 gm. per day, or 7% of total calories. Fat intake is less than 10% of total calories. Blood pressure and cholesterol level remain virtually unchanged in these people from youth to advanced age, with cholesterol levels clustering around 100 mg.[18] Necropsies have been performed on 600 natives and only one death was attributable to coronary heart disease, while very few plaques were found in any of the arteries. Hypertension is as rare as coronary heart disease; in fact, upon reaching middle age, there is a drop of about 10 mm. in the average diastolic pressure, and a drop in weight of about 10 pounds.

The lack of authentic age records poses difficulties in most studies of primitive peoples, making it difficult to assess potential life span in the absence of coronary heart disease. This problem was not encountered in studies in Ecuador, where local parishes of the Roman Catholic Church maintain baptismal records going back many generations with great care. In one Ecuadorian village of 800 people, with over 400 adults (i.e., over 15 years old),[19] 38 persons were over 75 years, a number were over 100 years, and the oldest, a male, was 121 years old. The adults work all their lives, often into their 90's. Diet consists of simple foods, mainly carbohydrates, with 9% protein and 8% fat. Beans,

corn, brown rice, and considerable quantities of fresh vegetables and fruits provide the major source of calories; animal protein is eaten only once or twice weekly. Cholesterol levels were found to range in the 140-160 mg. area. In ECGs made of the 20 oldest persons, only two were found to have any evidence of coronary heart disease.

The Ethiopian diet and levels of serum lipids fall about midway between those of primitive peoples and the typical Western population.[20] Their food intake, consisting of grain primarily, is supplemented by legumes and other vegetables, some fruit, meat, fish, eggs and additional fat. The combination provides 12% in protein, 18% in fats, and the balance in carbohydrates. Blood values of about 150 men and women between ages 30 and 70 years were found to correspond with their diet. From 20-50 years, the cholesterol level averaged 160 mg.; from 50-59 years, it rose to 186 mg.; and at 60 years and over, it dropped to 176 mg. Since autopsies are not permitted, X-ray studies of the aorta were made on 52 persons from 50-80 years old. Signs of coronary heart disease were found in 30 of these people. About the same number had ECGs that could be interpreted as positive for coronary heart disease. Government records indicate that 1.5% of all recorded deaths are due to coronary heart disease.

The freedom from coronary heart disease enjoyed by some population groups permits them to develop an unusual cardiovascular conditioning. A tribe of Indians in Mexico was recently studied[21] whose diet consists of corn, beans, squash, wild plants and occasional fish or meat. This tribe of 50,000, mainly farmers, have a national sport similar to kick-ball, in which a wooden ball is kicked continuously for distances of 100 miles or more--just for fun. The pace averages 6-7 miles per hour, and the only reason a runner drops out prematurely is because of leg cramps or urinary problems. No one questioned could remember a dropout because of shortness of breath or chest pain. Chest X-rays of runners showed hearts of normal size and contour; there was no "athlete's heart" or enlarged heart. ECG studies after a race showed no signs of chamber enlargement or any other abnormality. Blood pressures of

runners were taken during the race after 14 miles had been run; diastolic pressure was found to be lower than resting levels, even though pulse rates were averaging 155 during the run. These observations lead us to conclude that we have hardly scratched the surface of man's physical capability when in his healthy state!

Over 25 investigations of populations consuming low-fat diets show a low cholesterol level and a consistently low rate of coronary heart disease. No exceptions have been found.[22]

Native populations adopting civilized diets lower "immunity" to coronary heart disease

Is it possible that the populations studied that seem to be exempt from a high incidence of coronary heart disease are biologically unique, as some have claimed, and that diet is not the prime factor responsible for their low rate of coronary heart disease? If this is the case, members of these populations should enjoy similar immunity to coronary heart disease wherever they live, regardless of dietary changes that may occur in their new homelands. Studies on the migration of native groups to areas where they consume more fat have been made which help to answer this question.[23]

Japanese were studied in Japan, then in their adopted homeland of Hawaii where fat intake is intermediate, and finally in their last place of residence in Los Angeles, where the amount of fat they consume is similar to that in Western diets. In Japan, fat accounts for less than 10% of total calories (except for physicians, whose level averaged 22%!); Hawaiian men averaged 30% of their total calories in fat; and those in Los Angeles consumed close to 40% of their total calories in fat. Cholesterol level was found to be linearly related to percentage of fat intake, and death rates from coronary heart disease in the group studied (men aged 40-49 years) were found to parallel the rise in fat intake and increase in cholesterol level. Thus, in Los Angeles, the death rates among Japanese are comparable to those of Caucasians.

Comparison of arterial damage in young subjects from areas of high and low incidence of coronary heart disease

Coronary heart disease had been thought by many to be a disease of middle and advanced age. A study made during the Korean War (1953) dispelled these illusions.(24) Autopsies were done on 300 American soldiers killed in battle in whom the coronary arteries were evaluated for coronary heart disease. Although the soldiers were as young as 18 years and had an average age of 22, gross evidence of atherosclerosis was found in 77%. In 20 cases, where the arteries had closures exceeding 50%, the average age was only 22.6 years. No evidence existed that hypertension contributed to these findings. Seven of the men had closures of 98+% of the coronary arteries, and five of these were 22 years old or younger. Plaque formation in these diseased coronary arteries was typical, with the intimal lesions resembling those normally seen in the United States.

A series of Japanese men in the same age group was analyzed; no luminal narrowing over 50% was found, in marked contrast to the findings in the autopsies of American soldiers. These autopsy results correlated with the low incidence of coronary heart disease in Japan. Reports at that time (1946-51) indicated only 14 cases of coronary heart disease out of 1480 autopsy reports in a population of 2,000,000.

If arterial damage is so advanced at 18 years of age, when does it start? From existing evidence, it commences in early childhood when the diet of our culture begins to govern our nourishment. "In our society an endless succession of fat-loading meals is the most important etiological factor in coronary heart disease. One effect of this kind of high fat diet is hypercholesterolemia, and this is so universal that the so-called norms are simply standards for preclinical coronary disease."(25)

How high is "safe" for blood cholesterol and triglycerides?

Many investigators are realizing that our "normal" cholesterol levels are not normal, but are pathological. A representative series of cholesterol and triglyceride values were determined in

1864 "normal" subjects and are given in the table below. The figures are for males, but females are quite similar.[26]

AGE	TRIGLYCERIDE MG./ML.	CHOLESTEROL MG./ML.
16-20	78	199
21-26	96	225
26-30	111	230
31-35	135	238
36-40	115	244
41-45	121	250
46-50	125	250
51-55	123	257
56-60	116	262
61-65	98	252

Values this high are not found in populations free of coronary heart disease; these values reflect an epidemic state in our society. The experience of Dr. Kannel of the Framingham Study led him to say: "moderate serum cholesterol elevations between 250 and 350 mg. constitute the bulk of the hypercholesterolemias that appear to be predisposing to the abundance of coronary heart disease as it appears in the population."[27]

The data amassed in Dr. Kannel's momentous study indicated that cholesterol level is the best indicator for predicting coronary heart disease. How high must this level be for a myocardial infarction to occur? It is unnecessary to guess. Ninety-one infarct cases were measured within 24 hours of their attacks; their cholesterol level values compared closely with the table of values for "normals" cited above.[28] Forty-one of the 91 cases had ischemia with chest pain, but no infarct symptoms; their cholesterol level averaged 245 mg. Nonfatal infarcts (37 cases) averaged 255 mg., and fatal infarcts (11 cases) averaged 266 mg. In the total group, cholesterol levels were as low as 180 mg. and over half had levels between 180 and 250 mg. At the time of their 3-month check-up following their heart attacks, the cholesterol level and triglycerides of the entire group was found to be higher than the initial values. The treating physicians were not apprehensive about these levels and made no attempts to lower them; they were accepted as being in the "normal" range.

The dilemma is well put by Dr. Kannel: "By usually accepted standards, hypercholesterolemia does not appear to be an essential feature of atherosclerotic disease in western civilization, as everyone appears to have high enough serum lipids to produce atherosclerosis. At the generally high lipid levels seen in Framingham and elsewhere in the U.S., the risk is simply proportional to the serum lipids.[29]

The information gathered from the various retrospective and prospective studies, some of which we have given here, is in agreement. The data point conclusively to this general dictum: low cholesterol levels (under 135 mg.) produce coronary heart disease-free populations; medium cholesterol levels (135 to 180 mg.) produce a low-to-moderate incidence of coronary heart disease; and Western U.S. levels (180 to 300 mg.) produce epidemic levels.

More evidence is derived from animal experimentation.

Fatal myocardial infarctions have been induced in primates by experimental diets

Animal experiments provide us with evidence of an entirely different nature--a direct proof corroborating the cause-and-effect relationship of diet and coronary heart disease. A fatal myocardial infarction due to diet-induced hypercholesterolemia was produced in an animal subject (monkey) for the first time in 1959.[30] It has been repeated many times since in primates, whose physiology is closest to that of man, as well as in other animals. The composition of the diet consumed in that earliest experiment was very similar to human diets (U.S.). Protein was 15%; fat (butterfat) was 42%; and cholesterol was 1.5 gm. per day. The cholesterol level of the controls in the experiment was maintained at 132 mg.; in the experimental monkey, cholesterol reached a mean level of 679 mg. (419-872 mg.). Xanthomatosis became evident on the tendons and skin of the monkey after two years on the experimental diet; and after 40 months on the diet, the fatal infarct occurred. The infarction was massive and involved about half of the left ventricular myocardium. Areas of damage showed healed, healing and acute infarcts all superimposed upon each

other. Six areas of the coronary arteries were partially or totally occluded. The appearance of the intima was strikingly similar to that in human arteries.

Further experiments confirmed these results. In one test, 69 baboons were separated into a control and experimental groups.[31] Fat content of the diet in the control group was 2%; in the experimental group fat content was 22% and, in addition, 15% of the diet consisted of dried egg yolk. After 18 months, the animals were sacrificed and their arteries examined. No lesions were found in the control animals, whereas the butter- and egg-fed experimental group had extensive lesions in all aorta samples taken. Although the experimental baboons were only three years old when sacrificed, these lesions resembled closely those found in old baboons who had died in captivity, as well as those of atherosclerotic human arteries. What is surprising is that the cholesterol level of the butter- and egg-fed animals averaged only 205 mg., an average figure for humans.

Ordinary human diets have also induced fatal myocardial infarctions in primates

One criticism of the cholesterol-feeding experiments is that the amount of cholesterol is higher than is found in the human diet. In an experiment with adult rhesus monkeys designed to overcome this objection,[32] dietary cholesterol was added in amounts comparable to the average intake of humans in the U.S., and fat was set at 40% of total calories, comparable to the average dietary intakes in the U.S. Four diets were given, varying only in the amount of cholesterol. After 18 months, the monkeys were sacrificed and the amount of cholesterol in their tissues measured. The data are summarized below.

Diet	Mg/100 Cal. Cholesterol Content	Cholesterol Level After 18 Months Mg./100 Ml.	Cholesterol Content of Carcass Mg./G.D. Wgt.
1	0	115	1.8
2	43	129	2.0
3	129	168	2.3
4	387	392	2.7

Increase in cholesterol intake was reflected in an increase in plasma and carcass cholesterol.

If the above study left any remaining doubts as to the role of diet in coronary heart disease, the next study to be cited should certainly have dispelled them,[33] for in this experiment nothing was added--neither cholesterol nor anything else. In this experiment with rhesus monkeys, coronary heart disease was induced just using a good average American diet. The study utilized two diets--one, the average American diet containing a daily cholesterol intake of 390 mg. and another, the prudent diet, modeled as closely as possible to the low cholesterol diet recommended by the American Heart Association. For average humans, the average diet would have been equivalent to about 1.5 gm. cholesterol and the prudent diet about 200 mg. cholesterol. Total fat intake, and especially saturated fats, were lower in the prudent diet.

After two years on the diet, cholesterol levels for the animals on the average American diet were 358 mg., while those for animals on the prudent diet of the American Heart Association were 250 mg. At autopsy, the differences became more apparent. On the typical diet, about 75% of the intimal area was damaged, whereas only 15% of the intimal area was damaged on the prudent diet. It should be noted that the so-called "prudent" diet produced 15 times the damage produced by the low-fat, no-cholesterol diets previously cited.[34]

<u>The relationship of hypocholesterolemia to plaque and xanthoma formation</u>

That plasma composition is the prime factor responsible for plaque formation was demonstrated in an experiment with dogs and rabbits[35][36] in which circulating hypercholesteremic blood caused plaque formation on synthetic vascular grafts made of such materials as dacron, teflon and nylon. No plaques appeared in the comparable synthetic vascular grafts of the control animals that were fed on normal animal feed (which is low in fat and has no

cholesterol), even after periods of time nine times as long as was required for the development of plaques in the experimental animals. The plaques that formed on the synthetic substrates were practically identical in appearance to those formed on living human intima.

Xanthomas in man have always been thought to be caused by hypercholesterolemia. Forty-three rhesus monkeys were used in an experiment designed to increase understanding of xanthomatosis and were fed a diet similar to that consumed by humans in the U.S.[37] Controls consumed a 20% protein and 4% fat diet; the experimental diet was 15% protein, 41% fat and, in addition, 1.2% cholesterol. Xanthoma formation started in five months; by ten months, 86% of the monkeys were affected. The appearance and extent of the cutaneous xanthomatosis was found to be statistically significant to the amount of hypercholesterolemia ($P<.001$). Cholesterol content of the tissues affected was as much as 100 times higher than in the controls.

The significance of extravascular storage of cholesterol as demonstrated by the formation of xanthomas remains to be explored.

Further corroboration: the cinearteriographic studies.
Direct human proof provided that "safe" cholesterol and triglyceride levels may coexist with atherosclerotic damage

About ten years ago techniques were developed making it possible to visually demonstrate narrowing and obstructive lesions in the coronary arteries by cinecoronary arteriography. This procedure has been used with thousands of subjects and it is now possible to analyze the findings so as to more clearly correlate lipid levels to arterial damage and to be able to predict coronary heart disease.

In one study, 723 men, all under 40 years of age, underwent cinecoronary arteriography[38] because of chest pain. If a coronary artery was found to have more than a 50% closure, it was considered significant. Forty-nine percent of the men were found to have an average of two main branches of the coronary arteries significantly narrowed.

The case of the youngest of the men, a 17-year old, typifies the difficulties in diagnosis. Here was a physically active male without symptoms or apparent cardiac abnormality. At a routine school examination an ECG was done and the tracing resembled an anterolateral myocardial infarction. Blood studies were made, but were considered quite normal: cholesterol - 184 mg.; triglycerides - 122 mg. The cineangiography revealed the unexpected--a total occlusion of the anterior descending coronary artery along with well-established collaterals. Three years later the young man was quite active and asymptomatic.

The case of this young man seems to defy understanding because under current clinical judgment he was in the normal lipid range and his problem would never have been suspected if it had not been uncovered in the routine exam. However, further perusal of the data helps to clarify the cause of his occlusion. The most important correlation to significant lesions, as demonstrated by cineangiograph findings, is to be found in the level of serum cholesterol, as shown in the table below.

Serum Cholesterol Mg./100 Ml.	Significant Lesions % of Total Cases
< 200	20
200-225	38
226-250	48
251-275	60
276-300	77
301-350	80
> 350	91

These results confirm the data in the primate studies previously cited, viz.: arterial lesions are directly proportional to cholesterol levels x length of time of exposure to these levels. The notion that a cholesterol level of 184 mg. (the 17-year old's level) is "normal" or safe has a very weak foundation. Populations where coronary heart disease is essentially nonexistent do not have levels over 135 mg. and this level persists throughout their lifetimes. Based on the levels occurring in these populations, normal cholesterol levels should be 70 mg. to 150 mg. and normal triglyceride levels should be 35 to 75 mg. In this range, in both

man and closely-related animal groups, coronary heart disease ceases to be a danger.

Problems related to current methods of diagnosis are clearly brought out by the case of the 17-year old, discussed above, and similar cases. Fifty percent of those with total occlusion of the right or circumflex coronary artery in the 723 men undergoing cineocoronary arteriography had no ECG evidence of myocardial infarction. Of the 60 men who had two arteries totally occluded, only 30% showed ECG evidence of myocardial infarction. Even with three coronary arteries totally occluded, only 25% showed ECG evidence of myocardial infarction. Cholesterol level in this group was a better predictor of coronary heart disease than was the ECG.

Lipid levels accurately reflect degree of atherosclerotic damage

To illustrate how accurately cholesterol and triglyceride levels can predict coronary heart disease, it is of interest to analyze the findings from another group of 450 men who had undergone coronary cinearteriography because of possible heart disease.[39] These men ranged in age from 28 to 70 years. The triglyceride levels alone had a predictive value of about 65% that of the cholesterol level; both triglyceride and cholesterol levels together had the best predictive value, but there was no single better predictive value than cholesterol level.

At a cholesterol level of 130 mg., coronary heart disease incidence was 11%; at 370 mg., it was 85%. These figures agree closely with the previous study and with other large studies.[40] At every increase in cholesterol level, there is a corresponding increase in the incidence of coronary heart disease as shown by direct visual evidence. At age 28, the lowest age studied in this group, a combination of cholesterol level at 140 mg. and triglycerides at 60 mg., gave the lowest amount of visual evidence of coronary heart disease--0.5%. With a cholesterol level of 360 mg. and triglycerides at 540 mg., the incidence of coronary heart disease rises to 72%, an increase of 140 times.

To prove the reliability of the findings cited above, a prediction test was done with a new group of 60 patients. The test

was performed on a double-blind basis, using the results of the study with the 450 patients as predictors. After blood tests were made, an independent score was arrived at for each subject based on age and cholesterol and triglyceride levels. Using these values as predictors, 35% of the group had probabilities of over 90% and, therefore, significant closures of the arteries were anticipated for these 21 patients. Actual arteriography showed that 20 out of the 21 had such lesions, a 95.2% successful prediction.

It is obviously unnecessary to guess whether elevated lipids can cause coronary heart disease--a 95% accurate prediction on a double-blind basis makes it a certainty. The only remaining question is how much coronary heart disease one wishes to have and at what age. The data from this study indicate that by "choosing" to have cholesterol levels over 140 mg. and triglyceride levels over 60 mg., one can accurately plan to develop coronary heart disease! No longer does one have to be surprised by an infarct.

The results of this study and others which we have cited provide a potent argument for creating new norms for cholesterol levels of a maximum of 160 mg., and of optimal levels under 125 mg.

How the atherosclerotic plaque is formed: a hypothesis

The environmental conditions in the blood which precede plaque formation

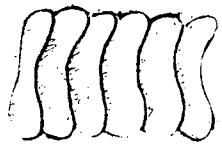
Sludging of erythrocytes due to high levels of serum lipids and effects on circulation

The previous studies have clearly demonstrated the cause-and-effect relationship between blood lipids (cholesterol, triglyceride) and coronary heart disease. However, the mechanism by which the actual disease process is created is not yet fully understood. Certain facts can be cited and gaps in knowledge hypothesized, nevertheless.

Diets containing fat in the concentration found in ordinary U.S. diets (40-50% of total calories) cause abnormal changes in the shape and size of erythrocytes as well as producing a clumping and adhesion between these cells.[41] Although this aggregation effect ("rouleaux formation") was first observed over 100 years ago, it

has failed to receive sufficient attention from present-day clinicians.

The harmful effects of rouleaux formation have been



Rouleaux Formation ("Roll of coins")

effectively demonstrated in a study with hamsters[42] whose cheek pouches are sufficiently transparent to permit the erythrocytes to be seen as they flow through the capillaries. After the hamsters were fed a large cream meal, the erthrocytes were observed to start to adhere to each other, then to the endothelium of the blood vessels. Rouleaux formation appeared first in small clumps, then in larger aggregates. This sludging of the blood gradually built up to a peak in about five hours. During these hours, for various periods of time, circulation slowed and in some capillaries stopped.

The cause of the circulatory stoppage is mechanical. It happens in this way. The erthrocyte is usually about 7.5 microns in diameter, but is able to pass through a 3.5 to 4 micron capillary by bending or folding at its very thin center. However, in the rouleaux condition, the aggregate formation now is 7.5 microns at its smallest dimension and is unable to fold like the single cell and pass through a 4-micron capillary. The clumping into rouleaux groupings also decreases the oxygen-carrying capacity of the cells severely as a considerable area of their surface is unavailable for oxygen transfer in this condition. Reduction of oxygen-carrying capacity in the hamsters after a large cream meal was as much as 35%. In an individual with angina or coronary insufficiency, a comparable reduction could be a serious problem.

Adhesiveness of platelets has also been experimentally demonstrated in humans by the feeding of a fatty meal.[43] Lipemia has been shown to be responsible for still another effect relating

to platelet activity. Considerable work has demonstrated that high lipid levels reduce the clotting time in man,[44] providing a stimulus for thrombi formation. In fact, pigs eating diets rich in egg-yolks will form larger thrombi from flowing blood than do controls on a low-fat diet.[45]

The ingestion of simple carbohydrates, such as sugar, raises lipid levels indirectly, producing the same effect on platelet stickiness as does fat intake.[46] Blood lipids are thus raised by either fat or simple carbohydrate ingestion, both of which are in excess in the average American diet.

Degenerative changes in erthrocytes due to high blood lipids and consequences

Red blood cells are known to be susceptible to degenerative changes depending upon the blood composition. If the cholesterol level is elevated in humans, the red blood cell membranes accumulate cholesterol, enlarge, and become distorted.[47] In animals, this phenomenon can be observed more closely.[48] When animals are fed diets to which cholesterol has been added, they develop an anemia due to hemolysis. There is a swelling of the erythrocyte membranes as observed in humans, which in the animals leads to destruction of the cells and deposition of cholesterol in various body organs such as the spleen, liver, kidneys, lungs, etc. This phenomenon was not lessened by intake of large amounts of protein or vitamin C or E, since it was not caused by nutritional deficiency but by the toxic effect of hypercholesterolemia.

Lipemia reflected in high concentration of cholesterol in arteries, providing basis for atheromas

Necropsy data have confirmed that the plasma cholesterol level is directly proportional to the amount of cholesterol in the artery linings. Twenty-one patients had blood samples taken one week before death and at necropsy their aorta intimas were analyzed for cholesterol content.[49] The relationship is shown on the next page in the table.

Cholesterol Last Week Before Death Mg./100 Ml.	Intimal Cholesterol (excluding residual cholesterol) Mg./100 Mg.
55	.66
158	2.15
193	2.86
279	3.78
330	5.00
426	8.32

The investigators calculated that for every 100 mg. increase of cholesterol level, intimal cholesterol increased by 1.8 mg./100 mg. of dry tissue. They found the lipoproteins in the plasma had penetrated through the intima down to the first elastic lamina, but had not penetrated the media. The pool of intact plasma lipoprotein in the intima seemed to be in equilibrium with the plasma lipoprotein. The cholesterol clearly enters the intima directly from the blood and in concentrations proportional to plasma cholesterol.

This concentration is greater within the plaques than it is within normal intima, as might be anticipated. In humans, the concentration of cholesterol and cholesterol esters in simple plaques has been determined to be almost twice that found in normal intima.(50)

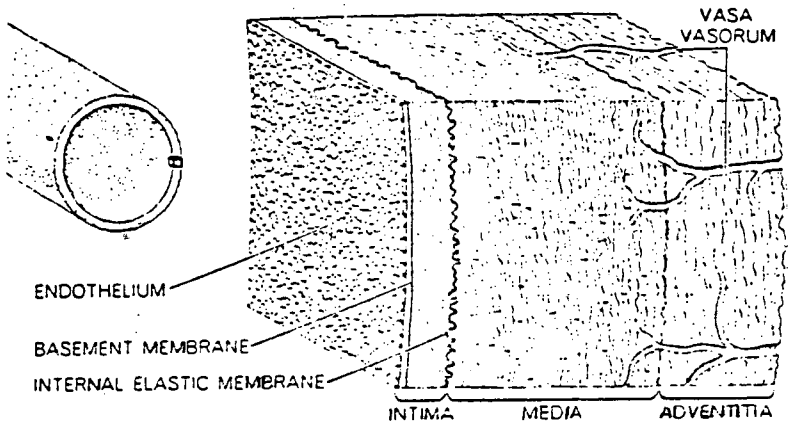
The so-called "normal" American lipid levels provide the environment for the development of plaques and the disease of atherosclerosis; the atheroma or plaque provides the mechanical means by which the morbidity and mortality of this disease is realized. Complete understanding of the plaques is still in the future, but enough is known to present a hypothesis of their development, as follows.(52)

The cycle of plaque genesis and destruction in the artery lining

Normal healing response (when cholesterol level is low)

The intima of an artery, when exposed to physical or chemical injury, responds by hyperplasia of the undamaged or surviving cells in the exposed area. This is dramatically shown with almost any

laboratory animal. Slightly scratch the intima and it will heal leaving a thin scar of no consequence--if the cholesterol level is around 100 mg. But if the same procedure is performed on an animal which has been fed enough cholesterol to bring its cholesterol level to 200+ mg., a full-blown plaque will develop. Certain structural features of the artery that are of interest in this context are illustrated in the drawing below.



In man, damage to the internal elastic lamina of the arterial intima occurs commonly and can be seen even in infants a few days old. Reasons for the fragmenting or rupturing of the lamina in isolated areas are speculative, but include flexing of the artery, twisting in body motions and general physical trauma. These breaks heal and form insignificant scars, causing no further problem, providing the cholesterol and lipid levels of the blood are not elevated.

<u>Pathological healing response and subsequent events (when cholesterol level is high)</u>

The fatty streak stage

If these blood levels are high, however, the cholesterol and lipids in contact with the ruptured lamina produce a condition that induces the sub-endothelial cells to ingest the lipid and cholesterol particles. These cells enlarge as they fill with these particles, multiplying as they continue to phagocytize the cholesterol and lipid particles in their cytoplasm. As they multiply, they spread on all sides, spilling over the still intact

lamina while at the same time ingesting all of the trapped cholesterol and lipid material within the enclosure. They are called "foam" cells due to their appearance when swollen with cholesterol and lipid particles.

At this stage, the injury is recognized as a "fatty streak". It is composed entirely of living material (whereas a plaque or occlusion practically never consists of only living cellular matter). The "streak" could remain indefinitely, not creating any harm, and is still reversible, as the foam cells contain enzymes to metabolize the ingested particles in time. Thus, at this stage, if the lipid and cholesterol levels of the blood drop, no harm has been done.

Fibrolipid plaque stage

If the lipid and cholesterol levels of the blood remain elevated, however, the foam cells will be overwhelmed with new cholesterol and lipids until they finally burst, spilling their contents with the cholesterol and lipids into the area around it. This initiates the fibrotic process by the fibroblasts, by which the simple fatty streak is converted into a fibro-lipid plaque through a process of fibrosis. At this point, the plaque is probably irreversible.

Studies demonstrate that cholesterol lying free in the spaces of a vessel wall always causes a hyperplastic and metaplastic reaction to the wall; it acts as a "neoplastic" agent in the intima. So that when the cholesterol levels remain elevated, the plasma will push through the plaque, constantly washing it with its irritating substances. Cells from the media will become involved as will adventitia cells eventually. Capillaries from the vasa vasorum will grow into the plaque to nourish it, and a fibrous cap will in time form on the lumenal surface, closing off the lumenal blood from the plaque. With the cap in place--now considered the "pearly plaque"--it can be dormant for long periods <u>if</u> the lipid and cholesterol levels in the blood are reduced to safe concentrations. If this happens, the plaque will grow no larger,

and as cholesterol and lipid are reabsorbed, it can regress to some extent.

Abscessing of plaque--final stage

If, however, lipid and cholesterol levels remain high, circulation from the adventitial capillaries continue to leak excessive quantities of cholesterol and lipids into the plaque. This further irritates the cells which keep repeating the destructive cycle until a huge abscess protrudes into the lumen at one end and into the adventitia at the other. The fibrous cap eventually degenerates and becomes very fragile. The plaque now consists of a core of cholesterol and lipids and dead cellular and fibrous substances, all in semi-liquid state. Because of its close physical similarity to a true abscess, it can be considered to be one. Its construction--the large cavity and fragile intimal protrusion--makes it subject to rupture at any time as the pulsation of the blood--100,000 pulses daily--acts as a gentle hammer on the weakly structured, mushy-centered lumenal protrusion.

The advanced plaque and complications it may produce.

Rupture of the plaque

The depth of involvement in advanced plaques reaches down to the adventitia. The large cavity has destroyed much of the muscle layer of the media and is filled with cholesterol crystals, debris and necrotic substances. Aneurysms and arterial blow-outs can easily occur under these conditions, which represent the end of the atherosclerotic process.

Under these conditions, the plaque is also very susceptible to rupture. Blood from the lumen may break the fragile cap and penetrate the abscess, forming thrombi from the fragmentation of the plaque. Debris from the rupture can circulate, becoming emboli, or if the ruptured debris stays attached to a partially detached cap, it can narrow the lumen considerably, or even totally occlude it.

If the rupture of the plaque forms an acute occlusive thrombus, it may kill the subject. If the acute occlusion does not

kill the subject, it usually becomes canalized or invaded by new blood vessels. These can arise from the vasa vasorum or from a branch of the coronary artery, if it is a coronary thrombosis. These new vessels can achieve a flow of 25% of the unoccluded artery, which is sufficient for the myocardium. They have a tendency to rupture because of a poorly developed media and adventitia, however, and because of this weakness are prone to hemorrhages which can produce a total occlusion. As a consequence, these thrombi are unpredictable and fragile and are probably most involved in terminal events.

Damage of emboli

Breakoff of plaques usually first becomes apparent in the retina. With the increased popularity of angiography, retinal emboli are being described with greater frequency. Cholesterol flakes from atheroma in the carotid artery are a large source of the emboli which appear in retinal vessels. These can cause visual loss temporarily if the fragment will pass through. Permanent loss may sometimes be prevented by development of collateral circulation.(53)

These same fragments are responsible for strokes or, minimally, for transient ischemic cerebrovascular events. It was formerly thought that moderate narrowing of the carotids will produce ischemia, but 90% closure is required before flow is sufficiently restricted to produce symptoms. The plaque fragments causing the ischemia may be seen by angiography.(54)

When enough plaques develop in the vascular system of the brain, senility develops. This was confirmed in a study of 60 patients in geriatric wards. Tests were given the patients to determine their degree of intellectual and personality deterioration, including evaluations of concentration, memory and general orientation. After their deaths, a count of plaques in the vessels of the brain was made and it was found that as the plaques increased, so did the degree of senility.(55)

Plaque fragments have been found in various locations in the body, including the spleen, adrenal gland, thyroid gland, bone

marrow, prostate, testes, liver and, of course, all of the major organ arteries.(56)

Partial occlusion of the lumen

Even without plaque rupture, the condition of a partially occluded lumen itself can produce death. When the coronary arteries become sufficiently narrowed, certain areas of the myocardium become partially anoxic locally. This can be observed in the heart muscle as a blue or bluish rather than pink area. Proximity of these two differentially oxygenated areas can produce an electrical imbalance that can result in ventricular fibrillation; no injury need be present. If corrected early enough, a heart in ventricular fibrillation can return to normal, apparently without damage. With a compromised coronary bed, not much physical effort is required to produce an ischemic condition, which in turn produces the electrical imbalance.(57)

II. SOME ERRONEOUS CONCEPTS CONCERNING THE DISEASE ORIGINS AND THEIR EQUALLY ERRONEOUS THERAPY IMPLICATIONS

Despite the abundant and convincing evidence establishing the etiology of atherosclerosis, medical researchers and practitioners have continued to proceed as though it were still shrouded in mystery; or, if the high-fat and high-cholesterol diet as causation is conceded to have some basis, other factors are thought to be of much greater significance. Part of the reason for the prevalent confusion and inability to assess the importance of the body of evidence we have reviewed, in our view, is due to entrenched misconceptions. We will now deal with some of these.

Stress as a causative factor in cardiovascular diseases.

The belief in etiological role of stress has wide acceptance

A discussion of prevention and treatment of coronary heart disease must take into account the widely-held viewpoint of professionals who contend that mental stress, in the form of anger, anxiety, aggressiveness, etc., is a cause of coronary heart disease. This school of thought has produced a system, in the last 15 years, by which individuals are classified as Type A (coronary-prone) or Type B (coronary-resistant).[58] According to this formulation, Type A represents the driving, aggressive, domineering personality, while Type B is passive, satisfied, relaxed, etc. While cholesterol and triglyceride levels are higher in Type A than in Type B individuals, that is thought to be the case because of the higher endocrine activity associated with aggressive behavior.

Diagnosis as to whether a patient is Type A or Type B is made on the basis of answers to a questionnaire, plus behavior exhibited while responding to the questions. (Type A should typically display mannerisms such as rapid and explosive speech, tense facial musculature, fist-clenching, abrupt body movements, etc.; Type B, conversely, would be slow, relaxed). Each answer and traits displayed while answering are given a weighted value on a scale and a diagnosis is then made. This method of diagnosing coronary-prone individuals has not been widely adopted, but is used in a few medical centers in the U.S.

While this diagnostic method carries a point of view to an extreme, the idea that stress is responsible for coronary heart disease is so imbedded in our conventional wisdom as to even have some legal standing. In workman compensation cases, if a doctor testifies in court that the stresses of a man's job caused his heart attack, the government must pay the damages. The image of the driving, hard-working executive or professional whose lifestyle brings on his heart attack is a popular one, and we are constantly warned about the dangers of not relaxing enough. From all sides we are urged to counteract the possible precipitation of a heart attack by emotional factors by taking stress-relieving drugs, such as headache remedies or tranquilizers. Part of our readiness to

accept stress as a causative factor in coronary heart disease may also be due to a natural reluctance to ascribe gluttony or gourmet habits to the demise of an individual. It is so much kinder to be able to say that death was the result of overwork, excessive worry about family, etc.

Though widely held, stress concept fails under careful analysis

The effect of stress in producing coronary heart disease has been tested in some interesting animal studies. Cockerels on a cholesterol diet[59] were subjected to unavoidable repetitive electric shocks, each preceded by a buzzer warner. Controls on the same diet but not subject to the shock treatment were compared over a period of several months. Though the shocked birds were emotionally affected, as was evidenced by their pattern of jumping and fluttering throughout the shock periods, there was absolutely no difference between the two groups of birds in double-blind graded evaluation of arterial lesions (or in blood lipid levels and weight), when sacrificed and examined at 5-, 8-, 14- and 20-week periods.

Continuous cold could be considered stressful and so was tried on rabbits.[60] One group was put in an environment where the temperature was kept at freezing (1 deg. C.) for a period of ten weeks, while another group was kept at a temperature of 25 deg. C. (77 deg. F.). At each temperature, some rabbits were fed a cholesterol diet, while others were fed a noncholesterol diet. At the end of the ten-week period, when sacrificed, all of the cholesterol-fed animals were found to have the same amount of atheroma, regardless of the temperature at which they were kept. Likewise, the noncholesterol-fed animals from both temperature groups were also entirely comparable. Cold as a stress-factor producing atheroma was not affirmed by this experiment.

Studies involving human groups likewise fail to uphold the stress theory. A five-year prospective study carried on among 270,000 Bell Telephone employees was set up to determine whether Type A (coronary-prone) individuals who work their way up to higher executive posts are more likely to have heart attacks.[61] Results

indicated that men at the top management level had a lower risk of coronary heart disease than men at lower levels. Dr. L.E. Hinkle, who directed the project, commented that the study "didn't come out the way I anticipated. Heart disease is not greatly influenced by the tensions of adult life in an industrial society." He further said that the findings "provide no evidence that men who are promoted rapidly, frequently, or recently, or men who are transferred to new departments or new companies, have any added risk of coronary heart disease."

During World War II, the populace of Nazi-occupied Austria endured all of the stresses and emotional problems found in wartime living.(62) Yet in a review of 24,546 autopsies, it was found that seven times as many heart attacks occurred in post-war Austria in 1958 than in the war years of 1944 or 1945.

Even using the data of the proponents of the Type A-Type B concept, it is found that the higher incidence of coronary heart disease occurs in the subjects manifesting the milder expressions of Type A behavior, rather than in subjects with more extreme Type A traits,(63) as would be expected if this theory were true. The theory does not even hold up using the evidence of the proponents!

At best, an emotional basis for coronary heart disease could be considered a possible minor factor, although the advocates of the stress theory have yet to prove their case.

Cholesterol synthesis in the body as a factor in blood cholesterol levels.

The confusion concerning the importance of exogenous cholesterol arises in some cases from a lack of understanding of the facts concerning cholesterol synthesis in the body. Dr. Irvine Page, renowned coronary heart disease specialist from the Cleveland Clinic, evidenced this confusion in a keynote speech entitled "Atherosclerosis--a Commentary" made before an international meeting. Dr. Page belittled preventative dietary approaches with these words: "The first suggestion was a low cholesterol diet. Of all the stupid things anybody could do, this was it, because everybody knew cholesterol was synthesized by the body. If

cholesterol is withdrawn from the diet, the body synthesizes enough cholesterol to make up the deficit." (What deficit, we may ask?) "The body, as usual, is smarter than the person who inhabits it. I tried the low cholesterol diet and lost weight as well as friends, and then woke up to the fact about nine months later that I was getting nowhere."[64] (The last comment has a sadly ironic aspect because Dr. Page experienced a myocardial infarction a few years after abandoning the low-cholesterol diet).

However, the facts concerning cholesterol synthesis in the body are quite different than Dr. Page supposes them to be. Although dogs have the ability to suppress as much as 95% of their endogenous cholesterol synthesis during ingestion of large quantities of exogenous cholesterol, man's ability in this regard is quite limited.[65] Various estimates of man's endogenous synthesis rate are from 250 mg. to 1500 mg., averaging 500-800 mg. per day.[66][67] To determine the extent to which high cholesterol intake might depress synthesis so as to offer some protection against hypercholesterolemia, five human subjects were put on a cholesterol-free diet for up to six months to permit a stabilization of the testing condition.[68] They were then fed a high-cholesterol diet of 3,000 to 3,500 mg. per day (the cholesterol was mainly derived from egg yolks) for periods up to 3 months. On both the low- and high-cholesterol diets, the amounts of newly synthesized cholesterol in the serum stayed the same. The results clearly support the investigators' statement that the endogenous daily production of serum cholesterol does not vary even with tremendous differences in cholesterol intake (0 to 3500 mg. per day).

Other studies confirm this statement. Thus, conclusions from another study[69] were: "No significant relation could be found between dietary intake and total body synthesis" and "Cholesterol synthesis is so weakly responsive to changes in dietary cholesterol as to be unresponsive."

Cholesterol synthesis in the body is clearly of minor significance in the matter of blood cholesterol levels, as these studies indicate.

The basis for standard values used in physical testing

The primary responsibility of the medical community is to preserve the health of the populace and to prevent disease and degeneration. These goals are monitored by means of periodic examinations at which time certain mechanical and chemical tests are made, the results of which are then compared to established standards. If a patient's test results fall within the standard range he is considered to be "healthy" and is advised to continue his present life-style until the next regular examination, unless illness should intervene. The obvious premise upon which this entire approach is based is that the standards with which the patient's tests are compared are correct. But are they?

The basis for standard values used in physical testing. nutritional regimen as set forth in the U.S. by the National Research Council Food and Nutrition Board, which includes recommended intakes of protein, fat, carbohydrates, vitamins and minerals--since all of the nutrients we consume affect the blood components measured in various tests made in determining the patient's state of health. The blood component standards, in turn, have been set by agreement with various medical bodies in the country, providing the basis for the evaluation of population health.

In these tests for blood component levels and in other tests, certain ranges are assigned as normal. The assigned ranges are shifted upwards for each decade of life--so that, by this system, a man who is 50 and is in the normal range would be abnormal if he were 30 and had these same values. Implicit in the system of different assigned ranges of normality for different age groups is the belief that there is a gradual deterioration of function in all respects as one ages. However, population studies around the world indicate that not all groups follow this pattern of decay, and in certain groups there is little significant change whether people are tested at age 20 or 80.

It is necessary to ask which pattern is "normal"--maintenance of function with aging or progressive decay?

Again, cholesterol levels are accepted as normal ranging as high as 300 mg.%. Yet the Framingham and other studies clearly demonstrate that persons with values of 260+ mg. have from 2.5 to 6 times the death rate for coronary heart disease than persons with values of 220 mg. or less.

Why then is a value of 260 mg. considered normal? The reason for this--it turns out, is that when it was first decided to adopt standards, there was agreement to use for the standard values the average values existing among the various age groups. Thus, through a dubious circular reasoning, the standards adopted were reflections of an ongoing disease state present in epidemic form in our population. It is time our standards were questioned!

As though the currently accepted standards were not bad enough, there have been proposals made recently from high quarters which would make them even worse. D.S. Fredrickson, a Director (1970) and key decision-maker at the National Institutes of Health, and his collaborators have suggested these as "normal" limits:[70]

AGE	CHOLESTEROL MG.%	TRIGLYCERIDE MG.%
0-19	120-230	10-140
20-29	120-240	10-140
30-39	140-270	10-150
40-49	150-310	10-150
50-59	160-330	10-190

Values were derived by population samples of "normal" subjects with no evidence of metabolic disease whose triglycerides were less than 100 mg. (The 200 mg. limit for triglycerides was a "second thought." In an earlier evaluation, Dr. Fredrickson was considering a triglyceride level of 400 mg. as the "upper limit" of normal.)[71]

The cholesterol levels accepted as normal by Dr. Fredrickson call for questioning. It has been proven by cineangiography that the upper limit proposed for ages 50-59--330 mg., produces 400% more arterial lesions than the lower limit.[72] Other studies which correlate coronary heart disease and cholesterol level show a rate of 111% at 130 mg., as against 85% at 370 mg., with all values proportional in between.[73]

The proposed normal limit for triglycerides of 190 mg. also need challenging. Let us recall the San Francisco study with over 3,000 men, in which triglyceride levels of over 176 mg. produce 300% more coronary heart disease than levels under 100 mg.(74)

Numerous studies cited elsewhere in this book point to the danger of these high "normal" values. Yet these are the new "improved" standards which Dr. Fredrickson is proposing be used for comparison with your values at your next physical exam(--so that you can be found "normal" while on your way to coronary heart disease!).

The physical examination as a protector of health.

Diagnostic tests used vary widely

Having questioned the established standards used for comparison in preventative check-ups, we turn to other aspects of the great civilized ritual--the physical exam--to ascertain their effectiveness as presently constituted in protecting public health.

A striking discovery concerns the variation in diagnostic testing procedures used among physicians. While automatic screening tests have become widespread in many health insurance and group medical plans, as instituted in industry, unions, the military, etc., screening tests have not been as popular with individual physicians, despite their proven usefulness in detecting disease states. Some authorities, in fact, have concluded that frontline medical practice is not geared to prevention(75) and that even when screening tests are used, many physicians ignore the abnormalities reported.(76)

In one indicative survey, 202 internists and general practitioners were questioned about the kinds of tests they would give patients in a thorough examination.(77) When presented with 24 possible screening tests, there was wide divergence of opinion among the physicians as to which tests they would employ. Ninety-seven percent would order a urinalysis, but only 56% would order a hemoglobin test, the balance calling it an "unwanted test". Half of the 24 possible tests were "unwanted" by over 50% of the physicians.

As to one of these tests, a cholesterol determination (--so important in the detection and treatment of coronary heart disease), 55% said it was not their usual practice to have this test performed, and 1/3 of the physicians who used the test said they ordered it only when there were clinical indications of coronary heart disease.

Proper preventative medicine practices would not defer this test until hypercholesteremia had produced clinical symptoms. Serum cholesterol levels are 95% accurate as predictive tests (as demonstrated in a double-blind clinical study confirmed by arteriography),[78] yet over half of the physicians questioned in this survey on diagnostic tests wanted for a complete physical examination chose not to avail themselves of a cholesterol level determination. The test needs to be routinely given--and the standards for comparison need reform!

Coronary heart disease deaths are not prevented by examinations

There are tragic implications in the failure to diagnose and treat coronary heart disease in its incipient stages. A study[79] of all sudden deaths of a nontraumatic nature in Baltimore during a 12-month period in 1964-65 illustrates this. In subjects in this study at the lower age range--from 20 to 39 years--22% of sudden deaths were due to coronary heart disease; in the upper age range--from 40 to 64 years--61% of sudden deaths were due to coronary heart disease. Half of the subjects dying of coronary heart disease had had no previous history of heart disease revealed to them in coronary episodes or through diagnostic testing. Twenty-four percent of those who died from coronary heart disease had seen a physician within a week before their death--yet with death less than days away, clinicians failed to prevent or predict the fatal attacks.

The efficacy of so-called "preventative medicine" (i.e., routine physical examinations) to lower coronary heart disease deaths is again indicated by the following study.[80] One hundred eighty-three sudden deaths over a five-year period were investigated in Albany County, New York. The victims were

autopsied and their medical and personal histories studied in an effort to gather information suggesting methods of predicting and averting sudden death. Results of the autopsies were surprising, showing much advanced damage. Acute myocardial infarcts were found in 47% of the cases, the infarcts being judged to be from six hours to one week old. In many of these cases, old or healing infarcts were also present. Among the 53% who showed no recent infarcts, about 70% of these had recent thrombi. Despite all this previous damage, none of the group had had any warning that they had been in imminent danger. Six had gone to physicians within three weeks of their death and had not even received a diagnosis of coronary heart disease.

Out of 101 males in this study who had died within an hour of their attack, only 15 had not felt well for periods from one to seven days before their deaths, and some of the 15 had attributed their feeling ill to "colds". So unaware were these 101 men of danger that 34 were at their usual work; 18 were driving a motor vehicle; 10 were in diverse activities such as jogging and attending a Christmas party. Out of 35 who died at home, only four were home because they weren't feeling well.

Still another case in point[81] is that of a 37-year old Navy pilot who had reported for his routine physical examination free of symptoms of obvious abnormalities. He complained, however, about having experienced a very short period of partial aphasia about a year earlier, and to explore this, an electroencephalogram and a carotid angiogram were taken. The results of these tests, however, and of all other clinical studies were normal. Carotid pulses were found to be full and equal bilaterally; heart exam was normal, including x-rays and fluoroscopy; ECG was normal both in resting and exercise tolerance tests (the latter was a 3-minute Harvard step test, more taxing than the usual Master step test); weight and blood pressure were normal; cholesterol level was average--229 mg., and other lipid levels were considered normal.

Following this very complete examination, the Navy pilot was returned to full-duty status. Three weeks later he was dead due to an acute myocardial infarct. During autopsy, extensive plaque

damage was found in the right and left coronary arteries, with the occlusion in the left coronary. The occlusion was adjacent to an advanced plaque and appeared to be the result of its rupture.

Very few physical examinations are as thorough as was that of this Navy man, but thorough as it was, it had no predictive value. It was an utter waste of clinical time and facilities, unproductive from the examining clinicians' standpoint, tragic from the patient's standpoint.

Another very significant study involving Navy and Marine personnel[82][83] was undertaken by Dr. C.J. Pepine, Director of the Cardiac Catheterization Lab of the U.S. Naval Hospital in Philadelphia, in an effort to learn more about the "evolution from silent to symptomatic coronary heart disease". Pepine had observed that 30% of Navy patients dying of natural causes are usually under 40 years of age, have no history of coronary heart disease, yet die of its effects. Pepine hoped to make earlier diagnosis of the disease possible through learning about its natural history as it evolved. To do this, he proposed to take asymptomatic subjects and run angiographic studies on them at two-year intervals so that the studies could be correlated with symptoms as they became manifest.

The 41 volunteers who participated in the study were Navy flyers or Marines on active duty, under 40 years of age, all certified to be in good health by current Service diagnostic techniques--as good as any in the country--with a first degree relative with the disease, and themselves hyperlipemic.

The results of the first angiograms--expected to reflect the absence of symptoms--were truly shocking. Nineteen of the 41 had advanced coronary heart disease; 16 had 2 or 3 coronary arteries with over 50% narrowing. The most advanced disease state was found in a man who was running 5 miles daily as part of the Marine Corps physical fitness program. (His program was changed at once, as were the fitness programs of many of the others who were running 2-3 miles daily as part of their activity.)

In commenting on the findings of the angiograms and other tests--other tests were made as a result of the unexpected and spectacular disclosures of the angiograms--Dr. Pepine said: "It

seems clear that cardiac ischemia can exist without symptoms, confirming our impressions from electrocardiographic studies in this group". (This statement is disputable. Not only were the subjects hyperlipemic, but xanthomas were found in them without exception--a telltale sign not taken too seriously, unfortunately.) In a two-year follow-up study, it developed that three of the men had suffered myocardial infarctions, and in four of the men that were recatheterized, the disease was found to have progressed.

Dr. Pepine reported: "None of the existing diagnostic techniques appear to be sensitive enough to detect asymptomatic coronary artery disease. In addition to all the other techniques, we employed echocardiography in most of the series and found that it, too, did not identify any of the subjects with angiographically proved CAD (coronary artery disease)". (Author's emphasis)

The problem of early diagnosis thus appeared far from a resolution to Dr. Pepine, who expressed the hope that in another five years he might "have enough data for useful conclusions".

The failure of conventional diagnostic tools to identify asymptomatic coronary artery disease is demonstrated again and again. The present approach which attempts to prevent coronary heart disease deaths by the practice of routine physical examinations is marked by futility because coronary heart disease can produce death before it offers convenient warnings either to the physician or the victim.

Until the diagnostic significance of elevated lipid levels is recognized (all of the so-called "asymptomatic" subjects in Dr. Pepine's study had hyperlipemia), coronary heart disease deaths will not be averted by physical examinations. You can, however, insist that blood lipid tests be included in your physical examination. Suggested tests and safe ranges are given in the chapter on Recommendations.

Diagnosis aside, prevention depends upon implementation of measures to lower lipid levels. Unless that is done, the epidemic of coronary heart disease will continue at breakneck speed.

Fredrickson's "five lipid classification system."

The National Institutes of Health's D.S. Fredrickson, whose recommended new cholesterol and triglyceride levels for use as standards were earlier discussed, has also proposed a new system of classification of hyperlipidemias and hyperlipoproteinemias into five main types, separated on the basis of their chylomicra and various lipoprotein fractions. Each group would have its own method of diagnosis and treatment. As Dr. Fredrickson accepts a genetic etiology of the elevated lipid condition, the treatment rationale is based upon the counteracting of an unavoidable physical condition by the use of lipid-lowering drugs and specially formulated diets.

The classification system has been widely acclaimed and publicized throughout the country, is being followed at the National Heart and Lung Institute (now National Heart, Lung and Blood Institute), and has been recommended as a worldwide standard by the World Health Organization.(84)

The concepts underlying the design of the diets recommended by Dr. Fredrickson are entirely unsound, as can be seen in an analysis of his writings (see "Familial Hyperlipoproteinaemia" by Fredrickson and Lees in the text Abnormal Lipid Metabolism). In a section entitled "Possible Biochemical Defects in Type III" (Types III, IV, and V, in Dr. Fredrickson's system, are all related in that carbohydrates will raise the pre-B-lipoprotein level in these individuals), the co-authors discuss a phenomenon "called carbohydrate induction of hyperlipemia". Citing examples of this, they say: "An important effect of diet on plasma glycerides was first noted in 1950 when Watkin et al found that a high-carbohydrate, fat-free diet increased the average serum glyceride concentration in a group of hypertensive patients on a rice and fruit diet. In 1955, Hatch et al extended these observations, showing that one-third of a similar group of hypertensive patients with no obvious defect in lipid metabolism became grossly hyperlipedemic on a rice and fruit diet and rapidly reverted to normal on the resubstitution of fat for carbohydrate in the diet." Fredrickson and Lees conclude: "Carbohydrate induction is therefore a mechanism common to all men and perhaps many other species. It

becomes pathological when it occurs on ordinary diets." (our emphasis)

As we will show, the authors' conclusions are based on some misconceptions concerning the effects of simple and complex carbohydrates in relation to blood triglycerides. The only carbohydrates referred to by Fredrickson and Lees in their discussion are complex carbohydrates. These, however, can only have the effect of lowering the triglycerides. It is only the simple carbohydrates (e.g., sucrose and fructose) which can raise the triglycerides--there are no exceptions! Yudkin[85][86] has been raising triglycerides for 10 years using sucrose on young and old, male and female. The effect of sucrose on raising of the triglycerides is documented in many studies.[87-94]

A comparison of the effect of sucrose, a simple carbohydrate, versus starch, a complex carbohydrate, on hyper-triglyceridemia[95][96] was seen in striking fashion in the case of a 44-year old man with a triglyceride level of 1200 mg. When placed on a 64% carbohydrate, 19% fat diet for five weeks, in which all of the carbohydrate was starch, his triglyceride level dropped to 400 mg. When his diet was changed by replacing 230 gms. of bread with sugar (sucrose), with the sugar providing about 30% of his caloric intake, his triglycerides rose to 840 mg. after another five-week period.

Fredrickson should have hesitated about concluding that a complex carbohydrate food such as rice can raise lipids, if only because 700,000,000 Chinese, among other peoples, whose diet uses rice as a staple, dispute this! Could this influential investigator's erroneous conclusion about the effect of complex carbohydrates on lipid levels been due to a careless reading of his references? Watkins et al used a diet of rice and fruit and sugar! Sucrose actually provided 47% of total calories in the Watkins diet. Or perhaps Fredrickson thought the sugar was not significant because he regarded it as no different from other carbohydrates. As a third possibility, could he have ignored its significance on the grounds that this much sugar, or more, occurs in "ordinary diets"?

That this last possibility may have been the case is suggested by another study in which Fredrickson participated[97] which was designed to test the question of "carbohydrate induction"--raising of the triglycerides by elevating of the carbohydrate level--involving 107 patients. The study cites a reference in support of this hypothesis[98] in which a diet of 88% of total calories was comprised of carbohydrates, primarily sucrose. It is no wonder that in Fredrickson's study, the carbohydrates of the diet, making up 80% of total calories, were lumped together in this catch-all manner: "the carbohydrates consisted of mixed simple sugars, complex sugars and starch." No percentages, no further descriptions of the sugars. It is obvious that he considers this mix as normal. As he states in the study: "There is a similar lack of firm data supporting a predictable and sustained effect of substitution of one carbohydrate for another." Without reading the conclusions of his study, the results could be foreseen: carbohydrates (his to mix) induce lipid elevation.

The fact of the matter is that Dr. Fredrickson's Types III, IV and V would not even exist on complex carbohydrates!

As a consequence of these misconceptions, Dr. Fredrickson is forced to adopt some startling dietary recommendations--55% of total calories in fat! Since he has concluded that carbohydrates produce lipidemia, they must naturally be reduced; lipids, in consequence, are increased. By this strange logic he advises raising the fats consumed in the U.S. from the present 40% of total calories to a proposed 55%, still hoping to reduce blood fats!

In a Bantu study,[99] increasing the fat level from 15% to 40% for one year increased triglycerides from 84 mg. to 141 mg.; back on the 15% fat diet for 30 weeks, they dropped to 75 mg. Increasing fat intake will produce more candidates for Dr. Fredrickson's groups III, IV and V; it will not reduce blood fats.

The five lipid classification system does not stand up under scrutiny: there are only two types of lipid abnormalities--high cholesterol and high triglycerides. With the recommended diet of 100 mg. cholesterol daily and no simple carbohydrates, practically everyone in a matter of weeks or months can drop to a normal range.

Primitive populations on comparable diets have no hyperlipidemia; it is a "Western" phenomenon. The five lipid types are an arbitrary, artificial grouping that formalize high cholesterol and high triglycerides into a new specialty--invented at the National Institutes of Health.

The artificial distinctions of the five types of hyperlipoproteinemia may fool the clinician, but will not deceive the pathologist. Necropsy findings in a Type III case were reported[100] and the pathologist was especially curious because only one other Type III case had been reported as coming to autopsy. All he found were lipid-containing atheromas of the type normally seen in the general population. In his report he stated that Type III produces just ordinary atheromas, and that any suggestion that the atheroma of Type III and that of ordinary coronary heart disease are of different pathogenesis is not supported by his findings.

The atheromas are the same, and the etiology of Types I, II, III, IV and V are the same--fat and cholesterol intakes, American portions!

III. A PROPOSED DIET THERAPY

Certain facts become evident from the investigations that have been reviewed which bear reiteration in summary form:

1. Newborns (human) have cholesterol levels below 100 mg.
2. Populations (human) wherein coronary heart disease has not been found have cholesterol levels from 80-130 mg. and maintain these levels throughout life.
3. Primates on cholesterol-free diets have cholesterol levels between 100-130 mg. at necropsy and are found to have less than 1% intimal damage. On an average U.S. diet without added cholesterol, primates develop plaques covering 50% of their aortic intimas within two years. Even on an American Heart Association moderate ("prudent") diet, where the cholesterol level rose to only 219 mg. after two years, intimal damage was still one-third that of the group on the U.S. diet. (The prudent diet brought about a "normal" cholesterol level of 219 mg., yet produced 15 times the artery damage of a diet that keeps the cholesterol level at 135 mg.) (The relevance of the conclusions using primates as subjects is based on the similarity of their cholesterol levels and their responses to dietary cholesterol and fat.)
4. Western populations where coronary heart disease is epidemic have cholesterol levels ranging between 170 mg. and 300 mg. as normal values. The death rate for coronary heart disease and the cholesterol level parallel each other.
5. Intimal artery damage in humans parallels the rise in cholesterol levels, as has been directly demonstrated by angiography. At levels below 140 mg. cholesterol and 60 mg. for triglycerides, the threat to the arterial intima disappears.

All the evidence points to one conclusion: coronary heart disease does not appear if the cholesterol level is kept below 140

mg. and the triglycerides under 60 gm. This goal is not difficult to achieve. When the new nutritional lifestyle is adopted and its benefits become widespread, we will wonder why the change was resisted for so long.

Regression of atherosclerosis in primates using low-fat, low-cholesterol diets

The prophylactic program for coronary heart disease is clear; but what about the multitudes in whom damage has already occurred?

The dismal picture concerning plaques and their potential for damage is brightened somewhat by experiments which show that symptom regression in atherosclerosis can be achieved under certain circumstances. Studies with pigeons, rabbits, dogs, monkeys, etc. demonstrate two basic principles:

1. Feeding the animal cholesterol, even in small quantities similar to amounts consumed in the U.S. diet, will cause plaques and consequent atherosclerosis to develop. The damage is proportional to the cholesterol level--the higher the level, the greater the damage.

2. If the cholesterol-elevating substances are deleted from the diet, there is always some regression of plaques after a certain period of time.

The studies reported here will concern only primates.

Fifteen rhesus monkeys were started on a diet program.[101] Three were on a normal monkey low-fat chow (C); two groups of six each, P and R, were on a cholesterol-butter supplemented chow. The diets were followed for 12 weeks. The controls (C) and the P group were sacrificed, and the R group was changed to the control diet of chow for 32 weeks, after which the R group was sacrificed. The cholesterol levels and area of plaque damage in the aorta are noted in the table.

Group	Cholesterol Level 12 Weeks	Cholesterol Level 44 Weeks	% Surface Involvement of Aorta Intima
(C) Control	142		4%
P	565		51%
R	559	129	21%

The R group was able to reduce their plasma cholesterol level to control values merely by elimination of the cholesterol and butter from their diet. This reduction even after the limited period of 32 weeks caused a regression of plaques of 40% of that found in the P group.

The response of humans to such a diet elimination program is similar, as will be discussed in a later section.

A comparison of low-fat, low-cholesterol diets and low-cholesterol 40% corn oil diets.

Forty adult rhesus monkeys were started on a low-fat, cholesterol-free diet for six weeks.[102] After this time, ten continued as controls (C), and the remaining 30 then started an atherogenic diet for 17 months. At the end of this period, the 30 were now divided into three groups of ten. Of these, group I was sacrificed and examined for baseline atherosclerosis; group II was put on the control diet; and group III was started on a cholesterol-free, 40% corn oil diet. The test continued for 40 months, at the end of which time all of the animals were sacrificed for coronary artery analysis.

The diet of the three groups is summarized below:

	Atherogenic	Low-Fat	Corn Oil
Protein	16%	19%	15%
Carbohydrate	43%	77%	45%
Fat	41%	4%	40%
Cholesterol	1.2 gm.	0	0

(Food values given are in percent of total calories; cholesterol value is % by weight)

If one looks critically at the atherogenic diet, it appears little different from the U.S. diet, except that the cholesterol intake is probably four times higher than most would consume. The low-fat diet resembles that of primitive populations, except for the relatively high protein intake.

Cholesterol levels observed in the study are listed below.

Cholesterol Levels (mg./100 ml.)

Group	Start	17 Mos.	40 Mos.
I - Atherogenic Diet for 17 mos.	138	701	
II - Atherogenic Diet for 17 mos. followed by low-fat, cholesterol-free diet to 40 mos.	142	712	136
III- Atherogenic Diet for 17 mos. followed by 40% corn oil, cholesterol-free diet to 40 mos.	140	703	138
Control - Low-fat, cholesterol-free diet continuously	143	140	135

Despite the high cholesterol level of 700+ mg. reached by the animals after 17 months, within 60 days after the return to a cholesterol-free diet, their plasma cholesterol levels had dropped to control values (<150 mg.). The effectiveness of diet in lowering cholesterol levels is strikingly demonstrated in this study.

Artery damage observed is indicated in the table below, expressed as % of total narrowing of lumen:

Group	Main Coronary	
	Left	Right
Control	1	1
I (Atherogenic)	60	56
II (Low-fat)	17	14
III (Corn oil)	25	26

The control monkeys had essentially no damage. Those on the atherogenic diet had 58% of the coronary artery lumens closed. The two regression diets (no cholesterol) both showed considerable

reduction in the number of plaques as compared to the atherogenic diet.

No ulcerated plaques were found; the principal lesions were plaques with a fibrous cap. Damage was restricted to limited areas of the media. Some of the atherogenic group developed cholesterol clefts, but none were found in the other groups.

Cholesterol was isolated from the plaques and the results are noted below:

Group	Cholesterol	Cholesterol esters
	(Mg./G. of tissue)	
I (Atherogenic)	12	33
II Low-fat	6	6
III (Corn oil)	5	9

Plaques in this stage of development lose most of their cholesterol (free and esterified) on a cholesterol-free diet. The low-fat diet produces superior results both as to regression of plaques and reabsorption of lipids from plaques. The corn oil diet at its maximum regression still showed 50-80% more narrowing of the coronary artery lumens than the low-fat diet. This evidence makes questionable the dietary recommendations of the American Heart Association encouraging high unsaturated fat intake.

Since even severely ulcerated plaques[103] are in equilibrium with the plasma and an exchange of the lipids thereby takes place, there is reason to believe that reduction of even the relatively advanced "pearly plaques" can take place as suggested by this study.

Some recommended but futile dietary reforms to prevent atherosclerosis

"All things in moderation" is the theme of current medical recommendations regarding nutritional change. It will not work and there have been tragic examples attesting to the failure of this approach. Norman Joliffe, originator of the Anti-Coronary Program in New York, started his diet plan based on a "moderate" reduction of cholesterol and fats as a means of reducing coronary heart

disease. Hundreds were attracted to this program and many are adhering to it today--but not Joliffe. He died of a heart attack a short time after he started the program--probably a victim of moderation.

Irvine Page,[104] internationally-known expert on coronary heart disease, made this statement in 1959: "On a low-cholesterol, low-fat diet, I went from a hypercholesterolemic coronary type to really low cholesterol levels for me, and then my lipids came back up after my wife and I got sick of the whole business." A few years later, Dr. Page had his heart attack.

One physician, in bed on the 11th day after an almost fatal heart attack, experienced a cardiac arrest.[105] Though in a semi-conscious state, he later recalls having heard the nurses' voices, the doctors' frantic measures to save his life, the emergency procedures, his blurred view of the surroundings. Paralyzed in limb and speech and unable to respond, he heard everything, as though in a dream sequence fantasy. Finally regaining consciousness after three days and realizing he was hungry, he persuaded the nurse to feed him an egg flip (300 mg. cholesterol) then and there, and another that evening (300 mg. cholesterol). "These assuaged my acute pains of hunger until the following day, when I was spoon-fed the most delicious scrambled egg that surely this world ever produced!" (Another 400 or so mg. cholesterol down the hatch!) One can imagine the quality of nutritional advice given by this physician and others whose understanding is not much better. Little wonder that 20+% of Americans 17 years old already have a cholesterol level of 260+ mg.[106]

What is the quality of the nutritional advice given by the American Heart Association? An indication comes from the proceedings of a recent symposium on angina and coronary heart disease sponsored by the Association, which were published as a supplement to their official journal.[107] The symposium, addressed by several experts, covered prevention, treatment, diagnosis, etc., but in its published proceedings of 187 pages, the total discussion on diet or nutritional aspects of these disease states took approximately 1/10th of a page! All of three

sentences--with this conclusion: "Lowering the levels of cholesterol and triglycerides are laudable long-term goals, but little influence on angina has been demonstrated."

This lack of enthusiasm for a dietary approach to cardiovascular therapy is reflected in the AHA official recommendations: cholesterol intake-not more than 300 mg. per day; total fat intake-not more than 40% of total calories; P/S ratio = 2.[108] Little is expected by the AHA from diet and little will be achieved using its recommendations!

A dietary regime that will succeed

An impressive body of data supports the view that fat and cholesterol intake have a surprisingly volatile effect upon the serum cholesterol. In trials where diets have failed to reduce lipid levels sufficiently, it will be seen that the diets were not low enough in fat and/or cholesterol content. Such misleading data confuse the physician, who concludes that cholesterol-lowering drugs are the only answer. Because this problem will be developed later, only one example will be given now.

Dr. Donald Berkowitz, an esteemed investigator of the Temple University Medical School has concluded after some seven years of testing diet against Clofibrate to assess their relative effectiveness in reducing blood lipid levels that dietary approaches to the problem are simply impractical, based on tests he devised. The tests by which he arrived at his conclusions are persuasive: 50 subjects in a six-month test program, 25 of whom were taking Clofibrate with no dietary restrictions and the other 25 of whom were on a cholesterol-lowering diet set up by Dr. Berkowitz. Results? Yes! The Clofibrate group reduced their cholesterol level 26% against an 11% reduction in the diet group. Triglycerides were reduced 46% in the Clofibrate group as against 9% in the diet group.

Why the poor showing by the subjects on the low-cholesterol diet when other tests have demonstrated that cholesterol levels can drop 25L% in four days by dietary means alone?[109] One look at Dr. Berkowitz' diet and the answer is obvious. Forty to forty-

five percent of total calories in fat and 350 mg./day of cholesterol!

At this level of dietary lipids, one marvels that the triglycerides were lowered even 9%! On a diet of 30% of total calories in fat with approximately 350 mg. of cholesterol, there was no change in cholesterol level in a short period, but it is possible that in six months an 11% drop could be achieved. The Berkowitz diet ignored practically everything known about the relationship of fat and cholesterol intake to serum cholesterol level. Yet this investigator concludes: "These results indicate that attempts to lower blood lipids by dietary control alone were not successful. ...The data are not meant to infer that changes in the diet are incapable of decreasing hyperlipidemia since it may be argued that nonresponse was in fact due to nonadherence to the new diet." However, he states, even where total adherence to the dietary regime can be assured (as in institutions where meals are especially prepared for the patients), the maximum reduction in cholesterol was 14%.

Another set of conclusions emerges from those studies in which fat and cholesterol intakes were dropped sufficiently; let us look at some of these.

Cholesterol intake and cholesterol levels

Cholesterol intake is probably the most significant factor in elevated cholesterol levels. When normals start on a low-cholesterol diet, their cholesterol levels drop to low values fairly rapidly. The most recalcitrant patients are those who are already hyperlipidemic. Due to their high plasma and tissue total lipid levels, the length of time to achieve a drop to normal levels takes months or even a year or more.

Five patients with lipemia were studied on a cholesterol-free diet with 35% of total calories in corn oil.[110] They were on the cholesterol-free diet for four weeks, then went back to their normal diet for three weeks. The next four weeks they went on the 35% corn oil diet and, in addition, took 1 gram of cholesterol. On the cholesterol-free diets, all of their cholesterol levels dropped

significantly, but on the cholesterol-added diet, their cholesterol levels rose in spite of the cholesterol-lowering effect of the corn oil. The results are summarized.

	Start of Diets	Cholesterol levels mg./% After no choles. 35% corn oil - 4 Weeks	After 1 gm.Choles. 35% corn oil - 4 Weeks
Entire Group	359	226	263
Youngest Member (26 yr. old)	379	251	255
Oldest member (53 yr. old)	320	181	212

All subjects dropped significantly in only four weeks on a cholesterol-free diet. The youngest and oldest members of the group had comparable drops, but when cholesterol was added to the diet, the older patient's cholesterol level rose much faster.

Fat-free and cholesterol-free diets for short periods can be much more effective than most clinicians believe possible, as is shown by this study and others, one of which will now be summarized.

Forty subjects, mostly medical students, plus some older staff members, went on a fat- and cholesterol-free diet for only 16 days.(111) Blood values were taken every 4 days for 16 days and are given in the table.

	Cholesterol Level mg./%				
	Start	4 days	8 days	12 days	16 days
40 subjects	210	152	150	148	147
59 yr. old*	370	266	268	242	238
39 yr. old*	269	186	187	172	165
40 yr. old*	322	302	281	230	235

*staff members not included in "40 subjects" average

To carry this experiment further, 93 university students started the fat- and cholesterol-free diet.(112) They stayed on

the diet for 8 days, then were divided into eight groups. Each group took different intakes of cholesterol per day. All of the groups added 30% of total calories in butterfat, and the non-butterfat cholesterol intake ranged from 0 to 4,493 mg. The new diet with the butterfat and cholesterol lasted 16 days. Results are summarized.

Serum Cholesterol Values Mg./100 Ml.

Fat and Cholesterol-free Diet			30% total calories as fat (butterfat) and added cholesterol as noted in mg. cholesterol/day for 8 days							
Start	4 days	8 days	0 mg.	95	153	293	634	1295	2494	4493
201	147	147	183	187	189	193	207	216	251	232

The rapidity of the effect of fat and cholesterol intake upon serum cholesterol has not been generally appreciated. Few realized it is possible to drop the cholesterol level 25% in four days, or to raise it 25% in eight days with a 30% butterfat but otherwise cholesterol-free regimen. More surprising is the ability to raise the cholesterol 72% in only eight days with a 2.5 gm. daily cholesterol intake. The highest cholesterol intake produces a slight reversal in the blood level, but this was probably due to temporary saturation.

It becomes quite apparent that the goal of a cholesterol level below 150 mg. is no insurmountable task, and that it certainly requires no help from the pharmaceutical industry, despite Dr. Berkowitz' conclusions.

Fat intake and lipid levels

When the low incidence of coronary heart disease among such groups at the Bantu is accredited to their low-fat diet, many argue that their immunity is a racial characteristic--but this is merely wishful thinking! This is shown by the following study.

Long-term inmates in a South African prison were selected to test their response to a 40% fat diet.[113] Half were whites; the other half were native Bantus. Average age was 37 years and all

were tested to exclude any with apparent abnormalities. Their diet in the prison had 15% of total calories in fat. For the test, fats were raised to 40% of total calories, with butter providing 25% of the fat content. The results after periods of 21 weeks and 51 weeks on this diet are shown.

Triglycerides mg./%

	Control Diet 15% fat	40% fat* 21 weeks	40% fat* 51 weeks	15% fat 30 weeks
Whites	86	103	119	85
Bantus	84	109	141	75

*25% of content in butter

The triglyceride values of Bantu natives not only are affected by fat content but overreact as compared to whites. Although they were at the same level as the whites in the beginning, by 51 weeks the Bantus' triglycerides were 20% higher; and after 30 weeks on their control diet they were 12% lower than the whites.

The Korean War provided the opportunity to compare white and Korean soldiers with respect to their response to diets containing different levels of fat, as reflected in the lipid values of their blood. The army diet of the Korean soldiers contained 15% fat, compared to the American soldiers who consumed 40% of their total calories in fat. The low lipid levels of the Korean soldiers rose to U.S. standards when these soldiers were given the U.S. army diet.(114)

The response to low- or high-fat diets is no different in any group--it is a universal response. Immunity to coronary heart disease can only be based on adherence to low-fat diets.

Exercise can be helpful as an adjunct to proper diet

Although proper diet is the key preventative step in eliminating coronary heart disease, exercise is necessary to maintain body functions, circulation and well-being at high levels. Alone, however, exercise will not bring lipid levels to safe values, as shown by the following study.

Two hundred ninety-eight men between the ages of 30 and 59 were tested extensively on exercise programs in order to determine if long-term physical activity could change cholesterol level.[115] This group was compared to others in various parts of the world. The conclusion: "The results of the present study (Cleveland) and the comparisons with the Finnish populations support the view that diet, rather than the level of habitual physical activity, predominantly determines the serum-cholesterol level." This study assumes major significance because of the participation of Herman Hellerstein, one of the pioneer experts in the use of exercise for rehabilitation of infarct patients, whose work began at the Cleveland YMCA in the late 1950's.

The role of exercise as an adjunct to proper diet in warding off cardiovascular problems is discussed in detail in the chapter on exercise, but a few general statements are in order at this time.

First, acute infarction after severe effort is rare in undiseased hearts. At the recent Olympics in Mexico City, dozens of collapses took place during events which required great endurance effort, but no deaths occurred. Even in the average population with its rampant coronary heart disease, acute infarction after severe effort is the exception rather than the rule. In one of the largest studies on acute infarction,[116] 2% died after unusual effort and 52% died during rest and sleep.

Exercise is critically important to establish collateral circulation in our plaque-ridden populace and has been demonstrated to bring about positive measurable improvement in coronary collateral circulation where insufficiency has been established, either due to obstruction or lumenal narrowing of lumens.[117] In groups on a conventional diet conducive to coronary heart disease, inactive subjects have a 200% greater risk of developing coronary heart disease than do physically active subjects.[118]

A satisfactory exercise program can be very simple. Start walking! Gradually work up to 1/2 to 1 hour of continuous walking per day, walking at a brisk pace. This is adequate for life. If one wishes to achieve maximum benefits from exercise, start running

for long periods of time at a speed that is not taxing. The distance should be gradually increased over a period of time, so that one is eventually running continuously for 15 to 20 minutes minimum. A run of this kind daily will keep one in good condition. An hour or two of continuous running once weekly will drive the pulse down below 50 per minute in most people, regardless of age.

IV. THE AMERICAN HEART ASSOCIATION UNSATURATED FAT DIET: THE FALLACIES

The current recommendations of the American Heart Association calling for a moderate reduction of cholesterol and substitution of unsaturated for saturated fats grew from decades of research. The observation that vegetable oils lowered serum cholesterol levels--even when the total fat intake was at prevalent U.S. standards of 40-50% of total calories--was made in the early 1950's. Many seized upon this as providing a possible solution to the problem of cholesterol control, the importance of which was gaining increasing recognition at that time. Here was an approach that held out the possibility that one need not forego his usual diet nor endure the privations of a low-fat, low-cholesterol diet to secure immunity from coronary heart disease--one need merely substitute unsaturated for saturated fats.

The food industry--ever sensitive to situations influencing profits--quickly responded. Those foods high in unsaturated fats (e.g., mayonnaise and margarine) were touted before consumers as panaceas for the dread disease. Other products turned up in new forms, with unsaturated fats substituted for saturated fats in ice creams, sauces, and other favorite edibles. Where nature had determined the chemical character of the foodstuff, as with meat or eggs, the industry's ingenuity came to the fore and we were offered eggs from chickens fed a diet high in unsaturated fats so as to produce egg yolks higher in these "desirable" fats and meats from animals whose fat composition reflected the high concentration of unsaturated fats in the feed they received.

(The distinction between fats as to whether they are saturated or unsaturated is one of convenience, depending upon the relative proportions of saturated and unsaturated components, both kinds of which are present in all fats, animal or vegetable. This arbitrary classification of fats as saturated, neutral or unsaturated is made according to iodine number, a figure based upon the number of grams of iodine that will dissolve in 100 grams of the fat, which provides a gross indication of the degree of unsaturation. A useful though arbitrary classification by iodine number is the

following: saturated fats, iodine number 0-70; neutral fats, iodine number 70-100; unsaturated fats, iodine number 100+.)

Though there were already impressive results showing the positive effect of low-cholesterol, low-fat diets in controlling cardiovascular disease at the time, these results were overlooked in the spate of enthusiasm that developed over the prospects for controlling coronary disease with unsaturated fat-based diets. This enthusiasm persisted, resulting in a negative attitude towards other dietary approaches, as typified by a 6-29-68 Lancet editorial: "A simple low-fat diet, in which fat accounts for less than 20-30% of the total calorie intake reduces elevated serum-cholesterol levels in most people, but it is monotonous and is unlikely to be adhered to for a long time." The stage was being set for twenty years of wasted efforts in an attempt to reduce coronary heart disease through diets which substituted unsaturated fats for saturated fats with no reduction in total fat content.

The preoccupation with the substitution of unsaturated fats for saturated fats--all else remaining unchanged--has dominated the nutritional world since the American Heart Association sanctioned this approach by adopting it as its principal preventative recommendation, ignoring the negative results of the many diet programs in which it had been tried. Unfortunately, a magic cocktail of oil will not cure or prevent atherosclerosis. The available evidence clearly demonstrates the utter futility of this approach to which endless manpower hours and funds have already been committed, and which is the basis for future projects such as the costly national-scale 10-year program--the National Diet-Heart Study--proposed by the National Heart and Lung Institute.

A review of the research on unsaturated fat diets

One of the longest of these programs, lasting 11 years, was undertaken in Oslo, Norway.[119] For the study, over 400 men aged 30-64 years, all of whom had had a first myocardial infarction, were divided into two groups. Both groups received the same amount of calories in fat--about 40% of total calories--but one group received these calories in unsaturated fat, the other in saturated

fat. The cholesterol intake was 264 mg. per day in the experimental group (unsaturated fat) and 600 mg. per day in the control group (saturated fat). The cholesterol levels of the subjects of both groups started around 300 mg., but in the experimental group dropped to 240 mg. by the end of the first three months, where it remained for five years, while in the control group it continued unchanged at 300 mg.

A comparison of sudden deaths in the two groups showed an identical rate, almost 25% of each group. However, those on the experimental diet had a lower myocardial infarction mortality rate than did the controls. Based on conclusions from studies that followed, the lowered cholesterol level was probably responsible for the reduced infarction rate on those on the experimental diet.

Another study, this one carried out in London,[120] was done with men under 60 who had recently recovered from a first infarct. Half the group of almost 400 subjects ate their normal fare while the other half had a special diet using soya oil substituted for the saturated fats. Their diets and beginning and ending cholesterol levels are indicated below:

	Special Diet	Controls
INTAKE PER DAY:		
Protein	80 gms.	88 gms.
Fat	125 gms.(46%)	115 gms.(46%)
Cholesterol	258 mg.	588 mg.
CHOLESTEROL LEVEL:		
Start	272 mg.	273 mg.
6 years later	239 mg.	269 mg.

The soya oil in the special diet was calculated to produce a fat ratio of polyunsaturated/saturated of 1.8/1. The U.S. diet has a P/S ratio of 1/5. The American Heart Association recommendation for a period of years has been 2/1.

Still hoping to prove their case as to the alleged benefits of the high unsaturated fat diet, advocates of this approach eagerly seek a "definitive answer" from the proposed National Diet-Heart

Study, a mammoth program which would test hundreds of thousands of people on special diets over a 5-year period, at least. Fat intake would closely follow the American Heart Association recommendations: saturated fats would be decreased, unsaturated fats would be increased, total fats would not drop below 35% of total calories.

The proponents of the National Diet-Heart Study have not heeded the conclusions of the London and Oslo trials,[121] which have, in effect, already proven the points that the proposed study would seek to clarify. A summary of these conclusions is given below:

	LONDON DIET	OSLO DIET
Soya oil gms./day	85	75
P/S	1.8	2.4
Sudden deaths	Dieters & Controls, same	Dieters & Controls, same

In the London trial, other relationships became apparent that discouraged the investigators:

1. Total deaths due to coronary heart disease--no difference between dieters and controls
2. Major relapses--no difference between dieters and controls

The London investigators concluded: "Indeed, the results of this trial alone lend little support to the suggestion that a diet of the kind used (high unsaturated) should be recommended in the treatment of patients who have suffered a myocardial infarction. Taken together with the results of the Oslo trial, there is no indication that this type of diet affects mortality."

The futility of the high-calorie-level unsaturated fat approach was again demonstrated in a study in which 80 people followed three different diets for two years, the diets differing essentially in the relative quantity of saturated vs. unsaturated fat. The control diet was predominantly saturated, the olive oil diet was neutral, and the corn oil diet was unsaturated. The results are summarized below:

TWO-YEAR TRIAL DIET

	Control	Olive Oil	Corn Oil
Cholesterol level end of 1st year	.3 mg.%	+12 mg.%	-30.8 mg.%
Cholesterol level end of 2nd year	-2.8 mg.%	-.9 mg.%	-19.9 mg.%
Total fat intake	33%	48%	52%
Major cardiac events	25%	43%	48%

As noted in the table, twice as many subjects in the corn oil group, which consumed the largest amount of fat, either suffered an infarct and survived or else died. The number of major cardiac events is proportional to the total fat intake, but is not related to either the cholesterol level or the saturation of the fat. The significance of the difference in the number of infarctions or deaths between corn oil and control groups approaches the conventional significant level (.1>P>.05). The possibility that a true difference of the same magnitude in the other direction could be missed by chance is less than one in one thousand. The investigators summarized: "corn oil cannot be recommended as a treatment of ischemic heart disease."

An analysis of the Oslo trial of 400 men reflects the relationship of cholesterol level and reinfarction:

CHOLESTEROL LEVEL MG. %	CORONARY HEART DISEASE RELAPSE RATE/1000 (REINFARCTIONS OR DEATHS)
<200	48
200-249	189
250-299	351
$\geq$ 300	471

These rates were applicable whether the subjects were on the unsaturated or control diets. A point for reflection is the acceptance by many standards of the 200-300 mg. cholesterol range as normal; yet subjects with a level of 300 mg. had an infarction rate of almost 1000% over those with a 200 mg. cholesterol level.

A U.S. study of 846 men[122] living in an institution where their food was especially prepared and monitored tried the

unsaturated fat approach, using a diet similar to that followed in the London and Oslo series. The men were examined and followed for eight years. Diet intake is shown below:

	CONTROL	EXPERIMENTAL
Fat (% of total calories)	40%	39%
Iodine # of fat	53	102
Cholesterol (mg./day)	653	365

Total mortality rates were the same for both groups--consistent with results obtained in the London and Oslo studies. Rates of myocardial infarction or sudden death (primary end points of the study) in comparison between control and experimental groups were not statistically significant.

To confirm adherence to the test diet, linoleic acid concentration of the adipose tissue was determined before and after the eight-year period. About 11% linoleic acid was found at the start; at the end, this level rose to 34% in those on the unsaturated diet. Autopsy results, however, showed no difference in the degree of atheroma between the controls and the dieters.

Results of the long experiment were quite disappointing for the principal investigator, but certain conclusions were apparent to him. "It may not be desirable, necessary or safe", he said, to augment the diet with polyunsaturated fats; total fats in the diet should not be 40% as in the average diet, but "should be reduced to less than 20% and ideally it should be 10%."[123] This eight-year study was the longest clinical trial in the U.S. of a diet high in polyunsaturated fats. It would be well if the American Heart Association reflected upon the results and the dietary implications drawn by the investigator.

Further evidence concerning the validity of the concept of lowering of morbidity and mortality rates of coronary heart disease through diets substituting unsaturated for saturated fats is provided by many other studies.

In one,[124] 200 men aged 30-50 years, all with a history of previous myocardial infarction, were divided into three diet groups for a five-year program. The control group consisted of 100 men

who ate a normal U.S. unrestricted diet. Each of the other two diets had 28% of calories in fat, except that one diet was low in unsaturated fats and the other was high--even higher than the amount recommended by the American Heart Association. The table summarizes the diets:

COMPOSITION OF DIETS (Control Diet is estimated)

	28% FAT DIETS		CONTROL DIET
	S Diet (Saturated Fat)	P Diet (Unsaturated Fat)	C Diet
Protein	20%	20%	15%
Fats	28%	28%	40%
P/S	.29	2.5	.27
Cholesterol	396 mg.	260 mg.	600 mg.
Carbohydrates	52%	52%	45%

To create the desired degree of relative saturation and unsaturation, corn and safflower oils were used in the P Diet, and coconut and peanut oils were used in the S Diet. Coconut oil[125] has been well-established as causing an increase in cholesterol levels of plasma and arteries because of its almost completely saturated structure, making it an exception among liquid oils. Peanut oil,[126] though unsaturated, has been incriminated in several experimental diets as causing more atheroma than almost any other oil. The use of coconut and peanut oils together should have provided an unusually effective combination for producing atheroma. In addition, the S Diet included 50% more cholesterol than the P Diet. The only redeeming feature of the S Diet was that it was a better diet than the C (Control) Diet. The table summarizes five years' results.

SUMMARY OF RESULTS AFTER FIVE YEARS ON C, P AND S DIETS

DIET	SERUM CHOLESTEROL MG.%		SERUM TRIGLYCERIDES MG.%		C.H.D. DEATHS	RECURRENT INFARCTION
	Start	End	Start	End	End	End
C (40% fat)	248	250	165	200	16%	25%
P (28% unsaturated fat)	259	234	150	157	10%	18%
S (28% saturated fat)	262	243	140	147	8%	18%

The end results after the five-year period show that a polyunsaturated diet of 28% fat and 1/3 less cholesterol is no better and could be worse than a highly saturated 28% fat diet. The large differences appeared in comparison to the controls--50% more coronary heart disease deaths and reinfarctions occurred in the control group than in either 28% fat group. Total fat intake made the greatest difference rather than the type of fat. Saturated fats in quantities normally consumed and unsaturated fats in quantities recommended by the American Heart Association and in the National Diet-Heart Study proposals are equally capable of great harm in the body.

This was also demonstrated in a study with a group of firemen,[127] average age of 43 years, who were without any history or clinical suggestion of coronary heart disease. After an overnight fast, they drank a formula milk shake in which 55% of the calories were primarily from butterfat. Immediately before drinking the mixture, a particular area of the conjunctival capillaries was photographed; four hours later the same area was rephotographed. In the four-hour period, the triglycerides rose from 109 mg. to 231 mg. The increase consisted mostly of chylomicra formed from the fat which were close to reaching their peak level. The photographs taken before the drink showed the capillaries to be functioning, normal in appearance, and with erthrocytes flowing freely through them. In the photographs taken

four hours after the drink, there was considerable interference with erthrocyte flow and complete interruption of their circulation in several areas. This was due to erthrocytes adhering together forming sludged masses as well as blockage by the capillaries. It was exactly what Swank [128] had described as "rouleaux formation" in hamsters under the same conditions. This experiment clearly showed that saturated fats in quantities not very different from those consumed in an average U.S. meal can block capillaries--creating possibly serious complications in patients whose circulation is already compromised, as in angina and coronary heart disease.

The same experiment was then repeated substituting an identical amount of unsaturated fat (safflower oil) for the butterfat in the original milkshake, all other procedures being the same. A comparison of the blood values with the saturated and unsaturated fat experiments is given:

	PLASMA TRIGLYCERIDE -MG.%		
	FASTING	4 HRS. AFTER MEAL	9 HRS. AFTER MEAL
Saturated fat drink:			
Low level subject	34	150	75
High level subject	227	399	206
Unsaturated fat drink:			
Low level subject	32	76	76
High level subject	197	410	410

Results showed that the subjects with the lowest and highest levels of triglyceride did better on the saturated fat (butterfat) drink than did comparable subjects on the unsaturated fat (safflower oil) drink. After nine hours the butterfat group had dropped considerably from the peak reached at four hours, unlike the safflower oil subjects whose elevated triglyceride values had not yet started to drop after nine hours. This circumstance could be a problem for patients with compromised circulations. As would be expected, the circulatory changes after the safflower oil drink were just as severe as those produced by the butterfat drink, with

sludging and interruption of flow occurring in the identical sites in the same capillaries.

The investigator's understandable concern was reflected in this statement: "The present studies did not demonstrate any difference in postprandial disposition of unsaturated fats as compared to relatively saturated fats...Interference in bulbar conjunctival flow due to sludging also, as Gittler earlier has reported, could not be lessened by the substitution of the unsaturated for the relatively saturated fats. If such interference in flow also occurs in the critically important collateral vessels of the coronary circulation in cardiac patients, then the ingestion of unsaturated fats could lead to disaster as readily as ingestion of saturated fats. This possibility particularly looms as a potential danger in view of the fact that the contemporary clinical fashion (author's note: read American Heart Association and National Diet-Heart Study Program) is not to advise the reduction of all fats in the diet but only the substitution of unsaturated for saturated fats in the diet."

This advice was given in 1965. It should have dampened the enthusiasm for diets high in unsaturates, but did not, despite the cheering from the bleachers by the dairy industry. The vacillations of this group, as observed in the reactions of the National Dairy Council, provide an amusing sidelight to the great saturated fat vs. unsaturated fat debate. When the first correlation was made between coronary heart disease deaths and total fat intake,[129] the National Dairy Council, sensing danger in the form of commercial reverses, challenged the concept.[130] The research had indicated that saturated fats (in our consumption patterns predominantly butter and dairy products) raised cholesterol levels, and unsaturated fats lowered these levels, a situation most threatening in its implications to the dairy industry. When an esteemed investigator demonstrated that unsaturated fats could be dangerous to health because in reducing cholesterol levels they frequently did so by redistributing the cholesterol from the plasma to the tissues, The National Dairy Council exulted in this turn of events which shifted the onus of

guilt away from saturated fats. Their annual award was duly presented to the investigator, who was "particularly cited for defining the qualitative and quantitative significance of fats in the diet of man."(131)

Unsaturated fats do lower serum cholesterol, but there is much evidence that they also raise the cholesterol content of plaques, arteries and tissues, and, in fact, deposit more cholesterol in the arteries than do saturated fats. Nevertheless, the National Diet Heart-Study program proposes placing thousands of persons on high unsaturated fat diets.

The evidence as to the harmful potential of unsaturated fats

Early studies which established the harmful potential of unsaturated fats began with rat experiments,(132) in which the animals received 40% of their calories either from butter (saturated fat) or peanut oil (unsaturated fat), together with a fixed amount of cholesterol. It was found that the cholesterol level in the plasma rose with the butter and cholesterol diet and declined with the peanut oil and cholesterol diet, but tissue analysis revealed that those on the peanut oil and cholesterol diet had higher levels of cholesterol in the tissues than those on the butterfat-cholesterol diet.

The experiment was repeated using rhesus monkeys(133) and a diet in which fat constituted 25% of total calories (butterfat or peanut oil) and cholesterol, 2%. After 50 weeks the animals were sacrificed and their aortas examined. All the monkeys on the peanut oil-cholesterol diet and those on the butterfat-cholesterol diet developed atherosclerosis, but those fed the unsaturated oil (peanut oil) had a mean cholesterol content of 15.3 mg./gm. of aorta as compared to 11.4 mg./gm. of aorta for those fed the saturated fat (butter). The peanut oil had the same effect in animals in such diverse species as rats and monkeys.

Corn oil, too, acted in a similar manner in experiments with young cebus monkeys.(134) In this study, one group of animals was fed a diet of butterfat and cholesterol and another group was fed corn oil and cholesterol. After 45 weeks, the animals were killed

and various tests were made. The concentration of free cholesterol in the adipose tissue of the corn oil-fed group was found to be 150-200% greater than in the butterfat-fed group. Aorta total lipid in the corn oil group was 1.95% as contrasted with 1.65% in the butterfat group. Total cholesterol was 210 mg./100 gms. in the corn oil-fed monkeys and 185 mg./100 gms. in the butter-fed group.

Other studies[135] have reported that cholesterol-corn oil diets have led to greater tissue levels of cholesterol than diets of saturated fat and cholesterol. If, however, cholesterol is removed from the diet and only a high quantity of fats are consumed (44% of total calories), the effect on the arteries is considerably different. In rabbits, for example, which are among the easiest species in which to induce atherosclerosis, on a cholesterol-free diet, saturated fats in quantities of 45% of total calories produced only a very slight atherosclerosis. When cholesterol was added to the diet, gross atherosclerosis developed,[136] especially when the total fat content consumed was unsaturated (corn oil).

In the rabbit study referred to, a basic rabbit chow diet was supplemented with different fats, with or without added cholesterol, to determine relative effects. The table below summarizes the diets and their varying effects on serum cholesterol:

DIET	MONTHS FED	FAT % OF TOTAL CALORIES	IODINE #	SERUM CHOLESTEROL LEVEL MG.% START OF DIET	SERUM CHOLESTEROL LEVEL MG.% END OF DIET
Rabbit Chow only	12	10.6	122	60	60
+ Cocoa Btr.	11	44.8	32	70	73
+ Coconut oil	6	44.8	9	65	65
+ Hydrog. veg. oil	8	44.8	69	50	55
+ Hydrog. veg. oil & 25% choles.	4-1/2	44.8	69	50	391
+ Corn oil & 25% choles.	4-1/2	44.8	120 (est.)	50 (est.)	596

All the animals thrived on the various diets, the fats being well tolerated, but the true story was told at autopsy. At that time, a correlation was found between the serum cholesterol level and the cholesterol content of the aorta which was proportional to the severity of the atherosclerosis. It should be noted that in the cholesterol-free diets, serum cholesterol level was little affected. The following table summarizes the findings:

DIET	GROSS AORTIC ATHERSCLEROSIS GRADE 0-4	AORTIC CHOLESTEROL MG./GM.	LIVER CHOLESTEROL MG./GM.
Rabbit Chow only	.0	3.55	9.54
+ Cocoa Btr.	.4	4.52	15.00
+ Coconut oil	0	4.18	
+ Hydrog. veg. oil	0	2.43	
+ Hydrog. veg. oil & 25% Choles.	1.5	18.26	86.90
+ Corn oil & 0.25% Choles.	1.9	21.30	

The surprising results of this experiment are not so much that hydrogenated vegetable oil and cholesterol produced 700% greater aortic cholesterol than the oil alone, but that corn oil (unsaturated) was much more atherogenic than a saturated oil. This is the finding that the National Diet Heart-Study Program will spend $111,000 000 to discover!

A commentary regarding this study might be that since the cholesterol level rose, conditions with humans are different, since corn oil is hypochesterolemic. However, this reasoning cannot be well supported, since a considerable amount of cholesterol can be absorbed without changing the serum cholesterol level.(137)

Other studies(138)(139) have determined that animals fed unsaturated fats and cholesterol develop plaques that contain more cholesterol than is found in those animals fed saturated fats and cholesterol. In fact, the rate of disappearance of the initially introduced cholesterol was retarded in unsaturated fat-fed animals as compared with the saturated fat-fed ones. The ineffectiveness of unsaturated fats in preventing or retarding atherosclerosis is not a species difference, having been observed in other animals, including man.(140)

The evidence be damned! On with the National Diet Heart-Study Program

Despite the formidable evidence that the adding of unsaturated fats to the diet is fraught with serious dangers, the National Institutes of Health are pursuing with vigor their National Diet Heart-Study Program which would saturate the nation with unsaturates. Their committee report on recommendations for this mass field study[141] focuses on a single goal: "The avowed purpose of any prospective diet-heart study is to test for a reduction in the incidence of heart attacks by instituting an UNSATURATED (our capitals) fat-low cholesterol diet." To achieve this goal, they suggest four diet programs:

NATIONAL DIET HEART-STUDY PROGRAM PROPOSED DIETS

	CONTROL	E_1	E_2	E_3
Cholesterol (mg./day)	546	440	100	100
Fat (% of total calories)	40	40	35	35
P/S ratio $\frac{\text{Polyunsaturated}}{\text{Saturated}}$	.2	.6	4.2	.5
Iodine Number	54	74	129	69
Protein (gm./day)	97	109	98	93
Cholesterol-lowering capability	0	-7%	-30%	-13%

Their stated ideal would be to have a control group and two double blind groups--one that lowered cholesterol levels by 5-10%, and the other "aiming at maximal lowering, compatible with feasibility, perhaps as much as 20%." The best this program could achieve would be to keep the group of people they hope to save in the low 200 mg. cholesterol level range. However, as previous studies on unsaturated fat diets have demonstrated, this will not prevent coronary heart disease. What a waste of human and financial resources!

V. DRUGS, SURGERY, AND EMERGENCY CARE IN THE MANAGEMENT OF ATHEROSCLEROSIS

Once the physician has made a diagnosis that a patient is "coronary-prone" or demonstrates one or more of the "risk" factors, measures commonly advised include drugs for lowering cholesterol or high blood pressure, anticoagulants for protection against thrombi, surgery for angina or overweight, and, if diet recommendations are given at all, most likely they would be the A.H.A. recommendations, earlier discussed.

We turn now to the data on drug therapy in order to evaluate past successes or prospects for the future via the drug route.

AN APPRAISAL OF DRUG THERAPY

Lowering of blood fats by the lipid-lowering drugs.

Lessons from the National Heart and Lung Institute "Coronary Drug Project"

The National Heart and Lung Institute, which is planning the National Diet Heart-Study Program, also brought forth the "Coronary Drug Project".(142)(143) If the results of the Drug Project are indicative of the type of recommendations for therapy that will be emanating from the National Institutes of Health's N.H.L.I., we are indeed in trouble.

The primary purpose of the CDP (Coronary Drug Project), now in its later phases, has been to test the efficiency and safety of the best lipid-lowering drugs in the long-term therapy of coronary heart disease. To make these determinations, 8,341 men ranging in age from 30-64 years, all of whom had had a previous myocardial infarction, were selected by 53 CDP centers and divided into six groups for the following regimes:

1. Conjugated estrogens - 2.5 mg./day
2. Conjugated estrogens - 5.0 mg./day
3. DT4 (dextrothyroxine) - 6.0 mg./day
4. Nicotinic acid - 3.0 gm./day
5. Clofibrate - 1.8 gm./day
6. Placebo

The process of selecting the 8,341 subjects took four years, and was only one facet of the problems confronted in this most extensive trial of lipid-lowering drugs ever attempted. In the view of the N.H.L.I., the importance of this project warranted the extraordinary amount of time, expense, and huge involvement of professional man-hours in the staffing of the 53 clinical centers and the elaborate coordinating superstructure of staff, boards, committees, and central laboratories and supply centers, in which almost all of the personnel are M.D.s or Ph.D.s.

The rationale for this prodigious effort was the need to resolve the confusion surrounding the prescribing of drugs for hyperlipidemia in patients with coronary heart disease. Physicians, according to the CDP, "know that susceptibility to first episodes of premature coronary heart disease is directly related to serum levels of cholesterol... They are also aware that elevated serum lipids frequently can be reduced by available drugs. However, they lack the answers to key questions about these pharmaceutical agents: Do they prevent recurrent episodes of coronary disease and prolong life? What is their mechanism of action? Are they reasonably safe in long term usage?... Treatment of coronary heart disease by controlling hyperlipidemia makes sense only as years-long therapy--and questions about drug toxicity are especially gnawing under this circumstance... Finally the physicians' dilemma stemming from the uncertainty as to rationale, safety and efficacy--is compounded by awareness of the relatively recent unfortunate experience with triparanol." (Triparanol--MER 29--is to be remembered for causing cataracts and other toxic effects in patients, including many physicians who used this hypocholestermic drug.)

An obvious question is--why bother? Low-fat, low-cholesterol diets work now--no side effects, no toxic factors, no constant monitoring. But the medical profession is trained to think of therapy in pharmaceutical terms, and this project reflects this inclination.

So far, an average of 36 months has been compiled in this projected five-year drug assessment program. The results to this

point are not promising. The 5 mg. estrogen group (ESG2) was stopped after only 18 months. In this short period, this estrogen group had double the reinfarction rate and 50% more sudden deaths than those on placebos. The decrease in libido were a majority complaint. Several cases of thrombophlebitis and pulmonary embolism, all in excess of those occurring on placebo, contributed to the tally of toxic side effects.

The decision to abandon the 5 mg. estrogen program opened a discussion on whether to continue with any estrogen, since 1000 men were still on the 2.5 mg./day dosage. Various studies were reviewed where other groups had used estrogens for other reasons (prostatic carcinoma, cerebral vascular disease, etc.), and although the dosages used in these cases were much less than 2.5 mg./day, an excessive number of reinfarctions was still found to have occurred. It was nevertheless decided to continue the 2.5 mg./day estrogen group, but to monitor these subjects very carefully for cardiovascular complications. Results of this program, however, are not encouraging so far. A report on a 570-man subgroup from one of the 53 medical centers in the program indicates that the five-year 2.5 mg./day estrogen program produced no benefits and that cholesterol level rose 6%.(144)

The tentative results on DT4 (Dextrothyroxene) after 18 months did not look too hopeful either. Among the 1109 men on this program, a small number (26 men, 2.3%) exhibited FEVB's (frequent ectopic ventricular beats--10% or more of all beats) on the original ECG. This group experienced a 330% higher death rate than did the corresponding FEVB group on placebo. These findings did not discourage the CDP Project Policy Board sufficiently to cease experimenting with this drug, so the balance of the men continued. After 36 months, a year and one half after the first review indicated the problems with the FEVB group, the Data and Safety Monitoring Committee recommended that DT4 be stopped. While the drug was doing what was expected (lipids were decreasing--cholesterol levels had dropped 12% and triglycerides had dropped 15-20%--both drops statistically significant), an unexpected development was an 18.4% increase in death rates over the placebo

group, due to patients experiencing reinfarctions and death from all cardiovascular causes. In addition, numerous untoward effects were observed--e.g., lowered white blood cell count, raised alkaline phosphotase levels, tendencies towards hyperglycemia and glycosuria, and several other biochemical changes.

Clofibrate, to be discussed later, and nicotinic acid, are the two remaining drugs in the CDP drug evaluation program. A preliminary review of nicotinic acid is that contained in the report of the 570-man subgroup, which forecasts what can probably be expected when the complete results of the 8,341 subject study are in. The subgroup report revealed that sudden deaths occurred more frequently with nicotinic acid, and that those on the drug had a greater death rate from coronary heart disease--despite an initial drop in cholesterol level of 17% which leveled off finally to 10% below original values. It is no wonder that the subgroup study's director, in his report on the 570 subjects, said: "The results of the present study do seem to suggest that serum cholesterol values may well not be a significant indicator of survival or of future morbidity, once the disease has become manifest." Mortality rates for the five-year program among the 570 subjects--a combined result of 28.6% for all those on the various drug programs as compared to 28.7% for the placebo group, hardly warranted a more sanguine statement concerning the value of lipid-lowering drugs in the treatment of this subgroup.

The drop in cholesterol level due to a lipid-lowering drug coupled with an unexpected rise in death rate was also the subject of comment in a CDP official statement[145] in reference to DT4: "As anticipated in the original design of the study, DT4 successfully reduced serum lipid content... First, it is possible that serum cholesterol is no longer related to risk of coronary heart disease after one or more myocardial infarctions, in contrast to its significant association with first events of atherosclerotic coronary disease. (However) Repeated analyses of the CDP placebo group experience show that serum cholesterol level at entry is related to risk of sudden death, all coronary heart disease death, and death from all causes. Therefore it remains reasonable to

hypothesize that sustained reduction of serum cholesterol level by SAFE (our capitals) means may have a beneficial effect on long term prognosis for post infarct patients."

There are several questions raised by the CDP study results as well as by the official response to them. One question concerns the seeming paradox of lowered cholesterol levels produced by drug therapy or diets high in unsaturated fats which are coupled with unexpected increases in death rates. By contrast, lowering plasma cholesterol by low-cholesterol, low-fat diets are effective in reducing coronary heart disease incidence because the excess cholesterol is not brought into the body.

But Diet-Heart Study standards permit high cholesterol and/or high fat intake, which in either case will raise cholesterol deposition into the tissues. Drugs have unexpected results; triparanol (MER-29), for example, lowered cholesterol in the plasma, but the precursor, desmosterol, became stored in the tissues. Unsaturated fats have also lowered cholesterol levels in the plasma only to shift them to the arteries and tissues.

Lowering lipids in the plasma is meaningless unless it is known where they go. This problem does not exist if they are not introduced by cholesterol and fat in the diet.

A second question has to do with CDP statements concerning the results of the drug assessment program and their implications, which utterly ignore the studies using low-fat, low-cholesterol diets and their contribution.[146][147] These studies do, in fact, establish this dietary approach as the "safe means" for "sustained reduction of serum cholesterol level", the stated goal of the CDP investigators, but one would hardly be aware that they existed, so far as the CDP analysis of the overall problem is concerned. A further criticism of the CDP statements has to do with the potential danger to post-infarct patients who may interpret these sweeping remarks to mean that it might be just as well to abandon cholesterol-lowering diets while they await the results of further research (viz.: "...it is possible that serum cholesterol is no longer related to risk of coronary heart disease after one or more myocardial infarctions...")

That this indeed is the official view was indicated by Dr. T. Cooper, Director of the N.H.L.I., who said: "I think we need to get on with testing whether lowering blood lipids will prevent arteriosclerotic vascular disease in man... Such trials should strive for maximal lowering of lipids by any methods available, effective, appropriate to the patient situation, and safe, be it diet (35+% fat as proposed in Dr. Cooper's Diet-Heart Study), drugs, surgery, or any combinations thereof." Dr. Cooper's conclusion is a stunner: "The test is therefore not of diet or drugs or surgery--rather it is a test of the lipid hypothesis." Dr. Cooper is proposing a $112,000,000, 10-year Diet Heart-Study project which would include up to 20,000 people to try to breathe life into this tired and false hypothesis! One would think that the mass of data showing the failure of drug therapy to reduce coronary heart disease through lowering cholesterol levels would have laid this concept to rest. Yet Dr. Cooper is proposing this huge investment of time and money to "determine once and for all" whether lowering lipid levels will reduce coronary heart disease.

It requires no crystal ball to anticipate the results of present and projected studies:

1. At the end of the five-year, over 8,000-subject Coronary Drug Project, the conclusion will be: drugs are not as effective in lowering coronary heart disease relapse rate as low-fat, low-cholesterol diets.

2. At the end of the ten-year, 20,000-subject Cooper study, the conclusion will be: inconclusive; insufficient improvement through lipid manipulation by diet (high unsaturated fat) to warrant a national all-out change in dietary habits.

The kind of biased thinking which underlies the design of these stupendous research projects and which rules out the low-fat, low-cholesterol diet approach for control of coronary heart disease is typified in this statement of a prominent researcher[148] (Berkowitz--a champion of Clofibrate): "More specific dietary changes involving a reduction in the cholesterol intake together with either a low-fat diet or a 30-40% fat diet comprising mostly unsaturated fats have resulted in various degrees of success. A

recent review of 12 such dietary trials involving both normolipedemic and hyperlipidemic individuals has indicated that except for Morrison's subjects, a reduction in the serum cholesterol level of 15% was the maximum effect obtained with even marked changes in the diet in institutionalized and highly motivated patients. Experiences with the National Diet-Heart Study (preliminary trials) were similar, resulting in an average fall in the serum cholesterol level of 14%."

Berkowitz, for reasons unknown, failed to be impressed with the Morrison study--the only low-fat-and-cholesterol study of the 12, in which subjects consumed 15% fat and <100 mg. cholesterol daily, and the only study in which there was substantial improvement in life span over controls for those having had a previous infarct. Subjects in this group dropped their cholesterol level 30% and their triglycerides 50%, all without lipid-lowering drugs, but these results are not considered important by Berkowitz and others with similar viewpoints because of the tremendous resistance to changing fat intake from 35+% to < 15%--the level to which it must drop to achieve therapeutic effects.

The other dietary trials cited by Berkowitz were of the unsaturated type suggested by the American Heart Association and by the National Diet-Heart Study. Berkowitz is correct when he says these will not work, but he offers no alternative but lipid-lowering drugs and, specifically, Clofibrate.

Berkowitz' experimental procedure with this drug was to administer the Clofibrate for a period of three months. Subjects not responding were given a different drug, either DT4 (now discredited by the CDP) or cholestyramine resin. The property of this resin in limiting intestinal absorption of iron([149]) and promoting anemia was not of concern when it was administered for lowering of cholesterol level. This substance is an anion exchange resin and further investigations as to what other minerals it might absorb should be carried out.

Clofibrate is the one drug not yet commented upon in the CDP reports. Comments will be awaited with interest, but meanwhile, let us examine other evidence dealing with the effect of this drug.

Clofibrate, another lipid-lowering drug: the evidence so far

Clofibrate has gained popularity because in Berkowitz's experience with 50 patients over 6-8 years, he was able to effect cholesterol level reductions of 30% and triglyceride reductions of 50% (which is what Morrison accomplished with diet alone).

Other investigators with the drug have not done as well, however. In a large trial of 530 male subjects (Veteran's Hospital inmates diagnosed as having cerebrovascular disease), use of Clofibrate over a two-year period in a double-blind study brought cholesterol levels down 5% in the first two months, but for the balance of the treatment period cholesterol levels were no different than pretreatment or placebo levels (regardless of age or race). Triglycerides in these men dropped and remained at this level throughout the treatment period.(150)

Since any lipid-lowering drug therapy is planned for years, toxic factors become important. Preliminary observations indicate that Clofibrate produces hepatomegaly in rats and also decreases secretion of cortical steroids.(151) In humans, at a dosage of two grams daily, adverse effects were observed on blood properties,(152) and the decrease in platelet stickiness, an initial response, mostly disappeared after 4-5 months. A surprising effect was in fibrinolytic properties. Clofibrate, it has been claimed, has a favorable response on the "thrombogenic abnormalities", especially in clot lysis time. (A short clot lysis time would be of great benefit for those with occlusive vascular disease.) Blood lysis time was normal in 6 out of 8 patients (six hours or less). However, on Clofibrate therapy, some of the lysis times increased over 400% within six months. After the drug was stopped, the lysis time in every case returned towards the starting values.

When Clofibrate was combined with a steroid (Atromid), lysis times dropped temporarily in 15 patients. The reason soon became apparent when the steroid alone was given and was found to reduce the lysis time. This observation resolved some contradictory reports concerning the success of Clofibrate in lowering blood

lysis time. The success was due to the steroid with which it was combined! When the steroid was removed, Clofibrate was shown to be an antifibrinolytic drug. This antifibrinolytic action is probably related to the suppression of adrenal secretion of cortical steroids by Clofibrate.(153) Although it is only theoretical that a short blood clot lysis time is beneficial, administration of anticoagulants is based on this reasoning. Increasing the lysis time may be too much of a penalty exacted for reducing the cholesterol level.

Lipid-lowering drug therapy for juveniles: there are no limits!

If N.H.L.I. officials have their way,(154) drug treatment to reduce cholesterol level will be extended to infants. In treating hyperlipidemic children, Dr. Kwiterovich used a diet containing less than 300 mg. of cholesterol per day, noting a 14% drop in cholesterol levels; but by combining cholestyramine with the diet, Kwiterovich achieved cholesterol drops over 40%. (This investigator apparently failed to consider that 300 mg. of cholesterol per day in a child is equivalent to 1000 mg./day in an adult--hardly a low-cholesterol diet. Morrison's success(155) was based on 100 mg. cholesterol/day with adults, which would be the equivalent of 20-50 mg./day with children.)

At an American Heart Association meeting in November of 1970, Kwiterovich proposed using this approach with infants, automatically screening them using a sample of cord blood. If, at the end of 3 months, their cholesterol levels are not in the normal range, treatment utilizing cholestyramine resin would begin. This treatment would place babies on breast milk at a special disadvantage, since mother's milk has practically no iron at all, and the infants' minimal iron stores would be further depleted due to the propensity of the resin for absorbing any iron that might appear in the intestine as a result of shedding of cells, etc.(156) It might be easier to put the mothers on a low-fat and low-cholesterol diet and keep the infants away from N.H.L.I. and anemia!

Forty-six children, the youngest only 4 years old, have been placed on such "low" cholesterol diets and cholesteramine. The parents of almost 50% of these young children were found to have cholesterol levels as high as 410 mg., though only in their teens or early twenties. One 26-year old mother had angina; another, aged 35, had already had one infarction. Small wonder that these children--who shared their mothers' blood supplies as fetuses and the family diet as growing youngsters--manifest abnormal blood pictures so very early in life.

In August of 1971,(157) the proposal for screening infants became a reality when the N.H.L.I. awarded 34 grants totaling $16,400,000 to establish Specialized Centers of Research at 29 universities and hospitals in the country. Among the several avenues of investigation funded is the selection of children with high cholesterol levels and the evaluation of drugs that will lower these levels. These drug regimes are intended for time spans of years and possibly throughout life. It is incredible how far N.H.L.I. will go to avoid programs based on low-fat-and-cholesterol diets! The N.H.L.I. apparently subscribes to the prevailing opinion as articulated by the editor of a chapter on Cardiology in a recent text,(158) who said he would not advise patients to follow a low-fat, low-cholesterol diet because "of the great inconvenience to the patient (and) because of the abnormal--<u>for our society</u>--and tasteless--<u>by our standards</u>--diet. (Our italics). For these reasons, despite the strong tendency to follow the superficial logic behind it, it is my belief that the sanest attitude is to wait for evidence of effectiveness before subjecting already unhappy patients to an unpleasant diet."

It seems that in our drug-oriented society it is preferable to put infants and their mothers on a lifelong drug regime!

The anticoagulants.

<u>A tale of two clots</u>

The subject of anticoagulants in coronary heart disease therapy is one that most cardiologists would prefer to forget ever happened. It will no doubt be as disreputable a chapter in medical

history as the blood letting and physics of bygone times because the basis for anticoagulant therapy is equally nonvalid. In the case of anticoagulants, this erroneous hypothesis in which it is based owes its origin to a case of mistaken identity. It had been well established that a principal cause of myocardial infarction was coronary occlusion. When the occlusion incorrectly became equated with thrombosis, the problems started. The so-called "thrombus" found occluding arteries was not a thrombus and could not be affected by anticoagulants.

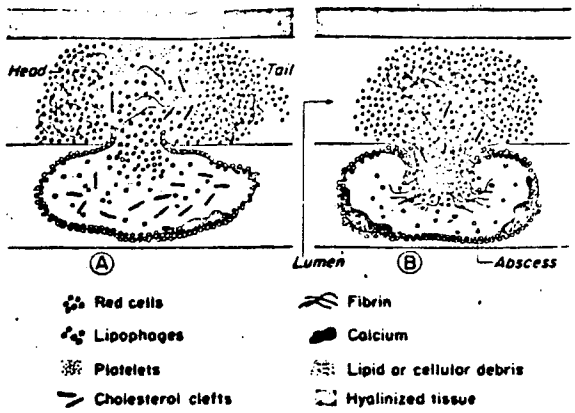
A few preliminary facts will prove helpful:

1. An anticoagulant prevents or delays clotting, or can cause lysis of a clot.
2. A clot forms when blood solidifies in the air. It is a fine fibrin mesh within which are red and white blood cells and platelets, present in similar proportions to their concentration in whole blood. Such a clot is commonly known as a thrombus.

In a poorly circulating deep leg vein with a stagnant blood stream, clots can form, and as they gradually circulate can cause a pulmonary embolism. This type of venous clot or "thrombosis" can be acted upon by anticoagulants. However, an occlusive thrombus is not affected by anticoagulants, as is a simple clot. An analysis of the thrombus formation will reveal the reason.

Origin of thrombus in atherosclerotic plaque

The so-called "thrombus" as found in coronary occlusions is not derived from a simple clot. Its origin is in the atherosclerotic plaque. Development of plaques have been described and characterized earlier in this writing as abscessed invasive structures, penetrating into the media and even into the adventitia. A simplified drawing illustrates this state.



A. Rupture of an atheromatous abscess and the discharge of some of its debris into the lumen leading to thrombus formation is illustrated. The "body" of the thrombus is composed chiefly of platelets and cellular debris and only a few erythrocytes and fibrin fibers. B. The rupture of the lumen into an abscess is shown. The thrombi following this type of rupture contain fewer platelets but many more erythrocytes and fibrin which also frequently enter into the abscess cavity. (American Journal of Pathology)

As noted in the dormant plaque, the abscess is lined by foam cells (engorged with lipids and cholesterol); filled with a gruel-like substance of semi-liquid lipid, cholesterol crystals and cellular debris; and topped with a fibrous cap, which has become hyalinized.(159) When a plaque ruptures and spills its contents into the lumen of the artery--if it is large enough--it will practically occlude the lumen. In most cases, at the plaque locations the lumen has been narrowed to less than 50% of its original size, so that rupture of the plaque will close most, if not all, of the remaining opening. The broken, but still attached plaque fragment, acts as a dam to the flowing blood. That fragment (which is partly the fibrous cap and partly the abscessed contents) becomes the nucleus of the thrombosis. The thrombus becomes

enlarged by masses of platelets which become enmeshed in the abscessed plaque fragments. Erthrocytes on both sides of the blockage, now surrounded by a fibrous network created by the platelets and blood fibrin, finish the job of forming the occlusive thrombus. The total development of the occlusive thrombus, whether it ruptures towards the lumen, as was described, or away from the lumen, as will be described shortly, can take anywhere from several hours to several weeks.

If the plaque ruptures inwards, away from the lumen, blood rushes into it from the lumen. The blood in contact with the lipid-and-cholesterol "gruel" and the ragged wall of the abscess form a chemical reaction which begins the thrombotic development. The cavity of the plaque now fills mainly with erthrocytes and some platelets and fibrin. A mixture of erthrocytes and "gruel" spills out into the lumen, which already being very narrowed, now becomes practically occluded. Flowing blood stacks platelets and fibrin into the occlusive spongy structure and erthrocytes pack against this mass, further enlarging it.

<u>The anticoagulants are ineffective against occlusive thrombi</u>

Seen in pathological conditions with natural anticoagulants

What effect can anticoagulants have on occlusive thrombi? Atherosclerosis patients who have been under the equivalent of anticoagulant therapy all of their lives (they are hemophiliacs) can provide us with an instructive answer. Some of these hemophiliacs have been documented with widespread atherosclerosis involving the coronary arteries.(160) In one case, a hemophiliac with a ten-year history of angina (six of whose male relatives were also hemophiliacs), finally experienced a myocardial infarction. The long history of angina in that case suggests considerable plaque buildup to establish the ischemia necessary for angina, ending with a plaque rupture to produce the infarct. In all these cases with hemophiliacs with atherosclerosis, it is obvious that clotting could have played no role in the development of coronary heart disease and that their natural inability to clot did not help to deter the progress of the disease, despite the fact that the

lack of clotting ability in these individuals was far greater than could be artificially produced with anticoagulant drugs.

Factor XII (Hageman factor) is important for the coagulation of blood and the formation of clots. Activation of Factor XII is considered the first step in the coagulation process. Yet a 59-year old physician,[161] with a confirmed myocardial infarction, had a severe deficiency of Factor XII. This was determined when he was being tested for anticoagulant therapy, and it was found that his whole blood clotting time was at least five times longer than normal. This is a much greater degree of anticoagulation than would be produced by drugs administered to prevent thrombosis. The patient's cholesterol level of 300 mg. and triglyceride level of 143 mg. would more likely be responsible for the infarct, rather than a "thrombus" or clot that could not form in this man's blood, given the severe deficiency of Factor XII.

The same study reports other infarctions with patients who not only have a Factor XII deficiency, but also Factor VIII (classical hemophilia) deficiency. Thus, a 26-year old hemophiliac who died was found to have had atherosclerotic plaques in his aorta.

Patients with rheumatoid arthritis sometimes develop a powerful circulating anticoagulant. A 57-year old male developed such a clotting defect,[162] which inhibited Factor VIII as much as in the most severe form of hemophilia (Factor VIII tested at 0% as against a normal of 40-240%). The clotting defect was first noticed by hemorrhages into the calf muscle. Not aware of any bruising or trauma, his problem was finally discovered by testing a few months later. The tests revealed no Factor VIII activity due to the presence of an inhibitor specially directed against this component. A year later, following many bleeding episodes, he was retested and the inhibitor was found to be 100 times more potent than the first time he was tested. Shortly after this, about 15 months after his clotting defect was discovered, he died of an infarct. Autopsy results revealed coronary arteries that were extremely atheromatous and narrowed. The aorta was densely covered with atheromata. Areas of the myocardium had old fibrotic scars and a recent infarction with fibrin in the inflammatory areas.

Smaller branches of the coronary arteries were occluded with fresh thrombi composed of laminated fibrin-platelet masses. The aortic thrombi were clearly noted to have fibrin platelet masses in the fragmented plaques, practically identical to the structure as described under "a simplified description of a 'thrombus'".

One must ask: how can fibrin-platelet thrombi exist in such an anticoagulant plasma? No anticoagulant drug treatment could ever be as effective against clotting as was the plasma of this 57-year old man. One's faith in anticoagulant treatment for infarction victims could well be undermined by this case alone!

Observed in animal studies.

Animal studies[163] confirm observations in humans as to the ineffectiveness of anticoagulants in coronary disease therapy. Four groups of rats were used to test the anticoagulant warfarin in its ability to affect the prognosis of coronary heart disease on an atherogenic diet. Two groups were placed on a low-fat, cholesterol-free diet, and the other two were placed on a diet in which butterfat comprised 40% of total calories and which supplied cholesterol. One group from each of the diet categories was given injections of warfarin sufficient to maintain blood prothrombin times at twice those of normal control rats. This is the value usually selected for humans. The experiment continued for 22 weeks, after which the rats were sacrificed and results noted.

DIET	WARFARIN	ISCHEMIC LESIONS HEART	KIDNEYS	CALCIFICATION OF KIDNEYS	MARKED RENAL PIGMENTATION
High fat	No	Yes	Yes	Yes	Yes
High fat	Yes	Yes	Yes	Yes	Yes
Low fat	Yes	No	No	No	No
Low fat	No	No	No	No	No

Warfarin has no effect on lipid levels. Both groups on 40% fat diets, whether on warfarin or not, had similar lipid values. All of the destructive changes showed up only in the groups on the high-fat diet. Kidney lesions were worse on the warfarin plus 40% fat diet than they were in the high-fat group without warfarin.

Thirty percent more lesions were found in the warfarin group. Other significant findings were these:

1. The cardiovascular and other damage was directly correlated with the high-fat diets, independent of the anticoagulant warfarin.
2. If warfarin has any effect on the ischemic lesions, it was to worsen them.
3. On the low-fat diets, with or without warfarin, no adverse changes were seen.

Experience in coronary patient therapy.

Since Wright's publication in 1948[164] of a large cooperative study on anticoagulants for the treatment of acute myocardial infarctions, anticoagulants became part of therapy in most U.S. hospitals. Several studies have been made subsequently and the total evidence points to no reduction of mortality or lessening of complications derived from the use of anticoagulants.

The absence of concrete evidence establishing beneficial effects from anticoagulant use is the subject of an interesting comment by the famed surgeon Michael De Bakey (1969):[165] "As far as anticoagulants are concerned, in general, here, too, we as surgeons are inclined to consider their use as an antithrombotic drug in much the same way as many of our medical colleagues do. To use it one must have faith in it. You don't need evidence if you have faith. Some surgeons have faith in anticoagulants and prescribe them, but I would say that most surgeons tend to be agnostics or atheists in this regard."

Dr. Hampton of Harvard sums up the problem (1969):[166] "I think we should remember that 20 years ago we also had the ideal drugs for myocardial infarction--the anticoagulants. Unfortunately, the assumption that we needed to stop clotting was wrong."

Hemophiliacs who suffer the ravages of coronary heart disease could not agree more with Dr. Hampton. It is unfortunate that large numbers of clinicians agree less. Perhaps they lack

sufficient familiarity with problems associated with this very routine therapy.

Heparin is widely used as an anticoagulant. Although patients have been on this drug for years and still continue to use it, they are troubled with adverse reactions. If the heparin is administered in reasonable doses for periods of more than 100 days, bone resorption can be noticed. Several cases have been reported where the resorption was so severe that spontaneous fractures of ribs or vertebrae occurred in as short a period as 6 months.[167] Biopsy showed soft bony matrix. Upon withdrawal from heparin, virtually all the patients were restored to their original condition with respect to this problem, experiencing satisfactory bone healing and no further fractures.

Even when patients are closely monitored, considerable risk is entailed with heparin therapy. In a coronary care unit[168] of a large Naval hospital, 42 cases of women--mostly over 50 years of age--who were receiving heparin, were reviewed. Forty-three percent of these women had bleeding episodes, of which 26% were quite severe. Although drug administration and control of bleeding were under strict hospital supervision, many bleedings occurred without any diagnostic evidence.

Retrospective studies of the patients' charts indicated that a warning in the form of pain occurred in every major bleeding episode about 48 hours before clinical evidence was available. If the bleeding was into the hip, in every case hip and leg pain was noticed. At this time, neither physical examination nor X-rays could determine what bleeding was actually taking place and was responsible for the pain.

Several other studies have indicated that women of this particular age group experience a 50% risk of bleeding on heparin therapy.[169] It would seem that patients not under constant hospital surveillance would be taking considerable risk by using this drug.

Long-term anticoagulant therapy leans to coumarin anticoagulants because they can be taken orally. The principal problem with coumarins, like any other anticoagulant, is that they

cause bleeding. Diabetics and those with coronary heart disease are in especial danger with anticoagulants because of their already fragile capillaries. Microaneurysms in these capillaries bleed spontaneously, and under the influence of anticoagulants, these minute hemorrhages--by continuing to bleed--can cause blindness[170] even after only 3 weeks of coumarin use.

One of the bright new hopes in anticoagulant therapy is urokinase.[171] It has stirred so much interest that a U.S. study is planned to begin in December, 1972, which will test urokinase, streptokinase, and placebo. This study will involve as many as 8,000 patients with myocardial infarction being treated in up to 70 institutions during 1973 and 1974.

A preview of possible results might be seen in the first controlled trial with urokinase. This Swiss-directed trial was conducted in six institutions in five nations and included 331 patients. Half the subjects were on urokinase and the other half on placebo (glucose). Dr. F.H. Duckert of the University Clinic in Basel said that the overall death rate was 16% "with no difference between the groups".

This report was announced at an international meeting where two reports on streptokinase were also made, which involved studies of 206 and 321 patients. In the larger study, Dr. P.M. Manucci, speaking for this group, said: "these results do not suggest that streptokinase therapy would reduce the mortality and the morbidity of myocardial infarction."

The chief ostensible reason for the use of anticoagulants is to prevent occlusive embolism. There is much reason to suspect that these drugs create embolisms, thereby producing the very condition they are intended to prevent. The purple-toe syndrome is an example of this situation, in which cholesterol emboli blocking blood flow to the extremities, eventually create a gangrenous condition. The blue mottling of the toe skin ("purple-toe") caused by the lack of circulation has been observed by several investigators.[172] Sixteen cases have been reported that describe the skin coloration typical of the purple-toe syndrome. In thirteen of these cases, tissue from the area was studied, and in

each instance cholesterol embolisms were found. The "purple toes" developed within 3-12 weeks after the start of the anticoagulant therapy in every case where anticoagulants were used, except one, where cholesterol embolism was noted in the foot area without the blue mottling of the toe skin. In this case, the patient died within 3 weeks after being started on the anticoagulant, not enough time for the discoloration to develop.

The embolisms as observed in the microphotos clearly show cholesterol crystals bridging across and firmly lodged in the lumen of small arteries, mostly in the range of 200 microns in diameter. It is possible that these cholesterol crystal emboli could originate from the contents of ruptured plaques. The fibrin network encompassing the plaque contents could soften under the influence of anticoagulants and the cholesterol crystals free themselves to be carried to small vessels which they could occlude. Thus, in small vessels where plaques are not found, anticoagulants could introduce plaque fragments, complicating the already distressing condition of atherosclerosis.

If a method is ever found to prevent the ruptured plaque contents from forming a thrombus, the result would be to disperse the fragments and cholesterol clefts or crystals through the vessels, thereby producing not one thrombus, but several smaller emboli. It would be difficult to choose between two possible causes of death--a single large thrombus or multiple thrombi. Either way points to the need for prevention of plaques. It is too late for therapy after plaque rupture occurs.

SURGICAL TREATMENT OF ATHEROSCLEROTIC COMPLICATIONS

Surgical procedures in cardiology and the force of fashion

We are not sufficiently aware, perhaps, of the manner in which new surgical practices become fashionable, hold center-stage for awhile, then recede as still newer practices gain ascendancy. Bed rest for infarct patients has in the past been required for several weeks. Even now traditional physicians adhere to a prescribed two weeks in bed, but younger physicians in line with the new thinking

on early mobilization of patients[173] require only a one-week bed rest. The practice of bleeding was in full sway 200 years ago when its use brought on the death of George Washington, and still crops up now and again in medicine, as it did years ago for the treatment of hypertension. Today, in some areas, it is still used for the relief of the pain of angina.[174]

Surgical treatments in coronary heart disease have flowered briefly, then under the revealing light of double-blind tests or large trials, withered and died. Carotid artery surgery to ream plaques out of narrowed sections and so restore proper circulation to the brain seemed logical, and many patients submitted to this procedure. Unfortunately, in the reaming process many plaque fragments broke off, creating occlusive emboli in multiple areas, which worsened the problem. Results of a large cooperative trial unexpectedly revealed that patients who underwent carotid artery surgery fared significantly worse than untreated controls, due to neurological brain damage caused by plaque fragments.[175]

Beck's myocardial abrasion procedure, originally claiming a 94% improvement over hundreds of cases, and Vineberg's mammary artery implant, claiming a 79% improvement, which enjoyed much popularity as methods for the revascularization of the myocardium,[176][177] are other surgical procedures which failed to withstand the test of time.

With respect to another surgical procedure, Dr. G.E. Burch, editor of the American Heart Journal, said: "Ligation of the internal mammary artery was the 'rage' a few years ago. That was supposed to be the thing. Somebody came along and did a sham operation, and the results were found to be just as good. So the whole thing stopped." And another fashion in medicine became passé.

We are now witnessing a diminution of enthusiasm for endoarterectomy, in which the kind of complications described in carotid artery surgery occur, due to the breaking off of plaque fragments which dislodge and produce multiple infarcts in the cerebral arteries and other parts of the body. In one case the

patient developed severe neurological abnormalities after the operation, dying a short time later.[178]

A 54-year old man,[179] who previously was normotensive, suddenly became hypertensive some weeks after endoarterectomy of the abdominal aorta. This was followed by several strokes with his death occurring a few days later. Autopsy confirmed the various infarcts.

The danger of disturbing existing plaques by the reaming out of the affected arteries, which can free atheroma fragments to travel throughout the circulatory system, is a problem in still another technique, catheterization (retrograde) of the aorta.[180] In this procedure, the incidental production of broken plaques and fragments thereof which may lodge in the kidney area, can cause renal failure or hypertension, as in the case of the 54-year old man discussed above.

Coronary arteriography is practically indispensable for bypass surgery, but the mortality figures on this diagnostic test have been running from 0.5 to 8%, depending upon the condition of the patient.[181] At the rate the bypass procedure is gaining in popularity, the death rate for diagnostic testing could run 10,000-40,000 people per year based on 1,000,000 persons examined annually by this diagnostic method.

Problems with currently used cardiac bypass methods

"This is the year of the 'jump graft'", according to Earle Mahoney, M.D., chairman of the American Heart Association's meeting in Anaheim, California in 1971.[182] The popularity of this newest of fashions in cardiac surgery is indeed growing: in 1969, 8% of all cardiac operations, and in 1970, probably 40%, were bypass procedures.

The "jump graft", which uses a saphenous vein bypass graft for coronary arteries, was first done in 1966. Its benefits--immediate symptomatic relief, disappearance of the ST depression with exercise, and other improvements--gained it almost instant acclaim. There have been no controlled studies as to whether this bypass will reduce or eliminate future infarcts, or would prolong life as

compared to conservative treatment. However, answers are slowly emerging from the patients who have undergone this form of surgery.

Saphenous vein bypass has been used for the lower extremity (femoropoliteal) and results have been tabulated for four years of experience. Twenty-seven percent of the group of patients studied who had the best results had occlusion of their grafts, but in the group with the worst results, 77% had closure of the bypass grafts. The problem of obstruction also appears to be the most serious problem, so far, with coronary bypass.

Although thickening of a vein placed in an arterial system was reported as early as 1906 by Alexis Carroll, it was not until 1971 that a pathological study characterized the thickening as an "internal fibrous proliferation". In this study, cases of 21 patients who had had the bypass operation and died were categorized depending upon the length of survival time following their operations. Twenty-nine saphenous veins were recovered and analyzed, disclosing no lesions for grafts less than one month old. In some month-old grafts, mild fibrous thickening had taken place, but in grafts four months and older, many complete occlusions were found. In one graft demonstrated to be almost completely open after 3-1/2 months, almost complete occlusion had taken place only three weeks later at the time of death.

Similar findings have been observed in other groups studied. At the Medical College of Wisconsin, their one-year experience on 67 patients was a 23% closure rate. In a New York University group of 145 patients, 30% of the grafts had closed after three years. At the Montreal Heart Institute, out of 127 vein grafts, 13% were occluded after two weeks, and a total of 32% were occluded after one year. These results at Montreal convinced them to "bypass" the procedure until more is understood about these discouraging results.

An attempt to analyze the reasons for the closure of the veins would appear to be a necessary step before the popularity for this procedure gets out of hand. A cooperative study was made of 317 patients who had undergone coronary bypass surgery.[183] The data suggested that the rate of flow in the veins was a major factor in

eventual closure. If the flow is less than 20 ml./minute, half the veins will close in less than three months; if the flow is less than 40 ml./minute, 1/3 of the veins will close in less than two years; if the flow is greater than 41 ml./minute, 90% of the veins will be open for at least two years.

These flow rates assume that the recipient vessel will not develop plaques which would narrow its lumen. The development of plaques narrowing the lumen is the reason the coronaries became occluded in the first place and the bypass operation performed. If the same plasma environment prevails, the recipient vessel will close and the operation will have been futile.

In two experiments with dogs, in which venous grafts (autologous) were placed in the arterial system, the animals were post-operatively divided into two groups: one received a high-cholesterol diet; the other, a cholesterol-free diet. In a year, all the animals on the high-cholesterol diet had developed severe atheroma in all the venous grafts. On the standard cholesterol-free diet, no atheroma was found on any of the venous grafts.[184] High fat-and-cholesterol diets provide the hostile plasma environment required to develop atheroma in both veins and arteries.

High blood fats also a factor in heart transplant cases

Dr. Philip Blaiberg had the distinction of receiving the first heart transplant.[185][186] His 24-year old donor had no atherosclerosis and his aorta was completely damage-free. The transplant kept Dr. Blaiberg alive for 19 months, when he succumbed to atherosclerosis. This denouement came as a surprise, since the problem of rejection of the new heart was considered to be the greatest threat to his life. At autopsy, when the transplanted heart and arteries were examined, there were some signs of rejection, but these were not serious. What was found astounded the pathologists: advanced atherosclerosis with every coronary artery occluded to such a degree that only a slit remained for the flow of blood. Sections of the coronary arteries revealed tightly

packed masses of cholesterol crystals impacted deep into the intima.

The pathologist ruled out the ordinarily suggested reasons for atherosclerosis, such as thrombosis, aging, excess of mucopolysaccharide, hemorrhage, etc., concluding from his observations that the damage could only have been caused by the high cholesterol level of the blood. At the time of the transplant, Dr. Blaiberg's cholesterol level was 315 mg., and it never dropped below 300 mg. in the following period until death. The pathologist reported: "The findings in this case suggest that the aorta and coronary arteries of a transplanted heart, unaccustomed to plasma with a high cholesterol and lipid content, take up these substances and retain them with unexpected speed and intensity, leading to extreme and universal luminal narrowing."... "This case adds another hazard where transplantation is undertaken on account of myocardial insufficiency from atheroma of the coronary arteries."... "I feel that patients with ischemic heart disease and high blood cholesterol are not suitable patients for heart transplantation."

The implications of the pathologist's statements are tinged with an unexpected bit of humor. If those with coronary heart disease are eliminated as prospects for transplants, who is left? The situation points out the futility of this approach and the need ultimately to control coronary heart disease by suitable prevention methods (in our view, proper diet). This is virtually admitted in the pathologist's closing remark: "It is indeed a sad irony that a brave pioneer should produce in the coronary arteries of this transplanted heart, the same disease that determined the dysfunction of his original heart."

It is tragic that no effort was made to reduce Dr. Blaiberg's cholesterol level either before or after the heart transplant. One reason for this neglect was the lack of understanding by the physician, Dr. Christian Barnard, concerning the relationship of cholesterol and lipids to atherosclerosis. In reviewing Blaiberg's death,[187] Barnard said that the patient "basically was not able to handle fats."

Fortunately for presently surviving heart transplant patients at Stanford University,[188] the problem of high lipid levels is starting to be recognized. These patients are now placed on low-cholesterol, low-fat diets, and in comparison to a control group on a conventional diet, their survival rate after one year has increased 50%. If this had been done earlier, before their transplants, the probability of their still having their original hearts would be good.

Dr. Barnard's understanding of the role of lipids in diet is not much different from that of physicians generally. It is his belief that the fat level of the Western diet is normal (40% of total caloric intake) and that people who develop degenerative diseases are "not able to handle fats." The fact is that no one can handle fats at this level, which is why we are in an epidemic state and will remain so until fat consumption drops to intakes low enough to prevent development of degenerative diseases--to less than 15% of total calories.

Cardiac bypass surgery--another passing surgical fashion?

The hard facts on bypass surgery are in.[189] One year after bypass 22% of veins are occluded, 18% of patients have suffered a myocardial infarction, and cardiac function is worsened in 50% of patients with previous myocardial damage. Well-controlled studies have shown that 3% of angina patients die each year; bypass figures seem to indicate 10% deaths per year.

Despite the higher mortality rate of bypass surgery as compared to conservative treatment, surgeons show great eagerness to use the procedure "preventatively". Asymptomatic patients who might possibly have an infarct are being advised to undergo the operation. At a recent conference of surgeons,[190] this enthusiasm erupted in statements summarizing the discussion such as these: "The magnitude of this work has such immense implications that it's a big statement to say that everyone who theoretically could benefit from this operation should get it." ...And again--with reference to the future of surgery in treating coronary heart

disease: "We're just a stone's throw away from the best swimming in the world".

These ardent advocates of bypass surgery have been challenged by a two-year study[191] of patients with so-called preinfarction angina. Of a group of 30 medically treated patients, 86% were alive at the end of the two-year period and "neither unstable angina nor its subgroups predicted the severity of coronary artery disease". Half the group had angina unrelated to activity and unresponsive to nitroglycerin. Patients such as these are considered prime candidates for bypass surgery.

One complication of bypass surgery is the loss of previous collaterals. In a study of 50 operations,[192] closure of the bypass in the first four months occurred in 14% of the cases; within 18 months, 30% had closed. In one patient studied before his bypass operation, the presence of an extensive collateralization of an obstructed right coronary artery was demonstrated by angiography. After the operation, the graft closed, and so did the collateral. His physician reported: "In essence, as a result of the procedure, the patient lost the natural bypass he had developed."

The facts show that there is indeed much to lose with bypass surgery, and very little to gain.

Some physicians are much more cautious about bypass surgery, having learned their lessons well from the mistaken enthusiasms of the past. Commenting on the relief of anginal pain due to bypass surgery, Dr. Eliot Corday[193] said: "Dramatic relief has been reported in 60 to 90% of angina patients. Unfortunately, the decrease of pain cannot be used as a guide because it has been shown that a sham operation of skin cutting results in significant relief of angina in 60% to 70% and that a placebo can give relief to anginal symptoms in 60%."

In another surgical context, 50 years after the acceptance of radical breast surgery, investigators are just beginning to question whether simple surgery with radiation might not be a more effective and less mutilating procedure. The caution here is very belatedly developing, unfortunately.

Dr. George Burch,[194] editor of the American Heart Journal, sums it up well: "Surgical procedures, like drugs, are therapeutic agents. They are introduced to improve the health of man and not to injure him. Saphenous vein grafts for coronary arterial diseases have an operative mortality of about 10%, a morbidity rate of about 25% or more (embolism, infarction, pneumonia, hemorrhage, and many other complications in health), associated pain and suffering of 100%, and a cost of $3,000 to $6,000 or more to the patient. The grafts do not cure the coronary artery disease, about 25% of the shunts close within 2 years, and the surgical procedure has never been subjected to any control studies such as sham operation or double-blind evaluation. Imagine any capable cardiologist prescribing a pill that had never been subjected to double-blind control studies, that might kill 1 out of 10 patients, hurt 25%, produce pain and suffering in 100%, cost $3-6,000 to the patient, and never cure him!"

Bypass surgery--the current medical fashion, like many before it, will also pass.

Still another surgical solution--the intestinal bypass

The danger of having surgeons implement means of lowering cholesterol levels rather than nutritionists is illustrated by the ileal bypass operation, in which (incredibly!) the distal third of the small intestine is bypassed in order to lessen the amount of nutrient absorption area available for digestion. Vitamin B_{12} is only absorbed in this bypassed area, but it is reasoned that the use of supplements can meet this problem in the post-operative patient.

Candidates for this operation are patients unable to lower their cholesterol levels below 250 mg. on drugs or the type of diet prescribed for them, and have even included some children.

The rationale for eliminating so many feet of small intestine is the control of coronary heart disease by the reduction of cholesterol levels. A surgeon who reported[195] on 38 ileal bypasses justified the use of the procedure on the basis of the supposed inefficacy of dietary control, stating: "reducing the

amount of ingested cholesterol seems to have very little effect on the level of serum cholesterol". The point of view that reducing the amount of ingested cholesterol has little effect on the level of serum cholesterol is challenged by many studies,[196-200] but even if this surgeon were right, lowering of the cholesterol level through the ileal bypass does not reduce the absorption of cholesterol and its continuing arterial destruction.

This was demonstrated in a series of 8 people whose coronary heart disease was confirmed angiographically. Ileal bypass surgery was performed on the group with the hope of improving their prognosis by halting any further atheroma development through lowering their cholesterol levels. Cholesterol values on all the patients did drop considerably after the bypass operation, and after a year angiography was again done. This revealed no resolution of arterial obstruction--in fact, in many areas there was clear evidence of further progression of coronary atherosclerosis.[201] Unfortunately, cholesterol absorption is not necessarily reflected in cholesterol level, as has been shown in various studies.[202] The results of the operations were ironic: the operation lowered cholesterol levels and increased atherosclerosis.

The dearth of understanding on the part of the groups performing this operation adds to the confusion. At the University of Minnesota, 70 ileal bypass patients reported a marked improvement in anginal pain after the operation had lowered their lipid levels considerably. The correlation of anginal pain and high lipid levels has been demonstrated as early as 1955,[203] as a result of the fats (chylomicra) causing sludging of the erythrocytes, thus lessening their carrying capacity.[204][205] The decreased oxygen in the tissues creates the ischemic condition including angina. This correlation apparently escaped the University of Minnesota spokesman, Henry Buchwald, M.D., Ph.D.,[206][207] who is studying flow patterns to see if a difference in viscosity between high and low cholesterol blood can be demonstrated. As to this possibility, he said: "We doubt it, but if this were true, it would offer an attractive explanation for

the decrease in angina following partial ileal bypass." Buchwald theorized that the reasons for the decrease in anginal pain may have been largely psychological and that his group might be "the best bunch of psychologists in the world."

Even though anginal pain may be decreased for reasons Buchwald and his associates fail to recognize, there is clear evidence that ileal bypass operations do not also deter the progress of atherosclerosis. Nevertheless, these operations continue on man, woman and child.[208]

THE TREATMENT OF ACUTE CORONARY PATIENTS--THE CORONARY CARE UNITS

Let us move from the surgeon's sphere to that of the diagnostician. Much of the magic in modern medical care lies in the complex equipment used. Physicians and patients alike are awed by coronary care facilities with elaborate equipment for monitoring ECG's and other parameters, all while the patient lies calmly in bed. The equipment fairly exudes an aura of life-saving qualities.

Fully equipped mobile emergency units including defibrillators, drugs to correct arrhythmias, and other paraphernalia directed to various aspects of acute coronary care bring coronary care facilities wherever needed--many sports arenas have their acute coronary "team", for example. There is much publicity touting acute coronary care and many are convinced that these heroic therapeutic measures have significantly reduced deaths from coronary attacks.

How significant is the coronary care unit in reducing mortality due to coronary heart disease? One report based on careful analysis[209] states: "The Coronary Care Unit impact on total coronary mortality can therefore at best be an order of 2-3%--a difference not readily measurable." The question must then be asked whether it would not be better if some of the large investments for coronary care units were substantially diverted for prevention programs to educate people to low-cholesterol and low-fat diets so that they would never need the care of the coronary units!

A good indication of the futility of this 11th-hour emergency approach can be gleaned from the records of the Framingham Study.[210] This study of 5,209 people aged 29-62 was started in 1948 and the subjects were examined every two years thereafter. In the first 14 years, 120 died of coronary heart disease, before reaching age 65. Two-thirds of these died within an hour of their attack. Not enough time to get to a hospital or a mobile unit. Anticipation of an attack would have been unlikely for most in any case, since 63% tested as free of coronary heart disease in their last examination. Forty-two of the 120 who died were able to reach a hospital, and of these, 38 were in the hospital for an extended period, receiving all the advantages that modern medical care could give them before they died.

In the hospital coronary care units, this is the typical routine that is followed in treating acute coronary cases as they are received in their emergency states--a routine that has been carefully worked out in advance so that a minimum of time is lost:

1. Relief of pain - morphine
2. Control of cardiac arrhythmias - lidocaine
3. Anticoagulant for prevention of thrombosis - heparin
4. A vasopressor, if patient is in shock - isoproterenol
5. Congestive heart failure - digitalis
6. Diet - 800 calories for first week, increasing to 1200

Unfortunately, each of these measures are fraught with problems.

1. Morphine tends to reduce the blood pressure and when given in repeated doses often causes hypotension. When combined with sedatives, anoxia of the myocardium increases, greatly increasing the possibility of ventricular fibrillation.[211]

2. Lidocaine has not proven itself in controlled studies. In one study with 203 patients[212] who were immediately placed on lidocaine, and in another double-blind study with 82 patients,[213] no differences were found in either study between the controls and those on the drug.

3. Heparin activates lipoprotein lipase which acts upon triglycerides. Free fatty acids are then released from the

triglycerides and so increase in the blood. Heparin injected after an overnight fast can cause a 300% to 1,000% increase in free fatty acid.[214] High free fatty acid concentrations have long been associated with increased arrhythmias and with death due to fibrillation. A further increase in free fatty acids is brought about by the release of noradrenaline which causes lipolysis of triglycerides. Blood-catecholamines (adrenaline and noradrenaline) are released as a result of fear and tension that may be aroused by the environment in intensive care wards.[215]

4. Isoproterenol in animal experiments produced destruction of the myocardium that was directly proportional to the dose. This was observed in a 50-year old man with a myocardial infarct. As the dose was increased, the S-T depression became more negative and he went into heart failure and died. The same symptoms occurred in a 3-year old child, but the dosage was quickly decreased, the S-T depression was reversed, and the child was saved.[216]

5. Digitalis to be effective must practically approach the toxic level.[217] Even under hospital supervision, toxicity occurs in 20% of hospitalized digitalised patients and of these 22% die. One of the problems is the wide variation of potency of the drug among different manufacturers, which caused the chief of the Food and Drug Administration to complain, "You're playing Russian roulette unless you have some assurance of tablet uniformity." The FDA has had to recall 94 digitalis preparations in less than 17 months because they failed to meet minimum specifications. Despite these problems, 5,000,000 cardiac patients are taking this drug.

6. Diet of 800 to 1,200 calories per day gives only 35 to 50 calories per hour. This places the patient in a state of mild starvation. A 154 lb. person,[218] for example, requires 72 calories per hour--1728 calories per day, at rest in a lying state. Even if the person were very obese, a minimum of 60 calories per hour--1440 calories per day, would be required. Insufficient calories force the body to draw upon the fat depots for energy, releasing free fatty acids. These are added to the free fatty acids created by the heparin (administered as an anticoagulant),

predisposing to an irritable myocardium with inevitable arrhythmias.

There is considerable advocacy in the medical profession for so-called preventative measures (i.e., drugs) against arrhythmias which frequently lead to ventricular fibrillation and death. Many have advocated routine atropine to protect against sudden deaths. This approach, however, is another that creates more problems than it cures. In a revealing study, 55 dogs were treated with atropine, after which an acute myocardial infarction was induced.[219] The unexpected happened--93% of the atropine-treated dogs had arrhythmias compared to 48% of the controls. The researcher commented: "Atropine never protected against the development of arrhythmias and in several instances increased their incidence significantly."

Because of the poor results in reducing the incidence of coronary heart disease by American Heart Association-type diets, a state of hysteria is developing concerning the dismal outlook for our older population. A typical editorial[220]--"When Primary Prevention is Too Late"--asks what about "the majority of ostensibly healthy persons above 50? The evidence is totally lacking, and the prospects are discouraging that modifying risk factors at this stage of life confers any benefit for coronary morbidity or mortality." The editor then makes a plea for aggressive prophylactic therapy for those who might have heart attacks (author's note: Isn't that everyone on the Western diet?), urging that this therapy be directed towards control of arrhythmias when the attack happens.

It came as no surprise to hear a prominent cardiologist suggest at a recent conference[221] that the population susceptible to coronary heart disease (everyone over 40 years: author's note) should carry a loaded energized syringe for self-administration of atropine or lidocaine in case one thinks he is having a myocardial infarction. This is the ultimate in instant mobile coronary care units--everyone his own mobile unit!

Fortunately, calmer heads prevailed at the conference. Dr. Michael Oliver of Scotland said: "We don't have enough information

to advise such patients to carry a loaded syringe. In the first place, we don't know what to put in the syringe; in the second, existing combinations of antiarrhythmic drugs are not uniformly effective or safe. I think this approach is premature."

Petrarch's advice[222] to the Pope in 1352 has a certain timeliness when we consider some of the "therapy" that has been foisted upon the public by medical practitioners, although its target was the physicians of the 14th century. He said: "I am much alarmed, gentle Father, to hear of your sickness, and this news sent a frosty shiver over my limbs. I know that your bedside is beleaguered by doctors, and naturally this fills me with fear. As Pliny said, 'In order to make a name for themselves with some novelty, they traffic with our lives. With them, not as with other trades, it is sufficient to be called a physician to be believed to the last word, and yet a physician's lie harbors more danger than any other. They learn their art at our expense, and even our death brings them experience: the physician alone has the right to kill with impunity.'

"Oh, Most Gentle Father, look upon their band as an army of enemies. Remember the warning epitaph which that unfortunate man had inscribed on his tombstone: 'I died of too many physicians.'"

ATHEROSCLEROSIS REFERENCES

1. Moss, U.J. Ballistocardiographic Evaluation of the Cardiovascular Aging Process. Circulation 36:434, 1961.

2. Morrison, L.M. Diet and Atherosclerosis. Ann. Int. Med. 37:1172, 1952.

3. Morrison, L.M. Diet in Coronary Atherosclerosis. JAMA 173:104, 1960.

4. Lyon, T.P. et al. Lipoproteins & Diet in Coronary Heart Disease. California Med. 84:325, 1956.

5. Keys, A., et al. Coronary Heart Disease among Minnesota Business and Professional Men followed 15 yrs. Circulation 28:381, 1963.

6. Keys, A., et al. Mortality and Coronary Heart Disease among men studied for 23 yrs. Arch Intern Med 128: 201-214, 1971.

7. Kannel, W.B., et al. Am. J. Publ. Health 55, 1355, 1965.

8. Keys, A. Coronary Heart Disease in Seven Countries. Circulation 41, Suppl. 1, 1970.

9. Quinlan, C.B.; Barrow, J. G. Prevalence of Coronary Heart Disease in Trappist and Benedictine Monks. Circulation 33, Suppl. III-193, 1966.

10. Westlund, K.; Nicolaysen, R. Scandinav. J. Clinical Lab. Invest. 18, suppl. 87, 1, 1966.

11. Rosenman, R.H., et al. Comparative Predicted Value of Three Serum Lipid Entries in a Prospective Study of I.H.D. Circulation 35, Suppl. 2-35, 1967.

12. Carlson, L.A.; Bottiger, L.E. Ischaemic Heart Disease in Relation to Testing Values of Plasma Triglycerides and Cholesterol. Lancet, 865, 4-22-72.

13. "The Geographic Pathology of Atherosclerosis", H.C. McGill, Jr., Ed. Lab. Invest. 18, 463, 1968.

14. Dunn, J. P. et al. Risk Factors in Coronary Artery Disease, Hypertension, and Diabetes. American J. Medical Science 259:309-322, 1970.

15. Walker, A.R.P., et al. Glucose and Fat Tolerances in Bantu Children. Lancet, p. 51, 7-4-70.

16. Bronte, Stewart, B., Keys, A., Brock, J. F. Lancet ii, 1103, 1955.

17. Hannah, J. B. Civilization, Race and Coronary Atheroma with Particular Reference to its Incidence and Severity in Copperbelt Africans. Central African J. Med. 4: 1-5, 1958.

18. Whyte, H.M. Aust. Ann. Med. 7, 36 and 47, 1958.

19. Leaf, A. Hard Labor Low Cholesterol Linked to Unusual Longevity. Medical Trib. June, 1971.

20. Longinov, A.S. Blood Cholesterol and Cholesterol ester levels in Ethiopians. Kardiologiya, 2, #1.

21. Steelquist, J., et al. A Tribe That Fascinates Cardiology, Psychiatry. JAMA. 208: 1617, 1969.

22. Enos, W.F. Jr., et al. Pathogenesis of Coronary Disease in American Soldiers Killed in Korea. JAMA 158: 912, 1955.

23. Keys, A., et. al. Lessons from Serum Cholesterol Studies in Japan, Hawaii, and Los Angeles. Ann. Int. Med. 48: 83-94, 1958.

24. Op. Cit. Reference 22.

25. Op. Cit. Reference 23.

26. Schilling, F.J., et al. Serum Cholesterol and Triglyceride. American J. Clinical Nutrition. 22: 133-8, 1969.

27. Kannel, W.B. Lipoprotein Pattern Doubted as Key to Heart Disease Risk. Medical Tribune p.18, 4-7-69.

28. Fyfe, T., et al. Plasma-Lipid Changes after Myocardial Infarction. Lancet p. 997, 11-6-71.

29. Kannel, W.B. Lipid profile and the Potential Coronary Victim. American J. Clinical Nutrition. 24: 1074-81, 1971.

30. Taylor, C.B., et al. Atheroscleroses in Rhesus Monkeys. Arch of Path. 76: 404, 1963.

31. Gresham, G.A., et al. British J. Exp. Path. 46: 94, 1965.

32. Armstrong, M.L., and Megan, M.B., et al. Plasma and Carcass Cholesterol in Rhesus Monkeys after Low and

Intermediate Levels of Dietary Cholesterol. Circulation Suppl. II, 43: II-III, 1971.

33. Wissler, R.W., et al. Atherosclerosis and Influence of Diet: An Experimental Model. JAMA 194: 37, 1965.

34. Op. Cit. Reference 31.

35. Tarizzo, R.A., et al. Atherosclerosis in Synthetic Vascular Grafts. Arch Surg. 82: 826, 1961.

36. Gonzales, I.E., et al. Relations Between Circulating Blood and Atheroma Forming on Dacron Protheses. Circulation Supp. II, 35: 2-13, 1967.

37. Armstrong, M.L., et al. Xanthomotosis in Rhesus Monkeys Fed a Hypercholesterolemic Diet. Arch of Path. 84: 227-37, 1967.

38. Welch, C.C., et al. Cinecoronary Arteriography in young men. Circulation 62: 625, 1970.

39. Page, I.H., et al. Prediction of Coronary Heart Disease Based on Clinical Suspicion, Age, Total Cholesterol, and Triglyceride. Circulation 62: 625, 1970.

40. Proudfit, W.L., et al. Selective Cinecoronary arteriography: Correlation with clinical findings in 1,000 patients. Circulation 33: 901, 1966.

41. Swank, R.L. A Biochemical Basis of Multiple Sclerosis. C.E. Thomas, Pub., Springfield, Ill., 1961.

42. Ibid.

43. Philp, R.B. and Wright, H.P. Effects of Adenosine on Platelet Adhesiveness in Fasting and Lipemic Blood. Lancet, p. 208, 7-31-65.

44. Op. Cit. Reference 41.

45. Mustard, J. F., et al. Diet and Thrombus Formation. J. Clinical Invest. 42: 1783, 1963.

46. Friedman, M. Pathogenesis of Coronary Artery Disease. McGraw-Hill Book Co., 1969.

47. Cooper, R.A., and Jandl, N.H. Bile Salts and Cholesterol in Pathogenesis of Target Cells in Obstructive Jaundice. J. Clinical Invest. 47: 809, 1968.

48. Cholesterol Induced Anemia in Guinea Pigs. Nutritional Rev. 30: 42, #2, 1972.

49. Smith, E.B. and Slater, R.S. Relationship between Low Density Lipoprotein in Aortic Intima and Serum-Lipid Levels. Lancet p. 463, 2-26-72.

50. Hollander, W. and Kramsch, D.M. Influx and Distribution of Intravenously Administered C^{14} Cholesterol in the Human Atherosclerotic Plaque. Circulation Suppl. III, 33: 15, 1966.

51. The Artery and the Process of Atherosclerosis. Plenum Press, New York p. 206, 1971.

52. Op. Cit. Reference 46.

53. Russell, R.W. The Source of Retinal Emboli. Lancet p. 789, 10-12-68.

54. Fields, W.S. Medical Tribune, 12-8-71.

55. Editorial - "Measures of Dementia and Senile Change". Lancet p. 88, 1-11-69.

56. Eliot, R.S. et al. Atheromatous Embolism. Circulation 30: 611, 1964.

57. Beck, C.S. and Leighninger, D.S. Death After Clean Bill of Health. JAMA 174: 133, 1960.

58. Friedman, M. et al. Coronary-Prone Individuals. JAMA 212: 1030, 1970.

59. Joyner, C.R. et al. Effect of Conditioned Anxiety Upon the Behavior, Blood Lipid Level, & Atherosclerosis of Cholesterol Fed Cockerels. Circ. Res. 9: 69, 1961.

60. Vahouny, G. V. et al. Effect of Cold on Experimental Atherosclerosis. Fed. Proc. Part I, p. 367, March, 1961.

61. Hinkle, L.E. Jr. Heart Disease Risk Lower Among Executives? JAMA 204: 41, 1968.

62. Barnes, B.O. et al. Artherosclerosis in 10,000 Autopsies & the Possible Role of Dietary Protein. Fed. Proc. 19: 19, 1960.

63. Friedman, E.H. Personality Type & CHD. JAMA 219: 385, 1972.

64. Page, I.H. Atherosclerosis--A Commentary. Fed. Proc. Vol. 18 #2, p. 47, 1959.

65. Ho, K.J. and Taylor, C.B. Control Mechanisms of Cholesterol Biosyntheses. Arch Path. 90: 83, 1970.

66. Cholesterol Absorption Versus Cholesterol Synthesis in Man. Nutrition Rev. 28: 11, 1970.

67. Taylor, C.B. et al. Human Serum Chol. Synthesis Measured by Deuterium Labeling. Arch. Path. 81: 213, 1966.

68. Ibid.

69. Op. Cit. Reference 66.

70. Fredrickson, D.S. et al. Fat Transport in Lipoproteins. N. Eng. J. Med. 276: 148, 1967.

71. Lees, R.S. and Fredrickson, D.S. Carbohydrate Induction of Hyperlipemia in Normal Man. Clinical Res. 13: 327, 1965.

72. Op. Cit. Reference 38.

73. Op. Cit. Reference 39.

74. Op. Cit. Reference 11.

75. Brown, H.J. Delivery of Personal Health Services & Medical Programs for the Poor. Milbank Mem. Fund Quart. 46 (pt. 2 #1) 203, 1968.

76. Williamson, J. W. et al. GE: Continuing Education & Patient Care Research: Physician Response to Screening Test Results. JAMA 201.938, 1967.

77. Bates, B. & Mulinare, J. Physicians' Use & Opinions of Screening Tests in Ambulatory Practice. JAMA 214: 2173, 1970.

78. Op. Cit. Reference 40.

79. Kuller, L. et al. Epidemiological Study of Sudden & Unexpected Deaths Due to Arteriosclerotic Heart Disease. Circulation. 34: 1056, 1966.

80. Scott, R.F. Asymptomatic Infarcts Found to be Common. Medical Trib. 12-22-1971.

81. Op. Cit. Reference 1.

82. Pepine, C.J. Severe Coronary Disease Seen in Asymptomatic Young Men. Medical Trib. 7-12-72.

83. Pepine, C.J. Coronary Heart Disease Discovered in Asymptomatic Men. JAMA 221: 241, 1972.

84. World Health Organization Bulletin. 43: 891, 1970.

85. Yudkin, J. Sucrose and Heart Disease. Nutrition Today. 16-20, Spring, 1969

86. Szanto, S. and Yudkin, J. Postgrad. Med. J. 45: 602, 1969.

87. Madison, L.L., et al. The Hypoglycemic Action of Ketones. J. of Clin. Invest. 43: 408, 1964.

88. Op. Cit. Reference 85.

89. Op. Cit. Reference 86.

90. Sugar and the Pill Makes Fat Faster Apart From Calories. Brookhaven Bulletin. Brookhaven Labs., Upton, N.Y. 1-2, 8-12-71.

91. Groen, et al. Effect of Interchanging Bread and Sucrose as Main Source of Carbohydrate in a Low Fat Diet on the Serum Cholesterol Levels of Healthy Volunteer Subjects. American Journal of Clin. Nutr. 19: 46-58, 1966.

92. Cohen, A.M., et al. Effect of Interchanging Bread and Sucrose as Main Source of Carbohydrate in a Low Fat Diet on the Glucose Tolerance Curve of Healthy Volunteer Subjects. American J. Clin. Nutr. 19: 59-62, 1966.

93. Campbell, G.D. Diabetes in Asians and Africans in and Around Durham. South African M.J. 37: 1195, 1963.

94. Ingle, D.J. The Production of Experimental Glycosuria in the Rat. Recent Progr. Hormone Res., 2: 229, 1948.

95. Op. Cit. Reference 91.

96. Op. Cit. Reference 92.

97. Glueck, C.J. et al. Immunoreactive Insulin, Glucose Tolerance, and Carbohydrate Inducibility in Types II, III, IV, & V Hyperlipoproteinemia. Diabetes, 18: 739, 1969.

98. Ford, S.F. et al. Interactions of Obesity & Glucose & Insulin Levels in Hypertriglyceridemia. American J. Clinical Nutr. 21: 904, 1968.

99. Antonis, A. and Bersohn, I. The Influence of Diet on Serum-Triglycerides. Lancet, p. 3, 1-7-61.

100. Holiman, J. L. Autopsy Findings in Type III Hyperlipoproteinemia. Arch. Path. 92: 415, 1971.

101. Tucker, C., et al. Regression of Cholesterol-Induced Atherosclerotic Lesions in Rhesus. Circulation, Suppl. II 63: 48, 1971.

102. Armstrong, M.L., et al. Regression of Coronary Atheromatosis in Rhesus Monkeys. Circulation Research 27: 59, 1970.

103. Field, H. Jr., et al. Dynamic Aspects of Chol. Metabolism in Different Areas of the Aorta and Other Tissues in Man. Circulation 22: 547, 1960.

104. Op. Cit. Reference 64.

105. Cardiac Arrest. Lancet p.262, 8-2-69.

106. Woods, J. W. and Penick, G.D. Arch. Path. 78: 234, 1964.

107. Symposium: Angina Pectoris. Circulation XLVI, Dec., 1972.

108. Diet and Heart Disease. AHA, NYC, N.Y., 1968.

109. Beveridge, J.M.R., et al. The Response of Man to Dietary Cholesterol. J. Nutrition, 71: 61, 1960.

110. Goldie, J.H. et al. Crystalline Cholesterol. American J. Clinical Nutrition, 22: 710, 1969.

111. Beveridge, J.M.R., et al. Dietary Factors Affecting the Level of Plasma Chol. in Humans: The Role of Fat. Can. J. Bio. and Phys. 34: 441, 1956.

112. Op. Cit. Reference 109.

113. Op. Cit. Reference 99.

114. Lee, K.J., et al. Soldiers on Low Fat Korean and High Fat U.S. Army Diet. Fed. Proc. 19: 236, 1960.

115. Salzam, S.H., Hellerstein, H.K., et al. Serum Cholesterol and Capacity for Physical Work of Middle-Aged Sedentary Males. Lancet, p.1348, 6-24-67.

116. Master, A.M., et al. Factors and Events Associated With Onset of Coronary Artery Thrombosis. JAMA 109: 546, 1937.

117. Hellerstein, H.K. Atherosclerotic Vascular Disease. Meredith Pub. Co. p.115, 1967.

118. Fox, S.M. III and Haskell, W.L. Physical Activity and the Prevention of CHD. Bull N.Y. Academy Medical 44: 950, 1968.

119. Leren, P. The Oslo Diet-Heart Study. Circulation 62: 935, 1970.

120. Controlled Trial of Soya-Bean Oil in Myocardial Infarction. Lancet, p.693, 9-28-68.

121. Op. Cit. Reference 119.

122. Dayton, S., et al. A Controlled Clinical Trial of a Diet High in Unsaturated Fat. Circulation. Suppl. II 60: #1, 1969.

123. Dayton, S. Study Urges Less Fats in Diet. L.A. Times

124. Bierenbaum, M.L., et al. The 5-Year Experience of Modified Fat Diets on Younger Men with Coronary Heart Disease. Circulation 62: 943, 1970.

125. Wissler, R.W., et al. Atherogenesis in the Cebus Monkey, Arch. Path. 74: 312, 1962.

126. Kritchevsky, D., et al. Cholesterol Vehicle in Experimental Atherosclerosis, Atherosclerosis, 14: 53, 1971.

127. Friedman, M., et al. Effect of Unsaturated Fats Upon Lipemia & Conjunctival Circulation. JAMA 193: 882, 1965.

128. Op. Cit. Reference 41.

129. Keys, A. Atherosclerosis: A Problem in Newer Public Health. J. Mt. Sinai Hospital, 20: 118, 1953.

130. National Dairy Council: National Food Supplies & Vital Statistics. Dairy Council Statistics 28: 1, 1956.

131. McCollum Award. American J. Clinical Nutrition 22: 1415, 1969.

132. Gresham, G.A., et al. Thrombogenesis & Atherogenesis in the Rat. Fed. Proc. 22: 1371, Pt. 1, 1963.

133. Getz, G.S., et al. Lipid Composition & Biosynthesis of Lecithin in Atherosclerotic Aorta of Rhesus Monkey Fed

Three Food Fats. Circulation, Suppl. II, 35: 11-13, 1967.

134. Op. Cit. Reference 125.

135. Gerson, T., et al. The Effects of Corn Oil on the Amounts of Cholesterol and the Excretion of Sterol in the Rat, Biochem. J. 81: 584, 1961.

136. Conner, W.E., et al. Relative Failure of Saturated Fat in the Diet to Produce Atherosclerosis in the Rabbit. Circulation Res. 20: 658, 1967.

137. Lin, T.M., et al. Absorption of Dietary Cholesterol in Man. Fed. Proc. 15: 120, 1956.

138. Friedman, M. and Byers, S.O. Effects of Saturated & Unsaturated Fat Feeding on Experimental Thromboatherosclerosis. American J. Physiology, 203: 626, 1962.

139. Friedman, M. and Byers, S.O. Effects of Feeding Saturated & Unsaturated Fats. Arch. Path. 77: 286, 1964.

140. Dayton, S., et al. Influence of a Diet High in Unsaturated Fat Upon Composition of Arterial Tissue & Atheromata in Man. Circulation, 32: 911, 1965.

141. Coronary Drug Project. JAMA 214: 1303, 1970.

142. Ibid.

143. Coronary Drug Project. JAMA 220: 996, 1972.

144. Schoch, H.K. Can Cholesterol Level Predict 2nd Heart Attack. JAMA, 220: 1550, 1972.

145. Op. Cit. Reference 143.

146. Op. Cit. Reference 3.

147. Op. Cit. Reference 4.

148. Berkowitz, D. Long Term Treatment of Hyperlipidemic Patients with Clofibrate. JAMA, 218: 1002, 1971.

149. Thomas, F.B., et al. Inhibition of Intestinal Absorption of Inorganic & Hemoglobin Iron by Cholestyramine. J. Lab. Clinical Med. 78: 70, 1971.

150. Quarfordt, S.H., et al. Lipid Response to Clofibrate in Cerebrovascular Disease. Circ. Suppl. II. 63: 214, 1971.

151. Op. Cit. Reference 75.

152. Chakrabarti, R., et al. Effects of Clofibrate on Fibrinolysis, Platelet Stickiness, Plasma-Fibrinogen, & Serum Cholesterol. Lancet p. 1007, 11-9-1968.

153. Azarnoff, D.L. Pharmacology of Hypolipidemic Drugs. Fed. Proc. 30: 827, 1971.

154. Questions Surround Treatment of Children with High Cholesterol. JAMA, 214: 1783, 1970.

155. Op. Cit. Reference 3.

156. Thomas, F.B., et al. Inhibition of Intestinal Absorption of Inorganic & Hemoglobin Iron by Cholestyramine. J. Lab. Clinical Med. 78: 70, 1971.

157. NHLI Grants Will Establish 29 Special Research Centers. Medical Trib. 8-11-71.

158. Modell, W. 1968-9 Drugs of Choice. p.370, C.V. Mosby Co., St. Louis, MO, 1967.

159. Friedman, M. Pathogenesis of Coronary Artery Disease. McGraw-Hill Book Co., 1969.

160. Stewart & Acheson. Atherosclerosis in a Hemophiliac, Lancet, 1: 1221, 1957.

161. Hoak, J. C., et al. Myocardial Infarction Associated with Severe Factor XII Deficiency. Lancet, p.884, Oct. 22, 1966.

162. Green, D. and Rizza, C.R. Myocardial Infarction in a Patient with a Circulatory Anticoagulant. Lancet, p.434, 8-26-1967.

163. Op. Cit. Reference 106.

164. Wright, I.S., et al. Report of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction. American Heart J., 36: 801, 1948.

165. Research on Acute Myocardial Infarction. Circ. Suppl. 4. 60: 252, 261, 275 and 238, 1969.

166. Ibid.

167. Griffith, G.C., et al. Jama, 193: 91, 1965.

168. Vieweg, W.V.R., et al. Complications of Intravenous Administration of Heparin in Elderly Woman. JAMA, 213: 1303, 1970.

169. Jick, H., et al. Efficacy & Toxicity of Heparin in Relation to Age & Sex. New England J. of Medicine, 279: 284, 1968.

170. Feman, S.S., et al. Intraocular Hemorrhage & Blindness Associated with Systemic Anticoagulation. JAMA, 220: 1354, 1972.

171. Duckert, F.H., et al. Urokinase is of Little Value for Thrombi. Medical Trib., 10-4-1972.

172. Moldveen-Geronimus, M. and Merriam, J. C. Cholesterol Embolism. Circulation, 35: 946, 1967.

173. Duke, M. Bed Rest in Acute Myocardial Infarction: Study of Physician Practices. American Heart J., 82: 486, 1971.

174. Armstrong, P.W., et al. Phlebotomy as a Therapy for Angina. Circulation Suppl. III, 39: 37, 1969.

175. Aetiology of Cerebrovascular Disease & Its Treatment. Lancet, p.238, 2-3-68.

176. Glenn, W.W.L. Some Reflections on the Coronary Bypass Operation. Circulation 45: 869, 1972.

177. Glenn, W.W.L. Heart Surgeons Assail Enthusiastic Surgery. Medical Trib., 12-8-71.

178. Price, D.L., et al. Cholesterol Emboli in Cerebral Arteries as Complications of Retrograde Aortic Perfusion During Cardiac Surgery. Neurology, 20: 1209, 1970.

179. Hypertension After Aortic Endarterectomy Complicated by Renal Artery Occlusion. JAMA, 215: 1163, 1971.

180. Sieniewicz, O.J., et al. Atheromatous Emboli to Kidneys. Radiology, 92: 1231, 1969.

181. Robinson, S.K. Coronary Arteriography. JAMA, 220: 727, 1972.

182. Use of 'Jump Graft' Spreads. JAMA, 218: 1887, 1971.

183. Walker, J. A., et al. Determinants of Angiographic Patency of Aortocoronary Vein Bypass Grafts. Circulation, Suppl. I., 45: 86, 1972.

184. Conkle, D.M. Atherosclerosis in Grafts. Medical Trib. 1-5-1972.

185. Thomson, J. G. Production of Severe Atheroma in a Transplanted Human Heart. Lancet, p.1088, 11-22-69.

186. Thomson, J. G. Atheroma in a Transplanted Heart. Lancet, p.1297, 12-13-69.

187. Pancreas Does Better Than Kidneys in Grafts. Medical Trib. 1-5-70.

188. Atherosclerosis May Shorten Survival After Heart Transplant. Medical Trib., 7-5-72.

189. Corday, E. Myocardial Revascularization. JAMA, 219: 504, 1972.

190. Op. Cit. Reference 182.

191. Merrill, A.J. Jr. Coronary Bypass for Angina Challenged by 2 Year Study, Medical Trib. 10-4-72.

192. Baltaxe, H.A. and Levin, D.C. Complications Noted after Saphenous Bypass. Medical Trib., 11-15-72.

193. Op. Cit. Reference 189.

194. Burch, G.E. Coronary Artery Surgery-Saphenous Vein Bypass. American Heart J. Editorial - July, 1971.

195. Surgery Advised in Uncontrolled Hypercholesterolemia. Medical Trib. 12-4-69.

196. Op. Cit. Reference 99.

197. Op. Cit. Reference 114.

198. Op. Cit. Reference 110.

199. Op. Cit. Reference 111.

200. Op. Cit. Reference 109.

201. Rowe, G.G., et al. Effects of Reduced Serum Chol. on Human Coronary Atherosclerosis. Circulation Suppl. III, 39: 22, 1969.

202. Op. Cit. Reference 109.

203. Kuo, P.T. and Joyner, C.R. Jr. Angina Pectoris Induced by Fat Ingestion in Patients with Coronary Heart Disease. JAMA, 158: 1008, 1955.

204. Op. Cit. Reference 41.

205. Op. Cit. Reference 43.

206. Eased Angina After Ileal Bypass Said to Defy Explanation. Medical Trib., 2-24-71.

207. Partial Ileal Bypass Leads to Relief From Angina. JAMA, 215: 1571, 1971.

208. Op. Cit. Reference 201.

209. Op. Cit. Reference 165.

210. Gordon, T. and Kannel, W.B. Premature Mortality From CHD. JAMA, 215: 1617, 1971.

211. Op. Cit. Reference 165.

212. Darby, S., et al. Trial of Combined I.M. & I.V. Lignocaine in Prophylaxes of Ventricular Tachyarrhythmias. Lancet, p. 817, 4-15-72.

213. Chapra, M.P., et al. Lidocaine Therapy for Ventricular Ecotopic Activity After Acute Myocardial Infarction. Br. Medical J., 3: 668, 1971.

214. Rutstein, D.D., et al. Heparin & Human Lipid Metabolism. Lancet, p.1003, 5-17-69.

215. Carruthers, M.E. Aggression & Atheroma. Lancet, p. 1170, 11-29-69.

216. Isoproterenol Overtreatment Perilous. Medical Trib. 9-21-70.

217. High Side Effects, Mortality Linked to Digitalis Therapy. Medical Trib. 2-2-72.

218. Metabolism. Published by Fed. of American Scientists for Experimental Biology. Bethesda, Md., 1968 - p.344.

219. Routine Atropine May Harm Infarct Patients. Medical Trib. 4-26-72.

220. When Primary Prevention is Too Late. Medical Trib. 1-5-72.

221. Op. Cit. Reference 165.

222. Saul, F.W. Pink Pills for Pale People, 1949.

ANGINA PECTORIS

Angina pectoris describes a characteristic pain in the chest area ranging from mild to extremely severe, and is generally thought to be the result of insufficient oxygen to the myocardium.

Extensive studies have revealed that atherosclerosis of the coronary arteries is most frequently associated with this disease. At least one major coronary artery has extreme narrowing or is occluded.

That O_2 deficiency is the primary cause of angina can be demonstrated in several ways. In the most direct demonstration, angina patients breathe in a mixture of lowered O_2 content. After a short period, angina is induced.

There are several indirect paths to the induction of angina. Intake of foods that will lower O_2-carrying capacity of the erythrocytes probably is most common. After an average U.S. meal of 40%+ of total calories in fat, large quantities of chylomicra, derived from the fat, pour into the blood over a period of several hours. As the chylomicra pour into the blood, an adhesiveness which holds many of the erythrocytes to each other in so-called "rouleaux" formations can be noticed. The greater the influx of chylomicra, the more and longer the rouleaux groupings. This sludging slows the circulation and in some cases may completely stop the flow of particular capillaries. This relationship between elevated lipids and erythrocyte aggregation producing this sequence of events was first observed in 1951.(1)

Tests on hamsters in which electrodes were implanted into the head of the animal to measure O_2 level in the blood have also confirmed the relationship with high fat intake in diet. After a large meal of cream, the available O_2 dropped 35% after 5-6 hours. This would correlate with the peak influx of the fat into the blood in the form of chylomicra. A control test using skim milk feedings reduced the available O_2 only 5%. Other studies showed that carbohydrates produced no changes in O_2 availability, and protein reduced the availability 10-20%.

One possibility for the lowered amount of 0_2 in the blood under conditions favoring rouleaux formation might be the reduction of the total surface area of the erythrocytes available for 0_2 exchange when they are adhered together. Another factor is blood flow slowdown associated with fatty meals. This slowdown has been measured and was found to be 20% less in the coronary arteries three hours after the meal.(2) The investigator suspected that the cause of the blood slowdown was the sludging of the erythrocytes.

The correlation of a high fat meal with oxygen insufficiency, demonstrated in the hamster studies, was repeated with a group of 14 angina patients. Here the indicator of oxygen insufficiency was the appearance of angina symptoms.(3) After an overnight fast during which time the patients were not permitted to smoke, ECG and blood tests were taken to establish control values. The patients were then given heavy cream to drink (40% butterfat by weight) with the amount of butterfat calculated at a ratio of .6 gm. per pound of patient body weight. Thus, a 150 pound patient would ingest 3 oz. of butterfat blended into his liquid drink. Following the cream meal, the patients were instructed to sit or lie quietly.

Control plasma lactescence was 45 units, but in half an hour the lactescence started to rise due to the pouring of chylomicra into the blood, reaching its peak in five hours at 260 units. This peak in lactescence coincided with the appearance of severe anginal pains in several patients. At this moment ECG studies confirmed the problem: there was ST depression and some T wave abnormalities. The attacks of angina were arrested with nitrates, and when these were ineffective, with heparin, I.V.

One of the patients went through this cycle four times. Each time his angina started about three hours after fat ingestion. Each time the pain was relieved with nitrates. In all of the patients, without exception, the individual lactescence curves followed the composite curve.

This same test was now repeated on three of the patients who had experienced anginal attacks after the fat drink, except that the drink they were given this time, while containing the same

number of calories, contained no fat. As these subjects sat quietly waiting for their anginal pain to appear, their plasma lactescence and ECG were constantly checked. After five hours, the plasma lactescence was unchanged from the control value of 45, and the ECG was still at control values. No angina or discomfort was experienced by any of the group.

A few years later, another group of investigators performed the same test on angina patients,[4] but in addition to producing angina after a fat meal, they monitored the conjuctival capillaries. Aggregation and sludging of erythrocytes were observed as the chylomicra reached their peak, so that correlation of the fatty meal, production of angina, and erythrocyte aggregation was now complete.

Observation of intravascular aggregation after a fat meal was again observed in a study on cats done about a year later, in which this phenomenon was seen to occur in the pial blood vessels in response to a fatty meal.[5]

The ingestion of sugar (sucrose) will produce changes similar to those produced by fat. Fifty-six angina patients were given 100 grams of sugar in water after an overnight fast. Thirty-nine of these subjects experienced an ischemic lowering and flattening of the ST segment and flattening or inversion of the T wave. The abnormal wave pattern developed 30-60 minutes after the sugar was ingested and coincided with the greatest hyperglycemia. To demonstrate that the abnormal ECG segments were indeed due to ischemia or 0_2 deficiency, 0_2 was given during the ischemic period and the ischemic segments returned to normal or near normal.

Ingestion of sufficient simple carbohydrates to cause hyperglycemia inevitably raises the triglycerides. As chylomicra are substantially triglycerides and the fat studies have indicated how efficiently chylomicra cause adhesiveness and aggregation of erythrocytes, the relationship of sucrose to erythrocyte sludging and consequent reduction of 0_2 seems to correlate.

Insufficiency of 0_2, sludging, and slowing of circulation can be detected in yet another way. Using very sensitive temperature detection sensors, 50 male angina patients were tested on a

treadmill in an attempt to induce angina.[7] Angina was induced in 22 of these patients with the symptoms demonstrated by ST depression in the ECGs of 21 of them. Of these, 17 patients demonstrated a lowering of temperature measured by instruments on the chest at the moment of angina. The lowering of temperature preceded the pain by as much as 90 seconds and disappeared a few minutes after the pain was relieved. Temperature drops of -2° C. (3.6° F.) were measured indicating a severe blockage of circulation.

Understanding of the condition of the coronary arteries of angina patients has been furthered by the use of cinecoronary arteriography. In a study done with 117 men,[8] 90% of those with typical anginal pain precipitated by activity showed a narrowing of at least 50% in one or more coronary arteries. Only 20% of those with cholesterol levels of less than 200 mg./100 ml. had significant narrowing (50% or more), but 81% had significant narrowing if their cholesterol levels were 275 mg.+/100 ml.

With the passage of time, the severity of the arterial damage observed in this group progressed:

Period of symptom observation	Arterial damage
< 6 months	1.5 arteries affected
6-12 months	1.9 " "
12-36 months	2.1 " "
more than 36 months	2.4 " "

It would seem logical that fats and simple carbohydrates which precipitate anginal attacks should be eliminated from the diet of angina patients as much as possible, as well as from the normal diet. Eliminating these two categories of food would also lower the cholesterol level (this is detailed in another section). Since the narrowing and closure of coronary arteries increase as the cholesterol level rises, this becomes important as a preventative measure. All the dietary advice indicated for coronary heart disease is also indicated for angina sufferers, since the formation of plaques is responsible for both conditions.

Once the change in diet is made so that no new plaques are formed and old ones regress to some extent, the next step is to encourage collateral circulation by means of a suitable exercise program, in order to eliminate the insufficiency or to reduce it as much as possible. The studies detailing the knowledge about collateral circulation development through exercise are contained in the Exercise chapter.

Angina pectoris is understandable as to cause and treatment. To recapitulate:

Cause. Atheroma (plaque) formation due to excess lipid and cholesterol in diet. Plaques narrow and sometimes occlude lumen of arteries, restricting circulation. Continued ingestion of simple carbohydrates and lipids cause chronic sludging, blockage of capillaries, and slowing of flow, producing O_2 starvation and ischemia--and angina.

Dietary treatment. Eliminate simple carbohydrates and lipids from diet (follow suggested diet in Recommendations chapter). This will prevent further artery damage and will begin process of plaque regression.

Activity treatment. A planned program to develop collateral circulation to bypass and supplement the damaged circulation system should be instituted. In time, as new circulatory paths grow, the angina should disappear, since sufficient blood flow would now be available for an active life.

ANGINA PECTORIS REFERENCES

1. Swank, R.L. A Biochemical Basis of Multiple Sclerosis. C.E. Thomas, Publisher. Springfield, Ill., 1961.

2. Regan, T.J. et al. Myocardial Blood Flow & Oxygen Consumption During Post-prandial Lipemia & Heparin induced Lipolyses. Circulation 23:55, 1961.

3. Kuo, P.T. and Joyner, C.R. Jr. Angina Pectoris Induced by Fat Ingestion in Patients With Coronary Heart Disease. JAMA, 1008, 1955.

4. Williams, A.V. et al. Increased Blood Cell Agglutination Following Ingestion of Fat, a Factor Contributing to Cardiac Ischemia, Coronary insufficiency, & Anginal Pain. Angiology 8:29, 1957.

5. Meyer, J.S. & Waltz, A.G. Effects of Changes in Composition of the Plasma on Pial Blood Flow. Neurology 9:728, 1959.

6. Kilinskii, E.L. & Vysokii, F.F. Production of electro-cardiographic changes in Sugar Tests. Vestnik Akademii Meditsinskikh Nauk SSR vol. 20, no. 10, p. 72, 1965.

7. Potanin, C. et al. Thermographic Patterns of Angina Pectoris. Circulation XLII:199, 1970.

8. Welch, C.C. et al. Cinecoronary Arteriography in Young Men. Circulation 62:625, 1970.

HYPERTENSION

I. "NORMAL" AND "ABNORMAL" WITH REGARD TO BLOOD PRESSURE

The ranges in relation to health and disease.

Hypertension by definition is a condition wherein blood pressure exceeds an arbitrary "normal" value. This value ranges from 140/90 to 160/95 according to most authorities. Some even claim that values can be considered normal above 160/95, indicating some flexibility as to what is considered "normal" for high blood pressure values.

The Society of Actuaries in 1959 published "Build and Blood Pressure Study", an analysis of blood pressure data on 4,000,000 living persons and 102,000 persons who had died. Conclusive results as stated by the study were that blood pressures in excess of 140/90 are abnormal at any age and lead to excess deaths that can be observed in the course of long term follow-up. As each increase in pressure increment in either systolic or diastolic pressure takes place, life expectancy is correspondingly shortened. A Metropolital Life Insurance Company analysis places life expectancy 16-1/2 years under normal for men 35 years old with readings of 150/100.(1)(2)

Various estimates have been made of the number of people fitting into the hypertensive classification in the U.S.; a conservative figure of 20,000,000 was given by Dr. Stamler of the Chicago Health Research Foundation and is below other figures that have been cited.

Hypertension is considered a principal cause of strokes, the third leading cause of death in the U.S., and responsible for over 200,000 annual deaths. In addition, there are those who do not die when having incurred a stroke, but suffer its disabling effects. It is not difficult to appreciate the immensity of the public health problem due to hypertension.

The remarkable pressure capacities of healthy arteries.

It is curious that pressures of the hypertensive ranges can be so destructive when one is aware of the high pressures generated by activity and exercise.(3) Weight lifting can within seconds raise systolic pressure from 105 mm. to 265 mm. Hg. Many occupations require the lifting of heavy weights all day long, and the systolic pressures of such laborers during their working periods are constantly above the hypertensive range. Athletes and runners, especially those who run for hours at a time, maintain systolic pressures above 160 mm. In a Pike's Peak run, pressures of 226 mm. were recorded. In 26-mile marathon runs, in which men well over 70 years old run for three hours or more, systolic pressures stay above 160-180 mm. during this time. Runs of this distance have been habitual for over 40 years with many people, and the problem of stroke never arises.

How much pressure can an artery stand? Does 160, 200, or 250 mm. approach the bursting strength of vessels? Some experiments with dogs provide much worthwhile data on this question.(4)

Twenty-one mongrel dogs had their blood pressure raised with an injection device designed at the National Heart Institute. Pressure was raised--and raised--and raised--and raised until the first signs of cardiovascular collapse were noticed at 5,800 mm. Hg. Pressure was continued until 6,000 mm., at which time the dogs died. Below 5,800 mm., the only changes noticed were bulging of the eyes and separation of the retina. Upon autopsy, no hemorrhaging of the cerebral vessels were found--there were no cerebral arteries or capillaries that were unable to stand 6,000 mm. of pressure. The investigator commented in amazement that "We never found an end point of pressure tolerance."

Healthy arteries don't break. Diseased ones do. Examining the etiology of high blood pressure reveals why these mildly elevated pressures, certainly no danger to healthy vessels, become catastrophic to damaged ones.

II. THE CAUSES OF HYPERTENSION

The role of plaques.

Since the start of the century, evidence has clearly indicated that renovascular lesions or constrictions, or occlusions, can cause sustained hypertension in both animals and man.(5) A group of 100 people with high blood pressure underwent surgery at Mayo Clinic after a study revealed occlusive areas in the renal arteries. These patients were found to have the same kind of atherosclerotic plaque damage in other areas of the body that were present in the renal arteries. Along with the widespread plaque damage, there were aneurysms and a few fibromuscular lesions that showed thickening of the media. Most of the narrowing was due to multiple plaques. The surgery resected or repaired diseased areas using various techniques, including dacron reconstructions, or in cases of too extensive atheromatosis, nephrectomy was used when repair was no longer thought feasible. Fifty-five percent of these patients became normotensive without medication. In another 29%, diastolic pressure was usually 90 mm. Only 16% still required some drugs, even though they were normotensive most of the time.

Thus, as the narrowing or occluding of the renal blood supply was repaired by these various surgical techniques so as to provide greater flow, the high blood pressure either disappeared or was greatly lessened.

This phenomenon was dramatically demonstrated in a 47-year old woman who in 1963 had normal renal function and was normotensive.(6) Four years later, she developed hypertension and was discovered to have a total occlusion of the left renal artery which resulted in loss of function in her left kidney. She rejected her physician's advice to undergo a nephrectomy, attempting instead to control her condition with drugs. One year later the left kidney function returned and her blood pressure dropped, without the use of drugs. Tests indicated that complete occlusion of the renal artery still existed, but collateral circulation had so thoroughly revascularized the area that she had practically normal circulation to the left kidney.

That plaques are a primary cause of high blood pressure was shown in a captive group of 32 psychotic patients,[7] all of whom had been under observation for as many as 10 years before their deaths. At autopsy, examination of the carotid, aorta and coronary vessels for atheromata revealed that the level of the systolic blood pressure was significantly associated with the degree of atheroma in all examined vessels, with the statistical significance being greatest with the cerebral vessels. This would help to explain the high incidence of cerebral aneurysm and blowout in high blood pressure, leading to stroke.

Plaque development from high lipid and cholesterol intake has been documented in other sections of this book. Renovascular hypertension is but one of its many clinical syndromes.

A nation-wide investigation of relationships between blood pressure and diet was done on about 12,000 inhabitants of Czechoslovakia,[8] who were representative also of the various geographic regions. A summary of some of the findings is given below:

Average Blood Pressure	Total Food Consumed per Day (K cal)	Animal Protein Gm./Day	Fat Consumed Gm./Day
Low	2911 (100%)	37.0 (100%)	84.4 (100%)
Medium	3049 (105%)	41.0 (111%)	104.5 (125%)
High	3178 (109%)	45.4 (123%)	112.6 (133%)

Those with high blood pressure consumed 9% more calories than those with normal pressure, but their cholesterol intake was 23% higher and their fat intake was 33% higher. The association of high lipid and cholesterol intake with hypertension was strikingly indicated.

The role of salt.

Salt intake has also been shown to be associated with hypertension. In Japan, where the salt intake (20 gm. per day) and the incidence of hypertension parallel each other, an effort to lower blood pressure has been in effect since 1957.[9] In a

program aimed at Japanese schoolchildren and their parents, the main efforts were an educational campaign and the serving of school meals utilizing minimal salt. Results of this program, conducted by the Hirosaki School of Medicine, substantiated the role of salt as an etiological factor in high blood pressure: systolic pressure of the children initially declined and did not rise during the 10-year period. (The "normal" and expected rise had been an average of 10 mm.) By contrast, about 6,000 persons not on this regime, who were also followed during the 10-year period, showed an increase of blood pressure and cerebrovascular accidents paralleling their salt intake.

Dr. Lewis Dahl has been preeminent in this country in efforts to reduce salt intake.[10] In his research he developed a group of rats, using inbreeding, who would become hypertensive when excessive salt was added to their diet. With a diet containing only the sodium normally present in foods, but lacking added salt, the rats remained healthy and lived an average life span. In an experiment with special relevance for infants and babies, the rats were fed with thirty different popular commercial baby foods. These common brands of baby food all contained a substantially higher sodium content than did the foods from which they were derived. Fed on these baby foods, the rats developed hypertension and had a drastically shortened life expectancy; whereas the control rats on the normal diet remained healthy. A special finding was that young rats were much more sensitive to the toxic effects of salt than the old ones. Transient feedings of salt for only two weeks in the young rats produced permanent and sometimes fatal hypertension.

Dr. Dahl believes that salt is added to baby foods so that the mother, whose taste is accustomed to foods of high sodium content, would not find them unpalatable. Thus the cultural toxicity is passed on from mother to child.

III. THE TREATMENT OF HYPERTENSION

Diet therapy abandoned as workable drug therapy sought.

Treatment for high blood pressure in the United States today is pharmaceutical. Previous therapeutical programs based on diet have largely been abandoned. A few decades ago dietary programs based on low salt and low protein were successfully employed, but with the popularity of hypotensive drugs, the dietary approach was practically forgotten. Dr. W.S. Hartroft,[11] a prominent researcher in the field for many years, in commenting on this change in therapeutic method from diet to drugs, said: "Such relatively abrupt changes of focus in medical science frequently reflect the enthusiasm of the moment rather than the considered judgment and experience of all involved."

Researchers have spared no effort to find the magic bullet or potion to treat the problem of high blood pressure. Yet the problem has been created by dietary abuses and can only be eliminated by dietary corrections. A serious drawback to the drug approach is the necessity for lifelong adherence to the drug regime if the chemotherapy is to be successful. Further, no drug is completely free of toxic effects. Inasmuch as nontoxic dietary measures for control and elimination of the hypertension are available, the choice of lifelong drug therapy should not be lightly made.

An insight into the development of a hypotensive drug[12] is provided by the work on veratrum viride. Veratrum has been used in folk medicine for hundreds of years but the margin between a hypotensive and emetic dose of the drug is almost zero. Violent retching, bradycardia and collapse would unexpectedly develop in many patients. In an effort to eliminate the emetic properties of the drug, Squibb Institute for Medical Research made extractions and purifications of the drug. One hundred two fractions were made. Over 400 separate oral assays were carried out in hypertensive hospital patients, but the work was unsuccessful and the project abandoned. Fortunately, none of the human guinea pigs

died as a result of these trials, but serious untoward effects could certainly have resulted.

Some years later around 1956 the chlorothiazides were developed. These drugs were enthusiastically received because they were as effective as low-salt diets in the lowering of blood pressure and were "much more acceptable to the patients than was the low sodium diet."[13]

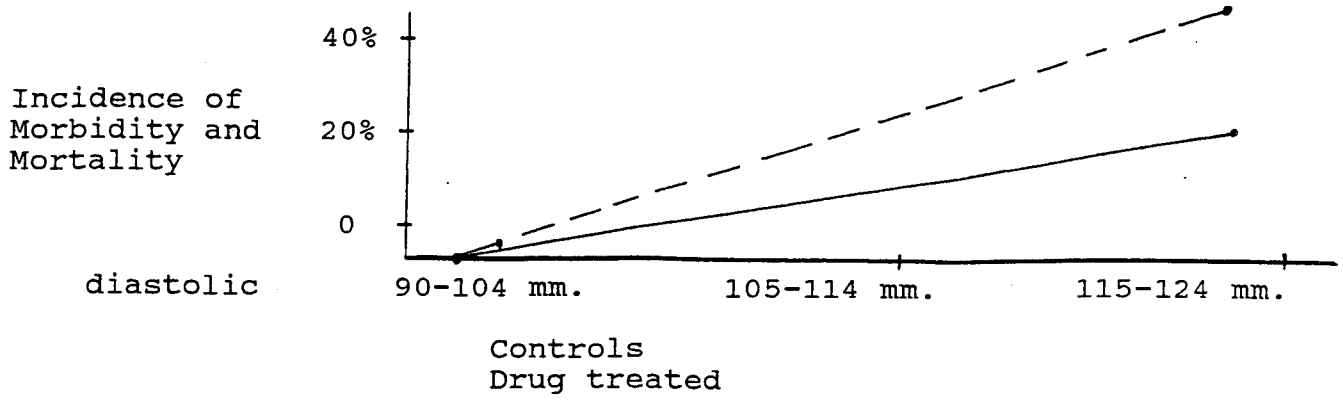
An evaluation of the pharmaceutical approach to hypertension.
Response to drug dependent upon extent of plaque damage

Although a number of trials have failed to show any benefits of drug treatment of high blood pressure, a recent large-scale study under the supervision of the Veterans Administration did show positive results.[14] The most striking improvements appeared in the highest risk cases.

	Diastolic Pressure			
	90-114 mm. Hg.		115-129 mm. Hg.	
	Controls	On Drugs	Controls	On Drugs
Died	19	8	4	0
Nonfatal complications	55	23	23	1
Length of trial	39 months		18 months	

The 115-129 mm. range was stopped at 18 months because of the high morbidity and mortality of the controls. The 90-114 group, if further divided into two sub-groups of 90-104 mm. and 105-114 mm., showed the 105-114 mm. sub-group to have significant improvement in the drug treatment over the controls. However, in the 90-104 mm. sub-group, there was no significant difference between drug-treated subjects and the controls.

In a projection of the results of this study based on a trial time of 39 months, we would see the following:



A hypothesis to explain the gradually increasing benefits with drug treatment as the diastolic pressure becomes more abnormal is based on concepts developed in the section of this book which deal with coronary heart disease. Those individuals with higher pressures have more extensive plaque damage and narrowing of the arteries, especially the renal arteries. The renovascular lesions, in addition to restricting the blood flow and providing the conditions for higher blood pressure, penetrate into the arterial layers, weakening them. The more extensive the plaque damage, the more the lumen will be narrowed, and the higher the blood pressure will be. Individuals with the highest blood pressures, having the plaques most deeply abscessed into their arterial walls, will be most likely to incur aneurysms of these weakened walls. In the advanced plaques, the media is destroyed and even the adventitia is penetrated, leaving only a section of the adventitia to withstand the pressures of the lumenal blood. In healthy arteries, as has been related, experiments with dogs have indicated that pressures of 6,000 mm. can be withstood; but plaque-destroyed arterial walls are subject to aneurysm and blowout at relatively low pressures of 200 mm.

If these relatively low but nevertheless critical pressures are allowed to continue, stroke and hemorrhage will occur frequently in the individuals with the highest blood pressures. The use of drugs or any other means to lower pressure will reduce the likelihood of blowout in the weakened sections of these badly damaged arteries.

Those individuals with pressures of 90-104 mm. would have much less plaque damage and penetration into the arterial walls. The lesser amount of lumenal narrowing would indicate smaller and less extensive plaques. Since arteries in this condition still retain considerable strength, a reduction from 22 mm. to 150 mm. or so with drugs would have little effect on them. These less severely damaged arteries probably have a breaking point of 300-700 mm. The type of plaque large enough to produce sufficient lumen narrowing to result in pressures of 115+ mm. probably would be found in arteries with a breaking range of 180-300 mm. Of course, as the abscess deepens in the plaque, blowout and hemorrhage will occur with the final breaking through of the adventitia. Some of these advanced plaques may be present in individuals from all the blood pressure groupings, but the general rule prevails that the lower the pressure the fewer and smaller the plaques and the less the damage to the arterial walls.

Myocardial infarction not prevented by drug therapy.

However, lowering of blood pressure with antihypertensive drugs does not lessen the likelihood of myocardial infarction, a possible denouement as the plaques continue to grow. As they enlarge, the fibrous cap containing the plaque contents may fragment, releasing either the contents or sections of the cap into the already narrowed lumen. When this occurs, it creates a sort of dam which leads to the aggregation of erythrocytes and platelets, causing the thrombosis responsible for many deaths. So despite the drug therapy, the conditions predisposing to infarcts proceed, nourished by the high levels of cholesterol and lipids, while the lowering of blood pressure only helps when the arteries have become so damaged that a pressure of 200 mm. is enough to break them. Thus, in the Veterans Administration tests which showed improvement in drug-treated groups as to incidence of strokes, kidney damage, etc., myocardial infarction and sudden death were not prevented.

The changing causes of death with high blood pressure patients in the last 30 years supports this thesis.[15] Cerebral hemorrhage deaths were three times as frequent as cerebral infarction deaths

30 years ago; now cerebral infarction deaths exceed those from cerebral hemorrhage. Antihypertensive drugs have lessened aneurysm and blowouts by lowering blood pressure, but have in no way impeded the advance of plaque formation and consequent infarctions. The fact that death rates from strokes are now third in rank among all causes of mortality demonstrates that antihypertensive drugs have only shifted the end point in the destructive process from aneurysm blowout and hemorrhage to plaque infarction. The death rate from strokes remains steadfast, however, despite drug therapy, and in fact has been accelerating at a striking pace, now merely postponed by a few years' grace.

Further evidence supporting the logic of the hypothesis offered above as to the palliative effect--and therefore insidious role of hypertensive drugs--is borne out by a study of 40 younger men with an average age of 35, whose diastolic pressures tested above 100.[16] Because of their youth--some were as young as 18--the examiner decided to make repeat readings over a period of several months. He determined that 12 of the 40 men gradually lowered their pressures from 105 to 88 mm.; the balance of the group were still elevated. The 12 were permitted to continue without treatment, but the other 28 were closely controlled on hypotensive drugs. These men were followed for seven years, during which time 11 developed non-fatal vascular complications, practically all of which were occlusive. The distribution of complications is significant: one developed in the group of the 12 untreated subjects; ten developed in the closely controlled group of 28. None of the complications involved failure of the vessel walls--aneurysm or blowout--and no hemorrhaging was evident. This is consistent with our hypothesis, because the men were young enough to have minimum plaque erosion of the arterial walls, hence there would be no breakthrough of the wall with subsequent hemorrhage. Using our hypothesis, we would expect that the group of 28 men, having the highest diastolic pressures, would have the more advanced plaque development. In this more advanced state, the plaques would be larger and more numerous, narrowing the arterial lumen to a greater extent than occurred in the group of 12

subjects. The greater narrowing of the arterial lumen, restricting the passage of blood, provides the conditions for high blood pressure. Individuals with the more advanced plaques would be expected to develop severe lumenal narrowing and plaque fragmentation leading to occlusion sooner than among those in the group of 12 with less advanced plaques. As predicted by our hypothesis, drug control of blood pressure prevented hemorrhage when the arterial wall had been sufficiently weakened to be capable of hemorrhaging, but meanwhile, the damage due to the evolution of plaque destruction of the arteries continued, nurtured by the continuing high levels of cholesterol and lipids which were unaffected by the drug treatment.

The findings depressed the investigator because he could now observe from his data that antihypertensive drugs might do more harm than good. "It could be that a tendency to excess arterial thrombus formation might coexist with the impulse towards persistent hypertension, even after artificial frustration of that impulse, or alternatively that the forced reduction of blood pressure might itself precipitate thrombosis and change in the vessel wall. Certainly the findings now reported do nothing to encourage the hope that hypotensive therapy can make any contribution to its solution (i.e., reducing the incidence of coronary heart disease--author's comment)." The investigator's first statement is predictive as to the plaque formation causing both the hypertension and the thrombus formation; the second statement is typical of the sad confusion that surrounds the treatment of hypertension by drugs.

The antihypertensive drugs--are they curative?

A stalwart in the defense of drug management of hypertension is Dr. E.D. Fries, who has devoted 25 years to antihypertensive drug research. Dr. Fries enthused in this statement: "It has been my good fortune to have been engaged in antihypertensive drug research at a time when it was making great progress. Success in this field was achieved by empirical methods rather than by brilliant insights." He continued: "These results justify the

belief that with continued efforts we can control all (author's emphasis) of the major cardiovascular diseases."[17]

How curative are the drugs in which Dr. Fries invests such faith and to which he so readily commits those suffering from high blood pressure?

To investigate the curative effect of antihypertensive drugs, a study was done with 60 patients who had been on drug therapy for as long as 20 years.[18] The subjects were taken off drugs abruptly and divided into two groups. No antihypertensive drugs were given to any of the subjects, but the subjects of one group were put on placebo. A summary of their blood pressure values during the testing period without drugs is given:

Type of Study	No. of Patients	Arterial Pressure Responses Increase	Return to Control	No change
Placebo vs. "No treatment"	17	11 11	6 6	0 0
All on Placebo	9	4	5	0
All on "No Treatment"	34	22	10	2
TOTAL	60	37	21	2

In the experimental group were patients with essential, renovascular and malignant hypertension, and renal parenchymal disease. In each group there were at least three incidences of these disease states. In the group of 17, blood pressures reacted the same whether the subjects were on "no treatment" or on placebo; 11 had their pressures rise to some value between the treatment level (when they were on antihypertensive drugs) and the control level (which was the value of their pressure before any treatment started); six of the 17 returned to the control value.

The 9 on placebo responded similarly. Four had their pressures increase towards the control value and five returned to the control value. In the group of 34, there were 22 who increased towards the control value and 10 who reached the control level. However, two retained approximately the lower level achieved during

the drug treatment. One of these two remained without treatment for eight years until his death of a myocardial infarction. (During the "no treatment" period, if blood pressure continued to rise to control levels in a short period--30 to 60 days--patients were returned to their drug treatment. At no time was their hypertension permitted to get out of control.)

An analysis of the mortality of these patients indicates no risk was incurred by taking them off drug treatment. Of the 14 patients that died, only one death occurred off drug treatment (the death cited above). Of the remaining 13, 5 died of stroke, 7 of coronary heart disease, and one of uremia. In the 13 deaths, hypertension was controlled at the period of the fatal illness. None of those who continued without treatment suffered any nonfatal complication up to the time of the report.

Based on this study, the best that can be said for the drug treatment is that the drugs suppressed the pressor mechanisms responsible for elevating the blood pressure. Any hope that the drugs can effect a curative action is not supported by these data.

And then there are the side-effects to consider!

Yet the drug therapy advocated for high blood pressure patients--even though its efficacy is questioned by the data we have cited--would be a life-long affair.

This is acknowledged by Dr. Fries, the staunch advocate of hypotensive drugs quoted earlier, who in the following statement also raises another problem: "Adherence of the patient is vital to a successful chemotherapy and his acceptance of lifelong treatment will depend on a simple regimen that is free of discomforting side effects."

One side effect is the elevation of serum uric acid.[19] This was noted in 1958 when thiazides became popular. Uric acid levels rose above 7 mg./100 ml. in 40-50% of patients treated with thiazides and related drugs. This becomes dangerous because tissue deposition of urate crystals occurs when serum levels rise above 6.5 mg.

In an effort to overcome the effects of uric acid elevation, Dr. Fries, the investigator, conducted some tests. He selected 24 patients with hypertension, putting them on various combinations of thiazide drugs for two months. At that time he introduced probenecid, well established for use in reducing uric acid levels. The specific results were these: after two months on antihypertensive drugs, uric acid levels rose to a mean of 8.14 from a starting pretreatment level of 6.4. The introduction of the probenecid at this time dropped the mean uric acid level to 5.86 after six months.

Results of the test satisfied Dr. Fries who was concerned about elevated uric acid levels because of his awareness that symptoms of arthritis have appeared during therapy with thiazides in patients without previous history of gout, and that exacerbation of acute gouty arthritis was a frequent occurrence during treatment with these drugs.

Since we are speaking in terms of a lifelong chemotherapy, the long-range effects of the drugs to be used for reducing the uric acid symptoms caused by the antihypertensive drugs must also be considered. Two principal uricosuric drugs are used in gout: probenecid and allopurinol. Both are considered to be without "discomforting side effects", but one of their long-term effects has been observed[20] to be crystal deposition in the muscles of users. These crystals contain metabolites of allopurinol, or--when probenecid is used--crystals of uric acid dehydrate.

In a study with gout patients, no crystals of either kind were found in those who had never taken these drugs. In other gout patients, although there had been no symptoms of muscle pain due to crystals, they had been taking the drugs for less than six years. Some of the tissues examined had 50 crystals per section viewed. In some patients with congenital deficiency of xanthine oxidase (allopurinol is a powerful inhibitor of xanthine oxidase), these same crystals were found, but in quantities of 200+ crystals per section. In these patients muscle discomfort upon exertion was experienced and various signs of myopathy were discovered.

To reiterate: all of the patients on the uricosuric drugs had crystals in their muscles; these crystals were not found in any untreated gout patients. This universal side effect is one that can be depended upon. Hypersensitivity to allopurinol was, unfortunately, fatal to a male patient who died 21 days after starting the drug, a victim of the ultimate "side effect".(21)

The recommendation for the use of any drug for a lifetime is fraught with danger. Even following 50 years of use, by the ton, ordinary aspirin is now known to cause internal bleeding.

Treating hypertension with drugs produces gout. Treating gout with drugs produces a possible myopathy. A vicious cycle with no end in sight, unless one goes back to the prevention of hypertension through the lowering of total lipids by dietary means, as discussed in detail in other sections of this book.

HYPERTENSION REFERENCES

1. Metropolitan Life Ins. Co. Blood Pressure: Insurance Experience & Its Implications. New York, 1961.

2. Dublin, L.I. et al. Length of Life, A study of the Life Table. New York, 1949.

3. Karpovich, Peter V. Physiology of Muscular Activity. W.B. Saunders Co., 1962 - Chapter 13.

4. Satinsky, V.P. High Pressures Fail to Break Cerebral Arteries. JAMA 210:1844, 1969.

5. Hunt, J.C. et al. Factors Determining Diagnosis & Choice of Treatment of Renovascular Hypertension. Circ. Res., Suppl II. 20:211, 1967.

6. Dobrzinsky, S.J. et al. Spontaneous Reestablishment of Renal Function After Complete Occlusion of Renal Artery. Arch. Int. Med. 128:266, 1971.

7. Evans, P.H. Relation of Longstanding Blood-Pressure Levels to Atherosclerosis. Lancet p. 516, 3-6-65.

8. Hejda, S. et al. Diet & Blood Pressure. Lancet p.1103, 5-20-67.

9. Reorienting Diet Cuts Hypertension in Japan. Med. Trib. 1-1971.

10. Dahl, L.K. - Letter to Editor. Nutritional Rev. 26:124, 1968.

11. Hartroft, W.S. Nutrition, Pharmacology & Hypertension. Nutr. Rev. 25:161, 1967.

12. Freis, E.D. The Chemotherapy of Hypertension. JAMA. 218:1009, 1971.

13. Ibid.

14. Ibid.

15. Prineas, J. & Marshall, J. Hypertension & Cerebral Infarction. Brit. Med. J. 1:14, 1966.

16. Stewart, I.M.G. Long Term Observations on High Blood Pressure Presenting in Fit Young Men. Lancet p. 355, 2-20-71.

17. Op. Cit. Reference 12.

18. Dustan, H.P. et al. Arterial Pressure Responses to Discontinuing Antihypertensive Drugs. Circulation 37:370, 1968.

19. Fries, E.D. & Sappington, R.F. Long Term Effect of Probenecid on Diuretic-Induced Hyperuricemia. JAMA. 198:147, 1966.

20. Watts, R.W.E. et al. Microscopic Studies on Skeletal Muscle in Gout Patients Treated With Allopurinol. Quarterly J. of Med. XL 157:1-14, 1971.

21. Kantor, G.L. Toxic Epidermal Necrolysis, Azotemia, & Death After Allopurinol Therapy. JAMA. 212:478, 1970.

PART II

THE ARTHRITIC DISEASES

GALLSTONES

CANCER

SIGHT AND SOUND:
VISUAL PROBLEMS AND DIET
HEARING LOSS AND DIET

EXERCISE

I. URIC ACID, AND GOUTY ARTHRITIS

High uric acid levels are associated with gout and gouty arthritis.

Gout and gouty arthritis are mediated by an elevation of plasma uric acid with symptoms usually appearing when blood levels are above 7 mg./100 ml. plasma. This level is reached by 5% of the U.S. population;[1] the incidence of the disease is proportional to the uric acid level.

Uric Acid Level	Gouty Arthritis Occurrence
6-6.9 mg.	1.8%
7-7.9 mg.	11.8%
8.+ mg.	36%

In the last few decades since the advent of antihypertensive drugs which elevate uric acid levels, additional victims of this ailment, which has been known for centuries, have been created. Gout was epidemic in England two or three hundred years ago and a perusal of the menus of the time explains the reason. Meat was eaten at every meal, with several varieties served and large quantities consumed. The high fat levels produced on this regime would be reflected in elevated uric acid levels, which over long periods of time would cause the gout symptoms, commemorated in the literature and art of the time.

The mechanism by which elevated lipids raise uric acid levels is most readily observed in fasting patients. In fasting, the reserve of plasma glucose is metabolized within a day or so and the body then calls upon free fatty acid as fuel. The increase in free fatty acids in the blood is followed by an increase in uric acid. A single 24-hour fast can produce this rise in uric acid. Gout has been observed after a one-week fast in several healthy persons, their uric acid levels rising from normal values to a mean of 14.7% and as high as 21 mg. percent.[2]

Factors inducing rise in uric acid levels.

Uric acid levels rise as total lipids rise

Normally, the rise of uric acid levels is tied to plasma lipid values just as in fasting, but the rise is more gradual, mimicking the rise in total lipids of the blood that occurs with aging as a consequence of the high-fat Western diet.

In a study of 34 persons with gouty arthritis and 28 healthy controls,[3] tests were performed to determine any association between lipids and uric acid level. (This study, as do others, report a particular lipid fraction of the blood, triglycerides, rather than total lipids; hence we will follow these.) The 34 had average uric acid levels of 8.8% mg. percent and their average serum triglyceride level was 142 mg. percent. This contrasted with the control triglyceride value of 100 mg. percent and average uric acid level of 5 mg. percent.

In another study of 100 patients with elevated lipids, results were the same.[4] Eighty-two percent of the patients with hypertriglyceridemia had uric acid levels averaging 7 mg. percent, whereas those with normal values had uric acid levels of less than 4.4 mg. percent. In a separate group of 25 gouty patients, 84% had hypertriglyceridemia.

Uric acid levels rise due to high purine content foods

Another pathway to elevated uric acid levels is by ingesting foods of high purine content, such as lentils, asparagus, mushrooms, animal products high in nucleic acid, and yeast.

This was demonstrated in a study in which five healthy males, average age of 30,[5] were fed a 2800-calorie formula diet. The protein was free of nucleic acid, using 75 grams of egg albumen per day or 11% of the diet by weight. After a stabilization period, the diet was supplemented with progressively larger amounts of yeast. Each amount was given for five days before the next increment was introduced. Results are noted below:

Plasma and Urinary Uric Acid of Men Fed 75 Grams Protein/Day
(Plus Added Increments of 2, 4, or 8 grams daily)

Average Value per Man	Added Yeast Intake, Grams per Day			
	0	2	4	8
Plasma uric acid, mg./%	4.9	6.0	7.7	9.4
Urinary uric acid, mg. 24 hr.	373	667	939	1,393

In only 15 days, on an average intake of 5 gms./day or 20 calories--less than 1% of total caloric intake--a uric acid level of 9.4 was reached. The effect of the high-purine food is dramatic, yet one is practicaly unable to find a textbook acknowledging dietary control as a means of alleviating gout symptoms.

Symptoms in gout are due to the uric acid crystals

As uric acid levels rise, crystals form, usually of sodium urate. These can be seen vividly in polarized light. In inflamed gouty joints, urate crystals have been consistently demonstrated in freshly aspirated synovial fluid.(6) Urate crystals, both naturally formed and synthesized, when injected experimentally into rabbits, dogs, and humans, produce an acute inflammatory response related to the dosage administered. Quantities of 20 mg. produce reactions typical of acute gout. When the investigators used themselves as subjects, injecting urate crystals into their knees, the inflammatory response that followed was so acute--with severe swelling pain and erythema--that only phenbutazone caused it to subside, local injections of procaine and hydrocortisone having failed.

There is no question about the ability of uric acid crystals to cause gout, whether precipitated under high lipid conditions in the body or introduced by injection. There is some speculation, however, as to the exact mechanism by which gout symptoms develop. One possibility is now described.

II. A HYPOTHESIS FOR THE MECHANISM OF GOUT SYMPTOM INITIATION

The release of lysosome enzymes from disrupted leukocytes initiates symptoms.

Leukocytes (polymorphonuclear) in the synovial fluid respond to urate crystals and other foreign substance as "enemies" of the body. The leukocytes instantly phagocytize the crystals by ingesting them into their cytoplasm.(7) Now in the cells, the crystals are taken into the lysosomes for digestion. The lysosomes are baglike organelles, normally spherical, and about .00001" in diameter, which contain enzymes capable of breaking down proteins, fats, carbohydrates and nucleic acids, but not urate crystals. The latter are toxic to the lysosomes and, in fact, to the entire cell. They cause cell membranes to rupture, releasing the intact crystals, digestive enzymes, and cell constituents into the synovial fluid. The proteolytic and other enzymes attack the synovial lining initiating the degeneration of the synovial lining and the subsequent arthritic condition.

Indirect evidence points to this autolysis of the phagocytes. Forty-nine puncture biopsies of synovial membranes were made. Gelatin was placed in fluid from each biopsy to establish the presence of proteolytic activity. The gelatin, pure protein, was broken down in 26 of these synovial fluid samples taken from inflamed synovia. Fluid from the other samples, from normal membranes, had no effect on the gelatin,(8) indicating that the proteolytic enzymes were only present in fluid from the inflamed linings.

These enzymes were identified as lysosomal proteases. Disruption of lysosomes would result in a substantially higher than normal level of lysozyme, one of the lysosome enzymes. Whereas normal serum contains an average of 9.7 g/ml. of lysozyme; serum from individuals with rheumatoid arthritis averages 14.1 µg/ml. In this study, 28 patients tested over 20 µg/ml.(9)

Fifteen of these patients were tested for lysozyme content of their serum and synovial fluid. The two tests, made simultaneously, indicated that the lysozyme level was over twice as

high in the synovial fluid as in the serum. Being rheumatoid, the serum lysozyme level of these individuals was already twice that of normals. Some of these rheumatoid patients had synovial lysozyme levels eight times higher than the highest normal values.

Bacteria as a cause of leukocyte disruption.

Damage to joints due to lysozyme enzymes destroying the synovial lining can be traced in bacterial and gouty arthritis. In gout, the urate crystal initiates the release of lysosomes. In other circumstances, certain bacteria, which are toxic to leukocytes and cause their dissolution, act in the same manner as the urate crystals in initiating lysosome breakdown. Hemolytic streptococcus (Group A), for example, initiates arthritic symptoms and rheumatic fever. After the disease has been overcome, the joint symptoms disappear.

The infectious theory of arthritis, which arose in the early part of this century, grew from the observation that many bacterial and viral infections and vaccines will cause joint symptoms, though these symptoms are transient. Innumerable tonsils and suspected teeth were separated from their owners in the vain hope of curing arthritis.[10] Joint problems originating with these transient causes disappear in a few weeks or months at the most, however, whereas rheumatoid arthritis may persist for a lifetime.

A hostile blood environment as a cause of leukocyte disruption.

In rheumatoid arthritis, results of bacteriological studies[11] have been overwhelmingly negative and strongly suggest that the disease is not caused by an easily identified organism. When inflamed joints are aspirated, the fluid aspirations are usually sterile, but various fragments including the cholesterol crystals[12] are found in the synovial fluid, whose role is not clearly established. Electron photomicrographs clearly show various unidentifiable particles being phagocytized by leukocytes in synovial fluid of patients with rheumatic arthritis. These photos also show the particles ingested in the lysosomes, but the enzymes are unable to digest them.[13] Leukocytes in the synovial

fluid are not particular about what they ingest--they have been found to phagocytize carbon, iron-dextran, gold and other inert substances as well as larger objects such as fibrin, cell fragments, erythrocytes, bacteria (e.g., Staph. albus) and other living organisms.[14]

In rheumatoid arthritis, a cause has not been identified. But according to our hypothesis, the symptoms are produced by the same basic mechanism that operates in gout. In the case of rheumatoid arthritis, however, it is not urate crystals that act as the toxic factor, but as we shall now attempt to show, it is a hostile blood environment that is responsible.

Lysosomes under certain circumstances undergo self-destruction, or autophagy. This can be seen when a cell dies, or when the cell is exposed to toxins, as an excess in Vitamin A. It also occurs when a cell is deprived of oxygen.[15][16] As the oxygen is gradually depleted, an increase of lysosomes is noted; after a few hours, an abnormaly large number of lysosomes can be observed.[17] After extended periods of 12 to 24 hours, autolysis becomes severe and goes as far as complete homogenization of all cell structures.[18]

Thus, a particulate noxious agent is not essential for lysosome destruction and consequent tissue inflammation. Anoxia in tissues can be an initiating factor. Partial capillary anoxia is constantly present in diabetics, prediabetics (hyperglycemics), and those with elevated plasma lipid levels (--normal under U.S. standards).

If mechanical or temperature trauma or some physiological condition producing edema is experienced by these partially anoxic joints, a localized condition of almost complete anoxia can result from the edema produced, creating the hostile environment bringing about the autolysis of leukocytes and the release of lysosomes. The "attack" would continue until the edema receded to the level of the original partial anoxia. After many repeated insults of this kind to the joint, the synovial lining would eventually be destroyed by the lysosome enzymes and the arthritic joint would irreversibly result from this destructive process.

This concept of the etiology of rheumatoic arthritis has considerable evidence to support it, as will now be shown.

III. CONDITIONS WHICH UNDERLIE ARTHRITIS

Hyperglycemia--a basic factor.

Hyperglycemia is present in rheumatoid arthritis and related conditions

Impaired peripheral capillary circulation in arthritis was observed many decades ago in World War I. In testing of 400 arthritic soldiers, a significant finding in the oral glucose tolerance test was that the more severe the arthritis, the more abnormal the test.(19) Using 100 grams of glucose, the average peak glucose level reached as correlated with the degree of arthritis was as follows: normals--135 mg.; mild--145 mg.; convalescents--150 mg.; moderate--170 mg.; severe--190 mg.

Hyperglycemia is also the hallmark of diabetes. These two diseases--arthritis and diabetes--have been shown to be linked by certain other evidence.

1. In vertebral ankylosing hyperostis, an arthritis of the spine, a numnber of studies have confirmed the association of diabetes with this form of arthritis. In one study of 100 patients, half were found to be either diabetic or hyperglycemic.(20)

2. In idiopathic ischemic necrosis of the femoral head (similar to Perthes' disease of children), 54% of an observed group were either diabetic or hyperglycemic; 80% in another series had elevated lipids.(21)

3. In "pseudo-gout", calcium pyrophosphate crystals produce a gout-like syndrome through a mechanism comparable to that by which urate crystals produce gout symptoms. In various studies patients with this disorder were found to be 40-60% diabetic.(22)

4. The Pima Indians in the western part of the United States have both one of the country's highest diabetes rates--34%--and also one of the highest arthritis rates. Among Pima Indian males, arthritis is 375% more prevalent than among their Caucasian counterparts, and among the females, the incidence is 150% greater.(23)

Causes of hyperglycemia and some consequences

The cause of hyperglycemia are explored in detail in the section on diabetes. To summarize the evidence presented there, the statement may be made that the condition is produced by simple carbohydrates such as sucrose (sugar), honey, fructose, etc., and elevated plasma lipids, especially triglycerides. The triglycerides may be endogenous or exogenous in origin. The elevated lipids are responsible for sludging of erythrocytes and rouleaux erthyrocyte formations, and consequent slowing of capillary circulation. In many cases, capillary circulation stops, completely occluded by chylomicra. Platelets are similarly affected.

Hyperglycemics utilize free fatty acids as their principal metabolic fuel because of the inadequate ability to metabolize glucose. The free fatty acids rise above normal, and since the platelets are able to bind the free fatty acids to their membrane surface, resulting in the surface becoming adhesive and prone to aggregation, the formation of thrombi can result.(24) Platelet aggregation is not necessary to the impairment of capillary circulation, as chylomicra--everpresent after a typical U.S. 45% lipid meal--can also create this ischemic condition.

The peripheral ischemia creates numerous symptoms--numbness, tingling of hands and feet, weakness, neuropathies and reduced MNCV (motor nerve condition velocity). These symptoms are exhibited also by diabetics and prediabetics (hyperglycemics), since all share in common--in varying degrees of severity--peripheral ischemia.

MNCV is well established as a consequence of hyperglycemia.(25) Improvement of MNCV was effected in one study in which treatment of the hyperglycemia resulted in normoglycemia. In the World War I study, it was noted that as the blood sugar returned towards normal, the arthritis receded.(26) Although slowing of MNCV has been extensively studied in diabetics,(27) arthritics are also found to have widespread neurologic damage based on their MNCV values.(28)

The neuropathy so widely found in both diabetics and arthritics probably has a common cause in capillary ischemia. Bell's Palsy gives us some understanding into the mechanmism involved, since the large facial nerve is affected in this condition, rather than the many small nerves affected in peripheral neuropathy. Two hundred cases of Bell's Palsy were investigated[29] for possible etiology. Viruses were sought with negative results, as were other possible causes--except one. A search for vascular causes revealed that half of the patients had capillary problems with such symptoms as pooling of blood, sludging, micropools and pathological forms of capillaries in their nail beds.

Hyperglycemia was suspected, and testing revealed that a very high percentage were diabetic, though 90% were unaware of their hyperglycemia. In the 10-19 age group, 45% had hyperglycemia. This percentile increased by age, reaching 100% in the 70-79 age group.

The investigator felt that the microangiopathy was responsible for the facial nerve death, due to decreased blood flow to the nerve resulting in ischemia and edema. The edema would compress the nerve because of its location in the rigid bony canal, where any increase in pressure would cause nerve damage.

The effect of generalized nerve damage shows up in newly diagnosed juvenile hyperglycemics.[30] A test using electricity to determine the minimum current the tongue could feel was tried on normals and newly diagnosed juvenile hyperglycemics. Normal subjects required a maximum of 30 microamps for a sensation of taste on the tongue, but the hyperglycemics required 300 microamps. The severity of this neuropathy suggested its origin long preceded its discovery.

Blood lipid levels--another basic factor.

Elevation of blood lipids by emotional factors

Emotional shock is known to bring on attacks of arthritis,[31] a phenomenon that is predictable according to the hypothesis earlier proposed.

The mechanism by which lipids are poured into the blood triggered by emotional reactions is clearly illustrated by observations of race drivers before and during a race.[32] Ten minutes before the starting gun, the drivers' blood levels are all normal, and after a final check, the drivers get into their cars to await the starting signal. Three minutes before the start, their catecholamines start to rise, and by the time of one minute to go have risen 500%. (The adrenals are here performing their ancient species adaptation function of preparing for battle or flight.) Most of this catecholamine is norepinephrine, whose vasoconstrictive properties are well-known. Simultaneous with the catecholamine rise is the rise in free fatty acid to 300% above normal. An hour after the race, the catecholamines and free fatty acid have dropped almost to normal, but the triglycerides are increased over 300% and remain abnormally high for several hours due to conversion of the free fatty acids to triglycerides.

This conversion of free fatty acid to triglyceride was demonstrated during electrophoresis by a transition from a free fatty acid band in the albumen area immediately after the race to a gradually increasing band of pre-Beta triglyceride which reached its peak an hour later. As the free fatty acid band decreased, the pre-Beta triglyceride increased.

Lowering blood lipids reduces peripheral ischemia symptoms

Whether capillary circulation is impaired due to triglycerides of endogenous origin triggered by emotional factors or by dietary triglycerides is unimportant; the results are the same. These results--numbness, tingling, paresthesia--all disappear if lipid levels are lowered.[33] Clofibrate, a lipid-lowering drug, was given to 9 patients with neuropathy due to hyperglycemia, while 6 patients were given placebos.[34] After a 12-month period, 7 of the 9 improved so that their pain and paresthesia disappeared. Only 1 of the 6 controls showed improvement. In 3 controls, peripheral circulation worsened and gangrene developed requiring leg amputation. In none of the clofibrate patients did vascular complications arise. While more effective means of lowering lipids

using diet rather than drugs are available, as detailed in other sections of this book, the benefits of the lowering of lipids are apparent.

Edema--still another basic factor.

A general statement can be made that is applicable to practically all joint arthritis not caused by specific particulate bodies (e.g., bacteria, crystals such as uric acid or calcium pyrophosphate crystals, viruses such as rubella, etc.).

Two conditions are necessary to initiate the inflammation of the joints. These are:

I. Compromised microcirculation producing partial anoxia
The anoxia would be caused by sludinging of erythrocytes and/or chylomicra mediated by elevated total plasma lipids. The subject may test hyperglycemic although total lipids may appear normal by U.S. standards.

II. Edema
The edema would be brought about by any one of several factors such as physical trauma, physiological causes such as the edema of menstruation, or by such drugs as oral contraceptives. The effects of the edema--superimposed upon the partial anoxia (Condition I)--produces close to total anoxia of the microcirculation, leading to autolysis of the leukocytes and subsequent dissolution of lysosomes. Destruction of the leukocytes would provide the enzymes which destroy the synovial lining.

In some circumstances, there is so much sludging occurring (Condition I) that sufficient edema is produced to fulfill Condition II without actual trauma or added physiological factors. The various kinds of circumstances causing the edema of Condition II will now be explored in detail.

IV. CONDITIONS PRODUCING EDEMA WHICH PRECIPITATE ARTHRITIS

Edema due to mechanical trauma.

Effects in normals

Edema produced by mechanical trauma drastically effects the flow of blood in capillaries. To test the effect of very gentle trauma,[35] the tip of a quartz rod was touched upon the transilluminated omentum of a monkey. So little pressure was applied with the rod that no blood vessels were ruptured. Before the pressure, erythrocytes flowed freely; after the pressure, they clumped and sludged for at least an hour until the sludge started to break and circulation resumed. The same test was repeated with other animals with the same results.

This is the sequence that is observed following even the mildest trauma:

1. Aggregation of platelets and chlomicra forming white masses. These "white emboli" can obstruct or occlude the capillaries and venules.[36]

2. Aggregation of erythrocytes within a few hours after the trauma.[37]

3. Decrease of venous return of cells. Capillaries become perfused with almost cell-free plasma because of cell stasis (plasma skimming), resulting in edema.[38]

4. Metabolic slowdown with decreased oxygen and carbon dioxide exchange with acidosis.[39][40] The acidosis would encourage crystal formation because of the reduced solubility of many minerals (e.g., calcium) as the environment becomes more acid.

Local microcirculatory failure due to occupational hazards (air-hammer workers, "housemaid's knee", other situations where vibration, percussion and pressure cause injury followed by edema) are well-known. What is not appreciated as injury is the mild trauma--typing, throwing, flexing joints for long periods in games, work, etc. The mild edema experienced with this kind of trauma goes unnoticed with good circulation, but with compromised circulation, it is enough to stop capillary flow in the traumatized areas for several hours.

Effect in individuals with impaired circulation

Charcot joints demonstrate the severe form of the combination of impaired circulation and sludging from hyperglycemia--with the superimposition upon this of a mild trauma--creating a hopeless degeneration. Joint areas of hyperglycemics are devoid of normal feeling and sensitivity as demonstrated by MNCV tests. Charcot joints are far advanced in this loss so that mild trauma is not felt or noticed. The joint is subjected to cumulative injuries, until the destructive changes that take place become irreversible. Eventually the only treatment left is amputation.(41)

Perthes' disease in children is a condition that resembles adult arthritis. Beginning with an apparently insignificant trauma in the hip or knee, there is then a transient ischemia, and finally an absolute ischemia associated with destruction of the femur head. The young victim then faces a lifetime as a cripple.(42)

Viewed through the revealing light of our hypothesis, the script in Perthes' disease would read this way:

1. A child with elevated lipids (perhaps normal by U.S. standards) and possibly hyperglycemic sustains a mild trauma in play or other activity;
2. The already compromised capillary circulation now superimposed by the edema of trauma produces an anoxia in the area;
3. Synovitis occurs because of the autolysis of the leukocytes and dissolution of the lysosomes, inflaming the synovial lining;
4. Transient ischemia is observed. This is a continuation of the severe anoxia produced by the combined edema of trauma and erythrocyte sludging of hyperglycemia. Continuous ischemia can cause death of the osteocytes, resulting in necrosis of the femoral head.

Treatment should immediately be directed towards reestablishing microcirculation and reducing edema. Only through lowering total lipids (and diet is the most effective way to accomplish this) can sludging be eliminated. Other ways to improve

circulation should also be initiated. Unfortunately, the only certain cure is prevention; trauma in a child with good circulation will not produce Perthes' disease.

The adult version of this condition is Idiopathic Ischemic Necrosis of the Femoral Head,[43] just as tragic and an equally avoidable condition. Two circumstances seem to be involved. As to the first, studies show that 54% of individuals with this disorder have hyperglycemia and 80% have elevated total lipids, including cholesterol, triglycerides, beta lipoproteins, etc. (all elevated even according to U.S. standards). Secondarily, most patients suffer from previous diseases such as osteoporosis or other degenerative diseases, and 20% report a history of microtrauma. Included here are such subjects as pneumatic drill workers and others sustaining traumas not sufficient to dislocate or fracture a bone.

The combination of the two reinforcing conditions produces a severe anoxia sufficient to cause the death of the femoral head due to oxygen lack. As in Perthes' disease, the "cure" is prevention--the lowering of total lipids by diet.

Edema due to physiological trauma.

Edema produced by physiological conditions without trauma can produce anoxia severe enough to bring on arthritis. The mechanism is clearly observed in immunization with rubella vaccines. Rubella vaccines have been given to thousands of women and children and a pattern of transient arthritic symptoms frequently appears in the joints of the arms and feet. Usually the symptoms last only a few weeks.[44]

A typical pattern of reaction in 159 subjects aged 6 to 33 years of age has been reported.[45] The group was checked initially and all were found to be without any detectable rubella antibody. After the vaccine was given, the seroconversions (rubella antibody with significant titer) averaged 95%. The data are summarized below:

Effects of Rubella Vaccine on 159 Female Subjects

Age	Seroconversions	Arthritic Symptoms	Arthritic symptoms when vaccine was given within 5 days of start of menstrual period (54 subjects)
6-12	100%	0%	0%
13-16	96	2	4
17-19	91	6	8 (est.)
20-24	93	25	44
25-33	94	50	72

These results are comparable to those observed in other studies. In one such study, 11,758 children were vaccinated and 0.4% developed arthritic symptoms.(46) In another group receiving vaccinations, 10% of the 15-17 year old subjects and 40% of the 30- to 40-year olds developed arthritic symptoms.(47)

The data may appear puzzling, but let us again interpret it with the aid of our hypothesis and the concept of the two prerequisite conditions:

1. Condition I. As the subjects advance in age, their total lipids rise. (We are discussing subjects who live in the U.S.; this would not necessarily be true in other areas.) The higher the lipids, the more chylomicra and triglycerides, and the more consequent rouleaux formation and erythrocyte sludging. (To formulate a maxim: The older the subject, the higher the lipids, the greater the sludging, the more severe the anoxia.)
2. Condition II. Edema of menstruation is well-documented and would be significant with the immunized female subjects. Weight gains of 2-6 pounds of fluid are normal. The edema, general throughout the body, worsens the anoxia of the capillaries. There is no mystery as to the reason women have 300% more arthritis than men(48)--they produce their own edema each month with their menstrual periods! Even without virus in the joints, the presence of edema alone could be sufficient to fulfill Condition II. However, joint circulation is further distressed by rubella virus in the area,(49)

which probably causes some lysosome dissolution. If microcirculation in these areas were excellent, the symptoms would be negligible; but as lipids increase the initial anoxia is greater and the superimposed conditions can produce manifestations of arthritis.

With use of oral contraceptives

The use of oral contraceptives can also precipitate manifestations of arthritis by fulfilling Condition II. As to the first condition, triglycerides are raised in 95% of the users of oral contraceptives,[50] and there is a shift of glucose tolerance towards hyperglycemia in 75% of users. Platelets become adhesive in a manner similar to that occurring in atherosclerosis, as a result of this blood picture. As to Condition II, edema associated with the use of oral contraceptives is more severe than that experienced in normal menstrual cycles. At the University of Michigan, 18 women on oral contraceptives who had rheumatic arthritis were studied.[51] Ten of them had a history of arthritis, tracing its beginning to a period just following the taking of the first pills. It was decided to have all 18 stop using the pill. In 15 out of the 18, arthritis either disappeared or improved. Four of the 15 resumed the pill and all four regained their arthritic symptoms.

Fluid filtration rates in normals and arthritics

When microcirculation is sufficiently impaired, both conditions I and II become fulfilled. This was demonstrated and measured in arthritics[52] using special instrumentation for capillary filtration rates. Normally some fluid passes through the capillary walls into the tissue. If the rate of filtration through the wall is greater than can be resorbed, edema develops. The rates for the arthritics and control subjects are shown below:

Amount of Fluid Filtering through Capillary Wall into Tissues

	.0028 = 100%	ml./min./mm./Hg./100 ml.
Controls	100%	.0028
Arthritics (no visible edema)	150%	.0042

Arthritics (with edema)	180%	.0052

Controls would be expected to show greater quantities of fluid filtering through the capillaries as they aged, due to the increasing plasma lipid levels with the years. The data confirmed this.

Fluid Filtration Rates Versus Age in Controls

Age (years)	Fluid Filtration	ml./min./mm.Hg./100 ml.
10	100%	.0020 (est.)
20	115	.0023
40	130	.0026
60	160	.0032

Thus, as the controls age, the 60-year olds start to show filtration rates similar to those of arthritics with the least amount of flow. Experiments were performed on the forearms excluding any joint (and thereby any inflamed synovia). After examining the edema fluid, it was conceded that the capillary endothelium had a normal permeability and the reason for the edema was unknown.

While the cause was not apparent to the investigator, the following explanation is plausible based on our proposed hypothesis. As the plasma lipid level increased, chylomicra content would also increase, resulting in a greater slowing and sludging of the capillary blood. When pressure rose due to the blockage, the plasma would be forced through the capillary walls in increasing volume. Thus, the plasma fluid filtration rate would be proportional to the lipid level of the blood; and although the capillary endothelium was normal, the internal flow pattern would not be.

V. SOME SYMPTOMS OF ARTHRITIS

Chronic edema.

The observations cited above concerning capillary wall fluid filtration rates in arthritics confirm the fact that arthritics can have a steady state of edema. This was also pointed out in 1947 when the relationship between erythrocyte sludging and edema was noted, especially in arthritics.(53)

Anemia.

Mild anemia of arthritis can be easily understood in the context of these circumstances. Abnormal, aged, and damaged erythrocytes are being constantly ingested by the phagocytic cells of the spleen and liver, guardians of the blood stream.(54) In the implantation of plastic valves in the heart, for example, hemolytic anemia frequently occurs as a result of damage to erythrocytes from the valves due to mechanical trauma.

While erythrocytes that agglutinate are thus being ingested, normal erythrocytes are completely ignored by the phagocytes. The tremendous capacity of the stationary phagocytes of the liver and spleen is indicated by some observations made with a monkey infected with malaria. Malaria parasites have the property of agglutinating erythrocytes. The infected monkey was observed to have clumps of parasitized erythrocytes throughout its system. In three hours 25-33% of <u>all</u> the monkey's erythrocytes were ingested and destroyed by its phagocytes.

Arthritics also have considerable generalized sludging of their erythrocytes(55) and the same mechanism can be assumed to be at work removing the clumped cells. A common finding with arthritics is a palpable spleen in 5-10% of the observed cases. These spleens are probably filled with "sludged" erythrocytes, whose withdrawal from the bloodstream creates the normocytic anemia so often found in arthritics.(56) Arthritic anemia is not responsive to iron therapy, since there is no iron shortage in the blood. In fact, the iron recovered from the destroyed erythrocytes provides a substantial storage reservoir.

Impaired capillary circulation.

Nonrheumatics are found with severe atrophic joint changes and destruction if they have had long existing hyperglycemia with coexisting neuropathy.[57] Poor circulation is a necessary condition for arthritis to develop. When destructive changes have taken place due to the partial anoxia, the muscles, skin and bone adjacent to the joint all show the ravages of atrophy.[58]

Recent advances in the techniques of measuring partial oxygen pressure (pO_2), pH, and lactate by microsampling further reinforce the hypothesis. A study of 102 synovial fluid samples from knee joints of patients were analyzed for pO_2 and other properties.[59] The pO_2 was significant and is summarized in the table below.

Mean pO_2 (partial oxygen pressure) in 3 Groups in 102 Synovial Fluids

Total	Disease	Mean O_2 Tension (mm. Hg.)	O_2 below 20 mm. Hg.	O_2 below 5 mm. Hg.	Zero O_2 Pressure
85	Rheumatic arthritis	26.53	27	8	2
13	Osteo-arthritis	42.92	0	0	0
4	Traumatic exudates	63.00	0	0	0

Those with rheumatic arthritis predictably have less oxygen available in the synovial fluid. Other studies confirm this observation. In a group of 22 patients with rheumatoid arthritis, only the severe cases had joint fluid pO_2 levels of <27mm. Hg.[60] Another group of 44 patients[61] were found to have lower values of pO_2 in inflamed joints. In fact, in 21 out of 22 patients with pO_2 levels of 25 mm. Hg., none could bear weight on the inflamed joint, attesting to the severity of the arthritis. As the pO_2 level dropped, the lactate level rose and the pH dropped, suggesting an anaerobic glycolysis taking place in the anoxic synovia.[62] When synovial membranes were biopsied (in 24 cases), greater damage was observed in those membranes where the fluid was lowest in pO_2.[63]

Leukocytic infiltration, obliterative microangiopathy, and fibrinoid necrosis were much in evidence.

The summary table on partial oxygen pressure in the synovial fluid samples makes clear the impossible situation of arthritics, where some joints have a pO_2 of zero. Complete obstruction of arteries and capillaries supplying arthritic joints have been demonstrated by angiography[64] so that the underlying mechanism has been observed. With the restricted O_2 supply due to sludging and the greater metabolic need due to increased leukocyte activity, very low O_2 tensions are inevitable.

On this point the investigator was predictive: "Anoxia-hypoxia might cause cell damage and death, and might also release lysosomal enzymes as shown by de Duve. If the leukocytes in the anoxic synovial fluid are damaged or die, the response of the organism will be hyperemia and massive leukocyte migration into the joint; increased oxygen consumption develops, and a new anoxia or hypoxic episode might be initiated."

VI. TREATMENT OF ARTHRITIS

Relief of anoxia is imperative.

If the inflammation is to recede, more oxygen must be supplied to the afflicted area. Elimination of sludging by lowering dietary lipid levels is one way to counteract the anoxia. Another method suggested is to bring additional oxygen into the sludged blood by hyperbaric oxygen therapy. Daily sessions of two hours at two-three atmospheres of oxygen for at least 20 sessions were tried on patients suffering from rheumatic joints and a variety of arthritic conditions.(65) At these levels oxygen becomes toxic and the patients must be closely watched. It is not known how much more oxygen can be absorbed by the erythrocytes, but whatever was absorbed was sufficient to produce "encouraging results" in 60 out of 75 cases. The therapy would not affect the basic erythrocyte sludging problem but would alleviate the severe anoxia in arthritic joints. An enumeration of various joint problems that respond to high pressure oxygen establishes the common bond of the joint inflammation syndrome--anoxia.

1. Rheumatoid polyarthritis. In 10 out of 13 patients, joint immobility and inflammation subsided.
2. Psoriatic arthritis. Four out of 6 patients had general improvement.
3. Degenerative rheumatism. Twelve out of 13 patients had good results.
4. Osteonecrosis of the femoral head. Five cases had substantial disappearance of pain.
5. Scapulohumeral periarthritis. Seventeen of 20 patients had complete relief from their symptoms.
6. Pelvic spondylitis. Six of 8 cases showed functional improvement.

Most of the beneficial results occurred with less than one month's exposure to oxygen or a total of 60 hours of treatment. If these patients went on a plasma lipid-lowering diet for the same one-month period, they would have received 24 hours of curative oxygen daily, instead of 60 hours per month.

An unenthusiastic appraisal of current therapy.

Treatment offered by physicians is based on reduction of the progression of the inflammation. For many years rheumatologists have been drawn towards the concept that immunological mechanisms are important in the pathogenesis of arthritic diseases. In an attempt to destroy or suppress the immune responses, cytotoxic drugs have been used for years. Results have been inconclusive, but now because of a controlled double-blind trial by eight clinics across the U.S., the value of this treatment can be assessed.(66)

Seventy-two patients were treated over 32 weeks in the testing program sponsored by the American Rheumatism Association. Half the patients received 150 mg./day of Cyclophosphamide, a popular cytotoxic drug; the other half received 75 mg./day. The high dose brought the progression of the joint erosions almost to a stop. The low dose group had insignificant improvement but experienced nearly as many adverse effects as did the high dose group. Adverse effects of the drug were considerable: 2 deaths from infections and one near death. One of the deaths occurred in the low dose group.

The deaths can be better understood when the effects of this therapy on the lymphocytes are noted. In the high dose group, the median lymphocyte count fell to 728, and 10% of the patients had values that were under 290. With so low a lymphocyte count, it is remarkable that so few deaths from infection occurred. The report states: "This trial has again demonstrated the high incidence of adverse effects seen with this therapeutic regimen. This, plus two deaths during the trial and long term dangers such as permanent sterility, induction of malignancies, etc., indicates that cyclophosphamide must be used with extreme caution and only in carefully selected patients." (Author's emphasis)

In view of the adverse effects anticipated with this therapy, one would hope not to be selected!

Since 1949, when Hench first used cortisone and everyone thought that the magic bullet had indeed been found, it has come to be used with more and more reluctance. The head of the Divisions of Rheumatology at the University of North Carolina Medical School

sums up the problems:[67] "Arthritic deterioration continues painlessly under coricosteroid therapy, and the conditions may be neglected until there is little that can be done... These drugs are used extensively, and I think the reason for this is impatience to do something right away. Orthopedic surgeons were especially likely to use steroids. Physicians who spend more time with their patients prescribed steroids less often... Persons who have jobs that are rough on their joints take steroids to get rid of the pain. They they keep on doing the same thing for one, two, or three years--and after that the joint is so deteriorated it's too late to do anything... There should be a philosophical acceptance that rheumatoid disease lasts a long time."

Some desperate and quaint treatments from the past.

It is of interest to observe the treatment by one physician of his own arthritis, since he was able to treat and follow it 24 hours every day. This London physician developed arthritis of the hip joints and right knee when he was 46 years old.[68] Sixteen years later, at age 62, he was still trying numerous approaches to the problem of his right hip and knee in an effort to avoid surgery. In the 16-year period, here is a list of the treatments he had undergone--a total of <u>16,000 treatments</u>--averaging 3 per day, 7 days per week:

1. Massage and manipulation--3 times daily
2. Exercises, in bed or bicycling or swimming
3. Daily surging faradic contractions (induced electricity) of the muscles surrounding the joint area
4. Over 100 intramuscular and pericapsular injections at weekly intervals
5. Deep x-ray therapy to the hip and knee
6. Physiotherapy, anti-arthritic medications
7. Use of crutches and sticks at appropriate times, with a raised heel under the right shoe.

Physician! Heal thyself! (This one really tried.)

In 1896, JAMA reported that in Australia rheumatic patients stayed at a particular hotel in order to receive a certain

treatment. When a whale was caught, the patients were rowed over to the works at which the animal was cut up. The whalers dug a narrow grave in the body, and the patients would lie in this for two hours as in a Turkish bath, while the decomposing blubber of the whale closed around the patient's body acting as a hugh poultice.

At least that treatment did no harm.

ARTHRITIS REFERENCES

1. Hall, A.P., et al. Epidemiology of Gout & Hyperuremia. A Long Time Population Study. American Journal of Medicine. 42: 27, 1967.

2. Alderman, M.H. & David, R.P. Hyperuricemia In Starvation. Proc. Soc. Exp. Biol. Med. 118: 790, 1965.

3. Feldman, E.B. & Wallace, S.L. Hyperglyceridemia on Gout. Circulation 29: 508, 1964.

4. Berkowitz, D. Blood Lipid and Uric Acid Relationships, JAMA. 190: 856, 1964.

5. Waslien, C.I. Uric Acid Production of Men Fed Graded Amounts of Egg Protein & Yeast Nucleic Acid. American Journal Clin. Nutr. 21: 892, 1968.

6. McCarty, D.J., et al. Crystal Deposition Diseases. JAMA 193: 123, 1965.

7. Arthritis Inflammation Linked to Leucocytes, Urate. Med. Trib. p. 13, 1-13-71.

8. Mitrovic, D., et al. Lysosomal Proteases & Local Inflammation. Rev. Rhum. 37: 741, 1970.

9. Lysozyme Level Offers Clue to Etiology of Rheumatoid Arthritis. JAMA 211: 763, 1970.

10. Pemberton, R. & Robertson, W. Studies on Arthritis in the Army, Based on 400 Cases. Arch. Int. Med. 25: 231, 1920.

11. Cecil-Loeb Textbook of Medicine, 1968, p. 1390-1410. W.B. Saunders Co. publishers, Philadelphia, Pa.

12. Op. Cit. Reference 6.

13. Inclusions May Explain Chronic Joint Inflammation. JAMA 197: 44, 1966.

14. Roy, S., et al. Bacterial Phagocytosis by Synovial Cells. Lancet p. 980, 10-30-71.

15. Lysosomes & Disease. Sci. Amer. p. 62, 11-67.

16. The Lysosome. Sci. Amer. p. 72, 5-63.

17. Confer, D.B., et al. Evolution of Lysosomes in Hypoxic Liver Parenchyma as Seen With the Electron Microscope. Arch Path 45: 533, 1964.

18. Becker, N.H. & Barron, K.D. The Chemistry of Anoxic & Anoxic-Ischemic Encephalopathy in Rats. Arch. Path 38: 161, 1961.

19. Op. Cit. Reference 10.

20. Modern Trends in Rheumatology. Appleton-Century-Crofts. p. 331, London, 1971.

21. Ibid.

22. Ibid.

23. Cobb, S. Frequency of the Rheumatic Diseases, p. 48. Howard U. Press, 1971.

24. Hoak, J.C., et al. Localization of Free Fatty Acids Taken up by Human Platelets. Blood 40: 16, July, 1972.

25. Ward, J.D., et al. Improvement in Nerve Conduction Following Treatment in Newly Diagnosed Diabetics. Lancet p. 428, 2-27-71.

26. Op. Cit. Reference 10.

27. Op. Cit. Reference 25.

28. Chamberlain, et al. Rheumatoid Neuropathy, Clinical and Electrophysiological Features. Ann. Rheum. Dis. 29: 609, 1970.

29. Korczyn. A.D. Bell's Palsy and Diabetes Mellitus. Lancet 108-10, 1-16-71.

30. Chochenov, R.H. Early Sense Impairment Seen in Juvenile Cases. Medical Tribune, p. 1, 7-7-71.

31. Toggart, P. and Curruthers, M. Endogenous Hyperlipemia Induced by Emotional Stress of Racing Driving. Lancet 363-6, 2-20-71.

32. Ibid.

33. Op. Cit. Reference 25.

34. Berenyi, M. R., et al. Treatment of Diabetic Neuropathy With Clofibrate. Journal Am. Geriatr. Soc. 19: 763-72, 1971.

35. Knisely, M.H., et al. Sludged Blood in Traumatic Shock. Arch. Surg. 51: 220, 1945.

36. Lutz, B.R. Intravascular Agglutination of the Formed Elements of the Blood. Physiol. Rev. 31: 107, 1951.

37. Op. Cit. Reference 35.

38. Knisely, M.H., et al. Slud38. Knisely, M.H., et al. Sludged Blood. Science 106: 431, 1947.

39. Lofstrom, B. Intravascular Aggregation & Oxygen Consumption. Octa Anest. Scand. 3: 41, 1959.

40. Bergentz, S.E., et al. Metaboliska Effekter Vid Inducerad Intravaskular Blodkroppsaggregation. Nord. Med. 1961.

41. Op. Cit. Reference 11.

42. Kemp, H.B. Venous Occlusion Thought to Cause Perthes' Disease. Med. Trib. 9-14-70.

43. Op. Cit. Reference 20.

44. Thompson, G.R. & Brackett, R.G. Rubella Vaccine Can Cause Transient Joint Pain. JAMA 210: 2169, 1969.

45. Swartz, T.A., et al. Clinical Manifestations According to Age Among Females Given HPV-77 Duck Rubella Vaccine. Am. J. Epidemiol. 94: 246, 1971.

46. Op. Cit. Reference 44.

47. Weibel, R.E., et al. Live Rubella Vaccines in Adults & Children. Am. J. Dis. Child. 118: 226, 1969.

48. Op. Cit. Reference 11.

49. Ogra, P.L. Arthritis Associated With Induced Rubella Infection. Journal Immunol. 107: 810, 1971.

50. Metabolic Effects of Oral Contraceptives. Lancet p. 783, 10-11-69.

51. Kay, D.R. & Bole, G.G. Rheumatic Symptoms Linked to Oral Contraceptive Use. Med. Trib. 11-71.

52. Jayson, M.I.V. & Barks, J.S. Oedema in Rheumatoid Arthritis: Changes in the Coefficient of Capillary Filtration. Brit. Med. J. p. 555, 6-5-71.

53. Op. Cit. Reference 38.

54. Ibid.

55. Ibid.

56. Op. Cit. Reference 11.

57. Schwarz, G.S. Atropic Arthropathy & Diabetic Neuritis. American Journal Roentgen 106: 523, 1969.

58. Op. Cit. Reference 11.

59. Lund-Oleson, K. Oxygen Tensions in Synovial Fluids. Arthritis Rheum. 13: 769, 1970.

60. Falchuck, R.H., et al. Respiratory Gases of Synovial Fluids. Amer. J. Med. 49: 223, 1970.

61. Treuhaft, P.S. & McCarty, D.J. Synovial Fluid pH, Lactate, Oxygen and Carbon Dioxide Partial Pressure in Various Joint Diseases. Arthritis Rheum. 14: 475, 1971.

62. Ibid.

63. Op. Cit. Reference 60.

64. Op. Cit. Reference 59.

65. Gilly, R. Hybaroxia Held Useful in Easing Rheumatic Joints. Med. Trib. 1-71.

66. Cyclophosphamide Use in Arthritics Questioned. JAMA 221: 645, 1972.

67. Weir, D.D. Drug May be Overused. JAMA 209: 19, 1969.

68. Tucker, W.E. Medical Treatment of Osteoarthritis. Lancet p. 741, 10-9-65.

GALLSTONES

I. DISEASE RELATIONSHIPS

Cholelithiasis (gallstones) is a disease[1] associated with populations on a Western diet. In the United States, it is estimated that 15,000,000 people have gallstones; they are found in 20% of routine autopsies. In most Asian countries where the fat intake is low, gallstones are infrequently found. In countries on a high-fat diet (U.S. Western type with 40+% of total calories in fat), the incidence climbs as the population ages. Infants and young children are almost never affected, but the incidence rises with age, so that one-third of the 75-year old population predictably has gallstones. The disease is serious insofar as it is closely associated with carcinoma of the biliary tract and gallblader: 50-90% of these malignancies are associated with gallstones.

The rise in incidence of gallstones with age is paralleled by a corresponding rise in plasma lipid levels, as was demonstrated in a study with a controlled population in the Western United States, the Pima Indians, in which 596 Pimas, aged 15 to 74 years, living in a section of an Arizona reservation, were examined for gallbladder disease.[2] The Pima Indians' diet has been documented[3] in great detail and because of their reservation abode could be observed as in a controlled study. Observation of this small population was particularly relevant because the Pimas have one of the highest rates of diabetes and arthritis, both diseases being associated with a high-fat dietary intake as discussed in other sections of this book.

The following table shows clearly that the incidence of both gall bladder disease and diabetes are very much age related in this group.[4]

PREVALENCE OF GALLBLADDER DISEASE AND DIABETES AS RELATED TO AGE

Age Groups	Gallbladder Disease Males	Females	Gallbladder and Diabetes Males	Females
15-24	0%	13%	0	0
25-34	4	73	0	15
35-44	11	71	0	33
45-54	32	76	25	48
55-64	66	62	50	71
65+	68	90	13	35

The lowering of the incidence in both gallbladder disease and diabetes at age 65+ is probably due to the excessive death rate of diabetics.

Obesity has been associated with gallbladder disease in several studies,[5][6] including the Framingham study. The Pima population studied was considerably above normal desirable weight; the men were 19% above, and the women 45% above.

Although their cholesterol level was low by U.S. standards, 180-190 mg.%, the triglycerides were elevated.[7] A control group of 32 without disease had values averaging 147% mg. as contrasted with a group of 59 with gallstones who had triglyceride levels averaging 164 mg.%. The level of 164 mg.% may have been less than it was before symptoms started, since there is a tendency to reduce levels of fat after an attack of cholecystitis. The elevated triglycerides would indicate a substantial intake of fat in the diet. This is borne out in a detailed diet study of 277 Pima females that reported the dietary fat content to be 44% of total calories, even higher than the U.S. average. Their total caloric intake of over 3000 per day together with a relatively inactive routine resulted in their weight being 157% of the desirable norm. By this standard, 97% were overweight.

II. ETIOLOGY OF GALLSTONE FORMATION

Imbalance of major bile constituents as cause.

In an effort to understand the etiology of stone formation, much research is being conducted. Study of stone as well as of bile composition is shedding important light on possible causative factors. A study of the bile properties was made on those Pima Indians undergoing cholecystectomy.[8] Almost all of the stones recovered were cholesterol-type. From the 30 patients from whom samples were obtained, the average hepatic bile contained a low concentration of bile salt and an excess quantity of cholesterol. The phospholipid level was also low. Normal values for phospholipid/cholesterol (P/C) are 3.4; those of the 30 patients averaged 1.6. Although the hepatic bile was optically clear after removal at the operation, after cooling and reheating, cholesterol crystals were found. The hepatic bile, based on its composition, was supersaturated.

Experimental evidence has revealed certain mechanisms of stone formation[9] in cholesterol stones--the major type found in Western civilizations--cholesterol is the major component. Normally, cholesterol is held in solution with bile salts and phospholipids. Its solubility is not materially affected by the several minor constituents in bile. Phase diagrams have been worked out experimentally that predict the relative amounts and ranges of cholesterol, bile salts, and phospholipids necessary for a solution to be maintained.

With this information, normal and lithogenic bile was analyzed; it was found that lithogenic bile is deficient in bile salt. In one study, the bile salt pool was 46% smaller than normal,[10] but in virtually every group studied, a relative reduction of phospholipids and bile salts and an excess of cholesterol were found. This produces a supersaturated bile which precipitates cholesterol in the gall bladder and eventually forms the stone.

Concentrations of these three major constituents--bile salts, phospholipids and cholesterol--were determined in patients

undergoing abdominal operations.[11] The patients were divided into two groups: 25 normals, those who had no history of biliary tract disease and in whom no stones could be found after examination of the gallbladder upon operation; and 66 abnormals, patients in whom stones were found. All the gallbladders were aspirated before withdrawing of a bile sample to avoid a sample of bile that was not representative. Normal biles were all found to fall within the solubility range as worked out in the phase diagrams, whereas abnormal biles did not and were all unable to keep the cholesterol in solution. The table summarizes these findings.

COMPOSITION OF NORMAL AND ABNORMAL BILE
(Millimoles per liter)

No. of Patients		Bile salt	Lecithin	Cholesterol
25	Normal Bile	135	38	11
38	Abnormal Bile - No cholesterol microcrystals	88	16	11
28	Abnormal bile with cholesterol microcrystals	98	18	22

The deficiency of bile salt and phospholipids (lecithin) can be noted in the abnormal biles compared to the normal bile. The contrast is especially clear in the bile with cholesterol crystals, where twice the quantity of cholesterol and one-half the phospholipids make the bile supersaturated and provide the basis for stone growth.

Previous studies reporting values for normal and abnormal bile constituents were analyzed and compared with this study and, as shown, once again the higher concentration of cholesterol and the lower quantities of bile salts created the abnormal stone-forming bile.

COMPOSITION OF NORMAL & ABNORMAL BILE IN PREVIOUS STUDIES
(Millimoles per liter)

	Bile Salt	Lecthin	Cholesterol
Normal biles	165	38	12
Abnormal biles	118	38	19

Drug therapy and surgery as inadvertent causes.

Cholesterol-reducing drugs have been implicated in gallstone formation. One of the most popular hypocholesterol drugs, clofibrate[12] (Atromid-S) has been studied for its effect on biliary composition. In one study, a group of six patients were placed on a control program for 6-8 weeks, then were given clofibrate for an additional 6-8 weeks, during which times phospholipids, cholesterol, and bile acids were measured. In five out of the six patients, a considerable drop in bile acids was noted, along with a small increase in cholesterol. When the concentration of the three principal components of the bile was determined, the bile composition was found to have acquired lithogenic properties.

Clofibrate works by inhibiting the synthesis of cholesterol in the liver, and in doing so, probably does not provide sufficient new cholesterol for conversion into bile salts, thereby rendering the bile too low in bile salts to keep the cholesterol in solution.

Another hypocholesteremic drug is cholestyramine,[13] a positively charged resin which binds acid bile salts. The resin does this so effectively that it decreases the size of the bile pool. This again creates a lithogenic bile due to insufficiency of bile salts to keep the cholesterol in solution.

Another mechanism by which the bile pool is lessened[14] is due to ileal resection. This procedure, the resection of the terminal portion of the ileum, prevents active transport of bile salts. Since 90+% of the bile salts in the small intestine are absorbed only by the ileum, the complications of this operation should be seriously considered. As a result of the lessened bile pool, the liver produces a bile with insufficient bile salts to keep the cholesterol in solution, again producing a lithogenic

bile. Patients with ileal dysfunction can only absorb in active transport 30-50% of bile salts in the intestine. In an extensive study[15] covering 72 patients with ileal disorders, 32% were found to have gallstones. Of 12 patients who had in previous years undergone ileal surgery, 9 had gallstones.

Effect of addition of bile salts to lithogenic bile.

There is little question about the importance of sufficient bile salts to keep the cholesterol component of the bile in solution to prevent crystals and gallstones. Recognizing the role of bile salt deficit in gallstones, experiments were tried in which stone patients were fed primary bile salts in the hope that this would normalize the bile relationship and restore the solubility of cholesterol in the bile. Further, by modifying the bile with additional salts, it was hoped that cholesterol in the form of crystals or stones might go back into solution.

The first successful attempt in humans to effect resolubilization of cholesterol stones in bile was done at Mayo Clinic.[16] The primary bile salt chenodeoxycholic acid was used; it was favored over cholic acid, and other principal bile salt, because it not only expands the bile pool but alters the bile composition to permit greater solubility of cholesterol. In the experiment seven female patients ingested up to 4.5 gm. per day of chenodeoxycholic acid for periods of up to two years. Four of the patients experienced either complete disappearance of stones or considerable reduction in their size. Side effects were mainly a dose-related diarrhea, due to irritation of the mucous membrane of the colon. Measurements after therapy showed the bile pool to be substantially larger and an increase in the proportion of bile salts and phospholipids to cholesterol in all patients.

This experiment was repeated in England[17] with 15 patients again using chenodeoxycholic acid. Composition of bile was measured at the start of treatment and after three months, when it was found that cholesterol solubility was increased because of the increased bile salts and phospholipids in the bile. After six months, the stones disappeared in three patients and three more

showed a decrease in stone size, while the other six were unchanged. There was a small increase in serum cholesterol and a 16% drop in triglyceride levels (probably due to the dose-related diarrhea). Six of the patients who had had microcrystals of cholesterol in their bile, no longer had them after therapy.

There is little question about the nature of the dissolution process: if the concentration of bile salts and/or phospholipids falls in relation to the cholesterol in the bile, the bile veers towards the lithogenic state. This process can be reversed by adding bile salts. Phospholipids (lecithin) have also been tried in the past but with dubious results.

To carry this concept further, gallstones in the common duct were infused with a bile salt solution by means of a continuous drip. A T-tube was put in place after cholecystectomy in a series of 22 patients. In 50% of them, stones were dissolved within two weeks.[18] Pouring bile acids directly on the gallstones accelerates the dissolution of the stones, but the process is the same as in the ingesting of bile salts.

III. DIETARY FACTORS IN RELATIONSHIP TO BALANCE OF BILE CONSTITUENTS

Role of cholesterol.

The question to be answered is: why does the liver produce insufficient bile salts and/or phospholipids, thereby creating a lithogenic bile?

For cholesterol to stay in solution in the bile, the concentration of cholesterol, bile salts, and phospholipids all must be within a fixed relationship. Since the bile salts and phospholipids act as the solvent (micelle), hypothetically either of two situations will cause supersaturation of the cholesterol in solution resulting in the formation of stones: lowering of the concentration of bile salts and phospholipids, or an increase in the concentration of cholesterol.

Such an increase in cholesterol concentration readily occurs in Western countries on the diet commonly consumed. In native populations where gallstones are unknown, ingestion of exogenous cholesterol is less than 100 mg. per day; in populations where gallstones are epidemic, cholesterol intake is 500-2,000 mg. per day.[19] The high intake is reflected in higher bile cholesterol concentrations, in both animals and man.

To determine the effect of dietary cholesterol on stone formation and bile cholesterol concentration, ground squirrels and prairie dogs were placed on test diets.[20] The control diet consisted of a monkey ration which was essentially all vegetables (6% fat, 0% cholesterol); the experimental diet was 50% monkey ration and 50% egg yolks (42% fat and 1.25% cholesterol--not very different from some Western diets). After a year, a liver tissue cholesterol content was measured, with results as shown below.

LIVER CHOLESTEROL LEVELS AFTER 12 MONTHS OF DIET
(Mg./100 gm. wet weight of tissue)

Animals	Control Diet (6% fat; 0% choles.)	Experimental Diet (42% fat; 1.25% choles.)	Choles. Increase
(17) prairie dogs	270 mg.	820 mg.	+303%
(11) squirrels	370 mg.	810 mg.	+218%

Cholesterol crystals or stones were found in 70% of the squirrels and 48% of the prairie dogs on the experimental diet; none were found in the controls.

When rhesus monkeys were placed on diets containing cholesterol in amounts comparable to some human diets,[21] their bile cholesterol concentration rose from 202 mg. to 500-600 mg., recalling the high values of 630-900 mg. reached by some humans on Western diets. In man, these values are high enough to produce stones because of the supersaturation of bile by cholesterol, even when bile salts and phospholipids are in the normal range.

Role of fats--saturated and unsaturated.

An unexpected etiology of gallstones arises from the diligent following of the American Heart Association's dietary recommendations, as revealed by a study sponsored by the Los Angeles Veteran's Administration. In this longest clinical trial of a diet high in polyunsaturates, modeled closely after AHA recommendations, recent autopsy findings[22] have revealed that those individuals who followed the program most closely were rewarded with an incidence of 34% gallstones compared to the controls' incidence of 14% (the same as is found in the general population).

Recent findings report that when healthy men who sere on a cholesterol-free diet change to a cholesterol-rich diet, the lithogenicity of the bile increases.[23] The new Veteran study findings puzzled the investigators, because the cholesterol intake of the unsaturated diet was 365 mg., compared to 655 mg. on the control diet.

The puzzle unravels itself in the light of concepts contained in the chapter of this book which deals with the dangers of large quantities of unsaturated fats in the diet, or in the study now to be described which shows how an unsaturated fat (corn oil) in the diet increased bile lithogenicity.

In the study,[24] rabbits were fed a diet of regular chow, to which fat was added to make up 44.8% of total calories. Cocoa butter was used with one group and corn oil with another. The corn oil-fed rabbits also had 0.25% cholesterol added to their diet. It was found that the corn oil permitted a massive invasion of cholesterol into the tissue regions, as shown in the table below. The excess cholesterol in the liver would tend to produce a bile supersaturated with cholesterol, thereby becoming lithogenic.

EFFECTS OF FEEDING SATURATED & UNSATURATED FATS

% of Total Calories in Fat	Type of Fat	Cholesterol Mg./G. Aorta	Liver
44.8	Cocoa butter	4.52	15.00
44.8	Corn oil	21.30	86.90

Diet-induced conditions producing fatty infiltration of the liver.

Fatty infiltration of the liver, usually in the form of triglycerides, is found in various conditions: overnutrition (obesity), undernutrition (e.g., kwashiorkor), and in normal-appearing persons (weight-wise), who may even test clinically normal.

In so-called "normals", following a Western diet of 40+% of calories in fat and relatively low intake of complex, but not of simple carbohydrates, the levels of plasma triglycerides become elevated, sometimes even by Western standards. As detailed in other sections of this book, plasma triglycerides become elevated by simple carbohydrates and/or dietary fat. Populations with low intakes of these foods have low triglyceride levels, 25-80 mg., while those on Western diets range from 100-200 by "normal" standards. Some resources even permit values up to 209 mg. to be in the normal range.[25] Maintenance of such abnormally high

triglyceride values (> 80 mg.), permits a gradual invasion of triglycerides into the liver. Both triglycerides and their products of hydrolysis, free fatty acids, are taken up by the liver[26] in proportion to their plasma concentration.

An accelerated demonstration of this takes place under fasting conditions.[27] After 24 hours, the plasma glucose is exhausted and free fatty acids from the lipid reserves are used for fuel. The free fatty acid level doubles or triples over normal (detailed in other chapters) and in a short time the bile becomes lithogenic. It is believed that the phospholipid secretion decreases as well as the bile salts. If the liver is invaded with lipids because of the very high level in the blood, the loss of function would be easily understood. Nevertheless, everyone seems to have lithogenic bile during fasting, whether normal or abnormal, in this investigator's experience.

Experiments with ethanol exaggerate this process of fatty infiltration.[28] After a single large dose of ethanol, free fatty acids are mobilized from the adipose tissue; immediately following this, there is increased hepatic triglyceride formation. Although fatty liver precedes the development of cirrhosis in alcoholics, diabetics can have massive fatty infiltration of the liver for years without developing cirrhosis.

In a study with rats[29] given ethanol as 36% calories and a normal amount of protein (18%), deposition of triglycerides in the liver varied in direct proportion to the amount of fat included in the diet. At 25% of calories in fat, hepatic triglycerides were 25 mg./gm.; at 35%, 50 mg./gm.; and at 43%--the average intake on a Western diet--70 mg./gm. Studies in humans show a converse process with the opposite conditions, i.e., low-fats diets reduce hepatic triglycerides.

Those prone to gallstones have high triglyceride levels,[30] which over a period of time produce a fatty liver, a reflection of the plasma environment. Liver biopsies were taken from 25 patients undergoing cholecystectomy and 24 patients undergoing surgery for peptic ulcer.[31] Those with stones were found to have 846% more triglycerides in the liver than those with ulcers--3.3 gm. per 100

gm. dry weight compared to 0.39 gms. In this study there was no correlation between sex or body weight; no evidence of nutritional deficiency could be found with any of the gallstone patients. Normal patients merely had to have "normal" triglycerides (<209 mg.) to have fatty livers.

Elevated triglycerides are also found in prediabetics and diabetics (see Diabetes), in whom the elevated plasma lipid level is the basic disorder, manifested in the hyperglycemia observed during the glucose tolerance tests.

The condition of elevated triglycerides is shared by hyperglycemics and those with cholelithiasis, and these two diseases frequently appear together because of the common etiology. Sixty-one newly diagnosed patients with gallstones were investigated for subclinical diabetes.[32] Glucose tolerance tests indicated 82% had abnormal glucose tolerance tests. Patients who had cases of existing diabetes and other metabolic diseases were excluded beforehand. The 61 had had no known symptoms indicating abnormal glucose tolerance. Out of this group, only 18% were moderately obese; the balance were either of normal weight (36%) or slightly overweight (46%).

Liver biopsies were done in 23 of the group and 21 were found to have fatty livers. Forty percent of those with fatty livers had from 15-80% fatty infiltration, which was significantly correlated with the hyperglycemia and elevated serum lipid levels.

IV. THE LIVER IN DISEASE AND HEALTH AND CHOLELITHIASIS

The role of the fatty liver is significant in cholelithiasis. The greater the fatty infiltration of the liver, the less its ability to perform functions such as manufacture of bile acids and phospholipids. In chronic liver disease with fatty infiltration, de novo synthesis of cholic acid, one of the primary bile salts, is lessened, resulting in a decrease of the total bile pool.[33] In a study with 3 normals and 13 patients with essentially nonalcoholic chronic liver disease,[34] it was found that most of those with liver disease had steatorrhoea. Although this is a common finding, the etiology has not been well known. Intestinal contents, following a meal containing fat, were aspirated from the proximal jejunum in the normals and patients with steatorrhoea. The patients were found to have subnormal bile concentrations as compared to the normals and were therefore unable to hold as much lipid in the micelle phase. No biliary obstruction was found or pancreatic deficiency. The investigator concluded that the steatorrhoea was due to a deficiency of bile salts.

The steatorrhoea of kwashiorkor with its associated fatty liver is well known. As soon as the liver returns to normal, the steatorrhoea disappears. Again, the fatty liver here is interfering with the production of bile salts.

Since biliary phospholipids are synthesized[35] from a separate pool in the liver and their synthesis is dependent upon the size of the bile salt pool, any lessening of the bile pool will lower the phospholipid content of the bile. The failure of the liver to produce normal quantities of bile salts prevents the normal catabolism of cholesterol to bile salts; in time the plasma cholesterol level must rise.

It is important for all these reasons for the liver to be in a normal healthy state. To restore it to this condition, a diet must be followed in which the total fat intake is less than 10% of total calories, cholesterol is limited to 100 mg. per day, and no simple carbohydrates are consumed, as recommended also in other sections of this book. On this program, cholesterol levels will drop below

160 mg. and triglycerides below 80 mg. At these levels, the fat will leave the liver as the hepatic triglycerides come into equilibrium with plasma triglycerides. Under this program, it is expected that existing gallstones will eventually dissolve, since the bile will return to normal with adequate bile salts to effect dissolution of stones.

Using the body's primary bile acids, rather than ingesting them, is more than just being practical. Feeding of chenodeoxycholic acid to dissolve stones ignores the root cause and will not prevent lithogenic bile from being secreted indefinitely. Even after cholecystectomy, stone formation in the common duct years later is not uncommon.(36)

Treatment without regard to cause can cause untold damage. A new procedure to remove overlooked stones from the common duct after a cholecystectomy has recently been reported.(37) If stones are found, the T-tube used to establish drainage from the common duct is removed and a catheter is inserted in the opening. The stones are fished out under fluoroscopic observation. Although the procedure requires no further surgery, the investigators were concerned about a 45-minute period under fluoroscopy for the patient. This amount of radiation is probably the equivalent to a lifetime of exposure.

Drug treatment also leaves much to be desired. The proposed breakthrough for the medical treatment of gallstones by the ingestion of bile acids is a life-time sentence of dose-related diarrhea with the prospect of becoming diabetic as a "reward" in the future.

GALLSTONES REFERENCES

1. Cecil-Loeb Textbook of Medicine. W.B. Saunders & Co., Philadelphia, PA. p 989-1003.

2. Sampliner, R.E., et al. Gallbladder Disease in Pima Indians New Eng. J. of Med. 283: 1358-63, 1970.

3. Reid, J.M., et al. Nutrient Intake of Pima Indian Women: Relationships to Diabetes Mellitus & Gallbladder Disease. American J. Clin. Nutrition 24: 1281-9, 1971.

4. Op. cit. Reference 2.

5. Friedman, G.D., Kannel, W.B., Dawber, T.R. The Epidemiology of Gallbladder Disease: Observations in the Framingham Study. Journal Chronic Disease 19: 273-292, 1966.

6. Sievers, M.L., Marquis, J.R. The Southwestern American Indian's Border: Biliary Disease. JAMA 182: 570-572, 1962.

7. Personal correspondence from the National Institute of Arthritis, Metabolism & Digestive Diseases, Phoenix, Arizona 9-28-72.

8. Small, D.M. & Rapo, S. Source of Abnormal Bile in Patients with Cholesterol Gallstones. New England Journal Med. 283: 53-7, 1970.

9. Bouchier, I.A.D. Gallstone Formation. Lancet p. 711-5, 4-10-71.

10. Vlahcevic, Z.R., Bell, C.C., Jr., et al. Gastroenterology, 59: 165, 1970.

11. Admirand, W.H. & Small, D.M. The Physiochemical Basis of Cholesterol Gallstone Formation in Man. Journal Clinical Invest. 47: 1043-52, 1968.

12. Pertsemlidis, D. Clofibrate Effects Studied. Med. Trib. 10-4-72.

13. Alpers, D., et al. Ileal Resection and Bile Salt Metabolism. JAMA 215: 101-4, 1971.

14. Ibid.

15. Danzinger, R.G., et al. Dissolution of Cholesterol Gallstones by Chenodeoxycholic Acid. New England Journal Med. 286: 1-7, 1972.

16. Ibid.

17. Bell, G.D., et al. Gallstone Dissolution in Man Using Chenodeosycholic Acid. Lancet p, 1213-6, 12-9-72.

18. Way, L.W., et al. Bile Salt Solution Dissolves Common Bile Duct Gallstones. Med. Trib. 5-17-72.

19. Khan, B., et al. Cholesterol in Human Tissues. Arch. Path. 76: 369-81, 1963.

20. Patton, D.E., et al. Biliary Cholesterol Deposits in Ground Squirrels & Prairie Dogs. Fed. Proc. Part 1, p. 248, March, 1961.

21. Op. cit. Reference 19.

22. Sturdevant, R.A.L., et al. Increased Prevalence of Cholelithiosis in Men Ingesting a Serum-Cholesterol Lowering Diet. New England J. Med. 288: 24-27, 1973.

23. Hofmann, A.F., et al. Can a Cholesterol Lowering Diet Cause Gallstones. New England J. Med. 288: 46-7, 1973.

24. Connor, W.E., et al. Relative Failure of Saturated Fat in the Diet to Produce Atherosclerosis in the Rabbit. Circulation Res. XX: 658-63, 1967.

25. Chem-Tech Labs. N. Hollywood, California.

26. Diazani, M.U. Liver Function & Plasma Lipids. Nutrition & Cardiovascular Diseases. Morgangni Edizioni Scientifiche, Rome, Italy, p1-46, 1970.

27. Op. cit. Reference 23.

28. Scheig, R. Effects of Ethanol on the Liver. American Journal Clinical Nutrition 23: 467-73, 1970.

29. Lieber, C.S. & De Carli, L.M. Quantitative Relationship between Amount of Dietary Fat & Severity of Alcoholic Fatty Liver. American J. Clin. Nutrition 23: 474-8, 1970.

30. Op. cit. Reference 7.

31. Sunzel, H. et al. The Lipid Content of the Human Liver. Metabolism 13: 1469-74, 1964.

32. Kremer, G.J., et al. Early Diabetic Metabolic Anomalies & Bioptically Established Fatty Infiltration of the Liver in Gallstone Subjects. Schweizerische Medicinische Wochenschrift 98(4): 110-3, 1968.

33. Ref. 8a of - Linscheer, W.G. Malabsorption in Cirrhosis. American J. Clin. Nutrition 23: 488-92, 1970.

34. Badley, B.W.D., et al. The role of Bile Salts in the Steatorrhoea of Chronic Liver Disease. Gastroenterology 56: 1136, 1969.

35. Op. cit. Reference 9.

36. Ibid.

37. Burhenne, H.J. Nonoperative Roentgenologic Method Credited With Removal of Gallstones. Med. Trib. 1-3-73.

I. SOME ORIGINS AND EVOLUTIONS

Cancer describes a multitude of malignant states; the possible etiology of many have been advanced, but in others remain beyond speculation. Some of the more important of the known carcinogenic agents will be discussed.

Respiratory carcinogens.

Smoking

Most lung cancer is associated with smoking. It is baffling that this form of self-destruction is practiced worldwide among literate peoples and is on the increase.

X-ray screening every six months of those in the risk group is a vain attempt to save the lives of smokers. The results of such a 10-year study[1] with more than 6,000 men in Philadelphia who had faithfully submitted to semi-annual X-ray examinations revealed the following: 121 new cases of broncogenic carcinoma had developed during this period; five-year survival rates were only 8% (the high death rate was due to the large percentage of cancers that had metastasized by the time they were detected); most of the men had no symptoms other than the normal smoker's cough.

The whole screening program seemed so unproductive to the investigators that they thought these programs should be abandoned, to be replaced by an educational program to discourage smoking. At a dollar cost of $5 per X-ray, there was an expenditure of $83,000 to detect each victim of lung cancer--an unreasonable outlay of funds for those who are willing to play Russian roulette using cigarettes as bullets.

Industrial carcinogens

Important in this category are organic solvents and such dusts as carbon, asbestos, and silica, as well as little appreciated dusts as sawdust.

Sawdust, because of its natural origin, has not been regarded seriously as a carcinogen. However, in a concentrated furniture-making area in England, a high incidence of nasal cancer was uncovered[2]--17 times more than was expected (a rate comparable to lung cancer among smokers). Investigation over a period of years revealed a possible mechanism.[3] Wood dust was found on the nasal septum and anterior area of the middle turbinate. The middle turbinate quite regularly showed squamous metaplasia. It was believed that the wood dust, lying on nonciliated epithelium, in contact for long periods with the mucous membrane of the turbinate, would provide the stimulus for the subsequent carcinoma.

Radiation as a carcinogenic agent.

Diagnostic X-rays

This cause of malignancies has been insufficiently appreciated by many physicians and the lay population.

In the 1940's, fluoroscopies were given in most physicians' offices, with little thought of any danger. In one retrospective study, a group of women treated for pulmonary tuberculosis at a sanatorium in Nova Scotia between 1940 and 1949[4] were traced back in the late 1960's to determine the effect of radiation used diagnostically in their care. Three hundred women, or 87% of the group which had undergone therapeutic pneumothorax were found. With these, fluoroscopic examinations before and after each air insertion had been made. In addition, 483 women treated at the same time but not exposed to radiation were also found.

Among the 300 women who had received radiation, 7.3% developed breast cancer, as compared to 0.8% of the 483 women who were not exposed to fluoroscopy. In at least 80% of the cases, the cancerous breast was on the same side of the body as the treated lung which was viewed by fluoroscopy. The cancer location was

predominantly found in the inner segments of the breast, instead of the usual location in the outer segments.

Leukemia risk in males was found in a large study involving 1,414 adult leukemia cases and 1,370 controls to have increased significantly with the number of diagnostic X-ray taken.[5] In those males having 21 more films made of the trunk, the leukemia risk was twice that of others having 20 or fewer X-ray films made. In many routine diagnostic X-ray studies, a dozen films of a trunk area are common, yet these studies indicate that even a single diagnostic series entails considerable risk.

Incidentally ingested substances as carcinogens.

Carbon, talc, and salt--three that are implicated in stomach cancer

A high occurrence of cancer of the stomach is found in Japan and in Iceland, but different carcinogenic agents seem to be responsible. Japan has probably the highest frequency of stomach cancer in the world: 54% of all male cancer deaths were of this variety. Iceland is a close contender, with 45% of all male cancers being stomach cancers,[6] as reported in 1959.

Geographical and cultural factors contribute to the relative isolation of Iceland, with the result that the population of Norwegian-Anglo-Saxon-Irish stock, coexisting there for over a thousand years (during which period very little immigration has taken place), has become so thoroughly integrated that no differences in ethnic origins are known, and the inbred population has developed very similar characteristics racially, socially, and culturally. Thus, genetic factors would be unlikely to explain differences in the incidence of stomach cancer observed in Iceland.

The dietary patterns in Iceland some 50 years ago, when most of the present carcinomas were starting to develop, were very different from those prevailing in Europe or the United States. Meat, fish, fats and milk products were the major diet items, with almost no fruits or vegetables consumed. Home-smoked mutton was the holiday delicacy served at most festivities. Salmon and trout were eaten in great quantities by farm families living by rivers and lakes, who preserved their excess supply by smoking the fish.

An Icelandic physician, aware that chronic hypertropic gastritis was common and noted in most of the stomachs examined in autopsy, reasoned that the carbon on the smoked surface of these popular foods, if carcinogenic, could initiate the tumor process in the stomach, since the smoked foods, being not easily digestible, would remain in the stomach for long periods. In a two-year experiment with rats using the typical farmer's diet, he obtained these results.:

FOOD	FREQUENCY	NO. OF RATS TESTED	NO. OF RATS DEVELOPING TUMORS
Smoked mutton	Daily	25	3
Smoked mutton	2-3 X daily	18	4
Smoked trout	2-3 X weekly	18	6
Salted mutton	Daily	25	1
Salted cod + 10 gm. standard food	Daily	25	0
Standard food	Daily	25	0

Smoked mutton eaten every day was so deleterious that 21 out of the 25 rats on this diet died in three months, as against a minimum life span of 441 days for rats on other diets. Of the remaining four survivors of this group, three developed tumors. When smoked mutton was fed only twice a week for the first year, and later three times weekly, 22% of the rats developed tumors. Rats fed smoked trout developed the largest incidence of tumors, 33%. One of these affected rats developed a typical leukemia, with enlarged spleen.

As a result of these experiments, the physician decided to study the recorded cases of stomach cancer from 1921 to 1959--1,655 cases. Their geographical distribution was plotted on a map of Iceland, locating high and low incidence areas. Upon investigation, it was found that the high incidence areas were those where the largest quantities of home-smoked meat and fish were eaten. Analysis of the smoked food revealed large amounts of 3, 4-benzopyrene, a strong carcinogen. One pound of smoked mutton--an amount easily consumed by many on a daily basis--was found to contain a quantity of benzopyrene equivalent to that in the smoke

of 250 cigarettes. (Another study at the University of Iceland seven years later determined that the quantity of 3, 4-benzopyrene in home-smoked food was twenty times higher than that in commercially smoked products.[7]

When natives moved from a low incidence area to a high incidence area, they developed cancer at the rate prevalent in the high incidence area. Thus, moving to the Westman Islands increased their incidence of cancer by 300%.

The possibility that other variables were responsible (e.g., soil composition differences, population density, heredity) was explored, but the smoked food hypothesis fit best.

The Japanese diet includes a number of carcinogenic agents, any one of which could be responsible for stomach cancer. Rice[8] is suspect because the cancer distribution seems to follow the areas of Japan where the rice is eaten. As Japanese migrate from their homeland and change their eating patterns, their incidence of cancer decreases.

The preferred rice in Japan is talc-dusted. Because of the association of talc with asbestos in the same mine deposits, contamination of the talc by the asbestos takes place, with dire consequences, as the latter substance is an established carcinogen. This has been demonstrated in studies relating asbestos to an increase in gastrointestinal tract cancer,[9] and by recent studies[10] in the asbestos industry in the Soviet Union where a mortality rate several times higher than that of the general population was found due to cancer, principally of the lungs and stomach.

Japan's leading position in the world with respect to the incidence of stomach cancer could also be accounted for by the high concentration of salt in the Japanese diet[11]--about 20 grams per day--probably the largest amount consumed per person anywhere. Animals fed such a salty diet have shown a high frequency of gastric inflammation and ulcers. Many Japanese investigators believe that this chronic gastric inflammation could be a factor in the development of stomach cancer.

The aflatoxins

It may be surprising that under certain conditions many popular basic foods are involved in the etiology of primary liver cancer.[12] The list of such foods is long: peanuts, cottonseed, soybeans, corn, rice, millet, wheat, sorghum, sesame, barley, peas, beans, cassava and sweet potatoes. The mechanism involved in the development of cancer has been widely investigated and the toxic factors have been isolated. These factors constitute a group of fungal metabolites called "aflatoxins" and are classified as B_1, B_2, G_1 and G_2 according to certain characteristics.[13]

Aspergillus flavus, the fungus producing the aflatoxins, is everywhere and grows on most common food plants. The aflatoxins are powerful hepatocarcinogens and quantities as low as one part per billion have caused tumors in animals.[14] This characteristic was revealed with the force of thunder in England when in 1960 the death of 100,000 young turkeys was traced to aflatoxin on moldy Brazilian peanut meal fed the animals, producing acute necrosis of the liver, "Turkey X" disease.

Since the incident, much experimentation has been done to explore the potential dangers of aflatoxin both in animals and man. The problem has great relevance to many populations subsisting on groundnuts as a basic food, as well as to those consuming much rice, which is often contaminated with a fungus. In Africa, moldy corn is eaten as a delicacy and it has been demonstrated that even cow's milk contains aflatoxins, if the cows have been fed moldy peanut meal.

The response of domestic animals to very small quantities of dietary aflatoxin is indicated in the following table:[15]

ANIMAL	LEVEL OF AFLATOXIN (ppm)	FEEDING TIME	TOXIC SYMPTOMS
Calves (weaning)	2.2	16 weeks	death
Steers (2 yrs. old)	.22-.44	16 weeks	liver damage
Cows (heifers)	2.4	7 mos.	liver damage
Pigs (4-6 wks. old)	.49-.69	3-6 mos.	liver damage
Chickens (1 wk. old)	.84	10 weeks	liver damage
Ducklings	.30	6 weeks	death

Even lower levels of aflatoxin become toxic when fed over long periods of time. In male rats, one part per million produced 100% tumor incidence in 41 weeks, but almost 1/100th of this minute quantity--.015 part per million (15 parts per billion)--produced the same incidence, 100%, in 68 weeks. It took over a year, but the insidious effect occurred on the same scale even with this infinitesimally small amount of aflatoxin.

Ducks fed aflatoxin at 30 ppb (parts per billion) developed liver tumors after 14 months in 8 out of 11 animals. In the case of trout, aflatoxin levels as low as 0.5-2 ppb over 10-24 months caused a significant incidence of liver tumors.

The extreme sensitivity of trout to aflatoxins provides insight into an unsolved mystery of a few years ago.[16] Primary liver cancer was discovered in up to 90% of American rainbow trout over three years of age. Detective work traced the probable cause to the use of a dry commercial ration which replaced the previous diet of wet viscera of animals, fish and horse meat. The dry feed, composed of substrates known to harbor fungus growth, was a likely possibility.

A similar incident occurred in which widespread cancer was produced in chickens due to a new commercial dry feed. Dry feeds are susceptible to fungal growth under poor storage conditions;[17] humidity of 75% with temperatures from 50^{o} to 110^{o} F. provides ideal growing conditions. Such conditions prevail commonly worldwide; unless storage conditions are available in which either the humidity or temperature are reduced below the growth minimums, most grains--and especially groundnuts (peanuts)--can be carcinogenic to humans.

Primates are affected by aflatoxins similarly to lower animals.[18] Reye's Syndrome (encephalopathy and fatty degeneration of the viscera) resembles aflatoxin poisoning in animals. In Thailand, many children died from this disease, revealing fatty degeneration of the liver and other organs as well as cerebral edema upon autopsy.

In a typical case of Reye's Syndrome involving a three-year old Thai boy who died of the disease, symptoms appeared only 12

hours earlier consisting of severe vomiting, convulsions and coma. Among the typical autopsy findings were severe fatty liver. Investigators who visited his home, a one-room grass and bamboo hut, found that he had eaten only one food for the two days before he became ill, a glutenous rice, which had been freshly cooked when he had first eaten it, then resteamed each morning. Aflatoxin was isolated from this rice when cultured by the investigators, and this derivative was then fed to 24 healthy female monkeys, 40 months old. All monkeys that had been fed from 13.5 to 40.5 mg. per kilogram of body weight died within a week. Their symptoms of illness and autopsy findings were identical with those of the young boy, following a pattern of similarity between Reye's Syndrome in humans and aflatoxin poisoning in animals.

Foods containing aflatoxin are found throughout Thailand, with geographical location paralleling the incidence of Reye's Syndrome. Although the disease is acute, based on animal experience lesser intakes of the toxin are known to produce hepatocellular carcinoma over longer periods of time.

Effects of low levels of aflatoxin were established in a study on Indian children,[19] where childhood cirrhosis of the liver is common. Vague gastrointestinal symptoms, the first symptoms, are followed by jaundice and hepatic coma. Peanut oil and rice taken from the homes of some of the children with these symptoms revealed aflatoxin contamination, suggesting a possible association.

Evidence confirming the cause-and-effect significance of the cirrhosis and the aflatoxin contamination was forthcoming from an Indian hospital handling children with kwashiorkor. From 1961 to 1969, 3,500 children had been treated, and experience had taught that cirrhosis is not a symptom of kwashiorkor. Symptoms of cirrhosis were first noted with a group of 20 children 1.5 to 5 years old who were under treatment. Part of the dietary regime consisted of a supplement of 1-2 oz. per day of a low-fat commercial peanut protein flour. When the children developed symptoms, the flour was analyzed and found to have 300 ug per kg. (0.3 ppm) aflatoxin. The 20 children were immediately taken off the peanut supplement, which had been consumed for periods varying

from 5 to 30 days. Detailed dietary histories, taken to determine whether aflatoxin-bearing foods might have been ingested prior to their hospital stay, revealed none, as these children from the lowest economic class lacked access to rice, peanut products, etc. Nor had the liver biopsy routinely taken by the hospital of all patients on first examination shown signs of cirrhosis, although the livers upon palpitation had displayed the soft hepatomegaly indicative of kwashiorkor.

Yet two months after ingestion of the infected food, 12 children had gross hepatomegaly and in others the typical leafy border was starting to be noticed. One of the 20 children was normal, but happened to be in the hospital and ate the infected food over a 30-day period; yet two years afterwards--the latest date of observation--this girl still retained the hepatomegaly. Three children of this group died of hepatic coma within 18 months. Of six children available for follow-up after two years, all showed hepatomegaly (3-5 cm.).

Although this study may be criticized for lack of controls, the fact is that 3,500 children treated in eight years prior to this incident showed no cirrhosis either clinically or upon biopsy, and the treatment course usually resulted in the fatty liver becoming normal within six weeks. By comparison, the cirrhosis of the 20 children evolved gradually from the fatty liver condition to fatty cysts to fibrosis and cirrhosis within a year.

Childhood cirrhosis in Indian children follows these identical histological changes. There was a direct correlation in liver damage in the group of 20 children with the period of ingestion of aflatoxin (5 to 30 days). It is of interest that a study of 250 cirrhotic children showed aflatoxin in the urine of 7% of them, and normals examined had aflatoxin in 10% of their urines. The presence of aflatoxins in a small percentage of the children indicates the cyclic consumption of toxic foods. Since the clinical symptoms do not appear for several weeks after ingesting the aflatoxin, no signs of aflatoxin need be found in the urine during the symptom period--the damage having been done some weeks

earlier and the aflatoxins perhaps consumed for only a few days or weeks.

This study goes far in establishing cause and effect of ingestion of small quantities of aflatoxin, 0.3 ppm causing cirrhosis in 5-30 days with intakes of only 1-2 oz. per day. This and larger intakes of toxic foods are common in many countries of the world where groundnuts are sold for human consumption.

In Africa, hepatoma is a common problem. Studies in Kenya[20] have implicated aflatoxins in the death of poultry, and the toxin was traced to groundnuts grown in Uganda. Groundnuts are a staple in the diet of humans in this part of the world; because of the animal deaths, concern was raised about the possibility of aflatoxins in the human diet. Test purchases in Uganda were made throughout an entire year, so that seasonal variations due to the rainy season and different times of storage might be evaluated. In all, 152 samples purchased at random from local stores and markets selling to the populace, were obtained for aflatoxin analysis.

Samples purchased during the rainy season proved to be the most highly contaminated, but NO sample was free of the aflatoxin fungus, Aspergillus flavus. The distribution of aflatoxin throughout the year was quite constant up to a concentration of .01 ppm. In the range of .01 to 1.0 ppm, however, twice the concentration of aflatoxins were found in the groundnuts during the rainy season than during the drier periods. Higher levels, 1-10 ppm and over were found only during or shortly after the rainy season.

Seventeen percent of all samples contained more than 1 ppm aflatoxin, and 6% contained over 5 ppm; in two samples over 10 ppm were found. It was thought that the samples could be graded as to their appearance in correlation with their degree of contamination with aflatoxin, and this worked out reasonably well, but there were exceptions. One sample of nuts, for example, which appeared satisfactory, contained 5 ppm of toxin.

Groundnut consumption is high in Africa. In a boys' school in Buganda, the average consumption per boy is 570 grams per week (1.26 lb.). In the Indian study[21] it was found that only 0.3 ppm

in 1/2 to 3 lb. of groundnuts was enough to cause a 100% incidence of cirrhosis and 15% mortality. With the findings of the Uganda study, widescale hepatoma is to be anticipated in areas of Africa. Recent studies grimly bear this out.(22)

Incidence of Primary Liver Carcinoma of Males
(rate/100,000)

Age Group	U.S. White	U.S. Nonwhite	Johannesburg	Mozambique
0-15	.2	.4	.6	15.0
15-25	.2	0	2.0	114.0
25-35	.3	1.2	10.0	156.0
35-45	.8	3.1	22.0	227.0
45-55	4.4	13.0	37.0	101.0
55-65	21.1	16.0	45.0	111.0
65-75	23.5	16.2	127.0	53.0
75+	38.3	32.4	59.0	-

These statistics become alive as one notes the constant reports of hepatoma emanating from Africa, of which the following, reported in 1970, is an example.(23) A 15-year old boy with a four-day history of abdominal pain was admitted to a hospital. The liver was palpable two fingers below the costal margin and was tender. He died two days after admission. On autopsy, the liver lesion showed great similarity to that produced experimentally in monkeys with aflatoxin. Samples of the family's cassava food stock were analyzed and found to have a high concentration of aflatoxin.

Other plant toxins

Other mycotoxins have been implicated in leukemia. Many Russians were found to have died in 1944 due to leukemia after having eaten bread made from grain infested with Fusarium. In an extensive study in Poland(24) covering 44 selected areas, an effort was made to determine whether there was an association between certain blood diseases and myocotoxins. These findings were made:

1. In houses of patients with leukemia, fungi were found including Aspergillus flavus, Fusarium, and others of the class of Imperfecti. These fungi all produce toxins when cultured.

2. In houses of healthy controls, these fungi were not present, or if they were, constituted a minor proportion of the fungi present, unlike those of the leukemia patients.
3. Leukemia patients' homes were damper and moldier than those of controls.

This study becomes pertinent in relation to a U.S. report, "Multiple Cases of Leukemia Associated with One House".(25)

Mycotoxins are responsible for several diseases in animals: moldy corn toxicosis in swine, facial eczema in sheep and cattle, and others in horses, poultry, etc.

Many plant toxins exist, but are beyond the scope of this writing. To mention one, that associated with the cycads--widely grown in the tropics and eaten by many natives and some Japanese--this toxin has been proven to form hepatomas experimentally in animals in low quantities, equivalent to that consumed in human diets. It is suspected of causing amyotrophic lateral sclerosis in humans.(26)

Nitroso compounds

The active carcinogens of the cycad are virtually identical to the nitroso compounds that have the property of inducing cancer after a single dose.(27)

These nitroso compounds have induced tumors in practically all organs of the rat and have been responsible for tumors in a wide variety of animals; it is suspected that they are equally toxic in humans.

Formation of a carcinogenic nitrosamine was demonstrated during a severe epidemic of liver disease in ruminants in 1961 and 1962. Feeding of meal made from sodium nitrite-preserved herring was directly correlated with the incidence of the disease. Samples of the incriminated herring meal were compared to meal without toxic properties. The former were found to have 30 to 100 ppm of nitrosamines, whereas there were none in the nontoxic meal.

Levels as low as 2 ppm of nitrosamines are sufficient to cause tumors in rats. These substances are formed from nitrites and

secondary amines and can be formed in vitro when mixed together in human gastric juice. Nitrites are commonly used as preservatives and food additives with such foods as cured and pickled meat products, cheeses, vegetables, cereals, canned products, etc. At an International Cancer Research meeting in Tokyo in 1972, Dr. J. Sander[28] stated: "We all ingest enough nitrite in food and food additives to produce cancer." It was noted at the meeting that nitrites as food additives have been banned in Japan; however, they are widely used in the U.S.

While the production of nitrosamines requires both nitrites and secondary amines, these conditions are quite commonly fulfilled. Powdered milk has a five times greater concentration of secondary amines than fresh milk, on a dry weight comparison. Sausages, made of various meats, are a potent source of secondary amines which form when these protein foods are cooked.[29] The possible relationship of these substances to cancer was commented upon by Dr. S. Epstein of Harvard Medical School who observed: "Reduction of human exposure to nitrites and certain secondary amines, particularly in foods, may result in a decrease in the incidence of human cancer."

Ammonia toxicity

Excessive quantities of meat in the diet can increase intestinal cancer by other mechanisms. Dr. W.J. Visek at a symposium in 1972 said[30] that Americans may be increasing their incidence of intestinal cancer by eating large amounts of meat. The mechanism for damage derives from the toxicity of the ammonia waste product formed as the meat is broken down in the body, unlike the process that occurs when nitrasamines are formed due to the joint presence of nitrites and secondary amines originating from cooked meat products.

Ammonia produced during protein catabolism is almost immediately detoxified primarily into urea. Urea enters the gastrointestinal tract as part of the body water, where it is hydrolyzed to ammonia and carbon dioxide by the intestinal bacteria which reside in the large intestine, due to the action of the

urease, a product of these bacteria. In animals which lack these bacteria, ammonia is not found in the bowel.

The larger the intake of protein, the greater the volume of ammonia produced. On a high protein diet, some cells may be exposed to harmful levels of ammonia during protein catabolism. Constant exposure to high levels of ammonia over many years could cause serious damage. Blood draining the colon normally has a ten-time higher concentration of ammonia than is present in an internal vessel such as the inferior vena cava. This concentration is higher than occurs in experimental animals subjected to ammonia intoxification, which has been observed to result in shortened cell life span, altered DNA synthesis, and general metabolic changes which are of disruptive nature.

Studies by Dr. Visek and others in the field[31] have shown ammonia toxicity in both man and animals. These findings are summarized:

1. Ammonia increases the susceptibility of cells to viral infection.

   In 72 hours of exposure to 20 ppm of ammonia, chickens exposed to Newcastle disease virus had twice the incidence of disease compared to controls. (Yet maximum safe ammonia concentration for man is considered to be 100 ppm.)

2. Ammonia can destroy white and red blood cells.

   This was demonstrated by injecting a minute quantity of urease into rabbits. Blood urea was hydrolyzed and the resultant rise in blood ammonia produced a 10-30% destruction of blood cells in an 8-12-hour period. Animals fed urea have shown the same decline of formed elements in the blood. Ammonia elevation of this degree can be produced by a high protein diet.

3. Suppression of ammonia increases survival to radiation.

   Only 21% of mice survived 800 rads of 30 days, compared to over 70% surviving where their hydrolysis of ammonia had been suppressed. In this situation, two

cell-destroying forces (radiation and ammonia toxicity) may reinforce each other.

4. Ammonia slows the growth of normal cells much more than it does malignant cells.
5. Ammonia concentration in the large bowel of man is usually higher than the levels that produce the damage cited in previous examples. These concentrations (as high as 300 µg/g of feces) can cause severe changes in the intestinal cells.
6. The highest incidence of malignancy of the bowel is found in the area of highest ammonia concentration. This type of cancer was responsible for 14.4% of all cancer deaths in the U.S. in 1964, leading all other causes of death due to cancer except pulmonary.

One way to reduce the ammonia content of the colon is to eat mainly complex carbohydrates. In animal experiments, complex carbohydrates (starch) caused faster growth and less urease activity than simple carbohydrates (sucrose). Sucrose intake was also accompanied by changes in colonic flora favoring higher production of urease.

In addition to the production of high levels of ammonia due to high protein diets, amino acid imbalance creates higher ammonia production.

Since ammonia fulfills so many of the criteria for a carcinogen, its association with cancer of the large intestine is of interest. A study of 7,078 cases of cancer of the large intestine was made in 1960 in which relationships to food consumed were noted. Patients with cancer of the large bowel were found to have consistently eaten more meat than did the controls.

Reduction of tumor incidence with low level of dietary protein

In several studies, low intake levels of dietary protein have been correlated with decreased incidence of tumors.

An Australian pediatrician[32] noted that children with low-protein diets and those who were suffering from malnutrition were remarkably free from tumors. To test this possible relationship,

he raised rats on various levels of protein, finding that inhibition of the growth of tumors did not occur on a diet exceeding 12% protein. Tumor inhibition started as the protein level dropped below 12% and was quite effective in the 6-10% range. The investigator concluded, "This is the basic principle upon which we postulate that moderate protein deficiency will depress the incidence of spontaneous tumors."

The same results were produced with animal experimentation in India.[33] Groups of rats were put on a high (20%) protein diet or a low (5%) protein diet and given daily doses of aflatoxin, a hepatocarcinogen. After a year on the diet the 20% protein group developed hepatomas or tumors in other organs in 50% of the rats (15), and the remaining 50% (15) had precancerous lesions in the liver. By contrast, the 5% protein group had no liver involvement; and of the 12 rats on this diet, only one developed a tumor (kidney). The low-protein level diet inhibited the aflatoxin carcinogenesis.

Another study with mice compared a 27% versus an 8% protein diet[34] in relation to cell-mediated immunity. When live pseudorabies virus was injected into each group, the mortality rate of the mice on the high-protein diet was twice that of the low-protein diet group. In addition, macrophages were found to be 50% more active in ingesting bacteria (Listeria) in the low-protein group, indicating increased anti-bacteria activity, also.

In skin grafting, graft rejection is a measure of immunity. When the mice on the low-protein diet were compared to those on the high-protein diet in the above study, it was found that the former rejected their grafts in 14.9 days compared with 21 days for the latter group.

These results showing varied manifestations of enhanced immune defense reactions due to a low-protein diet encouraged the investigators to predict that low-protein diets would be used in treatment of viral, protozoal and fungal infections, since immune defense against these agents is a function of cell-mediated immunity.

Visek's work[35] suggests that the improved ability of the animals to resist viral attack and other biological insults is due to reduced ammonia toxicity with a low-protein diet. Thus, in the radiation experiment, the suppression of one cell-destroying process (excess ammonia) increased the ability of the experimental animals to withstand the radiation. This increased resistance with regard to tumor formation and foreign toxins was also observed due to reduced ammonia content.

In other sections of this work we have reported on native populations who subsist on low-protein diets (3 to 8%) and do very well.

Dietary fat and cholesterol as etiological factors in cancer.

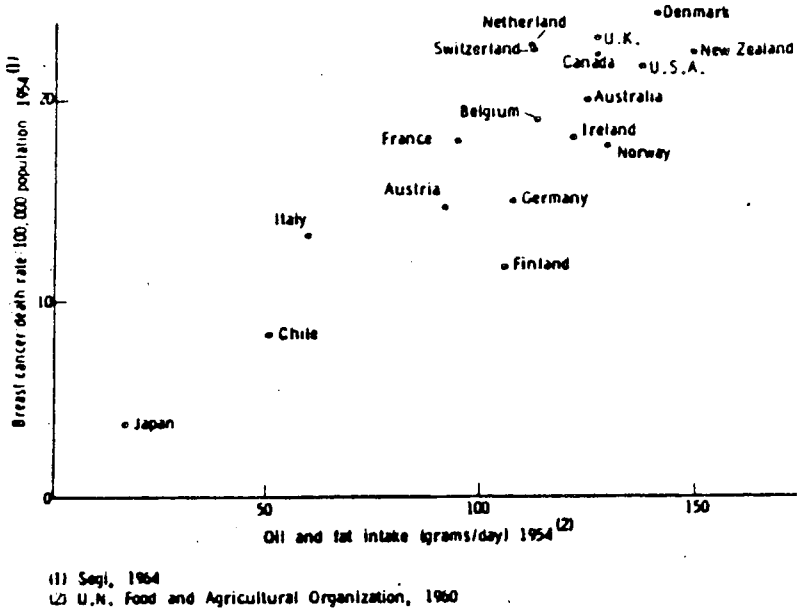
Breast cancer in relation to fat intake

Attempts to find some common etiology in malignant diseases have led to worldwide examinations of populations, where considerable variations in the occurrence of diverse malignancies have been observed. Environmental factors taken into consideration include standard of living, temperature, marriage customs as a possible factor in breast cancer, specific dietary intakes of protein, fat, etc.

One such view[36] which took into account many possible variables throughout the world, sought to establish factors consistently associated with breast cancer. Among the dozens of variables explored were marital status, number of children, length of nursing, age of first child, associations with other cancers or other degenerative diseases. To quote the reviewer: "One can plot the incidence of breast cancer against any number of environmental factors. The one correlation that shows up well and may be of etiological significance is that between breast cancer and the fat intake of women in various countries of the world. The postulation that a woman's fat intake relates to breast cancer is supported by a variety of animal experiments."

The following chart establishes this correlation.

CORRELATION BETWEEN OIL AND FAT INTAKE AND BREAST CANCER



(1) Segi, 1964
(2) U.N. Food and Agricultural Organization, 1960

This correlation was confirmed in a study(37) covering 24 countries. Over 90% of the population of the British Isles, both Eastern and Western Europe, Japan, Central and South America, and New Zealand were represented in this survey. Correlations with a significance of P <.001 were neoplasms of the breast and coronary heart disease.

A comparison of statistics reveals that breast malignancy death rates are highest in the two countries with the greatest fat consumption and lowest in the country with the lowest fat consumption.

COUNTRY	FAT CONSUMPTION Kg. per head per year	DEATH RATE FROM MALIGNANT NEOPLASMS OF THE BREAST (females) per 100,000 living
Netherlands	25.1	23.4
Denmark	25.0	24.0
Japan	2.6	3.8

Comparison of effect of saturated and unsaturated fats

Several of the early animal experiments establishing the relationship of dietary fat to malignancy were performed in the laboratory of Albert Tannenbaum[38] as early as 1942. The experiment reported below is more recent.

Two groups of 60 each virgin tumor-free mice were fed identical diets, except for the fat content. The experimental basal diet without the fat was given until the mice were 12 weeks old, when they were started on the diets containing fat, 2% for one group and 16% for the other. (These approximate primitive and "civilized" diets in human populations: 2% fat (by weight) = 4.5% of total calories and 16% fat = 35% of total calories.)

The progress of the two groups of mice is indicated on the table on the next page.

Influence of Dietary Fat on Formation of Spontaneous Mammary Cancer in DBA Virgin Female Mice

Age (Weeks)	Mean Weight (gms.) 2% fat	6% fat	Animals Alive and Tumor-Free 2% fat	16% fat	Cumulative Tumor Count 2% fat	16% fat
12	21	21	60	60	0	0
40	30	31	60	58	0	1
50	30	30	56	54	1	3
60	31	31	49	38	8	17
70	31	32	40	26	16	28
80	33	30	32	13	24	39
90	31	-	10	6	31	44
100	-	-	10	1	38	48
104	-	-	4	1	40	48

Unfortunately no controls without added fat to the diet were used, but other tests demonstrated a nonlinear effect of fat quantity vs. the tumor rate. For example, increasing the fat content from 2% to 7% enhanced tumor formation as much as an increase of 7% to 25%. In fact, another investigator found the same rate of formation of skin tumors in diets when fat content was raised from 27% to 61%. The maximum effect in mice seemed to occur at 16%. Fat added to the diet accelerated tumor formation whether the protein intake was minimal (7 calories per day) or near ad libitum (12 calories per day).

The type of dietary fat used did not seem to be important: tumor formation increased using lard, butter, wheat germ oil, coconut oil or hydrogenated cottonseed oil, but ironically, the popular unsaturated fat recommended by the American Heart Association for increased intake--corn oil--developed tumors much faster than olive oil or such saturated fats as hydrogenated coconut oil. Five percent corn oil was as effective in accelerating tumor growth as 20% of the other fats, such as lard, hydrogenated oils, etc.

Other studies have confirmed the phenomenon whereby saturated fats are observed to depress and unsaturated fats to accelerate tumor formation. A series of studies reported from 1967 to 1971 bearing on this finding are summarized.

1. The first test[39] evaluated the effect of the intake of different fats upon the composition of mammary tissue and on mammary cancer in rats. Female rats just weaned (22 days old) were separated into three groups, each of which was fed a separate diet. The diets, L (low fat, 0.5% corn oil), Coco (20% coconut oil), and Corn (20% corn oil) all were formulated with the same amount of minerals and vitamins and provided the same number of calories per day (reflected by a comparable weight gain on each dietary regime).

At 50 days, all the rats were given by stomach tube a single dose of 10 mg. of a carcinogen, DMBA (7, 12-Dimethybenz (a) anthracene). Two days earlier they had all been switched to a standard lab diet so they would absorb the carcinogen from the gut equally well, then were returned to their separate diets the second day after ingestion of the carcinogen.

After four months of observation, the animals were sacrificed. At autopsy, the tumors were resected and microscopically confirmed as adenocarcinoma before they were included in the table below.

EFFECT OF DIETARY FAT UPON MAMMARY CARCINOGENESIS AFTER DMBA INGESTION

Diet	Number of Rats	Tumor Incidence	Number of Tumors (all rats Incl.)	Latent Period in Days*
0.5% Corn oil	21	57.1%	1.5 ± .40	76.2
20% Coconut oil	21	66.7	1.6 ± .32	69.5
20% Corn oil	22	95.5	3.0 ± .52	56.5

*Latent period = time in days until appearance of first palpable tumors after feeding of DMBA

The significance of this test is the acceleration of the incidence of tumors with an unsaturated fat (corn oil) diet, while the same quantity of a saturated fat (coconut oil) diet showed almost no difference in its effect than the low-fat diet (0.5% corn

oil). This result follows very closely those of previous investigations cited in this study.

Comparison of mammary tissue reflected the fat intake as noted by the table below.

EFFECT OF DIETS ON FATTY ACID COMPOSITION OF MAMMARY TISSUE

Percent Composition of Fat

Fatty acid ester	Rat Mammary Tissue 0.5% corn oil diet	20% coconut oil diet	20% corn oil diet	Commercial Fat Coconut oil	Corn oil
Palmetic	28.5	29.5	19.9	14.4	9.3
Oleic	52.0	35.1	33.0	6.5	26.9
Linoleic	4.6	4.7	39.5	3.1	61.7

Linoleic acid elevation of the tissue is a major physiological change. This is the same type of change reported by Seymour Dayton[40] in his 8-year trial at the Veteran Center in Los Angeles.

In Dayton's experiment 800 men ate an average U.S. diet of 40% of total calories in fat. Half of them ate typical fats (iodine # 53), but the others had especially prepared meals high in unsaturated fats (average iodine # 102). Those who adhered strictly to the unsaturated diet had adipose tissue levels of 33.7% of linoleic acid, not much different from the rats of the study reported. Although the Dayton experiment was designed to test diet vs. atherosclerosis, it unexpectedly found more cancer deaths in the polyunsaturated group than the group on typical fats. The 20% corn oil diet for the rats (40% of total calories in fat) approximated the unsaturated fat diet in Dayton's study.

2. The second study in this group evaluated only corn oil as a dietary fat,[41] in two levels of consumption, 0.5% and 20%. Carcinogen DMBA was varied from 1 mg., 2.5 mg., and 5.0 mg. instead of the 10 mg. dose given in the first test. In addition, at the 5.0 mg. DMBA level, two new conditions were created. One diet, L-H, started with low fat (0.5%) until the DMBA was taken and then changed to high fat (20%); whereas the other diet, H-L, reversed

this procedure, starting with high fat, then switching to the low-fat diet after the DMBA was taken.

Before this test was designed, a study was run to determine whether different levels of DMBA were deposited in mammary tissues because of the difference in fat levels on the various diets. It was found that on the 20%-fat diet, the concentration of DMBA was not substantially different from that resulting from the low-fat (0.5%) diet.

The question was raised as to whether the high-fat diet "cooperated" with the carcinogen by preparing the tissue before the intake of DMBA, or whether its effect was due to its action after the DMBA was ingested. It was hoped the L-H and H-C experiment would provide the answer.

The procedure on the diet was the same as on the first test. Each group was fed its separate diet for 50 days, then all groups received a standard ration for two days before ingesting DMBA and for one day afterward. After four months of observation, all the animals were sacrificed. The results are summarized.

MAMMARY TUMOR INCIDENCE IN RATS ON HIGH- AND LOW-CORN OIL DIETS FOLLOWING INGESTION OF DMBA

Corn Oil in Diet	Number of Rats	Total tumor Incidence	Palpable tumors Incidence	Palpable tumors No. per rat	Latent Period (days)	DMBA dosage
0.5%	28	14.3	3.6	.03	111	1 mg
20.0%	30	26.6	6.6	.10	97	1 mg
0.5%	30	43.3	33.3	.4	84	2.5 mg
20.0%	30	76.6	56.6	.9	79	2.5 mg
Start L, end L (0.5%)	30	73.3	70.0	1.5	73	5 mg
Start H, end H (20.0%)	30	96.6	93.3	3.0	63	5 mg
Start H (20.0%) end L (0.5%)	30	73.3	66.6	1.6	68	5 mg
Start L (0.5%) end H (20%)	30	93.3	93.3	2.3	60	5 mg

These experiments confirm the previous ones in that the higher corn oil diet produced more tumors for each drug dosage than did the low-fat diet. The results were not unexpected.

The new information came from the H-L and L-H diets, by which it was found that even if dietary fat intake is at 20% corn oil before DMBA is ingested, if after ingestion fat level is reduced to 0.5%, the previous high-fat diet does not appear to affect the results: total tumor incidence is identical on L-L and H-L diets. Increased intake of fat <u>after</u> ingesting of DMBA provided the environment for accelerated growth of tumors.

3. The third study of this series sheds more light on the dangers of high polyunsaturated fat diets. This experiment[42] was designed in two parts in order to investigate degree of fat saturation vs. tumor formation. In part one, a uniform dose of DMBA (5 mg.) was given with four different corn oil content diets, 0.5%, 5%, 10% and 20%; in part two, the same dosage of DMBA (5 mg.) was given with ten different fats of varying saturations all taken at the 20% level.

Results were similar to those of previous studies. The 10% fat intake correlated with almost twice as many tumors as the 0.5%. The 5% level was only slightly worse than the 0.5% which seemed to indicate that 0.5% to < 5% is the safest intake level. Twenty percent was no worse than 10% which suggested that once a 10% fat level (20% of total calories in fat) was reached, tumor incidence is no worse. This accords with the results of Tannenbaum[43] who found that beyond 12-16%, additional fat seemed to have little effect on tumor growth.

Results of the second test indicated that there tended to be more tumors as the fat intake became more unsaturated. The dietary routine followed the other tests for this part of the experiment. Rats were divided into ten groups and all were fed 20%-fat diets for 50 days, then given a single dose of 5 mg. DMBA. Diets were continued for four months, after which the animals were sacrificed and checked for tumors. Fats used in the test ranged from coconut oil, butter, and tallow for the saturated types to corn oil and sunflower seed oil for the unsaturated types.

These three studies spaced over four years all agree on certain findings:

1. Addition of any dietary fat above minimum requirements increases the incidence of mammary tumors.
2. The more polyunsaturated the fat intake, the higher the incidence of tumors and the shorter the life span.
3. These effects are independent of total caloric intake which may not necessarily be true for humans.

The role of cholesterol--significant animal studies and some human experience

Cholesterol, as well as fat, has been implicated as a cause of mammary cancer. In one study, mice ingesting a Rockland rat diet and a supplement of boiled hen's eggs developed a high incidence of malignancies, whereas the controls, without the eggs, were unaffected. This led to a later study(44) to determine whether it was the white or yolk of the egg that was carcinogenic.

Two groups of mice were used. One was a group of virgin males and females, each sex separately caged. In the other group, the mice were permitted to breed. Each generation was bred only twice and then segregated into separate cages. In this group, the mice were made up of mice of the 3rd and 4th generations.

Each of the two groups was then divided into four dietary groups:

Group 1. Rockland diet only

Group 2. Rockland rat diet + hard boiled egg white

Group 3. Rockland rat diet + raw egg yolk

Group 4. Rockland rat diet + cholesterol and lard

In addition to the Rockland rat diet, daily portions were as follows for each 10-12 mice: Group 2, one egg white; Group 3. one egg yolk; Group 4, 75 mg. of cholesterol + 1 gm. lard.

The results of the study are tabulated on the next page.

RESULTS FOR VIRGIN MICE

Diet Groups	Number of Mice	Life Span (days)	Total Malignancies	Mammary Cancer	% of females
(1) CD (control)	20	675	1	0	
(2) CD + egg white	20	439	18	0	
(3) CD + egg yolk	21	497	19	0	
(4) CD + cholesterol and lard	19	697	9	0	

RESULTS FOR BREEDING MICE

Diet Groups	Number of Mice	Life Span (days)	Total Malignancies	Mammary Cancer	% of females
(1) CD (control)	97	677	16	0	0
(2) CD + egg white	152	422	130	0	0
(3) CD + egg yolk	139	355	121	23	33
(4) CD + cholesterol and lard	140	574	67	37	48

Both the virgin and bred mice had similar life spans on the control diet. Those on egg white developed no mammary cancer, but a high incidence of lymphosarcoma and lung adenocarcinoma, the latter so severe that a whole lung was frequently destroyed.

Mammary cancer followed a pattern more closely related to cholesterol intake. No first generation mice on the yolk or cholesterol diet, whether virgin or breeding, developed mammary tumors. These tumors began in the second generation and continued through the third and fourth.

By the third generation, the mice were so susceptible to mammary tumors that only the briefest exposure to cholesterol was necessary to induce them. The offspring of the third and fourth generations who were placed on the egg yolk diet (Group 3) from the time they were weaned were taken off the diet at the age of 4-6 weeks and were kept on the control diet (no cholesterol) until they died. Of this group of nine, six developed mammary cancer.

On the Group 4 diet (cholesterol + lard), 35 offspring of the third and fourth generations were removed from their diet at the

age of six weeks and placed on the control diet. Of these, 22 developed malignancies, 14 of which were mammary cancer.

Over 50% of the females exposed to both Group 3 and 4 diets developed mammary cancer, even though their exposure to these diets was for only 2-4 weeks out of a life span of 80 weeks.

An explanation for the mammary cancer sensitivity increasing in each succeeding generation comes from human experience. As the mother's blood cholesterol and lipids rise due to dietary intake of these substances, the higher levels are transmitted to the embryo's blood in pregnancy. Thus, in humans, although average cholesterol levels of newborn infants range from 50-80 mg.%, some infants have levels as high as 200 mg.% if their mothers' levels are sufficiently high.

In the breeding mice, in each succeeding generation the cholesterol levels would rise higher. In the first generation, the levels reached were not high enough under this diet to induce mammary cancer. In the second generation, they rose high enough for tumor induction after a lifetime of exposure. The third generation had such a high blood level from birth on that a few weeks of the egg yolk supplement was enough to stimulate the tumors. The young mice were doomed to die when they were at the human equivalent of 4-6 years of age, having eaten their cholesterol load for a period of time (in human terms to the 3rd and 4th year of life), and then stopped eating the cholesterol input for the rest of their days.

If this experience with mice has any application to humans, lowering cholesterol intake for life becomes mandatory.

Previous studies have indicated that cholesterol with lipids (egg yolk, cholesterol plus lard) induces tumors. In an effort to pinpoint the role of cholesterol alone, new studies[45] were devised. In these, mice were placed on two types of diets.

Diet 1 - Complete diet of Rockland mouse pellets and some fish meal, dried whole milk, yeast, etc. to contribute cholesterol to the diet.

Diet 2 - Cholesterol-free and fat-free diet.

Both diets contained all essential minerals and vitamins. Malignancies were induced by injecting cells of a fast-growing solid tumor Sarcoma 180 into the mice. Each mouse received a subcutaneous implantation of $1x10^6$ ascitic cells in the right flank. Up to the time of injection all mice were maintained on the complete diet. After the injection, the mice were separated into six groups of approximately 30 mice per group and placed on six different diets. After 10 days on each diet, the tumors were excised and weighed.

The diets were as follows: 1. the complete diet; 2. the complete diet + 2% cholesterol; 3. cholesterol-free and fat-free diet (CF-FF); 4. CF-FF + 1% cholesterol; 5. CF-FF + 2% cholesterol; 6. CF-FF + 3% cholesterol.

Results of these diets on the tumor growth are summarized.

EFFECT OF CHOLESTEROL ON THE GROWTH OF SOLID SARCOMA 180 IN CF_1 WHITE SWISS MICE COMPARED TO THE COMPLETE DIET (ROCKLAND)

Diet	Average Tumor Weight (gms.)	Tumor Inhibition	Tumor Stimulation
#1 Complete (Rockland)	1.61	0	0
#2 Complete + 2% cholesterol	2.03		26%
#3 CF-FF (cholesterol-free, fat-free)	.95	41%	
#4 CF-FF + 1% cholesterol	1.78		10%
#5 CF-FF + 2% cholesterol	2.15		33%
#6 CF-FF + 3% cholesterol	2.42		50%

On the complete diet which contained some cholesterol and fat, the addition of 2% cholesterol increased the tumor size 26%. On the CF-FF (cholesterol-free and fat-free) diet, tumors were inhibited by 41% from reaching the size attained with the complete diet.

This tumor-retarding effect was gradually cancelled by the addition of increasingly large amounts of cholesterol to the diet. Stimulation of tumor growth by cholesterol is vividly noted by the

increase in tumor weight as cholesterol intake rose. Final body weight on diets #4, #5 and #6 differed by only 3% compared to a tumor weight difference of 40%, indicating that addition of cholesterol only stimulated tumor growth, not body growth. The same trend was apparent in diets #1 and #2 where diet #2 produced no increase in body weight, but did produce a considerable (26%) increase in tumor weight.

As a result of these tests, the investigators reviewed other work relating to their study making these observations:

1. Malignant neoplasms contain a much higher percent of lipids than normal cells.
2. Lipids are used for energy; as much as 30% of energy requirements come from oxidation of fatty acids.
3. Tumors have a higher concentration of cholesterol and trap cholesterol from the host circulation to a greater extent than do normal cells.

These observations, in addition to their test results, provoked these questions by the investigators: Do hypercholesterolemic people have a higher cancer rate than normal people? Will an intake of cholesterol (as in the U.S. diet) stimulate the growth of human tumors? Is it possible to retard malignancies by feeding cholesterol-free diets to humans? (This treatment would stand alone in cancer therapeutics in not being harmful to the patient.)

These are probing questions and after two more years of experiments, the same investigators are closer to answers for these questions. Experiments were devised[46] with the same mice (CF_1 white Swiss) and the same two diets: Complete (Rockland) and CF-FF (cholesterol-free and fat-free); but this time, the mice would only be on these two diets. However, instead of a single tumor (Sarcoma 180), four different tumors were transplanted, in order to reveal whether cholesterol stimulation of tumors is restricted to Sarcoma 180 only, or generally stimulates malignant growth.

Implanting the tumors was done by subcutaneous injection and the period of tumor growth under the two diets varied from 14-21 days, after which time the tumors were excised and measured. With

the animals ingesting the complete diet serving as controls and using average size tumors as standards, it was found that all the animals on the CF-FF diet showed inhibition of all tumors. The results are summarized on the table below:

TUMOR INHIBITION ON CF-FF (CHOLESTEROL-FREE, FAT-FREE) DIET COMPARED TO COMPLETE (ROCKLAND) DIET

Experiments	Animals	Type of Malignancy	Avg. Tumor Inhibition	Significance of Tumor Inhibition
all	CF1 mice	Solid-Ehrlich	48%	99% Confidence Level
all	C57BJ/6S mice	Adenocarcinoma 755	54%	99% "
all	Sprague-Dawley rats	Solid Novikoff	40%	99% "
2,3,4,6,7	CF_1 mice	Sarcoma 180	46%	99% "

In every case, eliminating cholesterol and fat reduced the size of the tumor to half, and in all cases increased the life-span of these animals compared to those on the complete diet.

The diet was also tried on a strain of leukemia (L1210) using DBA/2S mice, and the CF-FF diet caused an inhibition as compared to the complete diet.

Due to the success of cholesterol-free diets in retarding tumor growth, it was thought that the same inhibiting effect might be achieved by the complete diet with hypocholesteremic drugs. Twelve drugs were tried, selected because of their success in lowering the cholesterol level in animals and man. The drugs inhibited tumor growth, but in most cases not as well as the CF-FF diet alone. The drugs were tried with the complete diet on all four tumors and, without exception, cholesterol-lowering by the drugs lowered tumor growth.

The investigators concluded: "These studies indicate that reduction of the availability of cholesterol, either by restriction in the diet, or by administration of hypocholesteremic drugs retards the growth and development of a number of transplantable animal tumors."

These findings assume a certain urgency in view of two separate studies that reveal the inability of malignant cells to produce endogenous cholesterol. Apparently this function is lost as part of the change from the normal to malignant state. Yet it is well-established that the concentration of cholesterol is higher in malignant cells and that cholesterol endogenously produced in the host is preferentially deposited in the tumor cells.

The investigators asked: "Will a cholesterol-free diet exert any appreciable restricting effect on the growth of cancer in humans, and will it prolong their lifespan?" There is an answer to this question: elimination of dietary cholesterol starves the tumor while doing no harm to the patient. The experience of a Canadian physician who reported a complete remission of cancer in four cases by lowering of their cholesterol levels[47] is germane.

The method he used involved cholestyramine, an iron exchange resin that cannot be absorbed but binds steroids in the gut, thereby reducing cholesterol. While diet alone will reduce cholesterol to much lower levels without the problems of resin therapy, the dramatic results achieved by lowering of cholesterol are nevertheless impressive.

Patient #1, aged 72 years, had cancer of the prostate proved by needle biopsy. After ten months on resin, cholesterol levels dropped from 302 mg. to 192 mg. and the prostate lost all of the enlarged, rock-like characteristics. Three years later, and still on treatment, no signs of neoplasm are evident.

Patient #2, aged 65 years, also had cancer of the prostate confirmed by needle biopsy, with the prostate hard and enlarged. He was started on resin and six months later the prostate appeared normal by digital examination. Three years later, by punch biopsy, the prostate was found to be almost completely benign with a few scattered neoplastic cells.

Patient #3, aged 73 years, with cancer of the prostate, after only one month of the resin intake had the prostate become almost normal. The cancer remained dormant for over a year until the patient died of nonrelated causes.

Patient #4, a 66-year old woman with advanced cancer of the ovary, had had previous unsuccessful radiotherapy. Six months after resin intake, her cholesterol dropped to 154 mg. and the large mass was no longer palpable.

That cholesterol crystals act as a "neoplastic" agent in humans has been documented previously in this work. Cholesterol lying free in the interstices of a vessel wall always produces a hyperplastic and usually a metaplastic cellular reaction. This reaction to cholesterol may explain the improvement noted in malagnancies when cholesterol is withdrawn from the tissues.

The Association of Malignancies, Nonmalignant Conditions, and Elevated Lipids

Elsewhere in this writing we deal with nonmalignant conditions, such as diabetes, hypothyroidism and hypercoagulable blood, which are associated with elevated cholesterol and lipid levels. An elevated cholesterol level is the precursor of many degenerative diseases.

Predictably, nonmalignant conditions are often found in association with malignancies. Vascular thrombosis and coagulation disorders are found associated with elevated cholesterol levels in the majority of cancer patients when systematic studies are made.(48) These blood patterns are mostly represented by the hypercoagulable state. In a group of 50, 25 normals had a coagulation time of 22 minutes, whereas the other 25, all cancer patients, had a coagulation time of 15 minutes ($P < .001$). A decrease of coagulation time of that magnitude has been produced by meals containing fat in a quantity comparable to the normal intake in many parts of the civilized world.(49) Meals containing such diverse fats as butter, corn oil, coconut oil, etc. all produced the effect as compared to a low-fat meal. In other tests, no difference in clotting time was shown whether the fats were saturated or unsaturated, as long as the total intake in calories was similar.(50)

Since hypothyroidism produces a high cholesterol and lipid level, it would appear to be a condition associated with cancer.

This association, in fact, has been found in a number of studies.[51] Repert,[52] in a study of 306 patients with breast cancer, found 12% of them with confirmed thyroid disease. This figure is at least ten times the expected incidence of thyroid disease in the general population. Loeser, in his study of breast cancer, found it far more frequently in hypothyroid patients or those hyperthyroid patients made hypothyroid by treatment, as compared to euthyroid women. Wynder found in his cancer patients much less history of hyperthyroidism than among his controls.

Diabetes or hyperglycemia are both conditions associated with elevated lipids (see Part III on Diabetes). Thus, it comes as no surprise to find an association of hyperglycemia with cancer in reports of almost 100 years ago.[53] In this series, Fruend in 1885 reported that out of 70 cancer patients, 62 tested as hyperglycemic. Reports made on the basis of more sophisticated testing methods used today show up to 80% of certain types of cancer with a diabetic glucose tolerance test. Out of a general cancer population at one hospital, more than 950 cases showed a general average of 36.7% testing diabetic in glucose tolerance tests. The criteria were set higher than for normal testing, otherwise the percent of diabetics would have been higher. In Repert's observation of 306 breast cancer cases,[54] he found 500% more diabetics than would be expected in the normal population. The high blood fat and cholesterol levels characteristic of the hyperglycemic condition, conducive to malignant growth as shown in the animal studies earlier cited, may also provide the environment for malignant growths in humans.

If it were possible to free oneself from the conventional belief that breast cancer has an endocrine etiology and to explore the concept that breast cancer is largely due to excess fat and cholesterol in the diet, it would be easier to understand a case history contributed by Pearson.[55] In a desperate attempt to control metastatic breast cancer, a woman was castrated, adrenalectomized and hypohysectomized. Administration of growth hormones was tried, and it exacerbated the cancer--a predictable effect if one assumes a lipid etiology. Growth hormone injection

is rapidly followed by a substantial rise of free fatty acid in the blood, which is sustained for long periods. If the glucose tolerance was normal before the growth hormone injection, after several hours it goes in the direction of a diabetic curve.(56) Had the medical personnel responsible for the care of this woman heeded the implications of some of the animal experiments described in this section, the patient might never have undergone endocrine ablation, so savage in concept and so utterly futile.

Estrogens in relation to cancer.

Estrogens are additive to the hypercoagulant state produced by elevated lipids and are responsible for hyperplasia of target tissues. In a British study completed in 1968, data(57) indicated a 700-1000% increase in thromboembolic deaths of those on oral contraceptives compared to other women. The role estrogens play in hyperplasia is becoming clarified as more evidence presents itself.

That thromboses are associated with malignant disease is well-established. In fact, it appears many times before any tumor can be found.(58)

In one study, 103 patients on oral contraceptives were examined as part of a routine program.(59) No carcinoma was found, but 84% had abnormal findings based on Pap smears and cervical biopsy studies. The abnormal changes were directly related to the length of time they had been taking oral contraceptives.

TISSUE CHANGES VS. LENGTH OF TIME ON ORAL CONTRACEPTIVES

Length of time on drug	< 6 mos.	6-12 mos.	13-24 mos.	> 24 mos.
Number of patients	27	28	28	13
% epidermization	58	73	78	85
% atypical metaplasia	17	32	30	46
% cysts	23	46	54	80

Incidence of cysts was directly related to breast cancer. Women with fibrocystic disease were found to have 260% more breast cancer than those without.(60)

In a group of women enrolled in Planned Parenthood Clinics, 27,000 on oral contraceptives,(61) and a control group of 7,000

using the diaphragm, it was found that the rate of carcinoma of the cervix was twice as high in the drug users. Animal studies confirm that high doses of estrogens lead to the production of cervical carcinoma.

The long-term effect of estrogens in stimulating hyperplasia is illustrated by vaginal cancer seen in daughters of mothers who had taken estrogens during their pregnancy to prevent miscarriage. Of the first eight such young women diagnosed, seven of their mothers had taken estrogen during the first trimester of their pregnancy. In the control group of 32 noncancerous patients, none of the mothers had taken estrogens at this period.(62)

There are no safe levels of estrogen.(63) A 3-1/2 year old girl played with estrogen-containing face cream and in six months could have been exposed potentially to 2,500 units, which is less than 5% of the accepted safe lower limit of exposure. She developed bilateral breast enlargement, deeply pigmented areolae, and her vaginal cytology was similar to a normal menstruating adult.

Estrogens act synergistically in the etiology of breast cancer with elevated lipid and cholesterol levels. Breast tumors can concentrate as much as 16 times the plasma level of estradiol,(64) and so stimulate the growth of malignant tissue.

Elevated lipid levels have been implicated in the etiology of breast cancer.(65) An additional mechanism(66) by which lipids may further contribute to the development of breast cancer is suggested in this hypothesis. As fat intake is increased, biliary steroids also increase and a larger volume go through the gut, eventually leaving through the large intestine. Gut bacteria have demonstrated their ability to produce estrogens from bile and cholesterol derivatives <u>in vitro</u>. Thus, substantial quantities of estrogen would be absorbed into the body to further stimulate growth in mammary tissue.

One possible reason why malignant tumors have a substantial appetite for the host's cholesterol is this ability to convert the cholesterol to estrogens.(67) Lowering fat and cholesterol in the diet can serve to starve the tumor by depriving it of growth-

stimulating estrogen, thereby reducing its growth, as demonstrated in the cited studies.[68-71]

Blood coagulation as a factor in cancer.

Experimental factors which increase the frequency of metastases and are associated with an increase of the level of lipids and cholesterol in the blood include[72] growth hormone, pregnancy, ACTH, hyperlipemia, and administration of cortisone.

Since all these conditions are associated with shortened coagulation time it has been implicated in metastases. A limited amount of success in reducing the frequency of metastases has been achieved with lengthening coagulation time. The major approach has been via anticoagulant drugs, rather than through elimination of the cause of the shortened coagulation time, the excess blood lipids.[73]

It has been established in both animal and human studies that fat intake, comparable to that included in the average U.S. diet, will produce adhesiveness and aggregation of formed particles in the body, and adhesiveness of the endothelium of the vessels and tissues bathed by the blood. These conditions favor metastases, in that they provide substrates to which they can adhere.

Dietary factors in cancer of the colon.

The dietary regime of cultures on low-fat and low-cholesterol foods bypasses many of the carcinogenic factors to which we on Western diets are exposed. Such diets have these noncarcinogenic aspects:

Low protein - Since little animal protein is consumed, protein intake is under 10% and cholesterol consumption between 25-100 mg. day;

Low fat - Vegetable sources provide much of the diet, keeping total fat intake below 15% of total calories;

High carbohydrate, mainly complex - Simple carbohydrate intake is minimal, since refined foods are not used.

The maintenance of a low cholesterol and lipid blood level offers the best protection against malignancies as the studies just

cited support. It also protects against cancer because it is high in residue.

Dr. Dennis P. Burkitt has stated[74-76] that the single most important cause of large-bowel tumors is a "refined carbohydrate diet". He further is convinced that the "low-residue" diet is responsible for appendicitis, diverticulitis, and even hemorrhoids."

These disease states parallel the incidence of colon cancer. In rural Africa, where the high-residue primitive diet is eaten, these diseases, as well as colon cancer, are found only 10% as frequently as in Western nations.

Dr. Burkitt has stated: "The most likely cause of bowel tumors seems to be carcinogens produced by bacterial action on bile salts or other normal bowel constituents." (An example of such a carcinogen from bile would be derived from cholic acid, which with mild dehydration, becomes apocholic acid, a definite carcinogen. Other bile acids such as deoxycholic acid have been demonstrated to become converted to carcinogens by intestinal bacteria.[77]

This is a special problem for populations on high-fat Western diets, 40+% of total calories in fat, since the higher fat content requires a greater secretion of bile, which in turn provides more opportunity for the production of carcinogens from bile by the intestinal bacteria.

Changing from a Western diet to one low in fats has been shown in diet studies to reduce the fecal concentration of bile steroids, since the secretion of bile is reduced. Fecal concentrations of bile acid steroids were 11 times higher in British and Americans on their normal diet than in Ugandans on a low-fat, high-residue diet.

Composition of fecal bacterial flora reflects the total amount of fat in the diet. Populations with high rates of colon cancer are on Western-type diets with 40+% of their total calories in fat, and have bacterial flora with a high percentage of anaerobic bacteria--the type most active in degrading bile to deoxycholic acid. Such populations have 100 times the quantity of bacteria able to produce deoxycholic acid compared to those populations in

whom colon cancer is rarely found and whose diet is largely low-fat and vegetarian, with little animal protein.

Race and/or climate have been ruled out as significant factors in this matter. A group of English people living in Uganda and consuming a normal Western diet were selected for fecal examinations. It was found that their fecal flora were practically identical with English people living in England on the same diet. American blacks living in Atlanta, Georgia, racially related to the Ugandan blacks, were found to have fecal flora which were the same, both quantitatively and qualitatively, as were found in white Americans in Atlanta.

Although rural Africans rarely develop cancer of the colon, when they move to a city and start eating Western meals, their rate of colon cancer matches the high rates found in Americans and Europeans. Japanese in rural area likewise have very few colon cancers; yet when they move to Hawaii or California, the incidence in their children is the same as that of the local population.

Evidence of this kind convinced Dr. Burkitt that not race, but diet is the causative factor in cancer of the colon. His recommendation is the high complex carbohydrate, low-fat, low-cholesterol diet that has been discussed previously.

There is still another factor involved in the matter of type of diet in relation to frequency of colon cancer: this is the short transit time from ingestion to defecation on a high-residue diet (about 35 hours for African villagers) compared to that for English students on a Western diet (89 hours). If bile-derived carcinogens were in the feces, they would be in contact with the sigmoid area 250% longer and in 1100% as concentrated a form on the Western diet.

It is in the six-inch passage between the rectum and sigmoid that most tumors of the colon are found. Dr. Burkitt's comments are relevant: "Any carcinogen ingested (as aflatoxin) or formed in the gut (bile-derived) would, in refined carbohydrate eaters, not only be present in a more concentrated form in small stools but would be held in contact with the mucosa for a prolonged period in a constipated colon."

To summarize the findings we have presented:

1. The composition of the bacterial flora reflects the amount of dietary fat;
2. The amount of fat in the diet is directly related to the amount of biliary steroids in the colon;
3. Intestinal flora are able to degrade the biliary steroids into carcinogens;
4. Populations on Western diet (40+% calories in fat) have the highest incidence of colon cancer, and those on low-fat diets have the lowest incidence of colon cancer.

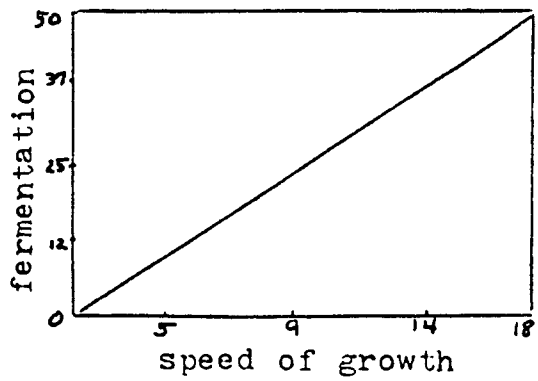
II. A MECHANISM OF MALIGNANCY

Warburg's studies of malignant cell metabolism.

Understanding the transformation of a normal to a malignant cell, starts with the work of Otto Warburg in the early 1920's.(78)

Warburg was investigating the metabolism of both normal and malignant tissue in vitro and noticed that their energy-producing systems were consistently different. Malignant cells produced much larger quantities of lactic acid, even under aerobic conditions. It was further observed that while embryonic tissue and other tissues (e.g., retinal) used glycolytic metabolism under anaerobic conditions almost to the extent of malignant cells, under aerobic conditions they reverted to normal glucose metabolism, whereas malignant cells still continued with glycolysis.

As Warburg and his various workers gained experience they developed techniques to measure the amount of oxygen used and metabolic products produced by normal and malignant cells.(79) It was found that normal cells from the liver and kidney in an adult animal, for example, gained 100 times more energy from oxidative respiration than from anaerobic fermentation, unlike malignant cells, which even under aerobic conditions gained their energy mostly from fermentation. The quantitative relationship between growth rate and fermentation in malignant cells was found, in fact, to be practically linear, as shown. Some malignant cells doubled



their mass in 3 days, others in 30 days--the rate of growth being directly proportional to their fermentation rate, with the fastest growing cells having the highest rates of fermentation, as illustrated in the graph.

Malignant cells created experimentally under oxygen-deficient conditions.

Once establishing that irreversible anaerobiosis is the one property of malignant cells that is different from normal cells, the next step was to discover what transformed normal cells to this condition.

The answer came after a 20-year search by Harry Goldblatt.(80) Aware of Warburg's work, he theorized that in normal tissues there might be cells or tissues that naturally have the ability to use fermentative mechanisms to a greater extent than their neighboring cells and could do so under anaerobic conditions. If repeatedly subjected to brief periods without oxygen, fermentative activity by these cells or their descendants might be encouraged. The lack of oxygen might even favor their growth, while slowing or stopping the growth of normal cells whose anaerobic metabolic capacities were less developed. If these conditions persisted, there was even the possibility that normal oxidative respiration, aerobic metabolic properties, would be lost. Would these cells with now only fermentative metabolic capability act like malignant cells?

These ideas haunted Goldblatt until 1950 when he was able to obtain sufficient funds to continue the work he had started in 1930. For his long-delayed project he selected a species of rat (Sloanaker-Addis strain of albino) that had not exhibited spontaneous malignancies for several years. Fibroblasts from the heart of a five-day old rat were cultured in several tubes, all under aerobic conditions. Out of the several cultures, we will trace the developments in one, #15-5. This culture was started on 3-15-50 and was divided into three groups as shown:

CULTURE # 15-5 (3-15-50)

N111		N120
Nitrogen: Average 1/2 hr. in 12 hrs.-- For 13 days between 4-13-50 and 4-25-51 Nitrogen: Average 1/4 hr. every 6 hrs.-- For 11 days between 7-23-51 and 10-15-51		Nitrogen: Average 1/4 hr. every 9 hrs.-- 3-15-51 3 days 4-16-51 3 days 4-25-51 3 days 5-7-51 3 days
Fibrosarcomas - 100%	CONTROLS No nitrogen; all normal cells after 2-1/2 years	Fibrosarcomas - 100%

Culture 15-5 always had adequate oxygen and was never exposed to nitrogen, but was kept in the same drum and incubator as N120 and N111. For the two-and-a-half years of observation, 15-5 grew normally without exhibiting characteristics of the malignant cell lines. During this period 15-5 was injected into 75 rats, 14 guinea pigs and 16 rabbits, subcutaneously and intraocularly, without the development of nodules or tumors. Usually, in two weeks time these cells were completely absorbed without a trace. In fact, after two-and-a-half years the cultures were indistinguishable from the original 15-5.

For exactly one year after their separation into individual cultures N120 and 15-5 were identical in appearance. Since they both originated from the same fibroblast culture, this was not unexpected. To test for any malignant characteristics in N120 for the first twelve months, 22 transfers were made, with subcultures taken at the time of almost all of the transfers. These cultures were transplanted in various animals, but the transplants had no effect and quickly disappeared.

Then, exactly one year later, on 3-15-51, N120 was exposed to nitrogen for various periods to produce an anaerobic environment. After the second exposure some cells with large nuclei and abnormal

characteristics presented themselves. After the third exposure, the cells were in a borderline condition for survival, but did recover after several days. After the fourth exposure, however, the first multinucleated cells were seen, and they were in good condition. From this time on, despite the fact that there was no further nitrogen exposure, the abnormal cells multiplied and after a period of months were considered malignant in appearance.

Whether they were actually malignant was soon established through transplantation. Four days after an implant, a palpable nodule was noted. In eleven days it became a firm nodule .6x.9x1.5 cm. When the rat host was sacrificed, the nodule was found to be a typical, moderately differentiated fibrosarcoma. Parts of this tumor were implanted and they reproduced themselves in consecutive implants, convincing the investigator that the serial transfer of these tumors could go on indefinitely.

N111 was exposed to nitrogen within 30 days of its separation from 15-5. Its evolution from normal to malignant fibroblasts followed the pattern of N120; each anaerobic period produced progressive degenerative changes in the direction of malignancy. Thus, although N111 was almost immediately exposed to anaerobic conditions after separation from 15-5 while N120 was cultured normally during testing for one year before exposure to anaerobic environment, the results were identical.

An anaerobic environment will encourage surviving cells with a tendency towards fermentation to develop this property and to lose the ability for aerobic respiration. Those cells which cannot make this change will die, while those which have been transformed have become irreversibly dependent upon fermentation.[81] Cancer cells had been created from normal cells simply by lack of sufficient oxygen to maintain aerobic respiration.

If any question still remains as to the ability of a normal cell to become malignant, this next series of experiments should erase any doubt.[82] A single mouse fibroblast was isolated and grown to a large culture. The culture from which the single fibroblast was isolated had a history of no tumors as demonstrated by injections into mice on several occasions. The large colony,

grown from the single cell on plasma substrate cultures in 82 days, was then divided into other substrates, and various substrains were grown. At the end of 1-1/2 years, some malignant and some normal cell lines were developed. Using the normal cell line, 40 mice were injected and not a single sarcoma developed; whereas in the malignant line, practically every culture produced a sarcoma after injection.

In still another significant study, embryonic mouse cells were placed in cultures in two different environments with respect to available oxygen. With sufficient oxygen they grew in vitro purely as aerobes, with no fermentation; when the oxygen was reduced sufficiently, in the time span of only two cell divisions--about 48 hours--they changed over to fermentative respiration, irreversibly, as was shown by the failure to return to aerobic respiration when the oxygen was again elevated.(83)

Ascites (Ehrlich) cancer cells have been grown in vitro even when the oxygen level is so low that 95% of their energy comes from fermentation. Ascites tumors in Leving mice are found to have such low levels of oxygen when probed with oxygen microelectrodes, that 95% of their energy requirements are supplied by fermentation.(84)

Normal animals do not have tissues that can live anaerobically, as do animals with malignancies. This is dramatically demonstrated with an experiment using tetanus spores, which can only germinate at very low oxygen levels. If these spores are injected into the blood of a healthy mouse, or even into a pregnant mouse, neither the mice nor the embryo of the pregnant mouse are affected; oxygen levels are too high to permit their germination. If, however, the tetanus spores are injected into a mouse with malignant tumor tissue, the mouse dies of tetanus. The spores are able to germinate and multiply within the anaerobically respiring tumors, eventually killing the host.

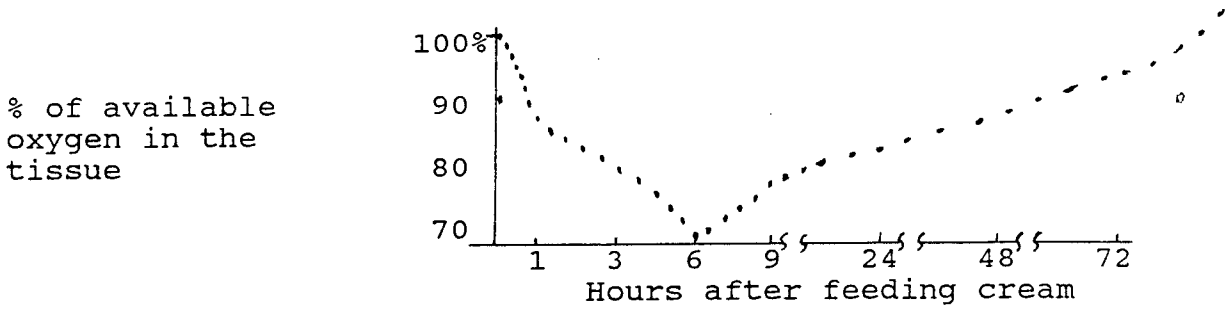
The question of whether a normal cell can develop into a malignant cell has been answered in the affirmative by many studies. The important question remaining to be answered is how such transformation of normal cells to malignancy may be prevented.

Anoxic conditions and malignancies in disease states.

The complete absence of oxygen is not necessary to transform cells to malignancy. Experiments have shown that only a 35% inhibition of respiration can bring about the transformation.(85) These oxygen levels can be found near the venous ends of capillaries. If these levels persist long enough, they provide the environment for malignancy.

One of the most predictable means of reducing the oxygen-carrying capacity of the blood is by that human cultural ritual known as the Western or American diet (40+% of total calories in fat). This has been qualitatively and quantitatively explored.

Swank(86) fed hamsters a large cream meal (controls were fed skim milk) to determine changes in available oxygen in the blood due to fat intake. Platinum electrodes to measure oxygen were implanted in the animals to make the determinations. Within 30 minutes after the cream drink, chylomicra started to pour into the blood, reaching their peak in about six hours. As they increased in the blood, the circulation became affected in two ways: 1. erythrocytes adhered to each other and to the endothelium of the blood vessels and rouleaux formations developed, preventing oxygen exchange from the adhered surfaces. 2. chylomicra and the rouleaux formations plugged the small capillaries to slow and sometimes stop the circulation. As a consequence of these phenomena, oxygen pressure in the affected areas was reduced almost to zero. By contrast, measurements in those hamsters taking the skim milk drink showed a reduction in oxygen of only about 5% when the maximum digestion of the milk had occurred.



Humans[87] react in the same manner to a drink of cream. Angina patients, after an overnight fast, drank a glass of rich cream, then sat and relaxed while the cream was digested. Just as in the hamsters, cholomicra poured into their blood, and in approximately five hours reached their peak. The plasma lactescence rose during this period so that at the peak the blood appeared to have a creamy reddish translucence due to the heavy influx of chylomicra. Also, coincident with the peak, several of the patients experienced an angina attack. Their EKG's were consistent in showing depressed and ischemic ST segments, indicating oxygen deficiency, although they were all isoelectric at the start of the test.

This experiment was repeated on yet another group, but this time the capillaries in the conjunctiva were observed.[88] At the beginning of the test the capillaries were all functioning with no observable narrowing of any passage. When the chylomicra were at their peak in 4-6 hours, several of the capillaries were completely blocked by chylomicra and possibly rouleaux formations. These blockages persisted for several minutes, some possibly long enough to provide an anaerobic malignant environment.

In all three experiments, those using hamsters and those with human angina patients and individuals in whom the conjunctiva was observed, when a nonfat drink equivalent in bulk and calories to the cream drink was given, no changes from normal were noted.

Impaired capillary circulation is rampant in diseases associated with high lipid levels, as diabetes, arthritis, etc. In a study that measured oxygen pressure in arthritis, over 30% showed joint synovial fluid oxygen pressure below 20 mm. Hg., and 10% were below 5 mm. Hg. A few joints were zero--no oxygen at all.[89]

Blockage of circulation in the bronchioles created by small thromboemboli have been associated with abnormal metaplasia. A study of 30 cases[90] selected to eliminate patients with cancer, infarction, and infection, retaining only those with pulmonary embolisms, sought to focus exclusively on patients in whom multiple thrombi could be studied in the smaller pulmonary vessels. Most of the cases revealed adenomatous hyperplasia and some developed

atypical metaplasia of the bronchiolar epithelium. One area of multiple foci of epidermal metaplasia was found to be adjacent to recent thrombi in medium-sized pulmonary vessels. The atypical cells were similar in appearance to malignant cells. It was estimated that the thrombi were only 3-4 weeks old.

To determine if the premalignant cells were a result of the thrombi, 62 rabbits were injected with thromboplastin and a control group with distilled water. Thromboplastin injections caused the greatest amount of thrombi to develop in three weeks. The rabbits were sacrificed at this time and it was noted that the average thrombus size was 5 to 50 microns. Control rabbits did not show any small bronchiole damage. The rabbits in which thrombi were induced were found to have the almost identical type and incidence of bronchiolar proliferation as found in humans and in the same association with the thrombi.

Comparing both human and rabbit lesions, the investigator concluded that the proliferative changes were created by the localized anoxia due to the emboli. He said: "the transition from basal cell hyperplasia to metaplasia...eventually to invasive cancer" was demonstrated in these studies.

In countries with a high incidence of cardiovascular deaths, high cancer rates coexist. Showers of thrombi from atherosclerosis could plant the seeds of future malignancies.

Impairment of cellular oxidative respiration and cancer growth and treatment.

Warburg's impressive body of research into the cause of cancer, based upon thousands of experiments, which brought him two Nobel prizes, may be very simply summarized:

1. "Cancer cells originate from normal body cells in two phases. The first phase is the irreversible injuring of respiration."
2. The second phase is the "long struggle for existence by the injured cells to maintain their structure, in which a part of the cells perish from lack of energy, while

another part succeed in replacing the irretrievably lost respiration energy by fermentative energy."

Oxidative respiration is damaged by insufficient oxygen and respiratory poisons. In the first instance, oxygen is kept from the cell; in the second, the cell is prevented by the poison from reacting with oxygen.

Arsenious acid is a strong respiratory poison. Arsenic is well-known as a carcinogen; it has been implicated in cancer of grape-growers who spray their vineyards with it and especially in cancers induced in psoriasis patients treated with arsenic preparations.

Hydrogen sulfide is a strong respiratory poison. Many of its derivatives, as thiourea and thioacetamide, have been used to preserve citrus fruit juices, and these have produced both cancer of the liver and gall bladder in rats.

Radiation, as a respiratory poison, is a two-edged sword. It destroys aerobic respiratory function, so that when cancer cells are irradiated, the small percent of aerobic respiration capability they possess falls below the minimum required for life and they die. Since the percent of aerobic capability varies considerably (it is proportional to their fermentative ability and growth rate), only the fastest growing cells die. At the same time, normal cells will have their aerobic respiration damaged by the same amount. During the course of time, descendants of these surviving normal cells will develop greater fermentation ability to compensate for the aerobic respiration function destroyed by the radiation and become malignant. Urethane, used in chemotherapy for leukemia, behaves similarly to radiation.

By increasing the oxygen level of the tissues, this second phase in radiation therapy or chemotherapy can be interrupted, since the transformation of normal to malignant cells takes place gradually over many cell divisions and further damage stops at any time the oxygen level is restored.

This can be illustrated in an unusual therapy for skin cancer.[91] A radiologist, unhappy with the massive destruction of

normal tissues by "cancericidal doses" normally employed by radiologists to treat skin cancer, discovered that skin cancers could be cured without radiation. His treatment consisted of defatting the skin, which permitted a 6% hydrogen peroxide solution to penetrate into the surface. No damage is done to normal tissues by this treatment but the malignant tissue is destroyed, as it cannot exist in a completely oxygenated environment.

Malignant tissues must be oxygenated to destroy the cancerous cells and restore the tissue to normal. This recalls Warburg's advice:[92] "the first precondition of the proposed treatment is that all growing body cells be saturated with oxygen."

Saturation of growing body cells is not possible if blood lipids are elevated. To have a minimum depression of oxygen with ingestion of foods, total fat intake cannot exceed 10-15% of total calories. The importance of minimal dietary cholesterol was discussed earlier in relation to the inhibition of tumor growth. As judged by population studies, for normals, a maximum ingestion of 100 mg. of cholesterol per day will keep one in a no-risk area. However, based on animal studies cited previously, a cancer patient should follow a cholesterol-free diet. The benefits may be more effective than obtained through selective killing of tissues by radiation or chemotherapy.

Tissue changes in the formation of malignancies.

Warburg's first precondition for the origination of cancer cells--the reduction of available oxygen to the cells--is found in the development of benign hyperplasia, as in scars, fibrous capsules, and cysts.

The deliberate initiation of malignancies in animals by circumstances that stimulate capsule formation confirm this effect of insufficient oxygen on the normal cell. Extensive animal experimentation has clarified many of the mechanisms involved in the development of malignancy.

In 1941, it was first noticed[93] that sarcomas developed around the site of a subcutaneously implanted plastic (bakelite)

disc in rats. Since then, various shapes, sizes and materials have been tried as implants, and certain common factors emerge:

1. The chemical nature of the implant does not affect the formation of the tumor;
2. The implant must be a minimum size and preferably in the shape of a flat disc with a smooth surface to produce a sarcoma.

Materials implanted that have produced sarcomas include metals, plastics, and glass. One test using cellophane sheets (2x3 $cm.^2$) in rats[94] was typical of the development of the tumor:

One week after the film was implanted, it was observed to be surrounded with a wide area of inflammation, and infiltrated by lymphocytes and macrophages, and by immature granulation tissue formed of young fibroblasts and many new capillaries.

Two weeks later the granulation tissue contained fewer capillaries and cells, but more fibers.

Four weeks later, in place of the granulation tissue surrounding the film, a newly formed connective tissue capsule of several layers of thin collagenous fibers appeared. Few fibroblasts could be seen between the fibers, but inside the capsule and at its internal surface, focal proliferations of young fibroblasts were observed.

Eight weeks later many young fibroblasts and macrophages were noted in the internal areas of the capsule, even though the thickness of the fibers increased and the capsule wall contained even fewer cells.

12th to 26th week was a relatively quiet period. The capsule wall now had three distinct layers, the middle layer revealing densely packed collagenous bundles in rows parallel to the flat surface of the film. Between these collagenous fibers were mature fibroblasts and blood-filled dilated capillaries, together with occasional groups of young fibroblasts. The internal layer consisted of cells very similar to the young fibroblasts observed during the first two weeks.

28th to 40th weeks found the middle layer even thicker and fewer cells within it. Profound changes could now be seen on

the inner surface of the capsule. In those animals who developed malignancies (30-60% of the group), focal proliferations of young fibroblasts observed close to the film surface became more numerous. The size and shape of the cells appeared very atypical as did the size of the nuclei. After 40 weeks the atypical cells in some animals covered the entire film surface. In other animals, these cells invaded the capsule and were found on the external wall. A fully developed sarcoma now was surrounding the cellophane film.

Close examination of these induced neoplasms indicated that sarcomatous elements had evolved from the fibroblasts since many of the normal characteristics of the fibroblasts could be identified in the malignant cells.

At the same time that the cellophane film was implanted, another implanting experiment in a separate group of rats was started, using minced cellophane (.1-.3 cm. wide). Both experiments produced very similar results in the formation of a capsule as well as in the other changes, with one exception. In the minced cellophane capsule, the middle layer never became wide, but remained a narrow, more porous structure. None of the capsules surrounding the minced cellophane became malignant.

Tests on the inner layer of fibroblasts revealed that the fibroblasts surrounded by the wide middle layer probably had less oxygen available to them. These fibroblasts, in the environment provided by the densely collagenized tissue, having inadequate oxygen, could result in the injury of some cells. The possibility of mitochondria damage was indicated. The investigator concludes that injury to some cells "might favor the selective multiplication of special, more resistant cell variants, which eventually become the malignant cells." An important characteristic of the new cells would be resistance to anoxia.

The investigator added: ..."development of tumors is observed only if there is a combination of cell proliferation, which creates material for selection, and changed environment which may create pressure for such selection." This pressure, as we have seen, is the anoxic environment within the inside of the capsule.

Measurement of metabolic enzyme activity(95) in the type of capsule having the wide collagen wall indicated a continuously decreasing level of activity over a period of six months. This decrease in capsules around cellophane implants for lactate dehydrogenase activity in a six-month period was 92%; for other enzymes it ranged from 80-90%. These metabolic changes create a tight barrier preventing normal exchange of metabolites, nutrients and oxygen.

Once the cells have been transformed to the malignant state, the implant can be removed and the tumor will develop, even four months after removal of the implant.(96) If the capsule is removed, no tumors develop, since the malignant cells are in the inside layer of the capsule.

Prevention of nutrient and oxygen exchange in the capsule, as the carcinogenic factor, is observed also in other experiments. Millipore filters,(97) 19 mm. in diameter and .15 mm. thick, in various pore sizes, were implanted subcutaneously in mice. After a year, fibrosarcomas developed and appeared to be inversely proportional to the pore size.

INCIDENCE OF FIBROSARCOMAS DEVELOPING AROUND FIBER IMPLANTS

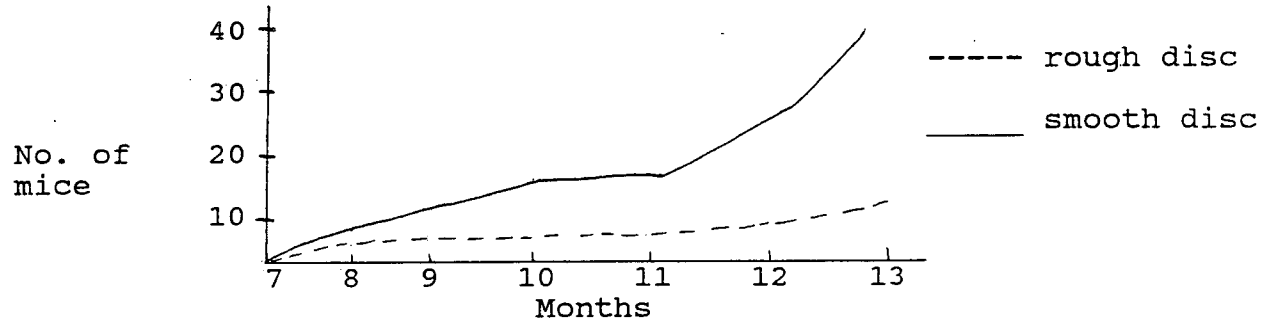
Total implant period	Pore size in filter			
	450 mμ	100 mμ	50 mμ	None
12 months	2.5%	26.5%	47.7%	33.3%
18 months	5.0%	52.9%	60.0%	

The largest pores, permitting the maximum exchange of nutrients, were associated with the lowest incidence of tumor growth. The investigator summarized: "These findings suggest that the potency of certain physical carcinogens may be directly related to their degree of interference with normal diffusion rates of specific nutrients or metabolites to or from the surrounding cells."

A more subtle test(98) was run using polyethylene discs 20 mm. in diameter and .4 mm. thick. One set of discs were used with

their original smooth surface, while another identical set had its surfaces filed until no smooth surface was left. Two groups of about 80 mice each received a smooth and a rough-surfaced implant. Although the first tumor was noted in 7-1/2 months, the experiment was continued for 13 months. Upon autopsy, it was noted that fibrous capsules formed around both kinds of inserts. On the rough discs, it was noticed that the fibroblasts followed the multidirectional scratches and seemed haphazardly and rather loosely arranged. By contrast, smooth implant fibroblasts were very closely packed in parallel rows and presented more of an impermeable barrier than the rough implant surface. Tumor incidence followed the degree of barrier developed by the capsule wall, and the difference was still increasing when the experiment was terminated. A decreased rate of transfer through a more dense capsule wall again demonstrated a higher association with the malignant state.

CUMULATIVE TOTAL TUMORS PLOTTED ON A MONTHLY BASIS



Further experiments clarify the importance of normal nutrient transfer. In one, quartz was implanted in rats in two forms, a disc about 2 cm. diameter and a similar volume ground into a powder.[99] The disc, as previous studies show, forms a barrier and also a substrate for fibroblasts to develop collagenous layers. Ground quartz, however, presents no barrier to the development of capillaries and nutrient exchange. Tumor incidence reflects the difference in the physical form of the implant. Eighty-six rats with disc implants developed 32 sarcomas (37%), while 200 rats implanted with the powdered quartz did not develop tumors.

These tests were repeated using glass instead of quartz and the results were the same: tumors with glass discs, none with glass powder.

In these induced tumor experiments, malignancy is developed if the normal exchange of nutrients and oxygen among the cells is inhibited by the dense avascular capsule. Under these circumstances, an anoxia is produced which favors the multiplication of cells able to exist in an anaerobic environment. These become the malignant cell precursors, a demonstration in vivo of the transformation of normal cells to the malignant state in Warburg's classic experiments.

Human cancer: the immediate causes parallel the animal experiments.

Previously cited studies have shown a strong association between cancer and ingestion of fats and cholesterol. It is curious that cholesterol, a substance naturally occurring in the body, can be suspected of having a role in cancer. Significantly, however, cholesterol in the body is not found in crystal form unless an abnormal state exists, as hypercholesterolemia or other pathological dietary-induced conditions. Crystalline cholesterol is not only abnormal, but toxic physiologically.

Local tissue response to cholesterol crystals[100] and various glycerides was studied in rabbits. Implants of gelfoam alone and of gelfoam impregnated with three separate glycerides, cholesterol and cholesterol ethers were subcutaneously implanted over the abdominal region. After 35 days, the implants and the surrounding tissue was analyzed. (Based on the studies cited, 35 days is insufficient time for malignancy development, but would indicate a trend.)

The gelfoam control and various glycerides produced a minimal response. Cholesterol, which was in solution in ether, had crystallized in situ, causing the most extensive lesions. These were characterized by an intense inflammatory response with many lymphocytes and macrophages and widespread fibroblastic proliferation. This response was similar to the start of the

malignant capsule around the disc implants described previously.[101] The behavior of cholesterol crystals apparently is comparable to the smooth surface discs in the experiments with mice.[102]

Three groups of 33 mice were each injected subcutaneously with olive oil and cholesterol. One group received 0.6 ml. of plain olive oil, the second an unsaturated cholesterol solution in olive oil (20 mg. cholesterol in 0.6 ml. olive oil), and the third a saturated cholesterol solution in olive oil (20 mg. cholesterol in 0.2 ml. olive oil). Only the saturated solution formed crystals *in vivo*. After 14 months the mice were examined for tumors. The findings are summarized.

INCIDENCE OF TUMORS IN MICE INJECTED WITH CHOLESTEROL AND OLIVE OIL

Tissue findings	SATURATED (20 mg. chol. .2 mg. olive oil)	UNSATURATED (20 mg. chol. .6 ml. olive oil)	OIL ONLY .6 ml. olive oil)
Cystic fibrosis	82%	42%	12%
Sarcoma at site	6% (p=.05)	0	0

Only the cholesterol injections in crystaline form initiated a malignant tumor. A study of the tissue sections of the sarcomas revealed that cholesterol crystals formed a baffle arrangement which effectively inhibited transfer of nutrients to the cells shielded by the crystals. The crystals, in a miniature way, act as the large disc implants that so consistently produce sarcomas by causing the transformation of normal cells to malignancy mediated by the dense fibrous wall of the capsule surrounding the disc. Few cells remained between the crystals as the space became filled with collagen, again closely following the pattern of the large disc sarcomas.

Evidence that this is a likely human etiology of cancer comes from a study of 110 surgically removed human cutaneous cysts. Five

were found to be malignant and only these five were found to contain cholesterol crystals.

In humans with gall bladder cancer, 90% are found to contain gallstones. As they occur in Western cultures, gallstones are composed mostly of cholesterol in crystaline form, which would identify the inflammatory source.

The mechanism by which cholesterol crystals initiate malignant transformation is probably similar to that occurring in silicosis and asbestosis.(103) Macrophages engulf silicate particles, but the lysosomes are unable to digest them and disintegrate, destroying the cell wall and spilling the contents, including the silicate particle. Another macrophage repeats the drama and dies, and still another, and in time fibroblasts quickly move in to encapsulate the necrotic area, trapping many living cells. The resulting fibrosis probably forms the barrier to the transfer of nutrients that produces the malignant environment.

Considerable relationship exists between cancer and fibrosis. Pathological fibrosis has been associated with malignancy.(104) Studies report pulmonary scar carcinomas developed adjacent to imbedded foreign bodies or within the scar tract in 11 instances. Lung carcinomas have been found after grenade splinter wounds. Nine fibrosarcomas have been reported as arising merely from surgical scars. Tuberculosis scars in a Japanese study showed a malignancy rate of 1,200% more than the normal population.

The mechanism of fibrosis as an etiology for malignancy lies in its presentation of an avascular tightly-packed connective tissue barrier to nutrients for the living cells trapped inside the scar or adjacent to it. It is, in effect, the equivalent of the disc implant described earlier in animal studies.(105)

An exhaustive search through the literature on the relation of carcinoma of the breast and fibrocystic disease noted that women with fibrocystic disease had 260% more breast cancer than normals. Eighteen percent of tissue removed in fibrocystic disease was malignant. A possible etiology for malignancy was the entrapment of epithelial cells in the fibrotic area. This could be initiated in breast tissue by cholesterol crystals acting as a "neoplastic

agent". The crystals stimulate macrophage phagocytosis and unsuccessful dissolution of the crystals by the lysosomes would fragment and degenerate the macrophages. Other macrophages would ingest the cholesterol crystals, with the same sequence of events, resulting in considerable macrophage death. Fibroblasts would be stimulated into action and a fibrous capsule or cyst formed.

III SOME CRITICISMS OF CANCER THERAPY TODAY

Treatment of breast cancer.

Tumor tissue, including breast cancer, is usually found to contain large amounts of cholesterol.(106) In one study, total lipid content of breast tumors was found to be 52%. Sterols related to cholesterol are found in breast cancers that are unknown in normal tissue.

Thus, the breast tumor has a strong association with high-fat and -cholesterol levels, which provide the mechanism for the development of the fibrous cyst due to the cholesterol-induced hyperplasia. In consequence, the lowering of lipid and cholesterol levels to achieve a low plasma level of these "neoplastic agents" would eliminate this cause of breast tumor. The most innocuous way in which this can be accomplished is through dietary management.

Treatment of breast cancer ignores all the findings relating to lipids and cholesterol and their role in malignancy. For the last 80 years Halsted's (radical) Mastectomy has been the treatment of choice. Until a few years ago, departure from this procedure meant ridicule and censure of one's peers and superiors.(107)

A leader in the struggle to minimize the trauma associated with this widely accepted treatment is George Crile, Jr. of Cleveland Clinic. By tracing Dr. Crile's activities since 1965, the evolution of the newer treatment can be seen. In 1965 at a meeting of the American Radium Society, Dr. Crile disclosed the results of a 5-8 year follow-up of 183 patients.(108) Of these, 61 had had radical mastectomy and 69 had been treated with simple mastectomy. Most of both groups had had postoperative irradiation. No endocrine ablation had been done in either group. Both groups had had primary tumors of similar size and the patients were of the same age range.

After 5-8 years, in the group which had undergone simple mastectomy, there were 64% survivors; in the group which had undergone radical mastectomy, there were 58% survivors.

Despite his revelationary results, Dr. Crile met opposition at the conference, where others were advocating the conventional

radical mastectomy and high voltage radiation of a minimum of 5000 rads delivered within five weeks even for uncomplicated earlier cancer.

At a National Conference on Breast Cancer in 1969, Dr. Crile reported on the dangers of radiation or dissection of the nodes in treatment of the axilla.[109] A study in animals revealed that damage to the nodes resulted in increasing the incidence of metastasis. In a group of 159 true stage 1 breast cancer patients without spread to the nodes, 49 were subjected to radical mastectomy and the remaining 110 were treated by simple mastectomy. None had radiation treatment. Although the ages of the women and sizes of the tumors were similar, the five-year survival of those undergoing the simple operation was 17% higher than those who had had the radical procedure.

Dr. Crile's position on radiation was further supported by a study of 48 patients[110] under 30 years old with breast cancer. All had negative axillary nodes and all underwent radical mastectomy, but only seven received radiation following their operations. At the most recent follow-up, only one of the seven who received radiation was alive (14%), contrasted with 31 of the 41 not radiated (75% survival).

One explanation for the poor results using radiation may be the lymphopenia produced by the radiation that lasts for at least a year.[111] At least three randomized independent studies have produced evidence of increased deaths from metastasis during the first year after radiation.

At the American College of Surgeons meeting[112] in the fall of 1970, Dr. Crile spoke to his critics: "Cancer can no longer be viewed as a devil to be exorcised as quickly and radically as possible", and routine radical surgery is performed "in a medieval spirit that disregards scientific data both here and abroad." In moving towards more enlightened treatment, Dr. Crile advocated "lumpectomy", local excision, which in the Cleveland Clinic has doubled in the last 15 years so that it now comprises 20% of all surgical treatment of breast cancer. Reviewing 56 selected cases

of lumpectomy, the five-year survival rate was 69%, no worse than simple mastectomy.

At the same conference studies were disclosed showing no advantage for either oophorectomy or postoperative irradiation after five years as compared to controls--survival rates were the same. Even when lymph nodes are at issue, "the use of postoperative irradiation offers no advantage", according to these studies. Nor was any difference in survival rates found with postoperative chemotherapy, using 5-FU at and shortly after surgery. In presenting these studies, the chairman of the conference noted that they had been contributed by 25 institutions and were under the direction of the NSABP (National Surgical Adjuvant Breast Project). As a result of these findings, he stated that he no longer uses irradiation, surgical castration or chemotherapy on his patients.

More recent disclosures from Dr. Crile in 1971 reported on 465 patients with operable stage 1 and 2 carcinoma of the breast.(113) Of these, 57 were treated by local excision of the tumor with very few involving axillary dissection or postoperative radiation. The balance were treated by mastectomy. The five-year survival rates of the groups were identical (67% and 68%).

In the Cleveland Clinic Quarterly, Dr. Crile posed the moral dilemma: Are patients with breast cancer giving their permission for surgery with what can ethically be defined as "informed consent"? Dr. Crile maintains they are not unless they are told the facts about the different therapies. For example, he points out that radical mastectomy is seldom used in England and Scandinavia because randomized studies in both countries have shown that survival rates are no different for simple or radical operations. While radical mastectomy in the U.S. is still used for most patients with operable breast cancers, Dr. Crile asks whether these patients know "there is no proof that any of the treatments, varying from local excision with or without irradiation, to ultraradical mastectomy with or without irradiation results in higher survival than any of the others."

Dr. Crile believes surgeons are under the moral obligation to advise their patients of these facts. If they knew the truth, he says, not many would accept "the deformity that results from the conventional radical mastectomy or the risk of lymphedema and limitation of motion that is so greatly increased when the axilla is dissected and irradiated."

The emphasis on drug research and therapy.

The absence of differential response to any of the conventional treatments used with breast cancer, as reflected in survival rates, may stem from the fact that no effort is made by cancer clinicians to eliminate one proven cause of tumor development. Fat and cholesterol dietary intake have been demonstrated almost without exception to have a primary effect on tumor growth and regression both in animals and humans.(114-124) Yet not the barest suggestion for diet modification appears in conventional treatment.

The hope for cancer cures through drugs proves elusive. Certain relatively rare cancers, such as acute leukemia, have achieved remissions over many months, but the common cancers, such as solid carcinomas of the alimentary and respiratory tract, have not responded well to drug therapy.(125) One reason for drug failure is the inability of the drug to get into the malignant area. An advanced cancer usually has so many ischemic areas with anoxic conditions and attendant necrosis, that drug penetration is insufficient to effect adequate improvement.

Drugs may be promising <u>in vitro</u>, but these conditions are not found <u>in vivo</u>. The very conditions that initiated the formation of the tumor--anoxia, ischemia and possibly a carcinogen--defeat the effectiveness of a drug treatment dependent upon adequate blood flow for success. This inherent contradiction is at the basis of the drug cure concept.

Even when drug cure seemed effective, the therapeutic response may be unrelated to a direct effect on the malignancy. For example: L-Asparaginase, an enzyme that destroys the amino acid L-asparagine, has had a measure of success in leukemia treatment.

But what is its mechanism? The original theory was that some tumors are dependent on an outside source of L-asparagine. The enzyme destroys the amino acid and so deprives the tumor of this essential nutrient. Some years after the treatment started, it was noticed that administration of L-asparaginase to cancer patients has an instant depressive effect on certain blood lipids, including cholesterol and triglycerides. Not knowing whether the lipid depression was related to the malignant condition, the enzyme was given to nonmalignant patients with atherosclerosis.(126) Twenty-one patients were given a single I.V. dose of L-asparaginase. Lipid levels started to fall in 3-4 days and reached their lowest in 10-14 days. Average drops of cholesterol were 1/2 of starting level. In one patient, the cholesterol dropped from 230 mg. to 58 mg. Cholesterol levels returned to original values in a month with most patients.

Animal and human experiments earlier cited indicate a reversal of tumor growth with the lowering of cholesterol level. There is more basis to the belief that the mechanism of L-asparaginase responsible for the improvement is due to the lowering of cholesterol than to any other action of the drug.

In another example, 13 children with acute leukemia(127) were treated with a low-protein diet (0.5 gm. of animal protein per kg. of body weight). Although the diet was started in the later states, mostly during relapse, 10 of the 13 improved. Compared with the controls, the patients on the diet low in animal protein had a markedly rapid disappearance of "blast" cells in the bone marrow. New relapses occurred, but remissions were effected in less time than with controls. This was significant because it is usually thought that every subsequent relapse is more resistant to treatment and lasts longer. Why should the lowering of animal protein intake have a therapeutic effect? This effect may be a result of the lowering of the cholesterol level with reduced animal protein intake, which has been shown to reverse tumor growth in numerous experiments.

The search for drug cures is as frantic and aimless as the action of a drowning man, desperately grasping at any straw. As

Dr. Schepartz, head of the National Cancer Institute, has said:[128] "No possibility is too ridiculous to be ignored." After 30,000 compounds have been investigated, he can be believed.

Sloan-Kettering Institute of New York, a leading cancer research center, is typical of the current approach. They have examined over 130,000 chemicals, cultures, and plant extracts in their relentless search for the "cure". Every possible substance, no matter how unscientific and irrational it may appear, is examined.

Even when drugs may seem promising and have been subjected to the most thorough evaluation, the drug approach has problems (in addition to the fundamental one already discussed, inability to penetrate ischemic areas). Immunosuppressive drugs are a good example. Used extensively on transplant operations to prevent rejection and also against a wide range of diseases, this family of drugs produces a basic response in the body--the depression of lymphoid tissue and reduction of white blood cells. The body's defense mechanism is rendered less effective and ordinary infections now become life-threatening.

Recent findings indicate that this weakening of body defense mechanisms includes also a reduced ability to destroy malignant cells. A study concerning the incidence of cancer in transplant patients bears this out.[129] Transplant centers around the world reported that an organ graft recipient on immunosuppressive therapy develops cancer at a rate 100 times greater than normals of the same age range. The cause for this increase was tied directly to the drugs. These cancers developed in 28 months on the average. When immunotherapy was stopped in three patients with widespread metastasis, the cancers underwent rejection. Five other controls still on the drugs were unchanged. All the living kidney donors in these transplant cancer cases were followed up for periods of almost 10 years, and none of them developed cancer. Their donated kidneys were cancer-free.

The malignant state developed when the defense system was destroyed. At least 30 cases of cancers developed in patients with nonmalignant diseases when they were treated with immunosuppresant

drugs. Twenty of them were patients with psoriasis, a condition where the capillaries have such poor circulation that the condition of anoxia necessary for continuous development of malignant cells already exists. Normally the white blood cells probably are able to control the slow evolution of malignant cells, but with the drugs paralyzing the white blood cell defense system, development of malignancies proceeded unhampered.

The drug approach in cancer cure overlooks the basic causes of the disease and hence can be considered more palliative--at best, or destructive, at worst--than curative.

Warburg pointed the way--but confusion abounds in cancer therapy today.

Warburg's concept (that cells may become malignant when respiration is damaged by anoxia or poison) received support in an unusual study. A German physician,(130) familiar with Warburg's work, reasoned that running or jogging should provide the best condition for thorough oxygenation of the tissues. Heart beat during jogging is usually doubled over resting, and with the accompanying elevated blood pressure, all tissues should be generously bathed with oxygen and nutrients. He sent a detailed questionnaire concerning the state of health to 1000 senior (over 40) distance runners who were worldwide members of the Association of Senior Long distance Runners. Four hundred fifty-four questionnaires were returned; some with comments by the senders' doctors. The ages of the respondents varied from 40 to 89 years, averaging 54 years old. Seven had had heart attacks and various other ailments, but only four had developed tumors, none of which were fatal. In contrast, in 454 men selected as controls and matched for age and other characteristics, 7 times as many tumors were found.

Similar conclusions were drawn from an animal experiment involving sedentary and active mice.(131) 7-12 DMBA was applied to both groups to initiate skin papilloma growth. One of the groups ran daily on a treadmill at 16 meters/minute for 20 minutes over a period of ten weeks before the 7-12 DMBA was applied. After the

application of the carcinogen, the exercise continued for 17 more weeks. The other group was kept in cages which permitted them only limited activity. Both groups were analyzed after the 17-week period. In all cases, the number of papillomas of the sedentary mice was greater than on the running mice. There were no deaths in the running group, but many of the sedentary mice died due to cancer growth.

This controlled animal study together with the human retrospective study of runners lays the basis for one principal reason for the activity program further developed in other chapters. Endurance activity acts both as prevention and therapy.

The light cast by these and other cited studies with their implications for cancer prevention and therapy is unperceived by many in the profession. Two physicians posed a question[132] to a group of experts on breast cancer. Both the question and the answers tell the tragic tale of cancer care today.

Question: A 53-year old woman has incurable carcinoma of the breast and her mother and two sisters also had breast cancer. In view of the family history of cancer, should her daughters be advised to have prophylactic mastectomy at about age 40?

(1) Answer: (consultant from Creighton U. School of Medicine)
"They might well be considered for prophylactic mastectomy at age 40 (or even younger under certain extenuating circumstances), particularly if they have cancer phobia because of the presence of the disease in their family."

(2) Answer: (consultant from from M.D. Anderson Hospital)
"We would have no quarrel with those who support bilateral simple mastectomy as a prophylactic measure, provided psychologic and other factors involved were completely satisfactory."

(3) Answer: (consultant from Columbia-Presbyterian Medical Center)
"The suggestion that the two daughters of the patient have prophylactic bilateral mastectomy is barbaric."

Answer 3 probably represents a minority view. Answers 1 and 2 show the desperation of failure and present the best reason why the dietary approach must be given serious consideration and a controlled study started. The first duty of a physician is that he do no harm; the therapy employed in breast cancer care comes under serious question in this regard.

CANCER REFERENCES

1. Weiss, W. X-Ray Screening No-Prognosis Aid in Lung Cancers. Med. Trib. 7-72.

2. Acheson, E.D., et al. Carcinoma of the Nasal Cavity & Accessory Sinuses in Woodworkers. Lancet p. 311, 2-11-67.

3. Nasal Cancer in Woodworkers. Lancet p. 253, 8-1-70.

4. Myrden, J.A. and Hiltz, J.E. Breast Cancer After Fluoroscopy. Med. Trib. 10-13-69.

5. Gibson, R.W., et al. Diagnostic X-Rays of Males Said to Raise Leukemia Risk. Med. Trib. 8-2-70.

6. Dungal, N. The Special Problem of Stomach Cancer in Iceland. JAMA 178: 789, 1961.

7. Gastric Cancer in Iceland. JAMA 204: 181, 1968.

8. Merliss, R.R. Talc-Treated Rice & Japanese Stomach Cancer. Science 173: 1141, 1971.

9. Selikoff, I.J., et al. Asbestosis & Neoplasia. Amer. J. Med. 42: 487, 1967.

10. Kogan, F.M., et al. Cancer Mortality Rate Among Workers of Asbestos Industry of Urals. Gig Sanit 37: 29, 1972 (Moscow).

11. Japan Investing in Programs for Early Cancer Detection. Med. Trib. 10-12-70.

12. Wogan, G.N. Aflatoxin Risks & Control Measures. Fed. Proc. 27: 932, 1968.

13. Lopez, A. and Crawford, M.A. Aflatoxin Content of Groundnuts Sold for Human Consumption in Uganda. Lancet p. 1351, 12-23-67.

14. Op. Cit. Reference 12.

15. Op. Cit. Reference 12.

16. Petering, H.G. Foods & Feeds as Sources of Carcinogenic Factors. Nutr. Rev. 24: 321, 1966.

17. Op. Cit. Reference 12.

18. Bourgeois, C.H., et al. Lab. Invest. 24: 206, 1971.

19. Amla, I., et al. Cirrhosis in Children from Peanut Meal Contaminated by Aflatoxin. Amer. J. Clin. Nutr. 24: 609, 1971.

20. Op. Cit. Reference 13.

21. Op. Cit. Reference 19.

22. Higginson, J. Cancer Res. 23: 1624, 1963.

23. Sereck-Hanssen, A. Aflatoxin-Induced Fatal Hepatitis? Arch. Environ. Health 20: 729, 1970.

24. Aleksandrowicz, J., et al. Mycotoxins in Aplastic & Proliferative Blood-Diseases. Lancet p. 43, 1-3-70.

25. Wray, B.B. Multiple Cases of Leukemia in One Household. JAMA 210: 1924, 1969.

26. Op. Cit. Reference 16.

27. Nitrites, Nitrosamines, & Cancer. Lancet p. 1071, 5-18-68.

28. Sander. J., et al. Nitrites & Amines Held Possible Cause of Cancer. Med. Trib., 3-22-72.

29. Epstein, S.S., and Lijinsky. Nature, 1-3-70.

30. Visek, W.J. Intestinal Cancer May be Increased by Meat Ammonia. Med. Trib., 9-20-72.

31. Visek, W.J. Effects of Urea Hydrolysis on Cell Life-Span & Metabolism. Fed. Proc. 31: 1178, No. 3, May-June, 1972.

32. Jose, D.G. Protein Deficiency in Diet is Linked to Enhanced Resistance to Tumors. Med. Trib. 5-10-72.

33. Madhavan, T.V., and Gopalan, C. Effect of Dietary Protein on Carcinogenesis of Aflatoxin. Arch. Path. 85: 133, 1968.

34. Cooper, W.C. Protein Deficit May Enhance Cell-Mediated Immunity. JAMA 216: 1431, 1971.

35. Op. Cit. Reference 31.

36. Wynder, E.L. Identification of Women at High Risk for Breast Cancer. Cancer 24: 1235, 1969.

37. Lea, A.J. Dietary Factors Associated With Death Rates From Certain Neoplasms in Man. Lancet p. 332, 8-6-66.

38. Tannenbaum, A. Nutrition & Cancer. Chapter. 12, "The Physiopathology of Cancer". Harper & Bros., New York, 1959.

39. Gammal, E.B., et al. Effects of Dietary Fat on Mammary Carcinogenesis by 7, 12-Dimethylbenz (a) Anthracene in Rats. Cancer Res. 27: 1737, 1967 (Part 1).

40. Dayton, S., et al. A Controlled Clinical Trial of a Diet High in Unsaturated Fat. Circulation Suppl. II XL: No. 1, July 1969.

41. Carroll, K.K., et al. Effects of Dietary Fat & Dose Level 7, 12-Dimethylbenz (a) Anthracene on Mammary Tumor Incidence in Rats. Cancer Res. 30: 2260, 1970.

42. Carroll, K.K. and Khor, A.T. Effects of Level & Type of Dietary Fat on Incidence of Mammary Tumors Induced in Female Sprague-Dawley Rats by 7, 12-Dimethylbenz (a) Anthracene. Lipids 6: 415, 1971.

43. Op. Cit. Reference 38.

44. Szepsenwol, J. Carcinogenic Effect of Egg White, Egg Yolk, & Lipids in Mice. Proc. Soc. Exp. Biol. Med. 112: 1073, 1963.

45. Littman, M.L., et al. Retarding Effect of Vitamin Deficient & Cholesterol Free Diets on Growth of Sarcoma 180. (29170). Proc. Soc. Exp. Biol. Med. 116: 95-101, 1964.

46. Littman, M.L., et al. Effect on Cholesterol-Free, Fat-Free Diet & Hypocholestermic Agents on Growth of Transplantable Animal Tumors. Cancer Chemo. Reports 50: 25-45-66 (Nos. 1 & 2).

47. Addleman, W. Cancer, Cholesterol, and Cholestyramine. New Eng. J. of Med. 287: 1047, 1972.

48. Miller, S.P., et al. Coagulation Disorders in Cancer. Cancer 20: 1452-65, 1967.

49. Blood Coagulation. JAMA 163: 223, 1957.

50. Tompkins, M.J. Effect of Long Term Feeding of Various Fats on Whole Blood Clotting Times In Men. J. Lab. Clin. Med. 64: 763-72, 1964.

51. Bulbrook, R.D. Hormone Assays in Human Breast Cancer. Vit & Hormone 23: 329-57, 1965.

52. Repert, R.W. Breast Carcinoma Study: Relation to Thyroid Disease and Diabetes. J. Michigan. SM Soc. 51: 1315-6, 1952.

53. Glicksman, A.S., and Rawson, R.W. Diabetes & Altered Carbohydrate Metabolism in Patients with Cancer. Cancer 9: 1127-34, 1956.

54. Op. Cit. Reference 52.

55. Op. Cit. Reference 45.

56. Catt, K.J. Insulin & Glucose Homeostatis. Lancet p. 353, 8-15-70.

57. Relabeling Oral Contraceptives. Sci. News Letter 93: 496, 1968.

58. Barden, R.P. Para-Endocrine Syndromes Associated with Carcinoma of the Lung, 100: 626-30, 1967.

59. Gall, S.A., et al. The Morphologic Effects of Oral Contraceptive Agents on the Cervix. JAMA 207: 2243-7, 1969.

60. Bryson, G., and Bischoff, F. The Limitations of Safety Testing. Prog. in Exp. Tumor Res. 11: 100-133, 1969.

61. Pill-Cancer Link Is Discounted by Two Panels. Med. Trib. 8-10-70.

62. Herbst, A.L. Daughters Cancers Linked to Mothers Use of Estrogens. JAMA 220: 653, 1972.

63. Bower, B.F. Safe Levels of Estrogen Are Wrong, Physicians Warn. JAMA 205: 33, 1968.

64. Hill, M.J., et al. Gut Bacteria & Etiology of Cancer of the Breast. Lancet p. 472, 8-28-71.

65. Op. Cit. Reference 37.

66. Op. Cit. Reference 64.

67. Adams, J.B., et al. Desmolase Activity of Normal & Malignant Human Breast Tissue. J. Endocr. 44: 69-77, 1969.

68. Op. Cit. Reference 42.

69. Op. Cit. Reference 44.

70. Op. Cit. Reference 45.

71. Op. Cit. Reference 46.

72. Cancer Metastasis & Blood Coagulation. Nutr. Rev. 23: 41-3, 1965.

73. Swank, R.L. A biochemical Basis of Multiple Sclerosis. Page 57-63. C.C. Thomas, Pub. Springfield, Ill., 1961.

74. Burkitt, D.P. Relationship As a Clue to Causation. Lancet p. 1237, 12-12-70.

75. Modern Diet May Play Role in Cancer of the Bowel. JAMA 215: 717, 1971.

76. A Refined-Carbohydrate Diet Is Linked With Colon Cancer. Med. Trib. 2-3-71.

77. Hill, M.J., et al. Bacteria & Etiology of Cancer of Large Bowel. Lancet p. 95-100, 1-16-71.

78. Warburg, O. The Prime Cause & Prevention of Cancer. English Edition by Dean Burk. Natl. Cancer Institute. Bethesda, Md., U.S.A.

79. Warburg, O. On the Origin of Cancer Cells. Science 123: 309-14, 1956.

80. Goldblatt, H., and Cameron, G. Induced Malignancy in Cells from Rat Myocardium Subjected to Intermittent Anaerobiosis During Long Propagation in Vitro. J. Exptl. Med. 97: 525-52, 1953.

81. Op. Cit. Reference 79.

82. Sanford, K.K., et al. The Development of Variations in Transplantability & Morphology Within a Clone of Mouse Fibroblasts Transformed to Sarcoma-Producing Cells in Vitro. J. Natl. Can. Institute 15: 215-37, 1954.

83. Op. Cit. Reference 78.

84. Warburg, O. Oxygen, the Creator of Differentiation, Biochemical Energetics. Academic Press N.Y., 1966.

85. Op. Cit. Reference 78.

86. Op. Cit. Reference 73.

87. Kuo, P.T. and Joyner, C.R. Jr. Angina Pectoris Induced by Fat Ingestion in Patients with Coronary Heart Disease. JAMA, 1008, 1955.

88. Friedman, M., Byers, S.O., and Rosenman, R.H. Effect of Unsaturated Fats Upon Lipemia and Conjunctival Circulation. JAMA 193: 11, 1965.

89. Lund-Oleson, K. Oxygen Tensions in Synovial Fluids. Arthritis Rheum. 13: 769, 1970.

90. Berkheiser, S.W. Bronchiolar Proliferation & Metaplasia Associated With Thrombeombolism. Cancer 16: 205-11, 1963.

91. Exner, F.B. Immunoresistance & Radiation Therapy. Med. Trib. 11-8-72.

92. Op. Cit. Reference 78.

93. Bischoff, F., and Bryson, G. Carcinogenesis Through Solid State Surfaces: Progr. Exp. Tumor Res. vol 5, pp. 85-133. Karger, Basel/New York, 1964.

94. Vasiliev, J.M., et al. Comparative Study of Alterations Induced by 7, 12-Dimethylbenz (a) Anthracene and Polymer Films in the Subcutaneous Connective Tissue of Rats. J. Nat. Cancer Inst. 28: 515-59, 1962.

95. Danishefsky, I., et al. Biochemical Changes in the Connective Tissue Pocket Surrounding Subcutaneously Imbedded Films. Cancer Res. 27: 833-7, 1967.

96. Op. Cit. Reference 93.

97. Goldhaber, P. The Influence of Pore Size on Carcinogenicity of Subcutaneously Implanted Millipore Filters. Proc. Amer. Assn. Cancer Res. 3: 228, 1961. - Further Observations Concerning the Carcinogenicity of Millipore Filters. Proc. Amer. Assn. Cancer Res. 4: 323, 1962.

98. Bates, R.R., and Klein, M. Importance of a Smooth Surface in Carcinogenesis by Plastic Film. J. Nat. Cancer Inst. 37: 145-51, 1966.

99. Op. Cit. Reference 93.

100. Spain, D.M., and Aristizabel, N. Rabbit Local Tissue Response to Triglycerides, Cholesterol, & Its Ester. Arch. Path. 73: 82-85, 1962.

101. Op. Cit. Reference 94.

102. Op. Cit. Reference 93.

103. Op. Cit. Reference 60.

104. Ibid.

105. Op. Cit. Reference 93.

106. Day, E.A., et al. Tumor Sterols. Metabolism 18: 646-51, 1969.

107. Fisher, B. In Consultation. Med. Trib. 3-31-71.

108. Five Views of Mastectomy & Radiation. JAMA 192: 27, 1965.

109. Possible Breast Cancer Risk of Oran Contraceptives Cited. Med. Trib. 6-5-69.

110. Postmastectomy Radiation Held Survival Risk. Med. Trib. 10-19-70.

111. Stjernsward, J., et al. Lymphopenia & Change in Distribution of Human B & T Lymphocytes in Peripheral Blood Induced by Irradiation for Mammary Carcinoma. Lancet p. 1352, 6-24-72.

112. Breast Cancer Therapies May Get Wide Study. Med. Trib. 11-20-70.

113. Crile, G. Jr., and Hoerr, S.O. Results of Treatment of Carcinoma of Breast by Local Excision. Surg. Gynec. Obstet. 132: 780-2, 1971.

114 - 124 Op. Cit. References 37-42, 44-47, 100

125. Testing Anti-Cancer Drugs. Lancet p. 827, 4-15-72.

126. Astaldi, G., et al. Effect of L-Asparaginase on Serum-Cholesterol. Lancet p. 1113, 5-23-70.

127. Halikowski, B., et al. Treatment of Leukemia by Amino Acid Imbalance. Lancet 3-27-65.

128. Seeking Cancer Cures. Newsweek - Aug. 31.

129. Starzl, T.E., and Penn, I. Some Posttransplant Cancer Tied to Immunosuppressives. Med. Trib. Oct. 25, 1972.

130. Van Aaken, E. Cancer in Runners. Translated from Leichtathletik Mag. W. Germany by Runners' World. Mt. View Ca. p. 42, May 1971.

131. Balke, B. Tumor Growth May Be Slowed by High Energy Expenditure. Med. Trib. 11-15-72.

132. Dollinger, M., and Tanaka, K.R. Management of Adult Daughters in Family With High Breast Cancer Incidence. JAMA 219: 391-2, 1972.

SIGHT AND SOUND:
VISUAL PROBLEMS AND DIET

The eyes are the windows of the body. Through them the internal circulation and most of the vascular problems arising in the body can be studied with minimal danger and discomfort to the patient.

The vascular problems observable through these "windows" are responsible for many kinds of degenerative ailments which have been discussed in previous chapters. They are also responsible for a group of visual disorders with which we deal in this chapter. These, like the systemic degenerative ailments, are reflected in a diverse symptomatology.

Incredibly, there is hardly a study to be found that relates the high-fat and -cholesterol Western diet to visual problems. The annual review on glaucoma published by the Archives of Ophthalmology discusses approximately 250 studies per year; yet in the period from 1966-72, out of over 1,500 studies which encompassed every aspect of glaucoma, it would be difficult to find one study which reported or suggested this relationship. Yet a good deal of evidence exists that incriminates the Western diet as the main etiological factor in the principal degenerative diseases of the eye.

Population studies discussed in the chapter on Atherosclerosis indicate that native populations on low-fat, low-cholesterol diets are essentially free of systemic degenerative diseases. Such diets also bestow freedom from certain forms of visual degeneration. Thus, in a survey of 805 Australian aborigines[1] whose diet is untainted by the sucrose and added fats of Western diet, not one case of glaucoma was found, though the subjects included elders over 80 years. In one 80-year old, no pathologic or senile changes were observed.

Populations on Western Diets are not as fortunate. In white Australians, unlike their aborigine counterparts, glaucoma and senile defects are common. In a U.S. study[2] conducted in Memphis, Tennessee, in which 13,155 individuals were examined, 2% had glaucoma. In a hospital for the aged, the incidence was 6%.

Comparison statistics from Sweden found glaucoma in 1% of individuals over 40 years of age, gradually increasing to 8.7% at age 70. Gradually increasing plasma lipid and cholesterol levels associated with aging in Western cultures are reflected in a parallel rise in such visual degenerative diseases as glaucoma, just as they are with a progressive increase in incidence of atherosclerosis (see Atherosclerosis chapter).

In this chapter, evidence is presented showing the relationship of several forms of visual degeneration to the abnormally high lipid and cholesterol levels produced by Western diets. These varied visual pathologies are due to ischemia or occlusion of blood vessels nourishing the eyes which effect specific neuropathies, often resulting in visual field losses and other visual disorders.

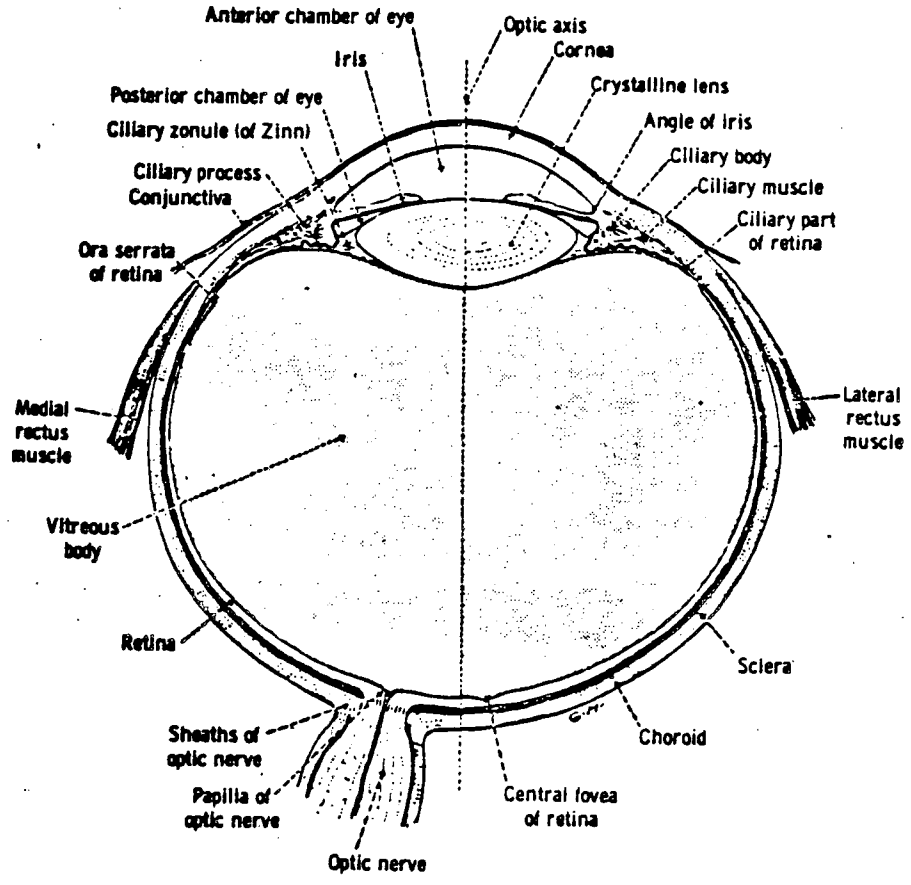
Statistics on the causes of blindness are of interest in this connection. Accidental blindness accounts for only ____%* of all cases of blindness; whereas blindness due to glaucoma, diabetic retinopathy, retinal detachment, cataracts, and other disease states preventable with a low-fat, low-cholesterol diet account for a total of ____%.* (*The author intended to gather these statistics.)

Ischemia and occlusive incidents responsible for visual ailments in many individuals are due to underlying atherosclerotic conditions. In time, atheromatous fragments form new emboli which may exacerbate the visual problems as well as create new complications. Meanwhile, the disease process is assiduously observed by the patient's ophthalmologist, who follows the year-in, year-out dance of the cholesterol emboli and prescribes palliatives in the form of drugs to control the optical symptoms they produce, but does nothing whatever to eliminate the growing emboli reservoirs--the atheromatous plaques. These continue to multiply and spread their contents throughout the vascular system, including the eyes.

Evidence of the presence of vascular problems may often be seen even without the aid of special instruments, as when grossly visible clues become apparent in a condition known as arcus

senilis, caused by deposition of lipid and cholesterol material. Deposition of such materials and their significance are of interest and will now be discussed.

Below is a drawing of the eye showing the principal parts that will be referred to in the text.



Section through right eye in horizontal plane magnified about 4 times. (After Eycleshymer & Jones. From Jones & Shepard: A Manual of Surgical Anatomy, Saunders, 1945.)

I. DEPOSITION OF LIPID MATERIALS IN THE EYES

A telltale sign: arcus senilis.

Arcus senilis is a common finding in Western cultures.[3] In Finland, practically every male over 40 years old examined had arcus. In a study of over 500 men and women in Glascow, Scotland, ranging from 30-69 years, arcus was found to be correlated with age and other factors.

The condition appears as an opaque greyish arc around the iris. In moderate arcus the arc is a narrow segment of a circle; in severe arcus the circle is complete and wider. It is due to a deposit of lipids, including cholesterol, triglycerides, and phospholipids found in the cornea and has long been associated with cardiovascular diseases. In the Glasgow study, the investigators were concerned with the relationship between arcus and serum lipid levels, as well as cardiovascular aspects. Results are summarized in the table below.

ADULTS WITH ARCUS SENILIS

Age Group	Normal Men	Normal Women	Males with Myocardial Infarction
30-39	14%	8%	27%
40-49	47%	30%	67%
50-59	71%	41%	70%
60-69	75%	67%	82%
Total Subjects	290	245	164

Males with myocardial infarcts had twice the incidence of arcus found in normal males in the 30-49 year age group. Cholesterol levels indicated that those with arcus had a significantly higher level than those without arcus. In a grading of severity of arcus versus cholesterol level in the 40-50 year age group, the following was observed:

SEVERITY OF ARCUS VERSUS CHOLESTEROL LEVEL
IN 40-59 YEAR AGE GROUP

Category	Cholesterol (Mg./100 Ml.)	Number of Subjects
No arcus	254	48
Moderate arcus	274	40
Severe arcus	286	32

The cholesterol levels of those without arcus and those with severe arcus differ significantly ($P < .01$). Since the observations of the arcus were made with the naked eye, the incidence of arcus was probably underrated and the differences in cholesterol level between those with truly no arcus and severe arcus were probably much greater.

This diagnostic sign (i.e., arcus) has been considered an inevitable result of aging. The investigator disagreed, citing these grounds:

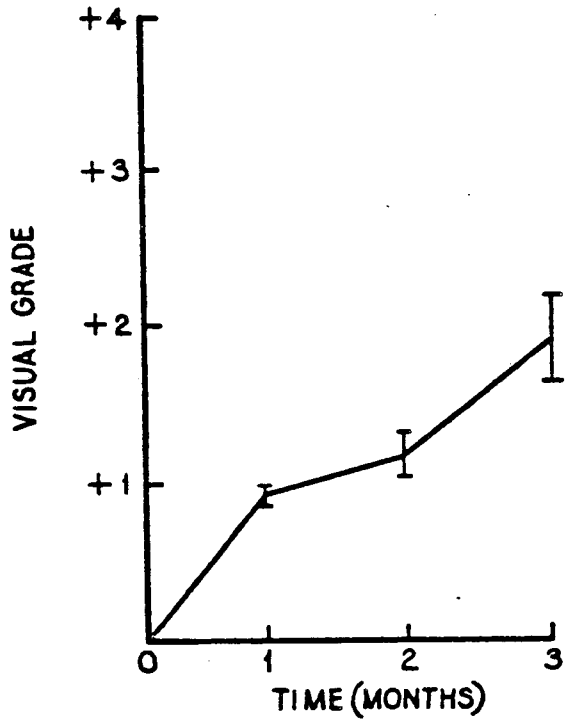
1. Sex incidence differs and is related to lipid differences;
2. Incidence varies in different populations;
3. In younger subjects with myocardial infarction or elevated lipid levels, arcus is more common.

The investigator concluded that the arcus must be an acquired lesion. Animal studies have established the correctness of this view.

The direct relationship of the severity of the arcus to dietary factors was established in a study with 20 male Dutch belted rabbits.[4] Five were controls, on a cholesterol-free, low-fat diet; 15 were on the same diet to which 1% cholesterol had been added. Results were tabulated after a three-month test period. A primary concern was to determine if there was a relationship between visible eye and aorta lesions. Corneal lesions were graded as to severity and plotted as to length of time on the cholesterol diet, as shown. (Grading was done by a worker who had no prior knowledge as to which animals were on which dietary regime.)

CORNEAL GRADING

Grade	Corneal Appearance
0	Clear
+1	Whitish deposit, 0.1 to 0.5 mm wide adjoining sclera. Deposit is not continuous.
+2	Deposit is continuous and forms a ring adjacent to sclera, 1 to 2 mm wide.
+3	Same as +2, but deposit is 2 to 3 mm wide. Only small part of iris is visible.
+4	Same as +3, but deposit is more than 4 mm wide.



Assessment of corneal lesions in cholesterol-fed rabbits. Abscissa: time on 1% dietary cholesterol. Ordinate: average visual grade per pair of corneas, graded according to criteria at left. Vertical lines indicate ± SEM.

The control animals showed no eye involvement. Those on the cholesterol diet showed initial lesions as early as 14 days; after 3 months most had continuous deposits ringing the cornea, 1-2 mm. wide. Each eye was then analyzed for cholesterol content of the iris, cornea and ciliary body tissues. Results were as follows:

EFFECT OF DIETARY CHOLESTEROL ON TISSUES OF THE EYE

Cholesterol Concentration (Mg./g.)

Diet	No. of Rabbits	Time (Mos.)	Cornea Abnormal	Cornea Normal	Iris	Ciliary Body
Control	4	3		.29	1.70	2.90
1% Chol.	4	1	7.15	.96	16.69	21.05
1% Chol.	4	2	8.63	.66	29.00	27.01
1% Chol.	6	3	12.10	.32	67.10	57.00

The abnormal portions of the cornea where the deposit formed was separated from the normal area, where no deposit was evident. Cholesterol content of the normal portion was similar to that of the controls.

In the analysis of the aortas, any atheromas found were separated from the aorta and tested for cholesterol separately. The remaining aorta wall, media, and adventitia were tested alone.

EFFECT OF DIETARY CHOLESTEROL ON AORTA TISSUE

Cholesterol Concentration (Mg./g.)

Diet	No. of Rabbits	Time (Mos.)	Atheroma	Media & Adventitia	Whole Aorta
Control	4	3			3.2
1% Chol.	4	1			4.5
1% Chol.	4	2	80.40	9.90	23.6
1% Chol.	6	3	95.30	9.80	29.6

The investigators summarized their findings:

1. The correlation between the amount of cholesterol in the iris and aorta is significant ($P < .01$).
2. A high degree of correlation was also found between the visual corneal grade and the corneal cholesterol concentration.
3. The tissue phospholipids paralleled the changes of cholesterol in both the eye and aorta at all time intervals studied.

Cholesterol crystal deposition in the lens.

Human studies[5] confirm these findings in yet another part of the eye, the lens. Cholesterol content of lenses of older adults

with high serum cholesterol levels were 10 to 15 times as high as a child's lens with a cholesterol level of 100 mg. percent, similar to native populations on low-fat diets. The table summarizes the findings:

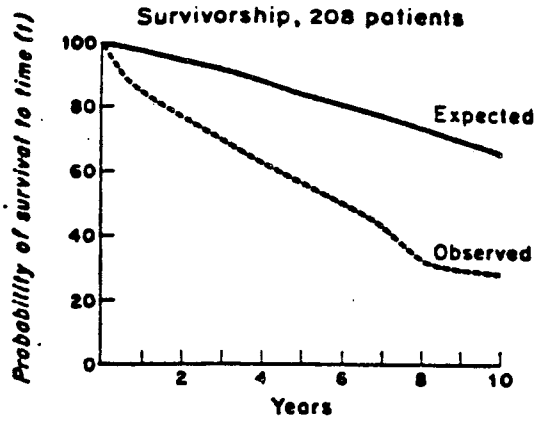
CHOLESTEROL CONTENT OF LENS AND SERUM IN CATARACT PATIENTS

Average Age (yrs.)	Type of Cararact	Average Cholesterol (Mg. %)	Average Serum Cholesterol (Mg. %)
.5	none	.08	100
74	immature	.947	565
65	mature	.804	484
82	hypermature	1.199	502

Crystals of cholesterol sparkling in human lenses with cataracts were reported as early as 1868; even urate crystals[6] have been reported in the cornea from patients treated for gout. The eye truly reflects the contents of the blood.

When the crystals of cholesterol are observed in the retinal arteries, the physician can be confident that it is a symptom of a widespread vascular disease. Retinal artery crystals usually result from showers of emboli originating from a large vessel with ulcerating atheromatous plaques.

A group of 208 patients[7] with retinal cholesterol emboli, aged 46 to 84 years, were followed year by year for periods as long as 10 years, after the initial discovery of the emboli. Survival rates during the first year were 13% less than would be expected in a normal population of the comparable age group; in the 5th year, they were 27% less; by the 8th year they were 40% less. Survivorship curves are shown on the next page.



Observed survivorship curve (broken line) for 208 patients with embolic cholesterol crystals in ocular fundus. Expected survivorship curve (solid line) for same age and sex distribution, Minnesota white population, 1950 Life Table. (Pfaffeubach and Hollenhorst).

Seven years after the first observation of the cholesterol emboli, 54% of the group of 208 patients were dead--which compares with 20% deaths for that age group in the average population.

At the time of initial observation of the emboli, 45% of the group were diagnosed as having carotid occlusive disease, a positive identification utilizing angiography and other techniques; 25% were found to have transient cerebral ischemia; and an equal number experienced central retinal artery or branch occlusion and amaurosis fugax (transient loss of vision), usually in one eye. The amaurosis fugax was always on the same side as the cholesterol emboli.

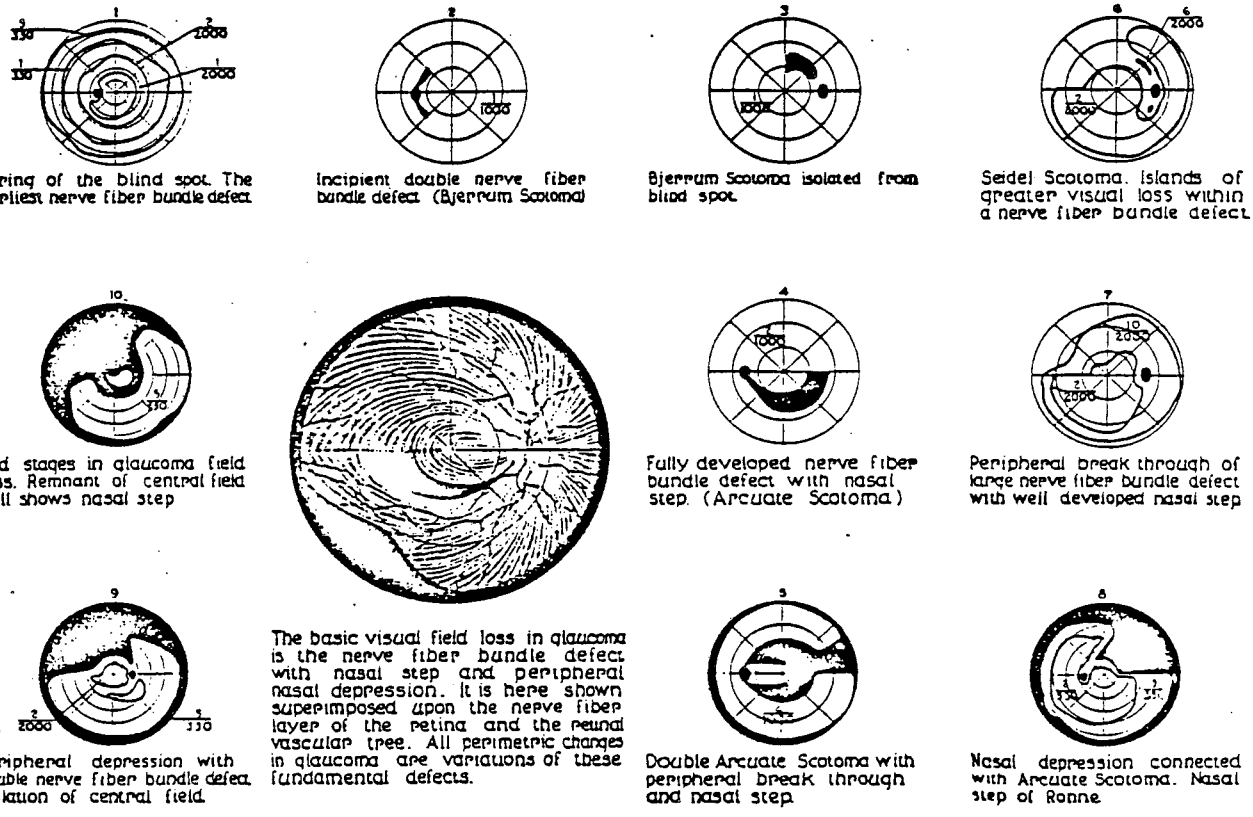
Having been introduced to some of the data showing deposition of lipid materials in the eyes and its association with systemic lipid levels and cardiovascular events, we turn now to a special problem: the mechanism by which the various visual complications caused by those lipids are expressed in visual field losses.

II. THE MECHANISM OF VISUAL FIELD LOSS DUE TO GLAUCOMA AND VARIOUS OTHER VASCULAR ETIOLOGIES

Patterns of visual field loss.

Visual loss in glaucoma is related to the patterns of the nerve fibre layer of the retina[8] as illustrated in this chart:

PRIMETRY OF GLAUCOMA
(Harrington)



Baring of the blind spot. The earliest nerve fiber bundle defect.

Incipient double nerve fiber bundle defect (Bjerrum Scotoma)

Bjerrum Scotoma isolated from blind spot.

Seidel Scotoma. Islands of greater visual loss within a nerve fiber bundle defect.

End stages in glaucoma field loss. Remnant of central field still shows nasal step

The basic visual field loss in glaucoma is the nerve fiber bundle defect with nasal step and peripheral nasal depression. It is here shown superimposed upon the nerve fiber layer of the retina and the retinal vascular tree. All perimetric changes in glaucoma are variations of these fundamental defects.

Fully developed nerve fiber bundle defect with nasal step. (Arcuate Scotoma)

Peripheral break through of large nerve fiber bundle defect with well developed nasal step

Peripheral depression with double nerve fiber bundle defect. Isolation of central field.

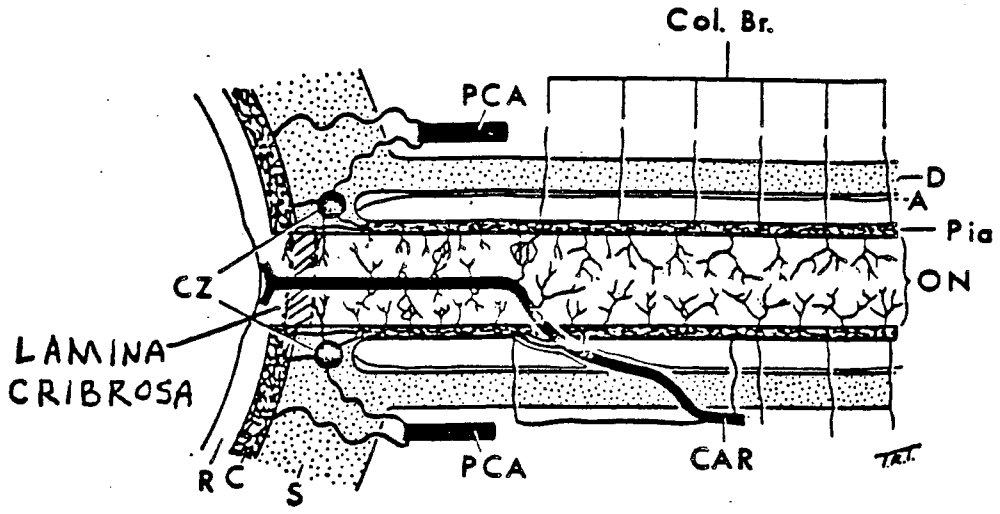
Double Arcuate Scotoma with peripheral break through and nasal step

Nasal depression connected with Arcuate Scotoma. Nasal step of Ronne.

Bjerrum's Scotoma (blind area) is illustrated in drawings 2, 3 and 4 and is the most usual visual field change in glaucoma. It can be traced to conform to the nerve fibre bundle of the retina, and therefore its etiology is considered to be a nerve fibre bundle defect limited to a particular area or sector of the retina.

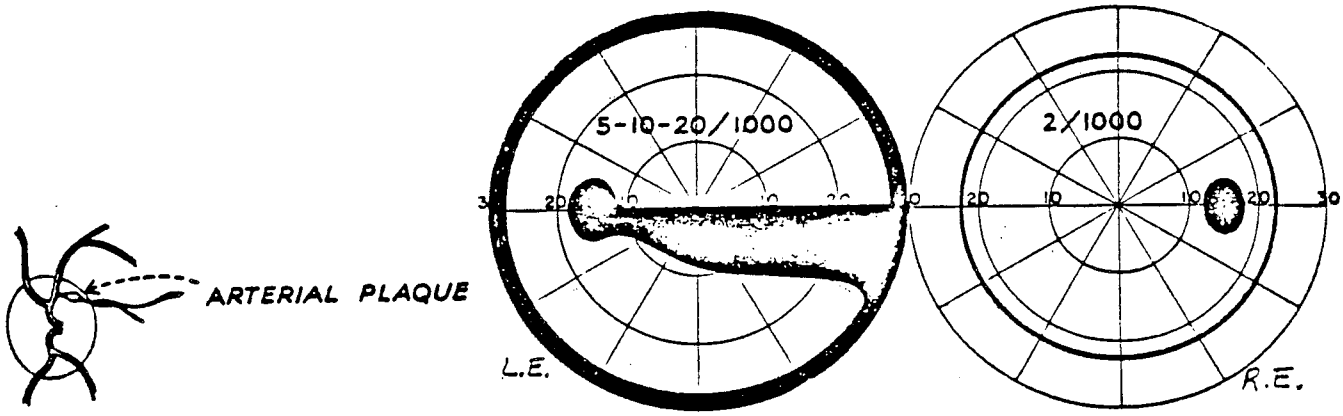
Many recent investigators[9] believe that these field defects are the result of insufficient circulation in the anterior optic nerve in the lamina cribrosa and circle of Zinn area (see drawing of circulation of optic nerve on the next page).

CIRCULATION OF OPTIC NERVE



Arterial supply of optic nerve. Central retinal artery gives off branches in dural sheath. There is no central artery of optic nerve. A, arachnoid; C, choroid; CAR, central artery of retina; Col.Br., collaterol branch; CZ, circle of Zinn; D, dura; OA, ophthalmic artery; ON, optic nerve; PCA, posterior ciliary artery; R, retina; S, sclera. (Hayreh. Brit. J. Ophth. 47: 651, 1963.)

Harrington states that circulation insufficiency can be caused by stenosis or partial or complete occlusion due to plaques in arteries farther away, as the carotid. When elevated IOP is present along with insufficient circulation, damage is rapid. He demonstrated this condition in patients with carotid artery insufficiency by pressing on the globe to increase IOP, thereby producing a temporary Bjerrum Scotoma. The drawing below illustrates this problem:



(See next page.)

Arterial embolus of lipid-debris type occluding a small branch of superior temporal retinal artery as a creamy white arterial plaque and producing localized retinal infarct. Field defect is atypical Bjerrum or nerve fiber bundle defect with steep margins and great density. Patient had left internal carotid artery occlusion with reduced ophthalmic artery blood pressure, as measured with ophthalmodynamometer, and a bruit in left neck. (Harrington.)

This condition would respond to the restoration of proper circulation, which would produce regression of the plaques creating the stenosis, as discussed in the Atherosclerosis chapter.

Harrington also reported hypertensive patients who developed Bjerrum Scotomas only after they were put on medication. As their blood pressure was reduced, blood flow declined. With the same IOP, insufficient blood was available to maintain a normal visual field.

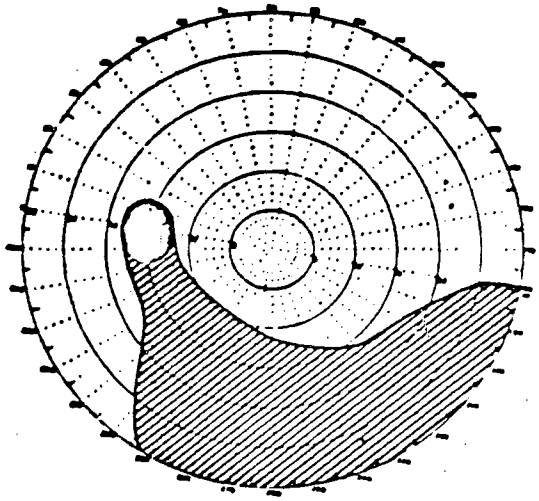
In an attempt to clarify the relationship of field defects to sectoral nerve fibre bundle defect, Hayreh[10] devised a series of primate experiments concentrating on the flow patterns of the ciliary arteries, the major blood source to the optic disc and also the choroid. To overcome the problem of the obscuring of the choroid by the circulation of the inner (nervous) layer of the retina, the blood supply to the retina was cut off by occluding the central retinal artery. With the inner retina now transparent, an injection of fluorescein solution was injected into the common carotid artery of the experimental monkeys on the same side of the eye being observed. Fluorescence fundus angiography of the pattern of circulation was then recorded through a fundus camera as the dye entered the vascular channels in the eye. Consecutive photographs taken every 0.8 second made it possible to plot the travels of the dye.

In observations of 24 eyes by this method, all showed a segmental distribution of the dye. In 80%, half the choroid and the optic disc filled with dye while the other half remained completely empty. Because the line of demarcation was so sharp, it was concluded that particular posterior ciliary arteries serviced only definite segments of the disc and choroid. In continued

injections, only 25% of the area filled, leaving a sharp line between filled and unfilled sections. The ability to see the particular areas served by various posterior ciliary arteries was possible because of the different times it took for each artery to fill its section. Upon repeated injections, all the areas eventually filled with dye.

These observations led Hayreh to propose a pathogenesis for nerve fibre bundle block defects such as Bjerrum Scotoma: "Each branch of the posterior ciliary arteries supplies a well-defined sector... Occlusion of one of the posterior ciliary arteries or its smaller subdivisions, therefore, would involve a sector of the lamina cribosa, the prelaminar part of the optic disc, and the retrolaminar part of the optic nerve... Atherscleratic changes in the posterior ciliary vessels which involve the optic nerve head and the area immediately behind the lamina cribosa (would) produce nerve fibre bundle defects, optic atrophy and cupping of the disc. This may stimulate glaucoma."

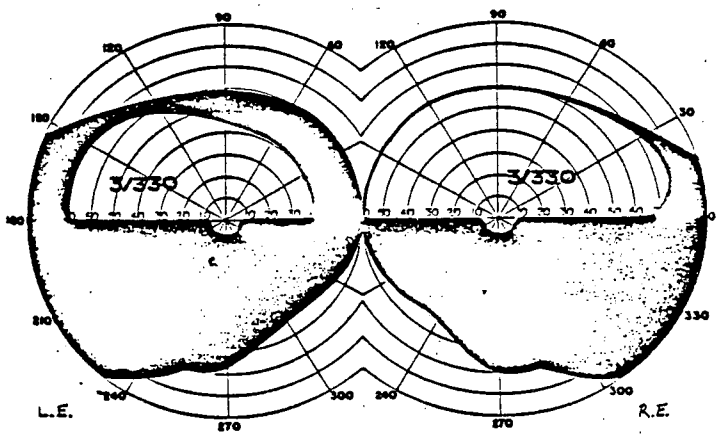
An occlusion such as described above would produce a field defect, though in these cases the retinal vessels are normal. A case illustrating this condition is shown below:



Visual field defect in the left eye of a 66-year old woman with temporal arthritis (reproduced by courtesy of Dr. J.F. Cullen). Target 5/2000 white. Visual acuity 6/9. (Hayreh.)

Another example would be Prechiasmal Altitudinal Hemianopia. In these cases the hemianopia is in the lower visual field,

comparable to the pattern achieved in Hayreh's monkey experiments. In some of the eyes a well-defined division was noted between the upper and lower areas of the disc and choroid culminating with a horizontal line. If one of the two main posterior ciliary arteries were occluded, this altitudinal field defect would be produced, though the retina would be unchanged. Such a defect is shown below:



Altitudinal hemianopsia associated with optic atrophy and peripheral sensory disturbance in patient with long-standing pernicious anemia. (Harrington)

Quandratic field defects are understood by the same mechanism. Occlusion of branches of dividing posterior ciliary arteries could cause various segmented scotomas, their size depending upon the area effected by the occlusion.

Circulatory relationships to visual defects.

Association of IOP, blood pressure, and filling of eye vessels to visual defects.

Insufficient circulation to the visual nervation accounts for diverse patterns of visual field loss. Sufficiency of circulation was now found to be dependent upon relationships of intraocular pressure (IOP), blood pressure, and the filling of the eye vessels, derangement of which could cause an inadequate blood supply to the nerves of the eyes. Hayreh, in further studies, investigated these relationships using the same technique--fluorescence angiographies, used with the monkeys in the earlier experiments.(11)

Two sets of variables were investigated: 1. Normal and low blood pressure; 2. Variable IOP from 5 mm. to 85 mm. The results are abstracted and approximated in the table below:

PATTERN OF VESSEL FILLING WITH VARIABLE BLOOD AND INTRAOCULAR PRESSURES

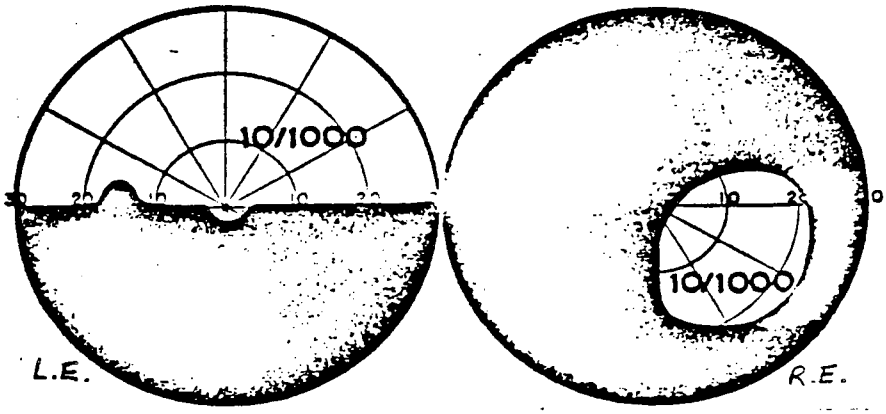
APPROXIMATE PRESSURES (MM. HG.)			FILLING OF VESSELS	
Systemic Arterial	Ophthalmic Artery	IOP	Choroidal	Optic Disc
150/75	110/65	30	normal	normal
110/60	80/54	15	normal	normal
35/15	25/13	5	normal	normal
150/75	110/65	50	slow-late filling	slow-late filling
110/60	80/54	35	slow-late filling	slow-late filling
62/35	45/31	20	slow and delayed	poor-only temporal side
150/75	110/65	85	very slow	poor-some vessels only partial
110/60	80/54	70	slightly	poor and slow
35/15	25/13	25	none	none

The results indicate that two basic situations may cause hypoxia in the optic nerve:

1. If the IOP rises sufficiently to overcome the blood pressure of the optic arteries;
2. If the IOP is normal and the optic arterial blood pressure drops. This condition may be due to stenosis or occlusion of a vessel feeding the eye, providing an insufficiency of flow and pressure.

Hypoxia in the optic nerve produced by circumstances creating the second of the two basic causative situations enumerated above would explain Harrington's observation[12] that hypertensives whose blood pressure has been reduced to normal by means of drugs may develop glaucoma, as well as the mechanism of post-hemorrhagic amaurosis (blackout).[13] In this latter condition, partial or complete loss of vision may occur within hours after a considerable

loss of blood, with visual defects and loss of field resembling those associated with glaucoma. Such visual field changes following hemorrhaging are illustrated in the following drawing:



Visual field changes secondary to exsanguination. Sudden and severe blood loss from hemorrhaging duodenal ulcer. Optic atrophy and permanent visual loss probably resulted from hypoxia in ganglion cell layer of retina.

Low tension glaucoma or pseudoglaucoma is also understandable as to basic causes producing hypoxia in the optic nerve, in the light of the above findings. It has been confusing to find individuals with normal intraocular pressure develop the typical visual field defects and optic disc changes that are found in glaucoma. Since the main tenet in glaucoma treatment is the reducing of an elevated IOP to the normal range, these patients presented a special challenge to the clinician.

In individuals with low tension glaucoma, very often a low blood pressure is also found. Arteriosclerotic optic atrophy, in which glaucoma often develops, is characterized by low blood pressure in the posterior ciliary vessels.(14) As the previous experiments demonstrated, the balance between the IOP and the blood pressure in the disc vessels is decisive in maintaining proper vision. When the systemic diastolic pressure is lower than the IOP, the disc and choroid arteries do not fill. If the IOP is 65%, filling is slow and sometimes only partial. When the IOP is less than 40% of the systemic diastolic pressure, filling is normal, regardless of the pressure. This was demonstrated in a monkey

whose blood pressure was lowered by IV injection to 35/15, yet had normal filling, though its IOP was only 5.[15]

All these observations provide a new view into glaucoma: in Hayreh's words, "One could define glaucoma as a disease in which the normal balance between the IOP and the blood pressure in the choroidal vessels supplying the optic disc and the retrolaminar part of the optic nerve is disturbed, resulting in vascular insufficiency in the optic disc and the retrolaminar part of the optic nerve, which produces visual field defects and optic disc and optic nerve changes." He goes on to say: "Thus a complete occlusion of the posterior ciliary artery produces ischemic optic neuropathy, while an incomplete occlusion produces glaucomatous changes. In both cases, the nerve fibre bundle defects are identical." With this new concept of glaucoma, we are able to understand the mechanism involved with some patients who were hypertensive[16][17] with normal or high normal IOP: when their blood pressures were lowered by antihypertensive drugs, they developed glaucomatous field defects; when their blood pressures were permitted to rise, their glaucoma became considerably improved.

The observations made by Hayreh in monkey studies have been confirmed in tests with humans. In one study with 58 patients[18] with severe nerve fibre bundle defects, three groupings of the patients were made:

1. Those with elevated IOP as compared to systemic blood pressure;
2. Those with relative obstruction in large vessel circulation and low blood pressure;
3. Those who had sudden blood pressure drops either due to hemorrhage or excessive anti-hypertensive treatment.

The condition of patients in the first group corresponded to the first of Hayreh's two basic situations associated with hypoxia of the optic nerve; the condition of patients in the second and third groups corresponded to the second of these two basic situations.

Two of these patients had IOP that never tested over 21 mm. and was as low as 12 mm. before any treatment. Other patients had IOP's up to 50 mm., yet the damage with all these patients was comparable regardless of pressure. Among the 58 patients, 60% were found to have clinically diagnosable vascular disease, but the other 40% were without any abnormal symptoms discoverable by a vascular neurologist using various laboratory studies. It was in this ostensibly "normal" group that a high percentage had elevated IOP.

The correlation of visual disorders and specific vascular supply.

The peripapillary choroidal vessels and their supply to prelamina cribosa area of the optic nerve

Fluorescein angiography studies in humans[19] also demonstrate as did the monkey studies[20] that particular ciliary arteries fill only certain segments of the choroid and disc. Three groups of patients whose glaucoma varied from no apparent defects to advanced degeneration were the subjects of a study in choroidal circulation. Angiograms were taken at different IOP's and observations were made of the arterial and capillary filling.

Group 1 - 11 patients with IOP between 26 and 36 mm. Hg. who had normal field and optic discs;

Group 2 - 16 patients with limited cupping of the disc and moderate field loss;

Group 3 - 8 patients with total excavation of the disc and severe field loss.

IOP was raised using a special suction cup to a level slightly above the systolic values of the ophthalmic artery and a dye was then injected IV. IOP was gradually dropped while angiograms were taken at closely spaced time intervals. The results were as follows:

FILLING OF CHOROIDAL VESSELS AT VARIOUS IOP

Normal IOP	Approx. 50 mm.	Approx. 80 mm.
Group 1 - No defects	Some defects close to	Defects close to,

		disc	but not touching disc
Group 2 -	Incomplete and delayed	Incomplete areas grow larger	Incomplete areas expand to disc margin
Group 3 -	Incomplete filling defect adjacent to disc in eyes	Filling defects become larger in area than in eyes with lower pressures	All but one patient had filling defects extending to disc margins

Filling defects were noted as sections of the choroidal circulation that did not fluoresce, indicating an absence of blood flow. In Group 1, defects were seen even under high IOP, separated from the optic disc, showing a fluorescence between the disc margin and the defect. This separation narrowed and gradually disappeared as the IOP was raised and observed in patients with more advanced glaucoma. Disappearance of fluorescence indicates the closing of blood flow in the particular vessels due to the elevated IOP.

Other studies have demonstrated that the peripapillary choroid is made ischemic much sooner at elevated IOP than other areas of the choroid. The primary source of blood to the prelamina criborosa comes from the peripapillary choroid, and even in normal eyes at elevated IOP, the optic disc does not fill unless IOP is reduced sufficiently to permit the peripapillary choroid to fill first. This is true even when the central retinal artery is filled.

Increases of IOP produced sections of no filling that became larger in the subjects as the pressure was increased. With advanced glaucoma, these ischemic sections were observed without elevating IOP. These ischemic sectors are the basis for visual field defects, and the field defects would be expected to be directly correlated to the location of the ischemic area.[21] Figure 7 shows the visual field loss directly attributable to localized ischemia due to an observable emboli.

In some patients, emboli and subsequent ischemia in the optic vessels occur over a protracted period of time. As the emboli are first seen, if not occlusive, there is no observable field loss. But as the circulation worsens, field loss develops; the position

of the loss can be directly correlated to the area of ischemia in the eye.

Two such cases will be described:[22]

A 62-year old man experienced sudden blindness in the left eye. In a few hours, his sight slowly returned, but the next day the blindness reoccurred. Upon examination, his right eye was found to be normal, but in the left fundus close to the disc and along the superior nasal artery a small infarct was noticed. At the first bifurcation of the superior temporal branch of the central retinal artery a reflecting yellow-white embolus was also noted, but it did not seem to impede the blood flow. Pressing on the globe through the lower lid caused the embolus to sparkle. Additional pressure partially collapsed the central retinal artery and the reflecting embolus flowed down to the disc. Pressure was immediately released, and instantly, with the fresh flow of blood, as the artery filled, the embolus was quickly floated to its original position, the superior temporal branch.

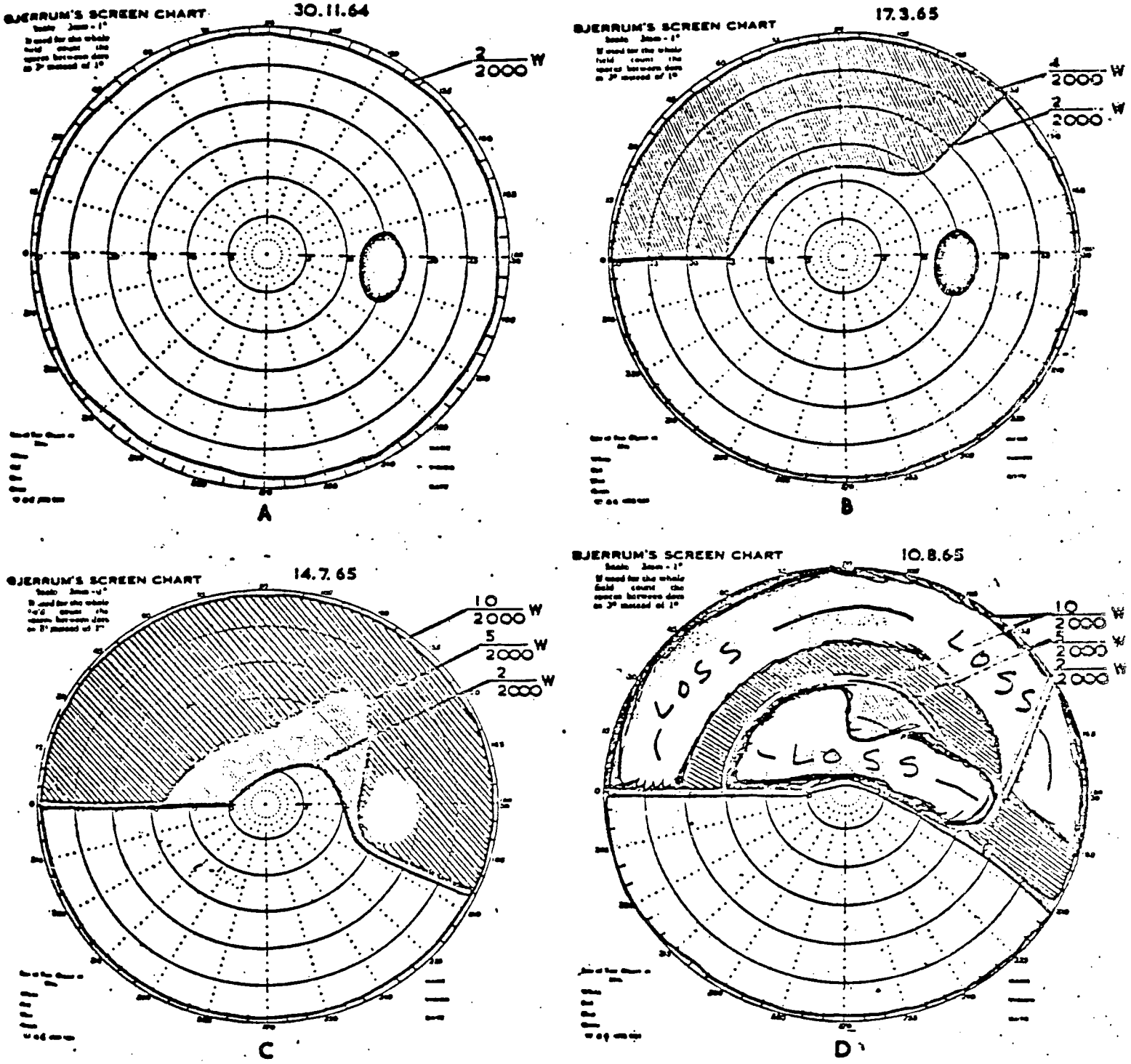
Field studies of the subject were made and a scotoma correlating with the size and position of the infarct in the superior nasal artery was noted.

Two findings in the case of this man are evident: 1. The correlation between the infarct and the loss of visual field, both as to size and location; 2. The appearance of emboli from distant plaques that became wedged in vessels. Subsequently the superior temporal branch emboli disappeared, but other plaque fragments over the months appeared and mostly disappeared. Some remained and formed permanent opaque areas in the vessel wall.

In the second case, also involving a 62-year old man, there was sudden blindness in the right eye. Upon observation, three sparkling plaques were noted at different bifurcation points of the central retinal artery. When the globe was gently pressed digitally, the plaques flashed in relation to the pressure. Visual field studies were made, but no defects were found. The progression of visual field loss is shown in the following figure, where A represents the no discernible defect stage. A few days later the arterial wall adjacent to the plaque at the inferior

papillary artery started to opacify, and after a period of weeks, several small infarcts (cotton wool patches) appeared in the area of the retina supplied by branches of the inferior papillary artery. The arterial wall opacities became more intense and spread to another branch fed by the inferior papillary artery. Visual field changes now started to develop (B). A progressive loss of field slowly took place limited to the area supplied by the

VISUAL FIELD CHANGES DUE TO ISCHEMIA OF INFERIOR PAPILLARY ARTERY



A-D Visual field changes. Analysis of these changes indicates progressive ischemia in the territory of the sclerosing inferior papillary artery with superadded acute absolute field loss after successive infarcts produced by occlusions of arterioles.

inferior papillary area (C). Superimposed over this field loss this field loss were sectors of acute absolute loss that directly correlated with the observed infarcts(D).

The proposition that plaques cause field vision loss is convincing when the eye is tested before the loss and at each stage following the appearance of emboli, as the loss progresses in relation to the size and position of the emboli. In this case, as the ischemic areas broadened, the visual field losses followed very closely. With both 62-year old subjects, the plaques or emboli originated from distant sites--their free movement in the arteries demonstrating that they were not derived from local plaques of the intima where they were observed.

Additional evidence of the embolic nature of these fragments come from other studies where pressure on the eye fragmented the emboli so that they completely passed out of the area, leaving no evidence of arterial damage. In one case of death from atheromatous embolism of the middle cerebral artery, 12 bright glittering plaques appeared several hours before death occurred, located in the ipsilateral retinal arteries. The plaques were examined after the patient's death and were filled with cholesterol crystals.

When atheromatous human plaques were injected into dogs and monkeys, the same glittering retinal emboli were noted that are so often seen in humans. The emboli were subsequently found to be cholesterol crystals.

Plaque breakoff as the etiological factor in these cases must be presumed, because of the inability to recover and analyze the emboli.

Visual Field Changes Due to Ischemia of Central Retinal Artery

An opportunity for positive proof of the composition and origin of such an embolus was created by sudden blindness in the left eye of a 74-year old woman[23] who had been under treatment for open angle glaucoma. When examined, the IOP in the left eye was found to be 30 mm.; it was 36 mm. in the right eye. Despite heroic measures utilizing vasodilators, anticoagulants, occular

massage, and antihypertensive drugs, the pressure of the blinded left eye rose. In six weeks it measured 82 mm. Because of the severe pain, the eye was removed.

The eye appeared relatively normal except for rubeosis iridis that had developed on the anterior iris surface, causing a secondary hemorrhagic glaucoma. In the central retinal artery, immediately posterior to the point of penetration through the lamina cribosa, an atheromatous embolus was found. It was calcified with many cholesterol crystals, but the wall in which it was lodged showed no atheromatous changes. The embolus had originated from a distant site and floated in the blood until the lumen narrowed enough to prevent its further passage. Its sharp edges swelled and partially destroyed the endothelium in the area where it had lodged.

Microscopic studies demonstrate that a plaque broken off from a distant artery may cause total occlusion of the ocular arteries, followed by blindness, and can also cause rubeosis iridis. The investigator concluded that the rubeosis is the direct cause of the secondary glaucoma in <u>all</u> cases of hemorrhagic glaucoma. This is confirmed in other reports.[24]

<u>Visual Field Loss Due to Ischemia in Temporal Branches of Central Retinal Artery</u>

A 50-year old man who had been treated for mild hypertension for 10 years became aware of a gradual loss of his field of vision.[25] He was found to have normal IOP (OD-16 mm.; OS-10 mm.) and normal outflow facility. Yet a well-developed rubeosis iridis was found in both eyes. Bilateral occlusions of the temporal branches of the central retinal arteries were noted, and the location of these occlusions matched the location and shape of the visual field defects.

Even in a patient with apparently normal clinical values, mild ischemia is sufficient to create the conditions causing considerable visual field loss. The occlusions were definitely demonstrated by fluorescein injection, but since they were limited to the branches, the circulation loss was small.

Thus, even with completely normal clinical values present, relatively little circulatory arrest can cause glaucoma. The ischemia in this patient was enough to stimulate the neovascularization of the iris, although it did not develop into a secondary hemorrhagic glaucoma. It could be called a benign course with a 25% loss of visual field, created from minute emboli due to plaque breakoffs at some distant site.

Retinal Detachment

Although it is recognized that emboli can create problems ranging from slight visual field defects to blindness, their role in retinal detachment has not been generally appreciated. A well-designed experiment on cats[26] clarified the mechanism of ischemia in the choroid and its relationship to retinal detachment. An emulsion of latex microspheres (6 u-14u diameter) was injected into a sector of the choroidal circulation. It covered about 20% of the fundus area. Because of the localization of the injection, the retinal vessels were not affected, nor was the inner (neurosensory) layer of the retina. Varying in duration from a few minutes to two days after injection, the inner retina directly over the occluded choroid sector detached from the outer retina (epithelium layer). In a short time the detachment became bulbous and sometimes spread to a greater area than the original choroid occluded sector. In 61% of the eyes, retinal detachment occurred. In only one of the 14 detachments was there any hole and tear, which would normally be expected in many cases. There was only one primary etiology--ischemia, by occlusion. An embolus from a distant plaque could have been equally damaging as were the latex microspheres.

To test the remote possibility that the propylene glycol, the carrier for the latex, could have been partially responsible for the detachments, some eyes were injected with the glycol alone. Of ten eyes so tested, no evidence of degeneration was found, even though they were followed for 10 weeks. One of the eyes developed some detachment that was thought to be caused by the injection raising the hydrostatic pressure of the vessels of the choroid,

creating a transudation. In a similar test of saline injections, no damage occurred.

Upon microscopic examination of the occluded choroid vessels, the latex spheres and entrapped erythrocytes were noted not only in the larger vessels, but in the choriocapillaries as well. Vessel walls appeared normal and there seemed to be no abnormal changes in other parts of the eye. IOP was also normal, and generally all 23 eyes changed only in the ischemic sector.

Visual field loss and lowered oxygen tension

The evidence associating various forms of visual degeneration with insufficient circulation suggests that the underlying problem is due to oxygen starvation of the tissue. The observation that various conditions tending to reduce oxygen in the blood will reduce the size of the visual field supports this view. Thus, smokers have been found to have reduced visual fields.

Smoking reduces oxygen content by producing carbon monoxide, which in turn forms carboxyhemoglobin. A 10-20% level of carbon monoxide can exist in the hemoglobin, thus restricting the oxygen-carrying capacity.(27) In a study of the effects of smoking on visual field, these results were found:(28)

1. Habitual smokers. For a two-week period, subjects reduced or completely stopped smoking. Field studies were made immediately before and after the two-week period. Tests at the end of the two weeks demonstrated an enlargement of the visual fields from 16% to 85%, with an average of 36%.
2. Nonsmokers. These subjects were tested and then they smoked for a two-week period and were tested again. The average field loss at the end of the test was 26%.

A more direct experiment correlating oxygen to size of visual field was done on twenty-year olds.(29) These subjects were trained for both perimetric field and flicker tests and considerable data had been gathered on their visual functions. To determine the effect of reduced oxygen level on their vision, they inhaled a gas mixture containing 5% oxygen instead of the normal

20%. There was no restriction on the number of inhalations per minute or the quantity of gas inhaled. After at least five minutes, measurements were started. The entire test took less than 15 minutes, during which time the subjects were seated comfortably with their heads resting on a head and chin support.

All subjects inhaling the reduced oxygen mixture experienced a shrinking of the visual field. One 25-year old man had a 20% loss of field in the upper temporal quadrant. In another 22-year old man, central flicker frequencies dropped 8 cycles or approximately 20%.

FFF field (flicker fusion frequency) testing is important in understanding glaucoma. Since the test was developed for practical application in 1950,[30] it has been widely used. Essentially the test consists of response to a light which is flickered at a constantly reduced frequency until it is first noticed to be flickering, at which critical point the frequency of flicker in cycles per second is noted. The light is moved throughout the visual field and the frequency response is mapped in the same manner as is done for perimeter charts.

Patients with early field loss in glaucoma are found to have a lower FFF[31] and many without any field loss are found to have an abnormally low FFF. In many instances low FFF will precede field loss, indicating low values in areas that later will show visual field loss. Thus, it can be a very sensitive indicator mapping future glaucoma damage.

The production of lower FFF simply by reducing oxygen tension in the blood of a subject only 22-years old sheds much understanding on the subject of glaucoma. Earlier, we have drawn attention to studies demonstrating visual loss from slight field loss to blindness, all with an etiology of various degrees of reduced circulation. Lowered oxygen tension of the blood produces effects similar to those obtained with reduced blood flow due to circulation impairment. The measure of the effectiveness of circulation considers total oxygen brought to the tissues per specific volume of blood. If, for example, the blood has 30% less oxygen, the result, so far as tissue nutrition is concerned, would

be the same as if the blood flow were reduced by 30%, though it contained the normal complement of oxygen.

Studies on humans show the validity of this concept. It is well established that raising the oxygen tension of the blood constricts both the arteries and veins of the retina.[32] In fact, under continuous elevated oxygen tension for 150 days, a 32-year old man lost his vision.[33] Examination revealed a complete stoppage of circulation due to the almost total constriction of the retinal vessels. Oxygen level was dropped gradually until he was breathing room air. After 5 months, one eye is still blind and the other can see only hand movements.

In one study, normal men were given pure oxygen to breathe for three hours.[34] During this period bilateral constriction of their visual field was noted, reaching its full shrinkage at the end of the three hours. It was also noticed that the retinal vessels had constricted considerably. As soon as they resumed breathing air in the room, the retinal vessels opened to their previous diameter and the visual fields enlarged back to normal. It was found that the constriction of the vessels reduced the flow of blood so much that even with the increased oxygen tension, the total oxygen was less than normal. This resulted in shrinkage of visual fields not unlike that in the subjects on 5% oxygen.[35] In the subjects of both studies the total oxygen available was less than normal.

A conclusion to be drawn from these studies is that total oxygen brought to the tissues must have 90-100 mm. oxygen tension as well as normal blood flow if visual efficiency is to be maintained at a maximum level.

Although visual field defects earlier discussed were of a sectorial nature due to loss of circulation in a specific section of the choroid, a reduced oxygen tension causes shrinkage of the entire visual field, since it affects the circulation of the entire eye.

Oxygen tension in the blood may be lowered due to other ordinary environmental conditions besides smoking. Elevation of blood lipid levels in animals and humans has been shown to be

associated with reduced oxygen-carrying capacity of the blood. The gradual elevation of lipid levels with advancing age in countries with high-fat diets (Western diets of 40%+ calories in fat) has been noted earlier.

In reviewing over ten studies analyzing arterial oxygen tension versus age of patients in the U.S., oxygen tension was observed to fall without exception as age advanced. Oxygen tension ranged from 100 mm. in the 20-year olds to a low of 58 mm. for a 68-year old. More representative values were from 90 mm. for the young, to 70-80 mm. for the aged, with medium values in between.(36)

These oxygen values correspond to shrinkage of visual fields occurring with aging in Western cultures. Perimetric and FFF tests on more than 400 normals aged 16 to 91 show this relationship.(37) A definite shrinkage in visual field occurred with every decade increase in age: the youngest had the largest field and the oldest, the smallest.

The youngest subjects were then given 5% oxygen to breathe and were retested. Their visual fields shrank to the same size as those found in the subjects aged 30-50 years. Tested for FFF, these young subjects under the influence of 5% oxygen tested as though they were 60-70 years old.

If lowered oxygen tension reduces field below normal, would 100% oxygen for a few minutes expand the fields greater than normal? This was tried, but the results in the young subjects were identical to those obtained with the breathing of normal air. Normal oxygen intake (ordinary air) permits optimal vision if the oxygen tension of the blood is 90-100 mm., as was the case in these young subjects. Below these optimal oxygen tensions, vision will shrink, regardless of the cause of the reduced oxygen tension.

We have observed lowered oxygen tension associated with multiple causes:

1. Smoking - oxygen level drops because of carboxyhemoglobin.(38)
2. Lowered oxygen content in air.(39)

3. Lowered oxygen tension in blood associated with aging.(40)

As the blood lipid level rises, the oxygen-carrying content of the blood drops. A high-fat meal typical of the Western diet is capable of increasing blood lipids and reducing oxygen tensions to 80 mm. or less in normals, so that shrinkage of field probably begins as early as the second decade of life, worsening as the individual ages. This particular phenomenon accompanies other degenerative changes that owe their origin to the dietary regime of our culture.

III. ETIOLOGY OF ELEVATED IOP

Significance in glaucoma.

Most clinicians treating glaucoma consider elevated IOP as the most important problem and attempt to bring it into "normal range". If they suspect a vasogenic factor, they may, in addition, use vasodilators or anticoagulants. Diet is not considered in the treatment.

Unfortunately, elevated IOP is just a symptom; even if it is controlled, the eye gradually worsens since the true cause is not considered. As Duke-Elder, a respected worker in this field, said in 1953,[41] "if the be-all and end-all of glaucoma resided in a raised tension and the raised tension itself were dependent upon the efficacy of drainage of the intraocular fluids, then surely the anxieties of five generations of ophthalmologists and the tragedy of blindness that has overtaken countless numbers of their patients could be mechanically relieved by sufficiently enthusiastic surgery." He later[42] reminded clinicians that glaucoma defects occur in the absence of elevated pressure, and that in the presence of elevated pressure both the optic disc and the visual field can remain normal for long periods of time.

Treating elevated IOP produces benefits as dubious as those obtained in controlling elevated glucose level in diabetics. The glucose levels of diabetics may be brought to normal and kept there by strict control but these patients still have a cardiovascular death rate 250% greater than normals. (See Part III, Diabetes). In analogous manner, those glaucoma patients who have been surgically treated to effect a normal IOP continue to lose visual field and progress towards cataracts faster than normals.[43] The realization that elevated IOP is just a symptom--comparable to the elevated glucose level of diabetics and that the real problem is vascular--has just begun to impress itself upon clinicians.

While a detailed analysis of glaucoma is beyond the scope of this writing, wide angle glaucoma (simple glaucoma)--the chief cause of blindness among adults in the U.S.--is understandable in the context of this discussion. Wide angle glaucoma is diagnosed

primarily upon demonstration of elevated IOP, usually combined with observation of visual field changes. Since visual field changes and the usual findings of glaucoma may also occur with normal IOP (low tension glaucoma), it is the contention here that IOP is not the causative factor, but another symptom. Elevated IOP is still the diagnostic sign most often alerting the examiner to glaucoma, however, although this disease can appear and worsen in the presence of normal IOP

The etiology of elevated IOP is unsettled at this time, but enough is known to permit a hypothesis to be proposed.

Increased blood flow in optic vessels as a factor in elevated IOP.

While elevated IOP has multiple etiologies, the opinion expressed here is that only two basic conditions are responsible for most cases of elevated IOP: 1. Increased flow of blood in the optic vessels; 2. Deficiency of the outflow facility.

To approach with proper understanding the problems associated with the first of these conditions--increased flow of blood in the optic vessels--clarification of the physiology of blood gas pressures is required. At a barometric pressure of 760 mm. of mercury at sea level and deducting 615 mm. for the partial pressure of water vapor and nitrogen, approximately 145 mm. is left for oxygen and carbon dioxide. Partial pressure of carbon dioxide (pCO_2) is about 40-45 mm. and of oxygen (pO_2) about 100 mm. During hypoventilation due to various causes, such as obesity, respiratory problems, or inactivity in sedentary individuals, pCO_2 rises and pO_2 drops, accordingly.

As pCO_2 rises, ocular blood flow increases and IOP becomes elevated. This phenomenon has been observed repeatedly in both animals and man, although most of the evidence derives from animal experiments.

In one study,[44] dogs were permitted to breathe room air, but rebreathed air that they had exhaled to decrease their oxygen intake and increase the carbon dioxide intake. Their total air intake thus consisted of part fresh air and part exhaled air. pCO_2

rose and with this rise the ocular pulse pressure increased from 15 mm. to 37 mm. Since the blood flow is directly related to the pulse pressure, a substantial increase of blood flow occurred. A summary of the results is tabulated below:

RESULTS OF BREATHING ROOM AIR MIXED WITH EXHALED AIR

	pCO_2	pO_2	Ocular Pulse	pH
Start breathing	40 mm.	80 mm.	15 mm.	7.30
Five minutes later	65 mm.	25 mm.	37 mm.	7.22

These results were confirmed using CO_2 and O_2 mixtures instead of ambient air.[45] Cats and rabbits were used in these tests and blood flow and IOP were directly measured upon breathing of various CO_2 mixtures. In one test, 12% CO_2 in O_2 produced an increased blood blow within two minutes after the start of inhalation. The flow increased almost 50% and remained at that level until the mixture was replaced by air. Simultaneous with the flow increase, the IOP increased, paralleling the flow increase curve. The IOP also maintained a 50% increase over starting value, returning to normal as the flow became normal. The pH dropped from a start of 7.4 to 7.1 at the peak of the blood flow and IOP.

Several drugs were tried, all of which increased ocular blood flow. In every case, as the ocular blood flow increased there was a parallel rise in IOP. One drug caused a decreased flow which was followed by a decreased IOP.

Another series of tests[46] with dogs confirmed these results and added new information. Mixtures of CO_2 and O_2 were used, and in one series, the results of 5%, 10% and 15% carbon dioxide mixtures were observed. The results are summarized.

EFFECTS OF BREATHING VARIOUS CO_2 AND O_2 MIXTURES
Change from base values using 100% O_2

Condition	IOP	Arterial Pressure	Venous Pressure
5% CO2	+35%	+151%	+66%
10% CO2	+85%	+93%	+47%
15% CO2	+75%	+173%	+111%
Asphyxia	+88%	+66%	+138%
Hyperventi-lation	-17%	-5%	-27%

At each increased level of CO_2, there was a corresponding increase in blood flow, as represented by the pressure rise, and another corresponding increase in IOP. Normal ventilation was considered to be a respiratory rate of 20 per minute. For testing hyperventilation, this rate was maintained, but the inflating pressure was increased. The additional volume of gas raised the pO_2 tension above the base value, which produced a blood flow and IOP less than base values. Asphyxia was achieved by switching off the air supply until apnea (cessation of breathing) took place. This condition created a substantial increase in blood flow and IOP.

Data from humans corroborate the conclusions reached in the animal studies: as CO_2 rises, IOP rises due to increased intraocular blood flow. In one study, ten normal patients were anesthetized with cyclopropane.[47] While the cyclopropane in the mixture was held at a constant percentage, the CO_2 content was varied from 25 to 96 mm. of mercury. It was found that a direct relationship existed: as the pCO_2 rose, so did the IOP in a direct proportion. When the pCO_2 was held constant and the anesthesia proportion was varied, it was found that the greater the anesthesia percentage, the lower the IOP and the cerebral blood flow. This response was also noted in another human study[48] of 39 eyes (24 patients), where general anesthesia was found to decrease ocular blood flow and IOP in a direct correlation. Hyperventilation also produced a lowered IOP, confirming the previous studies cited.[49]

The effect of ventilation was pursued further in a study of 31 patients under anesthesia.[50] When the anesthesia state

stabilized, CO_2 content of expired air was measured at the same time as the IOP. Patients were then hyperventilated and hypoventilated and similar measurements were taken. The results confirmed the previous studies, and are tabulated below.

RELATIONSHIP OF CO_2 IN EXPIRATORY AIR AND IOP

Condition	CO_2 Content at End of Respiration	Average IOP
Hyperventilation	3.8%	12.6 mm.
Normal Ventilation	4-5%	14.5
Hypoventilation	6%	16.3

Several other studies are cited by this investigator showing a general dilation and increased blood flow occurring in a direct relationship to a rise in pCO_2.

A further example of the direct effect of blood flow on IOP comes from tests using propranolol, a Beta adrenergic receptor blocking drug. When this drug is injected IV into both rabbits and humans,[51] the IOP drops significantly. In treatment with this drug, systolic blood pressure and heart rate are reduced and studies have reported a 25% reduction in cardiac output.[52]

This study has special relevance for hypertensive individuals in whom increased cerebral blood flow may raise IOP.[53] Autoregulation of blood flow maintains cerebral blood flow at a constant rate until the blood pressure exceeds the resting rate by 40%; cerebral blood pressure becomes elevated when resting blood pressure rises above this. The hypertensive condition leads to raised IOP; reduction of blood pressure reduces IOP.

The studies correlating lowered pO_2 and raised pCO_2 to elevated IOP assume importance because the majority of the population in the U.S. have less than optimal pO_2 tension in the blood. Groups at risk have been discussed previously; their pO_2 is physiologically too low, while their pCO_2 is too high, due to various mechanisms. They are:

1. Smokers--lose oxygen because of carbon monoxide;

2. Sedentary individuals--shallow breathing results from a low level of activity, which limits the amount of fresh air entering the alveoli of the lungs and so maintains a chronic state of elevated pCO_2;[54]
3. Hypertensives--autoregulation of blood flow will maintain cerebral blood flow at a constant rate until the blood pressure exceeds resting rate by 40%. Cerebral blood flow now increases greatly, and as studies cited have demonstrated, raise IOP abnormally.[55]
4. Ninety-nine percent of the U.S. population (those consuming a diet with 40%+ calories in lipids).

Throughout this book, evidence has been presented that people on the typical Western 40%+ fat diet, from children on up to the aged, have elevated lipid levels, which reduce oxygen-carrying capacity. This results in an elevated pCO_2, which raises IOP. Gradual shrinkage of the visual field may lead to glaucoma and even ultimately to blindness, due to ischemia and occlusions from atheromatous emboli.

Deficiency of outflow facility due to edema and elevated blood lipids (considered normal by U.S. standards) as a factor in elevated IOP.

Steroids mimic the process by which elevated blood lipids create resistance to aqueous drainage. In many cases where increased IOP has been reported due to the use of steroids, the elevation has been traced to a decreased outflow facility.

Two young women, aged 17 and 20 years, used topical corticosteroids in relation to irritation from contact lenses.[56] After a period of several months, each woman developed an elevated IOP. In both cases there was a decrease in outflow facilities with all eyes averaging .10u liters/min./mm. Hg (normal .28u liters).

In the body, a major corticosteroid is cortisol. It is produced with a diurnal variation, the peak level occurring at 8 a.m. and the lowest output at midnight. The difference between the high and low plasma values are in the range of 5 to 1.[57] This

cycle becomes of interest when IOP is checked throughout a 24-hour period in humans. Most eyes reach a peak IOP roughly correlating in time to the peak plasma cortisol level; by the end of the day, the IOP has fallen in line with the reduced plasma cortisol level. Normal eyes usually do not exceed 5 mm. Hg. from low to high in the 24-hour period, but glaucomatous eyes may fluctuate more than 10mm. Hg. and sometimes as high as 40 mm. Hg.[58]

In Cushing's disease, where there is an excess of cortisol secreted, the diurnal cycle practically disappears. Instead a constant plasma level of almost twice the peak normal level is secreted. The IOP is usually elevated in this disease,[59] and there are many similarities to glaucoma.

If a normal person ingests a corticosteroid, in 24 hours there will be a suppression of cortisol output. This does not occur with glaucoma patients, who tend to react like individuals with Cushing's disease. Over 100 patients were tested for this relationship in a study whose results are tabulated below.[60] Close attention was given to matching the normals to glaucoma patients as to age, sex, refractive errors, etc. The results are summarized:

PLASMA CORTISOL - BEFORE AND AFTER .75/MG. DEXAMETHASONE

Population	No. of Patients	Plasma Cortisol Starting Value	Plasma Cortisol 24 hours after Steroid	Percent Suppression
normal	73	25.80	18.47	28%
open angle glaucoma (no field loss)	52	29.75	25.01	16%
open angle glaucoma (with field loss)	42	27.25	25.74	6%

Patients with Cushing's disease show slight or no suppression of cortisol, much like those with open angle glaucoma with field loss.[61] Cushing patients with their elevated cortisol levels lose diurnal IOP variation and their IOP maintains the peak level. Patients with adrenal insufficiency requiring doses of

corticosteroids also lost diurnal variations of cortisol level and IOP, much like Cushing patients. Elevated cortisol is therefore one potent factor in raising IOP.

Other characteristics of Cushing's disease are of interest. They include: hypertension, hyperglycemia, fluid retention, hyperlipidemia, hypercholesterolemia, and elevated insulin level. Among these syndromes are the necessary conditions to create a decreased outflow facility. Fluid retention (edema) could create swelling of the collagen strands of the trabecular meshwork. This meshwork separates the canal of Schlemm from the anterior chamber, and swelling of these tissues would block the flow.(62) Yet if an adrenalectomy is performed, these abnormalities disappear since the cortisol is no longer elevated.

Patients with chronic diseases are usually found to have elevated cortisol values, and it is usual to find hypertension, coronary heart disease, and other degenerative diseases associated with both elevated cortisol and elevated IOP. In glaucomatous patients under standard medical treatment including miotics, no significant difference is found between their cortisol levels and those of patients who are not under treatment.

In the following hypothesis, an explanation is offered as to why plasma cortisol levels are elevated.

The high blood lipids resulting from the Western type diet (40%+ of total calories in fat) cause insulin to become less sensitive to glucose (see Part III, Diabetes), so that a higher insulin level must be maintained in order to metabolise the same quantity of glucose. This early hyperinsulinemia, a characteristic of hypoglycemia and newly diagnosed diabetes, stimulates plasma cortisol.(63) If .5-.15 units of insulin per kilogram of body weight is injected IV--only 8 units for a 60 kg. man--plasma cortisol will rise from 15 to 30 ug/100 ml. within an hour. Plasma H.G.H. (human growth hormone) will climb from 3 to 25 ug/ml., an 8-times rise. Free fatty acids (FFA) are immediately drawn from the adipose tissues, and as the FFA level rises, insulin becomes even less responsive to glucose. This vicious circle continues as the level of insulin rises still higher to cope with the glucose

metabolism: the higher insulin level raises the level of cortisol, then that of the human growth hormone, then the free fatty acid level, making insulin still less responsive to glucose, and so on. (This entire mechanism is detailed in Part III, Diabetes.)

Elevated insulin levels providing the impetus for the sequence of events leading to elevated IOP are brought about by both the simple carbohydrates that raise triglycerides and the high levels of dietary fat that generally raise all lipid levels.

Cortisol has independent effects on the plasma. Twelve patients were started on a daily dosage of 40 mg. of prednisone (a corticosteroid)[64] and after only one month their cholesterol had risen 91 mg./100 ml. and their triglycerides 24 mg./100 ml.--both highly significant increases. As would be expected, a substantial increase in insulin occurred, pushing the subjects towards hyperglycemia.

Another relationship that may be significant for outflow facility concerns circulating lipids in the blood, abnormally high on the Western diet.[65] In other sections of this book, evidence was presented on the effect of elevated lipids in the blood upon sludging and clumping of erythrocytes due to chylomicra.[66] Practically no work has been done to establish a relationship between these phenomena and outflow facility, however. With elevated blood lipids, transudation through the iris vessels would be possible which would provide a high concentration of lipids to partially block the trabecular area, thus increasing IOP.

Studies with rabbits[67] provide an insight into the mechanism. Rabbits were anesthetized and three small (2 mm. in diameter) sections of aortic wall or plastic fragments were placed on the iris of the right eye. Visible through the cornea, the effect of the implants upon the eye could be observed. All the rabbits were fed normal chow, but some had 2% cholesterol and 2% cottonseed oil added to their rations.

After nine weeks, their eyes (especially the irises) were inspected for any infiltration of lipids, and the intensity of lipid infiltration was graded from 0 to 4. A grade of one was given if any infiltration was observed and a grade of four if the

infiltration extended from the pupil to the limbus, practically the entire iris.

The rabbits on the cholesterol-free diet had no infiltration on the operated (right eye) or unoperated eye, but lipid infiltration was evident in all the cholesterol-fed rabbits. The average on the operated eye (right eye) was 3.7 and the left eye, 2.2. Shortly after the operation the radial iris arteries were noted to be dilated, apparently due to inflammation created by the implants. This dilation lessened, but continued throughout the test. Other experiments and confirming studies indicate that vasodilation was responsible for the almost 100% greater lipid infiltration in the operated eye.

In some of these studies, the first lipid accumulation observed in hypercholesteremic rabbit irises occurred at the periphery: in this area the arteries are worked the most, because of the intermittent "wrinkling" of the iris every time it dilates.

Both lipid and cholesterol deposition in the iris is caused by elevated blood lipids. If the iris vessels are dilated, as they would be with blood with elevated pCO_2, an increased deposition will take place. Such deposition not only remains in the iris but also freely exchanges with the aqueous humor in the anterior chamber.[68] Chylomicra in this critical area could block flow. Chylomicra vary in size from submicron to a micron, if they clump together. Probably the endothelial layer lining Schlemm's canal offers the most resistance to flow. Electron microscopy reveals passages in the pore structure of this inner wall to be in the range of .12 u to .44 u,[69] thus chylomicra could cause blockage in these small canals.

It is generally not appreciated how small a particle can block the trabecular meshwork. In the cataract extraction operation, it has been convenient to dissolve the zonular fibers supporting the lens, rather than rupture them. Alpha chymotrypsin, a proteolytic enzyme is injected into the posterior chamber; in a few minutes, the zonule is dissolved. Unfortunately, many cases of secondary glaucoma have resulted from this procedure. The dissolved tissue, particles of which are so small that they can only be seen by

electron microscope, were found to block the trabecular meshwork.[70] This occurrence has been confirmed using monkeys.

In capillaries, blockages and interruption of flow in humans, which have been observed and photographed,[71] are caused by chylomicra in bulbar conjunctival capillaries after a single drink of cream. This same blockage in the critical vessels of the iris can cause plasma skimming, a transudation of plasma resulting in a facility of flow into the anterior chamber, partially overloading the facility of flow through the trabecular mesh, and thus raising the IOP.

Elevated dietary lipids raise IOP in two ways:

1. They produce the environment conducive to elevated cortisol levels which produces edema;
2. They load the aqueous humor with lipids and additional fluid from transudation, impeding and slowing the outflow facility.

Lipid lowering and reduction of IOP.

Reversal of the hostile blood environment responsible for these effects can be accomplished by a low-fat, low-cholesterol diet. Some lowering of IOP has also been accomplished with lipid-lowering drugs, though with these there is the risk of known and unknown side-effects. Clofibrate has been extensively used for this purpose and although it has some effect on FFA and other lipids, there is little evidence that it reduces the edema or chylomicra generated by Western diets.

Hanesch observed[72] that patients with acute glaucoma had higher serum FFA during an attack than afterwards. He studied this phenomenon in 25 patients, measuring various lipid components and finding a substantial drop only in FFA: this drop measured 36% after an attack.

Clofibrate trial to lower IOP.

Pursuing this observation, Hanesch and Orban;[73] deliberately attempted to drop the serum FFA before or during the attack stage of glaucoma using a lipid-lowering drug, clofibrate, given in a

single dose of 1.5 grams. Ten patients tried the drug; the attack was relieved in eight of them. Half the patients experienced a substantial drop in their serum FFA and a drop in the viscosity of the blood within a few hours after taking the clofibrate. In every case there was a large drop in IOP by the 9th hour after the drug.

Cullen was encouraged by these results to try clofibrate on ten of his patients who had not responded to other treatment,[74] especially since he had achieved certain positive results with the drug in treatment for diabetic retinopathy for four years. Using the same single dose of 1.5 grams, five of the ten patients responded with IOP drops of as much as 17 mm. to 61 mm. in less than 12 hours.

An interesting observation was made on eyes with normal IOP. No significant drop was noted after drug intake. This was confirmed by Orban in both animal and human eyes.[75] In normotensive eyes, blood lipid levels are low enough so as not to be a factor in elevating IOP; therefore, a further lowering of lipid would have no effect. In later work by Orban, additional data on clofibrate-treated patients were presented: out of 60 patients with glaucoma, 32 had their IOP brought to normal, 15 had lowered IOP, and 13 were unchanged.[76]

The positive results achieved with patients with elevated IOP using clofibrate was not, however, duplicated by other investigators. Gloster[77] tried the single dose of 1.5 grams on 16 patients, unsuccessfully. He then took five of these patients and tried a schedule of 0.75 grams of clofibrate daily for periods of up to four weeks. These patients did not achieve any significant drop after the test period. Although these cases were somewhat different than Cullen's and Orban's, no apparent reason for the failure of treatment was advanced.

Ramsell tried clofibrate on ten of his glaucoma patients,[78] using a 2 gram dosage for a 30-day period. In one case, IOP dropped from 47 mm. to 23 mm., but the drug had to be stopped because of gastrointestinal discomfort. A sustained decrease of IOP was achieved with only 30% of the patients on the drug.

Other trials with clofibrate were made and are now being made, but the level of success is borderline. Benefits from clofibrate have been more consistent in diabetic retinopathy.

IV. DIABETIC RETINOPATHY

Elevated lipids as a factor.

The visual losses due to diabetes are especially merciless, proceeding relentlessly to destroy the victim's sight. As discussed in Part III, Diabetes, an elevated blood lipid level due to the typical Western diet initiates and characterizes the disease. As the blood lipids rise, the circulation becomes more sluggish, and in time the impaired circulation creates the environment for prediabetic and diabetic visual erosion, eventually leading to loss of sight.

Although it has been suspected that there was an association between diabetic retinopathy and blood lipids, little interest in this possibility was reflected in the research. A recent finding, however, has revived interest in this theory. A group of 37 diabetics[79] were examined and classified for retinopathy. Three grades were used: early, moderate and severe. Blood from these patients was analyzed by another investigator for platelet aggregation, and the degree of aggregation was noted. Neither investigator was aware of the other's results. When a comparison of the data was made, a direct correlation was established between the severity of the retinopathy and the degree of platelet aggregation ($.778 - P < .01$).

Why retinopathy becomes more severe when the aggregation of the platelets is greater is apparent. Sluggish circulation and clogged capillaries--the prerequisite conditions for retinal ischemia--were acknowledged; however, it was not clear to the research team why the platelets behaved in this fashion. Their solution was to propose using aspirin because of its property of interference with platelet clumping. There is a better way.

Several studies attest to this effect of diet on platelet aggregation. In 1958, patients with ischemic heart disease were placed on fruit and rice diets for only five weeks.[80] Platelet stickiness was reduced. In 1962, another group tested patients on a diet that included dairy fat and eggs, and found reduced platelet survival time as well as increased aggregation. Another study in

1967 tested both ischemic and normal patients for platelet aggregation before and after a breakfast that included 50 grams of fat. Platelet aggregation increased in all cases. In the normals, a 20-minute platelet count dropped from 85% to 53%; in the subjects with ischemia an initial value of only 60% (because of their already elevated lipid level) dropped to 48%. Young men on a high sucrose diet[81] for only two weeks were found to have a considerable increase in platelet aggregation--an anticipated response in view of the triglyceride rise produced by the sucrose.

Visual proof of the effects of a fatty meal on blood flow are seen in the microphotographs of men five hours postprandial.[82] Capillaries in the conjunctiva were photographed before and after the meal. While all capillaries were freely flowing before the meal, in five hours, at the peak of the chylomicra-loading of the blood, many capillaries had become blocked, the blockage lasting for several minutes in some cases. Whether the blockage was due to clumping of chylomicra, rouleaux formation of erythrocytes, platelet aggregation, or a combination of these factors, could not be investigated in living humans. But they have been explored in animals,[83] and all these factors have been found to be operative.

Unfortunately, the role of diet in the improvement of ocular circulation is not appreciated. One consultant, asked about new therapeutic approaches, did mention nutrition, ("...methods for improving the ocular circulation and hence nutrition of the optic nerve and retina, which may increase their ability to resist the damage inflicted by an elevated IOP"), but his suggestion was to use various drugs. His understanding of nutrition apparently did not include the effects of diet on circulation. With proper diet, not only would the optic nerve and retina be properly nourished but there would be no elevated IOP to "resist".[84]

Hypothesis of etiology of diabetic retinopathy.

The importance of the role of sluggish circulation in diabetic retinopathy has not generally been appreciated; hence a general discussion of the factors involved are of interest.

The evolution of diabetic retinopathy usually starts with retinal vein dilation,[85] and sometimes capillary dilation. The steady elevated pressure that dilates the vessel proceeds to cause microaneurysms, and upon their rupture, minute hemorrhages can be seen. The serum from these hemorrhages is reabsorbed, but the lipid constituents, because of their high level, are only partially reabsorbed. These lipids consolidate to become the exudates. The exudates--yellowish-white, hard and waxy in appearance--unquestionably fats, are derived directly from the plasma.

Exudates from the eyes of diabetic retinopathy patients have been analyzed. They stain as neutral fat using Sudan R. Further sections of exudates trace the particles of fat through various stages: engulfment by phagocytes to form foam cells, and dispersion in the deep layers of the retina.[86]

At this stage, the formed elements of the blood are in a continuous state of varied degrees of aggregation; the resultant ischemia in the tissues induces the development of new vessels. New vessel growth due to ischemia is a normal body process: in the eye, a response is rubeosis iridis; in coronary thrombosis and large plaques, collateral growth occurs (see Atherosclerosis chapter). A characteristic of the new vessel growth is the fragility of the vessels conducive to a tendency to hemorrhage.

Proliferative retinopathy, the growth of new vessels in the eye, is followed by severe changes leading to serious damage or blindness. The new vessels are usually supported by glial tissue, but they can grow in the vitreous body without support, like a delicate lacework (rete mirabile).

How do these stages appear to the clinician? Fluorescein angiography has been a visual aid in relating the observations to the etiology.

In the young diabetic, usually on insulin, and under treatment 10 to 20 years, a first sign in the retinopathy will be central retinal edema.[87] Angiography reveals capillaries in various stages of occlusion and dilation. At a later stage, microaneurysms form from which fluorescein dye leaks profusely. These sites will become the future hemorrhage areas where the first exudates will be

recognized. From this stage to blindness is a matter of two to four years, on an average: the course, says the investigator, is "rapid, bloody and blinding."

Underlying these pathological processes are extremely elevated blood lipids with fasting free fatty acids values of 2000-4000 eq./liter.

In older patients, 40 years and more, angiography reveals patchy microaneurysms in clumps and areas of hard exudates. The dye leaks out quite close to the exudates, following the route of the earlier hemorrhage that brought the lipids to the area. Dye will often leak out in areas where a cotton wool exudate (one which is not yet solidified) will later develop. The "soft" exudate develops and is reabsorbed, and vessels in the area will continue to leak dye into the former site of the exudate, demonstrating a continuing vessel defect.

Blood values indicate hypertriglyceridemia as the principal elevated lipid. Visual loss is gradual and follows the deposition of exudates, which will continue as long as the lipid level remains elevated. Some diabetics in this age group show more obstruction of circulation; in this group, damage can proceed at a rapid rate. Angiography shows the microinfarcts producing large areas of capillary blockage. Leakage of the fluorescein dye through the microaneurysms and the dilated vessels forecasts the hemorrhage stage soon to follow. Blood studies reveal elevated lipids and increased blood viscosity.

One pertinent finding was that the areas of visual deterioration were the same that were served by the smallest diameter capillaries; these would be most affected by formed body aggregation (platelets, erythrocytes, chylomicra). Hard exudates destroy the area of the retina that they occupy, so that even if they are reabsorbed, vision is not restored.

Although retinopathy is found with such circulatory diseases as atherosclerosis and hypertension, diabetic retinopathy has features almost exclusive to itself. An explanation might be found in the elevated glucose level of diabetics, a finding which accompanies a condition of elevated blood lipids (see Part III,

Diabetes). The higher the glucose level, the higher the blood lipids, which, in turn, produces the environment for platelet aggregation, erythrocyte sludging and rouleaux formation, and generalized circulation sluggishness.

Another accompanying symptom is edema, which follows as a result of aggregation of formed bodies. Transudation bypasses the blocked lumen and the resultant edema may swell the trabecular meshwork and reduce outflow, as well as producing a greater quantity of fluid in the ciliary processes. The edema increases the volume of aqueous humor, tending to raise the IOP.

These observations help to explain why hyperglycemics have[88] 300% more glaucoma than nonhyperglycemics. Other studies have found that 20% of diabetics who were unaware of any glaucoma had elevated IOP; and conversely, a group of 325 glaucoma patients were found to have 18% hyperglycemia. These figures exceed the expected incidence by many times.

As earlier noted, corticosteroids raise IOP in many patients. In one study,[89] topical steroids were applied to an eye in each of the subjects tested and measurements were taken for IOP changes. IOP response was classified into three groupings: 1. Nonresponders (nn) - those whose IOP changed little; 2. Intermediate responders (ng); 3. High responders (gg) - those whose IOP elevated substantially.

If edema is the mechanism by which outflow is impeded, then the more the hyperglycemia, the more the edema produced. If added to this edema is a fixed additional load of edema resulting from the cortisone, one would expect that those whose IOP readings were the highest after the cortisone application also had more hyperglycemia. Observations with 340 patients without overt diabetes are tabulated below.

GLUCOSE TOLERANCE AND TOPICAL CORTICOSTEROID RESPONSE IN 40+ YEAR OLDS

Group	No. of Patients	No. of Patients with Positive Glucose Tolerance
nn	50	1 (2%)
ng	70	3 (4%)
gg	100	17 (17%)
glaucoma	120	26 (22%)

Another series of tests were done with different groups, as follows:

TOPICAL CORTICOSTEROID IOP RESPONSE TEST

Group	No. of People	IOP Response 20 mm. Hg.	20-31 mm. Hg.	31 mm. Hg.
normals	300	58	36	6
open angle glaucoma	100	1	17	82
diabetic (n.p.r.*)	200	31	49	20
diabetic (p.r.**)	60	50	42	8

* no proliferative retinopathy
** proliferative retinopathy

The results show that in the normals where little initial edema existed, the edema produced by the cortisone brought only a small percentage of patients over the threshold of 20 mm. Hg. Those with glaucoma, in whom IOP was already elevated, responded to the additional edema by moving into the higher IOP levels.

Diabetics are influenced by an additional variable, high blood lipids. This impedes flow due to sluggish circulation, producing a lowering of the IOP, despite the steroid edema's lowering of the outflow. With proliferative retinopathy, the flow is even more blocked, reducing the IOP still further. In diabetic acidosis, the lipid and glucose blood levels are even more elevated; and in keeping with this hypothesis, the eyeball should be very soft, reflecting the abnormally lowered IOP, as indeed it is found to be.

Treatment of diabetic retinopathy.

Lipid reduction by means of clofibrate

An attempt to reduce retinopathy through lipid reduction by means of clofibrate was made.[90] Over a 3-year period, a highly significant decrease in hard, waxy exudates was demonstrated (P=<.00001). Cholesterol and triglyceride values dropped at the same time, permitting the exudates to be reabsorbed. (Unfortunately, hard exudates damage the area in which they are found and visual function is not restored). It was found that in 2/3 of the patients, new exudates were reduced or completely prevented from forming.[91]

The efficacy of lowering of blood lipids as a preventative measure is well-demonstrated by the results with clofibrate treatment. Low-fat diets have accomplished the same results,[92] but very little has been pursued in this direction.

Hypophysectomy--a radical treatment

Several approaches have been tried in treatment of retinopathy[93] since 1950. Substances used have included vitamins E, C and B_{12}, and such drugs as salicylate, lipotropics, cysteine, androgens, estrogens, and others. Procedures used have included X-ray therapy, adrenalectomy and hypophysectomy. All have been abandoned with the exception of hypophysectomy.

Hypophysectomy[94] (pituitary destruction) is a mutilating operation that has been practiced since 1952. The basis for it is the accidental finding that retinopathy decreased after a post hemorrhage infarct of a patient's pituitary gland. Since then a succession of surgical procedures for total hypophysectomy have been tried and essentially abandoned because of the high morbidity and mortality. The form now practiced is a pituitary stalk resection resulting in a partial loss of function. A short time after this version of hypophysectomy, retinal edema starts to reabsorb and a general vitreous clearing begins. In addition, new vessel formation seems to be lessened.

The probably mechanism involved in improvement in retinopathy following hypophysectomy is suggested by the finding that the requirement for insulin is lower after the operation.[95] Data cited in Part III, Diabetes, indicate that a lowered insulin requirement occurs with lowered blood lipid levels. Without the human growth hormone following hypophysectomy, there is a reduction in free fatty acids, and a resultant lowering of blood lipids. However, as the high dietary fat intake is unchanged, the diabetic state continues unabated. In a group followed for 8 years after hypophysectomy, 62% had died,[96] and generally the diabetes was no easier to control.

Without the pituitary function, lifetime replacement of steroids, thyroid, and gonadal hormones is the price to be paid, notwithstanding the loss of kidney function by lowering of the glomerular filtration rate. The benefits observed in retinopathy treatment following hypophysectomy can be obtained by nondrastic procedures which do not exact any penalties: lipid-lowering regimes[97] and especially low-fat, low-cholesterol diets.[98]

V. THERAPEUTIC MEASURES TO REDUCE IOP AND THE PROBLEM OF CATARACTS

The pharmaceutical approach to the treatment of elevated IOP has many dangers. Even modest therapeutic measures such as systemic anticoagulant treatment[99] for thrombophlebitis has caused blindness. Capillary fragility associated with disciform degeneration of the macula is characterized by intermittent bleeding and formation of exudates. When anticoagulants were introduced, the bleeding progressed into a severe hemorrhage, resulting in the loss of the eye. Anticoagulants are so routinely used that this patient's general physician neglected to advise the ophthalmologist that the drug was being taken; the use of the drug was discovered only after the damage was done.

The basic pharmaceutical approach to elevated IOP involves the use of compounds that produce miosis. These compounds also dilate the various vessels of the eye and increase the permeability of the trabecular meshwork. Instilled in the eye usually more than once a day, the patient regards his "drops" as harmless water solutions. Although these miotics are accepted almost universally as the principal treatment in elevated IOP, they are not without danger.

Cases of detachment of the retina, iritis, increased incidence of cataract and even increased IOP, have been reported with the use of miotics.[100] In one series of 45 patients with glaucoma, IOP could not be adequately reduced with the use of strong miotics several times daily. Pilocarpine (6%) and up to 1/4% of phospholine (echothiophate) were used. When these were abruptly stopped, in 28 of the 45 cases the IOP dropped to normal, and an additional 11 cases reduced their IOP. Only 6 of the 45 were not improved by stoppage of the drugs.

Miotic appearance of the pupils continued for several weeks, and as the pupil size slowly rose, so did the IOP. In those eyes where the IOP became elevated (6 cases), a weaker solution of philocarpine (2%) controlled the pressure.

Using a 2% solution of pilocarpine 3 or 4 times daily on some patients and 1/16 to 1/4% solution of phospholine, usually once a day, observations were made on the progression of cataract changes before and after treatment. The observation period ranged from 1 to 4 years and the results are summarized.

CORTICAL (NONNUCLEAR) LENS CHANGES OBSERVED OVER PERIODS UP TO 4 YEARS

			40-64 yr. olds			65-88 yr. olds		
Condition	No. of Eyes	Observation (yrs.)	Before	After	% Change	Before	After	% Change
nonglaucoma/no treatment	300	2.9	8%	11%	+38%	46%	54%	+17%
glaucoma, on 2% pilocarpine	286	2.3 to 3.9	6%	15%	+150%	59%	62%	+5%
glaucoma, on 1/16-1/4% phospholine	104	.9 to 2.1	6%	16%	+166%	59%	75%	+27%

In the younger age groups, lens opacities increased 400% for those on miotics compared to nonglaucomics with no treatment.

These findings were confirmed in another study of 198 eyes with chronic simple glaucoma.[101] Phospholine was used for periods up to 3 years, and the patients were observed up to 8 years. During this time over 2/3 of all types were found to have developed cataractous changes. There was some indication that discontinuation of the drug after less than 12 months treatment could prevent or slow the development of cataracts, but after 15 months of treatment, this possibility appeared remote.

Hyperemia is a characteristic effect of all miotics. In the rabbit study, hyperemia encouraged much more deposition in the iris than normal.[102] In humans, diffusional exchange between the iris vessels and the aqueous humor in the anterior chamber is considerable.[103] If the increased congestion of the blood vessels in the eyes of humans due to miotics permits the massive deposition of lipids in the iris vessels as it does in the rabbits,

and, as a consequence, the aqueous humor becomes hyperlipidemic by diffusion, then lipids will have substituted for glucose in the hyperglycemic condition, initiating cataract deposition as effectively as excess glucose.

The cholesterol content of cataracts supports this concept: as the cataract develops, its cholesterol content increases.[104] In this connection, the use of triparanol (MER 29) to reduce cholesterol levels[105] is of interest. A side effect of the drug in initiating cataracts was one reason for its removal from the market. Triparanol blocks the final step in the synthesis of cholesterol, the reduction of demosterol to cholesterol. Its use did produce a lowering of the cholesterol level, but this was counterbalanced by a raising of the demosterol level, which the plasma would not accept as normal. Excess demosterol was stored in the tissues and organs as well as in the plasma, and it may have acted in a manner similar to excess blood glucose in leading to cataract formation.

As people on Western diets age, their fasting blood glucose rises in response to rising blood lipids. At ages 40-64 years old, the rise is high enough to be considered abnormally elevated in a younger person. This hyperglycemia that accompanies aging could be one reason for "senile" cataract.

Senile and diabetic cataracts look identical. Although senile cataracts develop especially in people with atherosclerosis, both diabetes and atherosclerosis have as a common finding elevated blood lipids and glucose. In drug-produced alloxan diabetes in animals, a substantial hyperglycemia is noted. Cataracts develop in direct proportion to the blood glucose concentration, and in the mature hyperglycemic state, cataracts always develop.[106]

Sugars, in general, cause cataract, and lactose cataracts are well known.[107] In diabetics with continuous and substantially elevated hyperglycemia, a mature cataract can develop in 48 hours. In diabetics that have started to develop cataracts, further progression can be slowed or stopped with good control and restoration of normal glucose values. There is nothing unique about the diabetic cataract; it cannot be distinguished from the

"senile" type. In both groups--diabetics and aging "normals"--there is an excess of blood glucose.

In cases of inability to metabolize lactose, it becomes elevated in the blood like any other sugar; as the elevation continues, cataracts begin to appear. If milk or other foods containing lactose are no longer ingested, the cataract development will stop and may regress and disappear.

Thus, the best treatment for cataracts would be a dietary change: no simple carbohydrates and a low-fat diet. With this regime, blood glucose would return to the normal range and remain there.

Surgical treatment to reduce IOP may be successful for reducing pressure but is conducive to cataract formation. Several studies[108] acknowledge the increased incidence of cataract formation and progression in eyes that have had operations to reduce IOP. One study of 183 eyes, 83 of which were operated upon and 100 that were refused operation but continued with medical treatment, typifies the results. None of the 83 eyes required medication for control of IOP after the filtration surgery, whereas the 100 control glaucomatous eyes were medically treated for IOP control, some by use of phospholine, previously incriminated in cataract formation. Yet in the same extended observation period, only 8% of the eyes not operated on developed cataracts, compared to 39% of those that had undergone surgery.

INCIDENCE OF CATARACTS IN EYES WITH CHRONIC OPEN-ANGLE GLAUCOMA
(followed for 6 to 22 years)

Condition	No. of Eyes	Total Cataracts Pre-operative	Post-operative
bilateral glaucoma surgery	68	4%	35%
Unilateral glaucoma operated eye	15	0	53%
Unilateral glaucoma nonoperated eye	5	0	0
Control-unoperated bilateral	100	0	8%

In the unilateral cases, the unoperated glaucomatous eye acted as the control, and there were no opacities in 5 of the 15 eyes that were studied postoperatively. This was compared to the incidence of opacities in the operated eyes, where all developed cataracts within 2 to 11 years. There can be little question in these cases that the operation was responsible for the cataracts.

Justification for surgery weakens when it produces 400-650% more cataracts than occurs with medical management of IOP. Even in the control group of 100 eyes, where some cataracts were caused by the use of phospholine, the investigator acknowledged awareness of this risk but said the use was justified for control of IOP. However, as for his surgical experience, he said: "filtration surgery must be blamed for causing, potentiating or accelerating the metabolic changes leading to cataract formation." Yet he stated that to save functional loss of sight, his present knowledge left no alternatives other than surgery and miotics.

This chapter gives him an alternative. Ophthalmologists should heed the words of Dr. Bechrakis of the Institute of Experimental Ophthalmology who said each should ask "whether his patients do not suffer more from his treatment than from the results of their illness".(109)

SIGHT AND SOUND REFERENCES

1. Mann, I. and Rountree, P. Geographic Ophthalmology. A Report on a Recent Survey of Australian Aboriginals. Am. J. Opth. 66: 1120-34, 1968.

2. Early Detection of Glaucoma. Spectrum, a Pfizer & Co. N.Y.C. publication 12: 26, 1964.

3. Rifkind, B.M. and Dickson, C. The Incidence of Arcus Senilis in Ischemic Heart Disease. Lancet p. 312-4, 2-6-65.

4. Roscoe, H.G. and Vogel, A.W. Lipid Changes in the Eye Concomitant with the Development of Atherosclerosis in the Aorta in the Rabbit. Circ Res 23: 633-43, 1968.

5. Kaban, I.L. and Vass, Z. Nature of Human Lens Lipids. Ophthalmologica 154: 551-63, 1967.

6. Slansky, H.H. and Kuwabara, T. Intranuclear Urate Crystals in Corneal Epithelium. Arch Ophthal 80: 338-44, 1968.

7. Pfaffenbach, D.D. and Hollenhorst, R.W. Morbidity & Survivorship of Patients with Embolic Cholesterol Crystals in the Ocular Fundus. Am. J. Ophth. 75: 66-72, 1973.

8. Harrington, D.O. The Visual Fields. C.V. Mosby Co., St. Louis, 1964.

9. Ibid.

10. Hayreh, S.S., et al. Vasogenic Origin of Visual Field Defects & Optic Nerve Changes in Glaucoma. Brit. J. Ophthal. 54: 461, 1970.

11. Hayreh, S.S. Pathogenesis of Visual Field Defects. Brit. J. Ophthal. 54: 289, 1970.

12. Op. Cit. Reference 8.

13. Op. Cit. Reference 11.

14. Op. Cit. Reference 11.

15. Op. Cit. Reference 10.

16. Harrington, D.O. Amer. J. Ophthal. 47: pt. 2, 177, 1959.

17. McLean, J.M. Amer. J. Ophthal. 44: 323, 1957.

18. Feldman, F., et al. Cerebro-Vascular Studies in Chronic Simple Glaucoma. Canad. J. Ophthal. 4: 358, 1969.

19. Blumenthal, M., et al. Peripapillary Choroidal Circulation in Glaucoma. Arch. Ophthal. p. 31-38, 1971 or 1972.

20. Op. Cit. Reference 11.

21. Op. Cit. Reference 8.

22. Dark, A.J. Progressive Focal Sclerosis of Retinal Arteries: A sequel to Impaction of Cholesterol Emboli. Brit. Med. J. 1, 270-3, 1967.

23. Wolter, J.R., and Ryan, R.W. Atheromatous Embolism of the Central Retinal Artery. Arch. Ophthal. 87: 301-4, 1972.

24. Madsen, P.H. Glaucoma Following Occlusion of the Central Retinal Artery. Acta Ophthal. 43: 350-4, 1965.

25. Bresnick, G.H., and Gay, A.J. Rubeosis Iridis Associated With Branch Retinal Arteriolar Occlusions. Arch. Ophthal. 77: 176, 1967.

26. Collier, R.H. Experimental Embolic Ischemia of the Choroid. Arch. Ophthal. 77: 683-92, 1967.

27. Astrup, P. Scandinavian J. Clin. & Lab. Invest. Suppl. 99, 1967 or 1968.

28. Johnson, D.M. Preliminary Report of the Effect of Smoking on Size of Visual Fields. Life Sci. 4: 2215-21, 1965.

29. Wolf, E., and Nadroski, A.S. Extent of the Visual Field. Arch. Ophthal. 86: 637-42, 1971.

30. Miles, P. Flicker Fusion Fields, Technique & Interpretation. Am. J. Ophthal. 33: 1069-77, 1950.

31. Op. Cit. Reference 8.

32. Hickam, J.B. and Frayser, R. Studies of the Retinal Circulation in Man. Circulation 33: 302-16, 1966.

33. Kobayashi, T., and Murakami, S. Blindness of an Adult Caused by Oxygen. JAMA 219: 741-2, 1972.

34. Rosenberg, E., et al. Blood Gas & Neurological Responses to Inhalation of Oxygen at 3 Atmospheres. Proc. Soc. Exp. Biol. Med. 122: 313-17, 1966.

35. Op. Cit. Reference 29.

36. Neufeld, O., et al. Arterial Oxygen Tension in Relation to Age in Hospital Subjects. J. Amer. Geriatrics Soc. 21: 4-9-73.

37. Op. Cit. Reference 29.

38. Op. Cit. Reference 28.

39. Op. Cit. Reference 25.

40. Op. Cit. Reference 36.

41. Duke-Elder, S. Ulster Med. J. 22: 1, 1953.

42. Duke-Elder, S. "Glaucoma" p. 39 Blackwell Scientific Publ, Oxford.

43. Watson, P. Trabeculectomy, A Modified Ab Externo Technique. Annals Ophthal. p. 199-205, May, 1970.

44. Christensen, R.E., et al. Photoelectric Plethsmography. Invest. Opthal. 10: 247-51, 1971.

45. Bill, A. Aspects of Physiological & Pharmacological Regulation of Uveal Blood Flow. Acta Soc. Med. Uppsal. 67: 122-34, 1962.

46. Duncalf, D., and Weitzner, S.W. The Influence of Ventilation & Hypercapnea on Intraocular Pressure during Anesthesia. Anesth. Analg. 42: 232-7, 1963.

47. Hon, Y.H., et al. Effect of Carbon Dioxide on Intraocular Pressure In Anesthetized Man. Anesthesiology 25: 99-100, 1964.

48. Horven, I., and Syrdalen, P. Corneal Indentation Pulse & General Anesthesia. Acta Ophthal. 48: 59-66, 1970.

49. Op. Cit. Reference 47.

50. Meyer, H.J., and Opitz, A. Intraocular Pressure & CO_2 Concentration in Expired Breath. Klin. Mbl. Augenheilk. 156: 730-4, 1970.

51. Vale, J., and Phillips, C.I. Effect of DL & D-Propanolol on Ocular Tension in Rabbits & Patients. Exptl. Eye Res. 9: 82-90, 1970.

52. Frohlich, E.D., et al. The Paradox of Beta-Adrenalergic Blockage in Hypertension. Circulation 37: 417-23, 1968.

53. Hypertension & Cerebral Blood Flow - Editorial - Lancet p. 526-7, 3-10-73.

54. Karpovich, P.V. Physiology of Muscular Activity, P. 126 W.B. Saunders Co., Phila., Pa., 1959.

55. Op. Cit. Reference 53.

56. Burde, R.M., and Becker, B. Corticosteroid-Induced Glaucoma & Cataracts in Contact Lens Wearers. JAMA 213: 2075-7, 1970.

57. Catt, K.J. Adrenal Cortex. Lancet p. 1275-83, 6-13-70.

58. Lennon, R.G., and Turnbull, C.D. Diurnal Intraocular Pressure Variation in a Glaucoma Screening Program. Arch. Ophthal. 80: 714-7, 1968.

59. David, D.S., and Berkowitz, J.S. Ocular Effects of Topical & Systemic Corticosteroids. Lancet p. 149-52, 7-19-69.

60. Schwartz, B., and Levene, R.Z. Plasma Cortisol Differences Between Normal & Glaucomatous Patients. Arch. Ophthal. 87: 369-77, 1972.

61. Op. Cit. Reference 59.

62. Op. Cit. Reference 59.

63. Catt, K.J. Growth Hormone. Lancet p. 933-9, 5-2-70.

64. Kolterman, O.G., et al. Steroid Plasma Effects Studied in Rheumatism. Medical Trib. 9-71.

65. Friedman, M., and Byers, S.O. Some Local Factors Affecting Iridic Lipid Infiltration in Hypercholesteremic Rabbits. Am. J. Physiol. 197(4): 842-6, 1959.

66. Friedman, M., and Byers, S.O. Effects of Unsaturated Fats Upon Lipemia & Conjunctival Circulation. JAMA 193: 882-6, 1965.

67. Op. Cit. Reference 65.

68. Moses, R.A. Adler's Physiology of the Eye. P. 373, 344-5, 307 C.V. Mosby Co., St. Louis, 1970.

69. Kayes, J. Pore Structure of the Inner Wall of Schlemm's Canal. Invest. Ophthal. 6: 381-94, 1967.

70. Chee, P., and Hamasaki, D.I. The Basis for Chymotrypsin-Induced Glaucoma. Arch. Ophthal. 85: 103-6, 1971.

71. Op. Cit. Reference 66.

72. Hanesch, J., et al. Reaction of Blood Lipids During Acute Glaucoma. Klin. Mbl. Augenhk 148: 850-6, 1966.

73. Orban, T., et al. A New Concept of the Pathomechanism of the Glaucomatous Attack. Klin Mbl. Augenhk. 149: 847-58, 1966.

74. Cullen, J.F. Clofibrate in Glaucoma. Lancet p. 892, 10-21-67.

75. Gloster, J., et al. Action of Atromid-S (Clofibrate) on Intra-Ocular Pressure. Brit. J. Ophthal. 52: 793-800, 1968.

76. Op. Cit. Reference 75.

77. Op. Cit. Reference 75.

78. Ramsell, T.G., and Roth, J.A. Clofibrate in Chronic Simple Glaucoma. Brit. J. Ophthal. 53: 230-2, 1969.

79. Dobbie, J.G. Role of Platelets in Pathogenesis of Diabetic Retinopathy. Trans. Am. Acad. Ophthalmol. Otolaryngol 77: 43-7, 1973.

80. Besterman, E., et al. Diurnal Variations of Platelet Stickiness Compared with Effects Produced by Adrenaline. Brit. Med. J. 1: 597-600, 1967.

81. Szanto, S., and Yudkin, J. Postgrad. Med. J. 45: 602, 1969.

82. Op. Cit. Reference 66.

83. Swank, R.L. A Biochemical Basis of Multiple Sclerosis. C.E. Thomas, Pub., Springfield, Ill., 1961.

84. Lee, P. What is New & Important in Concepts of Glaucoma. Med. Trib. Sept. 6, 1972.

85. Newell, F.W. Ophthalmology. p. 388-90, 72, 387, 117, C.V. Mosby Co., St. Louis, 1969.

86. Blodi, F.C., et al. Stereoscopic Manual of the Ocular Fundus in Local & Systemic Disease. p. 69-71, C.V. Mosby Co., St. Louis, 1964.

87. Beaumont, P., and Hollows, F.C. Classification of Diabetic Retinopathy, With Therapeutic Implications. Lancet p. 419-25, Feb. 19, 1972.

88. Becker, B. Vascular Complications of Diabetes Mellitus. p. 43-50, C.V. Mosby Co., St. Louis, 1967.

89. Becker, B. Diabetes Mellitus & Primary Open-Angle Glaucoma. Amer. J. Ophthal. 71: 1-16, 1971.

90. Duncan, L.J.P., et al. Three year Trial of Atromid Therapy in Exudative Diabetic Retinopathy. Diabetes 17: 458-67, 1968.

91. Clarke, B.F., et al. Diabetic Retinopathy. Lancet p. 1255, 12-12-70.

92. Effect of Low Fat on Serum Lipids in Diabetes and Its Significance in Diabetic Retinopathy. Diabetes 17: 458-67, 1968.

93. Winter, F.C. Diabetic Retinopathy. JAMA 174: 143-6, 1960.

94. Daughaday, W., et al. Diabetic Retinopathy. JAMA 214: 1867-72, 1970.

95. Editorial - Pituitary Destruction for Diabetic Retinopathy. Lancet p. 415-6, 8-23-69.

96. Op. Cit. Reference 94.

97. Op. Cit. Reference 94.

98. Op. Cit. Reference 92.

99. Fernan, S.S., et al. Intraocular Hemorrhage & Blindness Associated With Systemic Anticoagulation. JAMA 220: 1354-5, 1972.

100. Abraham, S.V., and Teller, J.J. Influence of Various Miotics on Cataract Formation. Brit. J. Ophthal. 53: 833-8, 1969.

101. Axelsson, U. Glaucoma, Miotic Therapy, & Cataract. Acta Ophthalmologica 47: 1049-56, 1969.

102. Op. Cit. Reference 65.

103. Op. Cit. Reference 68.

104. Op. Cit. Reference 5.

105. Kummerow, F.A. Metabolism of Lipids as Related to Atherosclerosis p. 8, C.C. Thomas, Pub., Springfield, Ill. 1965.

106. Op. Cit. Reference 85.

107. Op. Cit. Reference 68.

108. Sugar, H.S. Postoperative Cataract in Successfully Filtering Glaucomatous Eyes. Amer. J. Ophthal. 69: 740-6, 1970.

109. Bechrakis, E. Intraocular Pressure & Facility in the Diagnosis of Glaucoma, A Critical Analysis. Ophthal. Res. 2: 96-103, 1971.

SIGHT AND SOUND:
HEARING LOSS AND DIET

I. HEARING ABILITY REFLECTS DIETARY PATTERNS

In all cultures following the Western diet, a loss of hearing occurs with aging. This loss is greatest at the higher frequencies.

In a study[1] comparing the hearing of adults in metropolitan areas of New York, Germany and Egypt, it was found that sounds at 14 KH (kiloHertz or kilocycles; equal to 14000 cycles) were not heard well. The subjects were uniform in their poor response; among those at 45 years of age and older, that frequency of sound could just be heard when amplified to 85 DB (decibels), equivalent to the sound of heavy traffic.

Even frequencies of only 6 KH were difficult to discern at 60 years of age for other individuals who lived in Wisconsin (the dairy state, it may be noted). In order to hear this low frequency they required a sound volume louder than ordinary conversation--65 DB. Ordinary male speech[2] reaches 8 KH and female voices reach 10 KH. Almost any common noise--footsteps, hand-clapping, musical instruments of many types--reaches at least 15 KH.

The quality of hearing disappears quickly as one ages, it appears. It must be asked, however: is hearing loss inevitable? Are the causes understood?

A group of investigators, whose work had led them to believe the high fat Western diet could be a factor in hearing loss, decided to test the theory.[3] They were acquainted with a study reported in a paper entitled "Dietary Prevention of Coronary Heart Disease" which had been presented at the 6th International Congress of Nutrition in Scotland five years earlier, in 1963. The study involved two mental hospitals[4] in Finland, most of whose patients were asylum cases and essentially permanent inmates. In one hospital the diet remained unchanged--about 500 mg. of cholesterol daily and fats mostly of the saturated type. The other hospital substituted unsaturated oils for most of the fats and reduced the cholesterol intake to 200-250 mg.% per day. After three years the

cholesterol level of the subjects at the control hospital was 267 mg.%, while those at the experimental hospital on the lower cholesterol diet was 220 mg.%. Other improvements were noticed on the lower cholesterol diet including longer blood coagulation time and only 1/6 the incidence of new coronary heart disease as confirmed by ischemic ECG's.

Five years after this dietary program had been initiated, the investigators conducted audiometric tests in the two hospitals, which included air conduction tests at 500-4000 CPS (cycles per second), bone conduction tests at 2000-4000 CPS and high frequency tests at 12 to 24 KH. Two age groups, 40 to 49 years and 50-59 years, were tested in the two categories of 136 experimental subjects and 142 controls.

In every test, the low-cholesterol diet group had better hearing than the higher cholesterol group. In fact, the subjects of the 50-59 year old low-cholesterol group had better low frequency hearing and equally good hearing at 12 KH than those of the 40-49 year old control group. The difference in hearing seemed to parallel the incidence of coronary heart disease, as well as the cholesterol level--predictable associations as an increase in ischemic disease could be expected to also limit the blood supply to the inner ear, and thus reduce function.

To gain further evidence on this point, another study[5] was arranged with young people, aged 10 to 29 years. Two groups were selected: one, from a hypercholesteremic area in East Finland where 40- to 59-year olds have a mean cholesterol level of 297 mg.% and the highest incidence of coronary heart disease in Finland; and the other, an area in Yugoslavia, where the 40-59 year olds have a mean cholesterol level of 183 mg.%, one of the lowest rates of coronary heart disease in Europe.

Tests were conducted from 12 to 20 KH, and the superiority of hearing ability of the Yugoslavs was evident both in age and frequency range. The poorer hearing ability of the Finnish youngsters reflects the start of their degenerative journey into atherosclerosis.

The same investigators decided to test high and low cholesterol and fat dietary populations in the Soviet Union.[6] Moscow was selected as the site of the population on a Western-type diet, rich in fats and cholesterol, where incidence of atherosclerosis is high. Rural areas of Georgia in the southern USSR was an ideal choice for the population on a low-fat, low-cholesterol diet. The Georgian diet uses a large amount of vegetables and fruit, and is low in fat. Little meat is eaten and this is boiled in water and the fatty liquid discarded. The incidence of atherosclerosis is low in the area and it is one of the rare places in the world where very old people (100+ years) are found in considerable numbers. (Their advanced age is documented by birth and baptismal certificates authenticated by the government.)

A selected group of 332 subjects from Moscow and 290 from Georgia were studied in four basic categories: children, 10-19 years; and adults, 40-49 years, 50-59 years, and 60-125 years. The children were tested only for frequencies of 12 to 16 KH and the surprising result was that there was no difference in hearing between the population groups in this age range. Adults tested as expected. Georgians on their low-fat, and low-cholesterol diets had far better hearing than their age counterparts in Moscow. At 4000 CPS, Georgian 50-59 year olds had better hearing than Moscow 40-49 year olds.

Of special interest were the tests on the 100+ year olds. The oldest, 125 years, could hear a 500 CPS whisper (38 DB) and in ordinary conversation could hear 4000 CPS (65 DB).

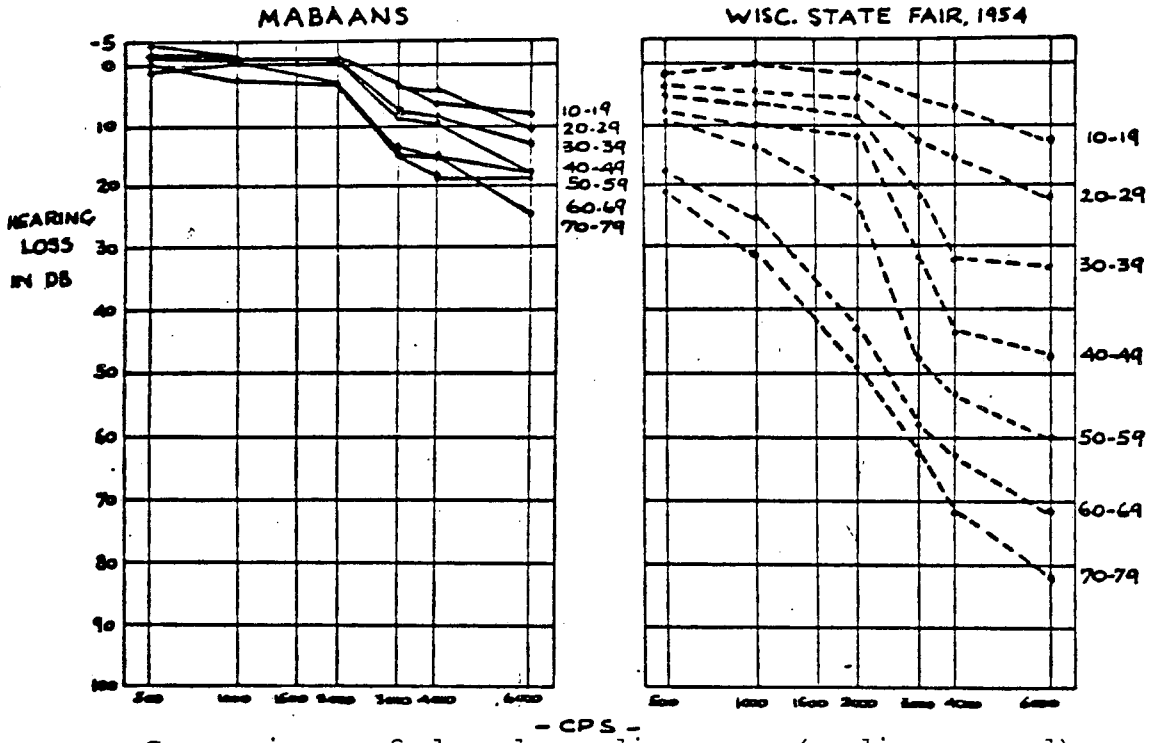
Another population existing on a low-fat, low-cholesterol diet that has been tested is the Mabaan tribe in the Sudan.[7] Their diet is inadequate by Western standards, consisting of ground millet (the major source of calories), some fish, nuts, wild dates, and almost no meat.

However, several benefits of the dietary regime were revealed by the tests. Cholesterol levels averaged 160 mg.%, systolic and diastolic pressure remained the same whether the subjects were 15

or 75 years of age, coronary heart disease was absent, and the tribespeople retained their agility into their 70's and 80's.

Hearing tests were made of seven decades of the Mabaan men, from 10-19 years to 70-79 years in frequency ranges from 500 to 6000 CPS. Identical tests made of men at the Wisconsin State Fair of 1954 (the butterfat state) were used for comparison. The results reveal that Mabaan men 70-79 years of age have better hearing than Wisconsin men 30-39 years--about as good as the 30-year olds; and the 60-69 year old Mabaans have better hearing than the 20-year old Wisconsin youths.

COMPARISON OF HEARING LOSS IN WISCONSIN AND MABAAN MEN



Comparison of decade audiograms (medians used).

While a 70-year old Mabaan man could hear a sound of 6000 CPS as a whisper (DB=25), his Wisconsin counterpart couldn't hear it unless it had the volume of heavy truck traffic (82 DB).

II. FACTORS AFFECTING CIRCULATION WHICH UNDERLIE HEARING LOSS

Reduction of circulation due to atherosclerosis.

Insufficient blood flow to the ears due to atherosclerosis will produce hearing loss. This was found to be the case with 12 aged patients upon autopsy. Hearing tests were made before they died and the audiometric data were compared to the autopsy findings.[8] The principal finding was loss of circulation due to atherosclerosis in the critical hearing vessels and secondary nerve damage.

Vascular insufficiency due to atherosclerosis and/or reduced oxygen content of the blood is the leading cause of hearing loss that occurs with age.[9] Although the loss occurs at all frequencies, the higher frequencies are affected most, as indicated by the studies cited earlier.

High frequency loss probably occurs because of inadequate circulation in the cochlear artery that terminates in the high frequency inner shell of the cochlea. The cochlear artery is an end artery derived from the internal auditory artery, which is a branch of the baselar artery formed by a junction of the vertebral arteries. The vertebral arteries often are the site of considerable atherosclerosis and the circulatory insufficiency from this source eventually lessens the blood flow to the cochlear arteries.

Hearing loss at higher frequencies cuts across class barriers, affecting all whose circulation has become compromised due to Western diet and any other possible factors. Unfortunately for the health of the nation, this includes physicians. In Honolulu,[10] 1000 consecutive auscultations of the heart were made by both registered nurses and physicians. It was found that the physicians heard only 1/3 as many high pitched systolic murmurs as were detected by the nurses.

Audiograms solved the puzzle. All of the doctors had high frequency hearing losses and thus were unable to hear the faint

heart sounds. These physicians were in the 40's and 50's as compared to the nurses, who were in their 20's. Atherosclerosis that develops and advances with age on a Western diet had robbed them of some of their hearing, as well as depriving their patients of more accurate diagnoses.

Smoking aggravates inadequate circulation to hearing organs.

With a compromised circulation, the added burden of smoking can worsen hearing in all frequency ranges. Smoking lowers blood flow in two ways: by vasospasm, and reduced oxygen-carrying capacity of the blood due to the creation of carboxyhemoglobin by the carbon monoxide.

At the Veterans Hospital in Topeka, Kansas, 126 male smokers were matched with 126 male nonsmokers and all were tested[11] for hearing. Frequency response was checked from 125 CPS to 12000 CPS for both air and bone conduction. At all frequencies, and especially the higher ones, smokers had a greater hearing loss ($P. <001$). The study demonstrated effectively that those subjects whose hearing organs received more oxygen--the nonsmokers--had better hearing.

Effect of increasing oxygen supply to hearing organs.

To test the effect of oxygen on hearing, Professor Miyake of Nagoya University in Japan subjected his patients with idiopathic or spontaneous deafness to oxygen therapy.[12] For one hour a day, the subjects were exposed to oxygen at 2 to 2.5 times atmospheric pressure. This treatment lasted from 7 to 15 days and was intended to increase the oxygen tension of the blood and thereby attempt to compensate for local oxygen insufficiencies.

Of 16 patients treated, more than 50% regained their hearing completely, and others tested improved substantially. Long-term effects of this treatment are not known.

Another way to improve circulation is through vigorous exercise. A group of 70 faculty and staff members of Purdue University set up an exercise program to test this concept.[13]

All underwent hearing tests before starting the program. After four months of regular, vigorous exercise, they were retested. Many demonstrated an improvement in hearing. In some the improvement was remarkable; in none was there a worsening of hearing.

Any way by which more oxygen can be brought to the hearing organ seems to effect an improvement in hearing.

Besides smoking, diet, and exercise, there are additional less common factors affecting hearing that can produce partial or complete deafness for brief periods or even permanently. Drugs,[14] for example, including neomycin, kanamycin, gentamycin, and even common aspirin, have been implicated. The effect of aspirin was found to be dose-related, usually transitory, and mostly affecting patients with rheumatoid arthritis, but not much information is available on drug toxicity in relation to long-term damage of hearing.

In common with defects in vision, hearing losses are largely initiated by inadequate quality and quantity of circulation. To effect improvements both in sight and hearing problems endemic in our aging population, changes in diet patterns that underlie the circulatory problems are required, together with proper exercise.

HEARING REFERENCES

1. Rosen, S., and Olin, P. Hearing Loss & Coronary Heart Disease. Arch. Otolaryng. 82: 236-43, 1965.

2. Lawrence, M. How We Hear. JAMA 196: 831-3, 1966.

3. Op. Cit. Reference 1.

4. Turpeinen, O., et al. Dietary Prevention of Coronary Heart Disease: Long Term Experiment. Amer. J. Clin. Nutrition 21: 255-276, 1968.

5. Op. Cit. Reference 1.

6. Rosen, S., et al. Epidemiologic Hearing Studies in the USSR. Arch. Otolaryng. 91: 424-8, 1970.

7. Op. Cit. Reference 1.

8. Hansen, O.C., et al. Pathological studies in Presbycusis. Arch. Otolaryng 82: 115-32, 1965.

9. Zelman, S. Correlation of Smoking History with Hearing Loss. JAMA 223: 920, 1973.

10. Gilbert, F.I. Paramedical Personnel Are Held Useful in Conducting Physicals. Med. Trib.

11. Op. Cit. Reference 9.

12. Miyake, H. Oxygen for Deafness. Med. Trib. 1-10-73.

13. Ismail, A.H. Deafness Linked to Heart Attacks, Strokes. Sci. News Letter 94: 641, 1968.

14. Boston Collaborative Drug Surveillance Program. Drug Induced Deafness. JAMA 224: 515-6, 1973.

EXERCISE

The "good life" as lived or aspired to in the retirement years by many in advanced societies is one in which the individual takes it easy and enjoys mostly passive entertainment. Movies, plays, television, table games, and spectator sports keep much of the population quite literally glued to their seats. Even younger individuals who are working drive to their jobs, frequently sit all day performing sedentary tasks at a desk or in a limited area, then drive home to eat their dinner and relax over a newspaper or with T.V. Activity that the body requires to maintain health is denied, and on weekends when such activity is possible, it is avoided for the "good life."

This passive lifestyle continues until the end for many people. With nursing homes and retirement facilities becoming popular, people are doing less for themselves, becoming inactive both mentally and physically. At this later stage of life, deterioration occurs rapidly with inactivity, and for many it can be a death sentence.

Only in recent years has there been any organized effort to promote exercise as part of a new lifestyle. However, for many people the attitude towards exercise is still exemplified by the remark attributed to a famous wit: "When I feel like exercise, I lie down until the feeling passes away."

I. EFFECTS OF INACTIVITY ON GENERAL BODY FUNCTIONS

To realize how inactivity affects the body and mind, observations on the effect of prolonged bed rest are of interest. In one such study, changes in cardiac function was noted after a continuous bed rest of 20 days.[1] The subjects were young men mostly in their early twenties and active athletes, who were in excellent physical condition at the start of the experiment. At the end of the bed rest period, several changes had occurred, as shown.

CHANGES AFTER 20 DAYS OF BED REST

	Before rest	After rest	% change
Maximum oxygen intake	3.39 liters/min	2.43 liters/min	-28%
Heart volume	860 ml.	770 ml.	-10%
Maximum cardiac output	20 liters/min.	14.8 liters/min.	-26%
Maximum stroke volume	104 ml.	74 ml.	-28.8%
Total blood volume	5.065 liters	4.7 liters	-5%

A very significant change was the 28% drop in maximum oxygen intake, since this measurement is the standard by which the functional capacity of both the respiratory and circulatory systems are judged. It represents the maximum oxygen that can be delivered to the tissues and is the measure of the aerobic work power of the body. This loss reduces the exercise capacity of the body to 72% of the level it had only three weeks earlier.

The maximum amount of blood the heart could pump per minute (cardiac output) was reduced 26% due to the 28% reduction in the stroke volume (amount of blood pumped per beat).

Another effect of bed rest is the decrease of red cell mass.[2] In a 35-day bed rest experiment, losses up to 15% of total red blood cell mass were experienced by young men. It was noted that a decreased rate of erythropoiesis, verified by serial reticulocyte count, was responsible. As soon as activity was started, erythropoiesis increased. In effect, bed rest creates an anemia whose only cure is activity.

Calcium loss from the bones becomes a serious problem with prolonged inactivity. Three healthy men in their 20's restricted themselves to complete red rest for 30-36 weeks.[3] Within a few days, the calcium balance became negative and continued to be negative for the entire duration of the bed rest and even during the first three weeks of activity after red rest before it finally became positive. During the bed rest period, 4.2% of the total body calcium was lost.

This loss was not evenly distributed among all the bones of the body: weight-bearing bones were found to have lost the greatest amount. In the central area of the os calcus (heel bone), losses of 25 to 45% of bone mineral were measured by gamma ray scanning. Upon resuming activity, bone density slowly increased. It may require years to restore the bone density to normal; and if the subjects are in their 50's or older and lack a regular, vigorous activity schedule, bone density may never return to normal.

If activity is a mechanism by which bone density is maintained, then lack of it should demonstrate decreased density, and activity in excess of normal amounts should create supernormal density. The first premise has been verified by the bed rest experiments; the second has been confirmed by field studies.

In tests with 69 athletes, bone densities of the femur were determined by the gamma absorption method.[4] The athletes were compared with nonathletes of the same age and were found to have significantly higher bone density. Measurements were then compared in the athletic group for possible correlation with the level of physical activity. It was found that density increased with increasing physical activity. For example, runners and skiers were found to have higher densities than swimmers. Since activity appears to govern bone density, superdensity of the bones can be achieved.

A correlation was also found between bone density and the power of the quadricep; greater muscle strength accompanied higher bone density. This finding was confirmed by a study[5] that correlated another bone and muscle system. In 46 routine autopsies, the ash weight of the third lumbar vertebral body and

the weight of the left psoas muscle were investigated to determine whether a relationship existed between them. It was found that the denser the vertebra, the heavier, and thus stronger, the attached muscle. Correlation was $P < .001$ and led to the concept that "the weight of a muscle reflects the forces that it exerts on bones to which it is attached, and a reduction or increase in muscle weight results in a corresponding loss or increase of bone."

When muscle use is limited because of immobilization or paralysis, both muscle and bone atrophy. In various disease states where myopathy is found, bone loss and fractures are usually associated with the myopathy. Loss of muscle strength during periods of total activity has been found to be 3% per day.(6)

Further evidence of the relationship between muscle use and bone density is found in a study with stroke victims.(7) These patients had experienced a partial or complete paralysis on only one side of the body. Various bones of the lower and upper arm in both the normal and partially paralyzed arms were evaluated for osteoporosis. Factors that had been difficult to assess previously, such as weight-bearing or calcium homeostasis, were not a factor here, since the normal arm acted as the control.

In the 25 patients participating in the study, the abnormal arm consistently showed localized osteoporosis. The loss of bone density was proportional to the loss in muscle power. It is thus possible to demonstrate that loss of bone density is not necessarily a result of aging, insufficient calcium intake, inadequate endocrine activity, or any of a host of factors heretofore suspected of causing the problem: simple disuse of muscle will cause osteoporosis.

In addition to bones and muscles, an organ system has a functional capacity that is directly related to its previous activity. If the rate of metabolic activity is increased, the functional capacity of the organ is increased; if an organ is put into continuous rest, it rapidly loses much of its function.

In addition to metabolic losses relating to bone loss and muscle atrophy, other tissue loss demonstrated by negative nitrogen balances of up to 3.5 gms./day have been observed.

Reduction of heart size, cardiac output and stroke volume, and loss of erythrocytes have been noted. After only 21 days of bed rest, the resting pulse increased 10 beats per minute, and following a 30 minute walk, the pulse rate increased 35-40 beats per minute. The increase in heart beat for the same amount of work was needed to compensate for the smaller stroke volume.

Bed rest has also been correlated with emotional responses typical of a stressful situation: anxiety, hostility, tension, aggression, etc., that can result in considerable personality changes.

While nervous system impairment is not normally considered a result of inactivity, it has been demonstrated. It is well-established that achievement of a high level of performance in any sport depends upon frequent repetition and much coordination of the particular movements required. Sensory input by the performer are constantly checked against performance, enabling errors in the physical motions to be corrected. This constant feedback is basic to the proper operation of the nervous system. Studies where sensory input is reduced show impairment of sensory perception, motor coordination and of general intellectual functions.

Inactivity increases in Western cultures as people age: those who are 50+ years old start to show the outward signs of nervous, metabolic and cardiovascular impairment. While the effects are not as severe as those produced by bed rest, this impairment has already begun as early as 25-35 years of age, increasing as the level of inactivity gradually increases. The problems produced generally do not respond to a magic pill, though persistent exercise such as walking or slow running for long periods could reverse some of this, such as the bone loss associated with the osteroporosis of later years.

Stimulation by activity of all organ and sensory systems is absolutely necessary for optimal functioning of the human organism. Even in normal freshman college women, physical fitness has been shown to make a considerable difference in chronic health complaints.[8] Physical as well as extensive physiological tests were given to 67 young women. The more physically fit of the group

were found to have fewer chronic complaints, e.g., menstrual discomfort, backache, digestive upsets, fatigue, colds and allergies. Physical tests showed no detectable differences in the group. The feeling of well-being achieved by physical activity in 18-year olds is no different than in the elderly population.

In a group of ten subjects aged 52- to 78-years old, exercise was tested against Meprobamate (400 mg.) for relative tranquilizing effects.(9) Fifteen minutes of walking, enough to raise the heart rate to 100 per minute, lowered the electrical activity in the muscles by 20%. This relaxation lasted for at least an hour. Both placebo and Meprobamate showed no difference from controls. Dosage of Meprobamate was kept low because of its hypotensive effect on elderly people. This would create further problems in impairment of motor control and driving performance, already a serious problem in the elderly.

Walking is a tranquilizer with only pleasant side effects! Other physiological benefits of physical activity are worth noting, also. Physical activity has an insulin-like effect and will reduce glucose levels in normals and diabetics alike. In fact, in a study(10) in which normal young men stayed in bed for up to three weeks, abnormal and significant glucose intolerance and hyperinsulinemia following oral glucose tests occurred in 12 days. Even as early as three days, the glucose tolerance test appeared abnormal.

One wonders how many individuals have been diagnosed and thereafter treated as diabetics as a result of having oral glucose tolerance tests taken after an illness or incapacitating condition kept them confined to bed for a week or more. Once insulin treatment--a lifelong program--is begun, the chance for discovery that such individuals were not really diabetic becomes remote.

Uric acid levels are also reduced by exercise.(11) This can be a significant factor in the later prevention of gout. It is of note that reduction of uric acid with exercise does not occur on a high-fat diet. As is discussed in other sections, the average diet, which is high in fat, inhibits glucose metabolism, as well as

fibrinolysis, and both are helped by exercise in the presence of a moderate- or low-fat diet.

II. EFFECTS OF EXERCISE IN PREVENTING CORONARY HEART DISEASE

Exercise as a factor in coronary heart disease.

Exercise is obviously significant in maintaining body functions, but can it prevent coronary heart disease?

Coronary heart disease is basically a result of plaque growth nourished by the high-fat, high-cholesterol Western diet (see Atherosclerosis chapter). Exercise can help offset the effects of this disease by developing collateral circulation to reestablish vascular pathways, replacing those blocked by plaques. If the plaque growth occludes a principal vessel supplying the heart, it is too late for exercise to help, however. In a race between the growth of plaque and collateral vessels, plaque will win. Unless a diet low in fat and cholesterol is followed to reduce or eliminate plaque growth, vigorous exercise may be more of a hazard than a help, due to the possibility of plaque breakoff in such activity.

How strenuously can one exercise? Normal hearts, even with the most strenuous exercise, do not die.[12] This was demonstrated during the 1968 Olympic Games in Mexico City, where frequent collapses of the athletes occurred, but no deaths. But when atherosclerosis is a factor, death is unpredictable. A 28-year old football player died during a game; upon autopsy, he was found to have generalized coronary atherosclerosis and a recent thrombus. Dr. Jokl cites 100 cases of unexpected sudden deaths during exercise in both young and old. At autopsy, the most frequent findings were coronary atherosclerosis and degenerative changes in the myocardium.

Even marathon runners, who run continuously for 26 miles, are not immune, as evidenced by the death of a 51-year old physician[13] in Southern California,--a long distance runner of many years--who died in his sleep.

Physical activity does provide advantages over inactivity to individuals who have had a first myocardial infarction. In a study of 301 such patients,[14] of whom about 1/3 had died in the first four weeks following the infarct, their level of activity both on

and off their jobs was noted from histories, and was classified as to degree of activity entailed. The results are indicated below.

PHYSICAL ACTIVITY VS. % DEAD IN 1ST 4 WEEKS AFTER 1ST MYOCARDIAL INFARCT

	Least active	Intermediate	Most active
% of patients (all men)	80	111	89
% deaths in 1st 4 weeks	49%	25%	17%

The least active of the group had almost three times as many deaths as the most active. This was no consolation for the 17% in the most active group who also died, but it indicates the importance of activity which promotes life-saving collateral circulation.

Further confirmation[15] comes from the Framingham studies that monitored several thousand people. The most sedentary group had 500% more deaths from coronary heart disease than the most active. In a larger study in New York covering a population of 110,000 people, it was found that sedentary smokers have 900% the death rate from coronary heart disease than physically active nonsmokers of the same age.

Another large-scale study noted differences in coronary heart disease incidence in men who have active jobs as compared with those with sedentary jobs. In this investigation, 2,180 railroad workers, of whom 875 had active jobs and 1,305 had sedentary jobs, were followed for 5 years. The active group had considerably fewer deaths from coronary heart disease than the sedentary group. Ninety-three percent of the two groups were subsequently followed for further observations. Some confusion arose when it was found that regardless of the level of activity, the 20% with the highest cholesterol levels had 323% more deaths than the 20% with the lowest cholesterol levels, indicating that the level of blood cholesterol was even more important than the level of activity.

Both low cholesterol values and an activity program are important in lowering the incidence of coronary heart disease.

Even under the watchful eyes of organized rehabilitation programs with physical educational directors and physicians in attendance, exercise without proper diet can be deadly. A 61-year old man[16] in such a program was running a mile three times weekly in addition to other exercise after only 9 months on the program. Tests on a maximal exercise test on three separate occasions had produced no abnormal findings. During a simple exercise, he fainted on the gym floor: within 15 seconds, three physicians failed to revive him despite heroic measures for almost five minutes, during which time he remained pulseless. He finally responded to defibrillation attempts and made a successful hospital recovery.

In strenuous activity, death from coronary heart disease does not necessarily result from a thrombus. In fact, considerable evidence suggests that this is a minor factor. In one pathological study, two years were spent in dissecting and analyzing the coronary arteries from 41 victims of acute myocardial infarction. In only two of the subjects did the thrombi appear to be cause for death. In 26 of the 41, no thrombi were found, merely old plaques. In the majority of the subjects, all three coronary vessels were found to be narrowed by plaques reducing the original lumen over 75%, and in many cases the reduction of the lumenal diameter reached 90%. The examination of the coronary arteries was exceedingly precise, with cuts being made every 5 mm. in order to locate all significant lumenal defects.

If death did not result from a sudden blockage of blood, what was the cause?

This question was pondered by a surgeon[17] who with his associates had performed over 5000 operations on coronary vessels, both on humans and animals. In his work with dogs, he observed that a heart supplied with uniform circulation from all of the arteries supplying it has an even pink color with the electrical potentials from the heart being essentially identical, making for an electrically stable heart. If one artery is tied so that the

volume of blood is insufficient to maintain the pink appearance of the heart (myocardium), this local area will cyanose and become blue in color. The electrical potential in the blue and pink areas adjacent to each other will exhibit up to a 20 MV differential; this differential will trigger an electrical instability causing fibrillation.

If one of the coronary arteries is partially occluded, a well-oxygenated heart--as indicated by its pink color--can be relatively safe under low levels of activity. At higher levels of activity, oxygenation will take place everywhere except at the portion of the myocardium served by the partially occluded vessel. In this area, the oxygen level will not be adequate, and a bluish color will be evident reflecting the lowered oxygen tension. The potential differences set up by the differences in oxygen tension may reach the threshold for fibrillation, causing death.

Of the many hearts examined by this physician after coronary heart death, one-third of the myocardiums showed no observable damage, and many of the remaining two-thirds had little enough damage so that they could have lasted for years if they had not been pushed to their fibrillation threshold.

This unequal oxygenation of a relatively undamaged myocardium during strenuous activity, with neither plaque breakoff nor a thrombus involved--just plaque growth narrowing the lumen of the coronary arteries--explains such catastrophes as that of the man who starts to shovel the snow in his walk and is dead within a few minutes.

In such hearts, the institution of new diet habits with low fat and cholesterol intake will stop formation of new plaques and cause regression of the damage to some extent, as is shown by primate studies. If these individuals will also undertake an adequate but careful exercise program, collateral circulation can develop which may provide an even distribution of blood in the myocardium during strenuous activity so that oxygen differentials no longer occur.

The following studies show how exercise achieves rehabilitation.

Rehabilitation of compromised circulatory networks with exercise.

In one of these studies using animals, 23 dogs had a surgically produced acute myocardial infarction by complete closing of the left anterior descending coronary artery.[18] This procedure usually produces an infarction of 15-30% of the left ventricle. Three days after the operation, 11 of the dogs were started on an exercise program consisting of running 30 minutes per day at 4 miles an hour on a 10% incline. After five weeks on this program, the exercise and the nonexercise control groups were tested for various parameters, then all were sacrificed and autopsied.

During the exercise period no deaths or complications occurred even though only three days had elapsed since the infarction. On the final test, the conditioned dogs demonstrated all the benefits of exercise as compared to the control group: lower heart rate, higher cardiac volume and generally better recovery. Autopsy findings showed considerable collateral growth in the blocked areas in both the exercise and the control dogs. No autopsy evidence of ill effects due to the exercise could be found.

Many of these exercise-induced changes can be demonstrated indirectly in humans. Ischemic ST depressions--the ECG evidence of narrowed or blocked coronary arteries, can be substantially influenced by exercise. Several studies bear this out.

In one study,[19] 618 men--260 of whom had documented coronary heart disease--participated in a conditioning program over a period of seven years. Expected changes such as lowering of heart rate and increasing maximum oxygen intake and cardiac output were effected; but, in addition, the ischemic ECG changes decreased in those subjects earlier exhibiting them, and in many on a maximal exercise program, the ischemic changes disappeared.

In another study, 44 United Airline pilots over 35 years old[20] who were found to have ST ischemic depressions were put on an exercise program consisting of walking which gradually was

increased to slow running. In all the pilots, their ECG's returned to normal and during a three-year follow-up, remained normal.

Some physicians who started patients with ischemic ST changes on exercise programs were able to achieve complete disappearance of ischemic changes[21] after conditioning, as demonstrated by retesting of the patients under maximal stress conditions.

Benefits of vigorous exercise are also reflected in reduced morbidity and mortality of infarct patients following such a regime as shown in one program started in 1964[22] and reported after being in effect for five years. The participants in the program were males who had had an acute myocardial infarction at least five months prior, were no older than 51 years, nondiabetic, with a diastolic blood pressure under 120 mm., and free of any problems that would prevent them from following a vigorous exercise program. Of 204 who qualified, only 77 decided to start the program; the other 127 were used as controls and matched for age, occupation and other criteria. Results of the program are summarized.

COMPARISON BETWEEN EXERCISE AND NONEXERCISE INFARCT PATIENTS (1964-9)

Group	Total	Nonfatal reoccurrences myocardial infarctions	Cardiac deaths
Exercise patients	77	1 (1.29%)	3 (3.89%)
Nonexercise	127	31 (27.92%)	15 (11.81%)

The controls experienced over 20 times as many new infarctions and 400% more cardiac deaths than those on the exercise program.

It might be thought that rehabilitation is possible only in younger people. A group of eight men and women[23] whose average age was 70 years were put on an exercise program that included three months of training on a stationary bicycle. After this period they experienced the same benefits that younger people do: lower heart rate, increased cardiac volume, and in retesting were found to be able to maintain a work load limit 76% higher than pre-exercise level. In addition, other advantages were noted such as

increased agility, muscular endurance and general improvements in coordination.

An individual case of a 65-year old,[24] who had an anterior myocardial infarction with a complete left bundle branch block, is of interest. After he had recovered from his attack, his doctor suggested that he contact his local YMCA for a gradual exercise program. Fortunately, he lived in Cleveland where one of the finest programs of its kind was taking form. This program was based on a gradually progressive overloading principle: start very slowly and daily push the body more and more. Each day's activity was designed to work just slightly beyond comfort, and gradually, over several months, the benefits of endurance exercise became apparent.

The program for this 65-year old consisted of running in place for 60 seconds (--he thought he would collapse!). After four months of conditioning, which included running, swimming and calisthenics, his resting pulse dropped from 98 to 58. On his 65th birthday--four years after the attack--he celebrated by running ten miles in 71 minutes--a tribute to the rehabilitative effects of vigorous exercise.

Collateral circulation developed through exercise.

The mechanism of rehabilitation is the increased blood flow made possible by development of collateral circulation in the ischemic areas. Animal studies made with rats clarify the relationship between exercise and capillary growth in the vessels serving the myocardium.

In one study, rats were permitted to run[25] one mile daily for 36 days; a control group had no exercise. A technique was devised to determine the size of the coronary arteries and all its branches (the coronary tree): plastic was injected into the thoracic aorta of the living rat until it filled all the coronary vessels and their branches; after the plastic hardened, the tissue was dissolved in 10% potassium hydroxide. The cast produced vessels as small as 40 microns, and its weight was used as a

comparison weight (cast weight) for the various conditions observed.

A comparison of the size of the coronary trees of exercised and nonexercised rats showed that the former group had a 27% larger coronary tree. Since nitrates are used extensively to produce a vasodilation in coronary heart disease patients, a group of rats was fed "Peritrate" (pentaerythrityl tetranitrate) at 480 mg./Kg. of diet. After two weeks on this diet, their coronary trees were measured and found to be no different than those of the control rats. The popular nitrate medication had no curative effect on the ischemia in this experiment, yet it is dispensed universally--while vigorous exercise, which does have a curative effect, is not encouraged by many physicians.

Further experiments on rats[26] running on treadmills and swimming under different regimes are summarized.

EFFECT OF EXERCISE ON THE SIZE OF THE CORONARY TREE

Condition	Body Wt.	Heart Wt.	Cast Wt.	Cast Wt. % (+-) Difference from from control
Running (no exercise)	466 gm.	1.59 gm.	2.68 mg.	
Running - 1.3 Km./day, twice weekly	469 gm.	1.45 gm.	3.98 mg.	+48%
Swimming (no exercise	344 gm.	1.23 gm.	3.58 mg.	
Swimming - 1 hr./day	315 gm.	1.19 gm.	3.69 mg.	+3%
Swimming - 2 hrs./day	300 gm.	1.19 gm.	4.31 mg.	+20%

In the running test, the coronary tree of the runners increased 48% in size over the nonrunning controls. Swimming did not develop as much collateral circulation as running, but a minimum swimming time did develop collaterals. One hour of swimming per day increased the coronary tree 3%, while two hours per day increased it 20%.

Rats of all ages are helped by exercise.[27] In an exercise program consisting of an hour swim each day, rats equivalent in age to human teenagers, 30 year olds, and 50+ year olds were tested. It was found that the rats of all ages increased their blood supply to the heart, and the extra coronary arteries (those that arise from branches of the internal mammary artery or the subclavian arteries and connect with the arterial branches of the coronary arteries) increased in size almost 300% more in the exercised rats than in the nonexericsed controls.

Even rats with an equivalent human age[28] of 90 years were helped. These rats were 22-months old, and were exercised with 4- and 8-month old rats. After a twelve-week program, the 4- and 8-month old rats had increased their capillary beds 10% and the 22-month old rat (the "90-year old human") increased 7%. Never too late, at least in rats.

The work that has probably the most significance for man was done in 1957.[29] Surgery was performed on 117 dogs and arterial constriction produced various degrees of myocardial ischemia. In resting dogs it was found that collateral circulation developed in proportion to the degree of constriction: there was almost no increase in collateral circulation in areas where the blood supply was the least constricted.

When dogs with mild constriction were exercised, they developed more collateral growth than the resting dogs with the greatest constriction. Evidence obtained in studying anastomoses in the hearts of anemic patients[30] strongly indicates that the dog experiments are valid for humans.

This finding that exercise is particularly effective in promoting collateral circulation that would not otherwise develop in coronary heart disease patients, is no doubt the explanation for the fewer deaths that occur among those who partake in exercise and experience their first acute myocardial infarctions.

As exercise provides increased circulation to the myocardium, it also increases vascularization elsewhere. Patients with intermittent claudication[31] (arteriosclerosis obliterans) found that an exercise program of 3-8 months provided a significant

increase in the blood supply to the affected leg. Pain upon walking either lessened or disappeared during this period.

Effect of exercise on lowering blood pressure.

Improved circulation in the body also lowers blood pressure. This was seen in a program with 23 hypertensive men (BP > 140/90 mm. Hg.)[32] who ranged from 42- to 60-years old. Many were on hypertensive drugs which were continued throughout the training. No dietary change was suggested nor was any other variable made so that any blood pressure changes would be due primarily to exercise.

The exercise program consisted of an hour of activity which included 30 minutes of a walk-jog progressive routine and which took place twice weekly. At the end of the 6 months, considerable drops in blood pressure were noted. The average systolic drop was 13 mm. and the diastolic drop was 12 mm. Some individual changes were substantial and are listed.

CHANGES IN BLOOD PRESSURE BEFORE AND AFTER TRAINING PROGRAM

	Before training (mm. Hg.)	After training (mm. Hg.)	Difference
Systolic	200	140	-30%
	175	140	-20%
	170	133	-21%
	145	125	-15%
Diastolic	135	115	-15%
	120	90	-25%
	105	82	-22%

Vigorous exercise is capable of bringing many hypertensive pressures down to the normal range with a very minimal program, only two hours weekly for six months, of which one hour per week was for the walk-jog activity. This study demonstrates how little activity is necessary to maintain a reasonable measure of fitness.

Although a low level of activity can maintain fitness, it must be lifelong and incorporated into the lifestyle. If not, fitness disappears. This was the experience of 12 men,[33] 20-years old, who trained intensively for six months. Vigorous gymnastics as

well as extensive running four to five times weekly produced substantial improvement in all fitness parameters (lower heart rate, increased maximum oxygen capacity, etc.). These same men were retested when they were 42- and 52-years old. They had not continued an activity program and no evidence of residual fitness was apparent. Their fitness had regressed to the level observed in sedentary men of the same age. The investigators in this 30-year long study concluded that fitness depends on habits of diet, exercise and smoking, and not on training in youth.

Effect of exercise on lowering of blood lipid levels.

Elevated blood lipids, particularly cholesterol and triglycerides, have been associated with increased risk of coronary heart disease. Early studies of blood lipids during exercise programs reported a lowering of lipids. Later studies found that a lowering occurred only if there was a weight loss.[34] Present findings do not support the position that exercise induces any significant lipid changes.

A group of 15 sedentary professional men ranging in age from 35 to 55 years started on an exercise program. This consisted of a program of calisthenics and running that became progressively more strenuous as the training continued. The men exercised six times weekly for six months. During the training period, the subjects were advised not to change their diet or smoking habits, so that any differences after the six-month period would be due principally to the exercise.

Results after the six-month training were disappointing. Cholesterol levels were reduced only in those who lost weight and when the weight was stabilized, their cholesterol levels rose even higher than the original values. Both serum cholesterol and phospholipids showed no significant changes during the training period.

Serum triglycerides dropped from pretraining level of 208 mg.% to 125 mg.% posttraining, but if more than three days elapsed since the last exercise period, this level returned to the pretraining value. This acute exercise-related drop was probably the factor

that caused confusion in other studies that reported lower triglyceride levels after exercise.

Other studies involving a larger number of subjects and endurance training for up to a year have failed to show a significant decrease in either serum cholesterol or triglycerides.[35] An extensive international study on the relationship of physical activity to blood lipid levels failed to show any correlation to exercise but did support the view that diet is the factor that determines serum cholesterol level.[36]

In Cleveland, 298 males between 30 and 59 years of age were tested for maximum oxygen uptake which would reflect their maximum physical activity. Blood lipids were analyzed and compared to the various levels of oxygen uptake. Even though the most active men had twice the maximum oxygen intake of the least active men, there was no significant difference in their serum cholesterol levels. The Cleveland men were compared to a group of farmers in Finland who were much more active than the Cleveland men, but were on diets very similar in total fat and cholesterol content. Both groups had similar serum cholesterol values. Other studies showed that "populations with different levels of habitual physical activity have similar cholesterol values when their dietary fat content is quantitatively similar." In these groups studied, all were the typical Western diet--fat, 35-40% of total calories and 350+ mg. cholesterol.

III. WHY DOES VIGOROUS EXERCISE IMPROVE MORBIDITY AND MORTALITY: A HYPOTHESIS

Vigorous exercise does increase the life-span. An analysis of the life-span of athletes listed in Who Was Who in American Sports shows clearly that life-span is related to continuous endurance exercise.

The summary follows:

LIFE-SPAN OF ATHLETES ACCORDING TO SPORT

Sport	No. of athletes	Mean age at death	% who lived past 50 years
Football	120	57.4	64.9
Boxing	107	61.6	75.8
Baseball	630	64.1	82.6
Track	23	71.3	87.0

Those engaged in track and field sports probably developed the greatest collateral circulation in contrast to those engaged in sports where the activity is intermittent. Sustained activity at levels of at least 70% of maximum for several minutes is necessary for maximum collateral development.[37-41]

Those who are active not only have less coronary heart disease, but when they do suffer an acute myocardial infarction, have the lowest death rate. These advantages can be explained by investigating the fibrinolytic activity in active and sedentary individuals.

The normal role of fibrinolytic activity is to maintain the balance between deposition and solution of fibrin in the process of tissue injury and repair. Its role in the internal formation of thrombi was not intended by nature, but is important in coronary heart disease.

Physical activity promotes plasma fibrinolysis in the body and the effect is a generalized one. Thus, if an arm were immobilized in a plaster cast, leg exercise would benefit it as well as the

exercising leg, as the fibrinolytic effect would occur throughout the circulation.(42)

The level of fibrinolytic activity depends upon the level of physical activity: a very low level of fibrinolytic activity occurs if the exercise is mild; but with a high level of exercise, even for very short periods, plasma fibrinolysis is effectively increased. As little as 1-1/2 minutes of vigorous exercise in 20-year olds doubled their fibrinolytic activity--an effect persisting for at least an hour.

The response of level of fibrinolytic activity to three levels of activity was tested in nine normal 20-year olds on a treadmill:(43)(44)

1. Maximum exercise - Level of running to produce exhaustion in five minutes. Oxygen consumption at this level was considered 100%.
2. Seventy percent exercise effort - Level of running to consume 70% of the oxygen used at maximum effect.
3. Forty percent exercise effort - Level of fast walking necessary to consume 40% of oxygen used at maximum effort.

Fibrinolytic action was determined by the area of lysis in $mm.^2$ of a bovine fibrin plate. Results of the test results are summarized in the table:

FIBRINOLYTIC ACTIVITY AT THREE LEVELS OF EXERCISE EFFORT

Degree of Effort	Length of time	Heart rate per minute	Fibrinolytic activity per $mm.^2$ of lysis	
			At rest	After exercise
100%	5 min.	175-220	98	676
70%	15 min.	152-195	129	421
	30 min.			626
40%	15 min.	110-135	85	158
	30 min.			196
8 a.m.-rest			66	
5 p.m.-rest			266	

Thirty minutes of effort at 70% of maximum is required to achieve the fibrinolytic activity produced by only 5 minutes of

maximum effort. Brisk walking even for 30 minutes produces less fibrinolytic activity than the body normally achieves lying in bed until 5 p.m.

Diets high in lipids (Western diets) can negate and suppress the fibrinolytic activity produced by exercise. This effect of dietary lipids is suggested by the diurnal variation of fibrinolysis. As discussed elsewhere, the peak cortisol diurnal activity affects many parameters in the body. Blood cortisol is highest at 8 a.m. and lowest at 5 p.m. Blood lipids mediated by the high cortisol level are raised and fibrinolytic activity is correspondingly depressed. It is not unexpected that if the lipids are elevated for any reason, they would be a factor in impaired fibrinolysis, a will be explained.

Considerable evidence exists demonstrating a relationship between elevated blood lipids and increased coagulation. In one of many animal and human studies showing this relationship, a low-fat diet for 3-6 months decreased or restored to normal a condition of hypercoagulability in a group of patients.(45) In another group of ten 30-year olds, clotting time was determined by feeding a fat-free breakfast one day and the same breakfast plus a glass of rich milk (the "fatty meal") on a second day.(46) The "fatty meal" increased the serum triglycerides from 81 mg.--their level after the fat-free meal--to 164 mg., and shortened the clotting time from 22.9 seconds (after the fat-free meal) to 15.6 seconds.

The correlation between elevated triglycerides and shortened clotting time has been studied and found significant ($r = -.65$). Shortened clotting time is found with elevated triglyceride levels even without a previous "fatty meal". Circulating chylomicra which are composed mostly of triglycerides cause a turbidity in the blood which when measured can be used to predict the clotting time. As the chylomicra increase, the clotting time shortens. Even in the elevation of triglycerides due to disease conditions, as in biliary cirrhosis, the fibrinolytic activity drops as the serum triglyceride level rises.(47)

Just how suppressive elevated triglyceride levels are to normal fibrinolytic activity even after severe exercise is borne

out by the following study[48] with seven normal subjects and eight with elevated triglyceride levels but no evidence of coronary heart disease. The subjects were tested after maximal exercise on a treadmill that exhausted them in five minutes. (The investigators were the same that conducted the previously mentioned studies[49][50] at 100%, 70% and 40% of maximal effort.) No change was noted in the normals as compared to the previous study, but there were surprises in the elevated triglyceride group. The table summarizes the results.

LIPIDS, FIBRINOLYTIC ACTIVITY AND RESPONSE TO EXERCISE

Group	Age yrs.	Wt. kg.	Triglycer. mg./100 ml.	Choles. mg./100 ml.	Fibrinolytic Activity mm.^{2} Rest	Exercise	Max. heart rate	0_2 consumption ml/min/kg. (exer.)
Elevated trigly.	41	81	458	223	97	263	179	37
Normals	42	79	92	209	100	665	179	40

Both groups were closely matched in age, weight, cholesterol level, heart rate, etc. Yet fibrinolytic activity after exercise increased 565% in the normals and only 165% in the patients with elevated triglycerides. This rise of 165% could be achieved by resting in bed until 5 p.m. and taking advantage of the diurnal rise.[51][52]

It should be noted that even though the maximum heart rate was identical in both groups, the maximal oxygen usage of the subjects with elevated triglyceride was only 90% of the normals. This can be readily understood since studies[53] have demonstrated that lipemia is associated with reduced blood flow in the coronary arteries and a reduced utilization of oxygen by the myocardium. The mechanism for the decreased 0_2 would be due to the rouleaux effect as explained in other sections of this book.

None of the subjects were on any medication[54] or had a history of angina, diabetes or any degenerative disease. Tests were all run early in the morning after a 14-hour fast to avoid as many variables as possible.

Findings that subjects with elevated triglycerides performing exhaustive exercise have no better fibrinolytic response than inactive normals puts both groups in high risk categories for coronary heart disease. These findings are also of interest in view of the recommendations of some physicians[55] that atherosclerotic patients begin their exercise 3 to 5 hours after their meals (Western type), since lipidemia is highest 3 to 5 hours following a meal. The reasoning is that since exercise increases fibrinolysis, it should be performed when the body needs it most. The futility of this expectation can be seen from this study. (The thought of decreasing dietary fat to avoid the whole problem must seem unnatural to these physicians!)

A hypothesis as to how activity lessens certain of the disastrous consequences of coronary heart disease for those on typical Western diets is as follows. As plaques develop and mature, plaque break-off inevitably occurs. Even after a plaque break-off, formation of a thrombus may take hours or days to happen. If the break-off is large enough to block a substantial portion of a vessel, cellular bodies including platelets will dam up against the plaque. In time, fibrin formation follows, heralding the formation of the thrombus. If sufficient fibrinolytic activity is present, the fibrin can be lysed and the development of the thrombus slowed or prevented. This will provide time for the growth of collateral circulation in the critical partially blocked areas, and hopefully, in time the blockage will break up due to the arterial pressure exerted against it, possibly to be reabsorbed before it creates too much havoc in the form of smaller emboli.

Often these occurrences are too late to help victims of Western-type diets, however, so that exercise alone will not suffice as a preventative for coronary heart disease. Unless low-fat, and low-cholesterol diets are adopted, exercise cannot achieve

its potential as a life extender and preserver of body functions.

EXERCISE REFERENCES

1. Saltin,B., et al. Response to Exercise After Bed Rest & After Training. Circulation. Suppl. #7, 38: #5, 1968.

2. Morse, B.S. Red Cell Mass Decrease Seen in Bed Rest. JAMA 200: 23,1967.

3. Donaldson, C.L., et al. Effect of Prolonged Bed Rest on Bone Mineral. Metabolism 19: 1071-84, 1970.

4. Westlin, N., and Nilsson, B. Physical Training May Create an Above Normal Bone Density. Med. Trib. 2-5-70.

5. Doyle, F., et al. Relation Between Bone Mass & Muscle Weight. Lancet, p. 391-3, 2-21-70.

6. Kottke, F.J. The Effects of Limitation of Activity Upon the Human Body. JAMA 196: 825-30, 1966.

7. Gorday, W.J., and Paul, B.J. Osteoporosis in Hemiplegia. Stroke 2: 41-7, 1971.

8. Gendel, E.S. Exercise Lack Seen To Cause Disability In Normal Women. Med. Trib. 3-2-70.

9. deVries, H.A., and Adams, G.M. Exercise & Meprobamate Compared as Tranquilizers. Med. Trib. 5-9-73.

10. Lipman, R.L., et al. Glucose Intolerance During Decreased Physical Activity in Man. Diabetes 21: 101-07, 1972.

11. Bosco, J.S., et. al. Reduction of Serum Uric Acid in Young Men During Physical Training. Amer. J. Cardiology 25: 46-52, 1970.

12. Jokl, E. Exercise & Cardiac Death. JAMA 218: 1707, 1971.

13. Royce, S.W. Jr. Pasadena, Calif. Member of Senior Track Club, California.

14. Frank, C.W., et al. Physical Inactivity as a Lethal FActor In Myocardial Infarction Among Men. Circulation. 34: 1022-33, 1966.

15. Abelson, P.H. Physical Fitness. Science 161: 1299, 1968.

16. Pyfer, H.R., and Doane, B.L. Cardiac Arrest During Exercise Training. JAMA 210: 101-2, 1969.

17. Beck, C.S., and Leighninger, D.S. Scientific Basis for the Surgical Treatment of Coronary Artery Disease. JAMA 159: 1264-71, 1955.

18. Kaplinsky, E., et al. Effects of Physical Training in Dogs With Coronary Artery Ligation. Circulation 37: 556-65, 1968.

19. Hellerstein, H.K. Exercise Appears to Benefit Patients With Heart Disease. JAMA 204: 28, 1968.

20. Kidera, G.J., and Smith, J.E. Exercise Aids In Converting ECG To Normal. JAMA 204: 31, 1968.

21. Westura, E.E. Physical Conditioning & the Abnormal Electrocardiogram. JAMA 199: 202, 1967.

22. Rechnitzer, P.A., et al. Long Term Follow Up Study of Survival & Recurrence Rates Following Myocardial Infarction in Exercising & Control Subjects. Circulation XLV: 853-7, 1972.

23. Barry, A.J., et al. Effects of Physical Conditioning in Older Individuals. J. Geront. 21: 182-99, 1966.

24. Curtis, C. Run For Your Life. Family Weekly, 153 N. Michigan, Chicago, Ill. 9-17-61.

25. Tepperman, J., and Pearlman, D. Effects of Exercise & Anemia on Coronary Arteries of Small Animals As Revealed by the Corrosion-Cast Technique. Circulation Res. 9: 576-84, 1961.

26. Stevenson, J.A.F., et al. Effect of Exercise on Coronary Tree Size in the Rat. Circulation Res. 15: 265-9, 1964.

27. Bloor, C.M., and Leon, A. Lab. Invest. 22: 160, 1970.

28. Tomanek, R.J. Exercise Boosts Circulation in Rats. Med. Trib. 8-69.

29. Eckstein, R.W. Effect of Exercise & Coronary Artery Narrowing on Coronary Collateral Circulation. Circulation Res. 5: 230, 1957.

30. Zoll, P.M., et al. Circulation 4: 797, 1956.

31. Skinner, J.S., and Strandness, D.E. Exercise & Intermittent Claudication. Circulation 36: 23-29, 1967.

32. Boyer, J.L., and Kasch, F.W. Exercise Therapy in Hypertensive Men. JAMA 211: 1668-71, 1970.

33. Robinson, S., et al. Training & Physiological Aging in Man. Fed. Proc. 32: 1628-1634, May 1973.

34. Holloszy, J.O., et al. Amer. J. Cardiol. 14: 753, 1964.

35. Rechnitzer, P.A., et al. The Acute Effects of Exercise on Serum Lipids of Patients With Previous Myocardial Infarction. J. Sports Med & Phys. Fitness 7: 177-81, 1967.

36. Salzman, S.H., et al. Serum Cholesterol & Capacity For Physical Work of Middle Aged Sedentary Males. Lancet p. 1348-51, 6-24-67.

37. Op. Cit. Reference 25.

38. Op. Cit. Reference 26.

39. Op. Cit. Reference 2.

40. Op. Cit. Reference 28.

41. Op. Cit. Reference 29.

42. Menon, I.S., et al. Effect of Strenuous & Graded Exercise on Fibrinolytic Activity. Lancet, 700-702, 4-1-67.

43. Rosing, D.R., et al. Blood Fibrinolytic Activity In Man. Circ. Res. 27: 171-184, Aug. 1970.

44. Rosing, D.R., et al. Moderate Exercise Seen To Increase Body's Fibrinolysis Only Slightly. Med. Trib., Aug., 1970.

45. Ulutin, O.N. Dietary Restriction & Coagulability of Blood. Lancet p. 48, 7-5-58.

46. Rifkind, B.M., et al. Serum Triglyceride Levels & Stypnen Time. Lancet p. 745-6, 4-2-66.

47. Jedrychowski, A., et al. Fibrinolysis in Cholestatic Jaundice. Br. Med. J. 1: 640-2, 1973.

48. Epstein, S.E., et al. Impaired Fibrinolytic Response To Exercise in Patients With Type IV Hyperlipoproteinaemia. Lancet p. 631-3, 9-26-70.

49. Op. Cit. Reference 43.

50. Op. Cit. Reference 44.

51. Op. Cit. Reference 43.

52. Op. Cit. Reference 44.

53. Regan, T.J., et al. Circulation 23: 55, 1961.

54. Op. Cit. Reference 48.

55. Angelino, P.F., et al. Physical Activity & Fibrinolysis. Minerva Med. 55: 2111, 1964.

PART III

DIABETES: PREVENTION AND CURE

A position paper on
abnormal carbohydrate metabolism
(hypergylcemia and hypoglycemia)

APPENDIX: RECOMMENDATIONS

AFTERWORD: A WORLD WITHOUT DEGENERATIVE DISEASES?

FOREWORD

Diabetes, in this view of abnormal carbohydrate metabolism, is a temporary or persistent disease state caused by inability of the body insulin to function at normal efficiency in the presence of elevated blood lipid levels. Unless the beta cells have become substantially destroyed by the action of exogenous insulin in the treatment of the disease, the condition will in most cases be cured by restoration of normal blood lipid levels.

This unconventional interpretation is supported in this paper by many references which are abstracted and cited. The section entitled, A History of Diabetic Therapy, describes the early successes (1929-1935) with a diet therapy which achieved a reduction of elevated blood lipid levels. This dietary approach was a reversal of the traditional high-fat, low-carbohydrate diabetic diet still in use today, and was employed with great success by I.M. Rabinowitch of Montreal, Canada, in the treatment of hundreds of diabetics--including many who had been insulin-dependent for years.

A theoretical foundation for the success of this radical diet therapy limiting fat intake was established by Himsworth of England, working contemporaneously with Rabinowitch. His studies indicated that the action of endogenous or exogenous insulin on blood glucose was adversely affected by blood lipids above physiologically normal levels induced by high-fat diets. Experimenting with diets of varying fat content, he discovered that as the fat content of the diet increased, insulin sensitivity and glucose tolerance decreased in a directly proportional relationship.

Despite these promising indications that diabetes could be cured and prevented by a low-fat diet, the sweep of events was to bypass the work of Rabinowitch and Himsworth. With the advent of the convenient oral hypoglycemic drugs, diabetic therapy settled quietly into regimens based on the use of insulin, the oral drugs and the traditional high-fat, low-carbohydrate diabetic diet; this complacent therapeutic orientation was to persist for many decades.

The rude awakening came in 1970, with the release of the shocking results of the University Group Diabetes Program (UGDP), a massive study carefully designed by leading diabetologists to evaluate the relative merits of the conventional modes of diabetes therapy, which revealed that no therapy was helping the diabetic patient!

Despite this revelation, most diabetologists today are still unaware that in the intervening years the foundation stone laid by Himsworth in creating a workable theory of abnormal carbohydrate metabolism has been added to by countless later researchers, until a solid fortress of evidence on the cause (and cure) of diabetes has been constructed. The therapeutic implications of this evidence, of course, lead straight back to Rabinowitch.

Some of this evidence supports the concepts that any factors, natural or induced, which raise the blood lipids sufficiently, will produce hyperglycemia. In the section entitled Creating the Diabetic State: Factors Raising Blood Lipids, studies are described which show that besides a high-fat diet, such conditions as strenuous exercise in untrained individuals, fasting, starvation, and severe illness may also have this effect; though a high-fat diet, generally being consumed over an entire lifetime, may produce the most lasting carbohydrate metabolism abnormality.

The precise nature of the defect in the diabetic's ability to metabolize glucose is discussed in another section, New Light on the Diabetic State. The studies cited here reveal that this defect is not due to an inability to handle glucose normally nor to a deficiency of insulin, but arises from a decrease in insulin sensitivity. This impaired sensitivity results in hyperinsulinemia as the body tries to compensate for the effects of the diminished ability of the insulin to metabolize glucose. The severity of the hyperinsulinemia is found to increase with the severity of the hyperglycemia. Hypoglycemia, in this view, exists as a lesser abnormality of carbohydrate metabolism and a preliminary state to hyperglycemia. In this disturbance, the efforts of the pancreas to compensate for the decreased insulin efficiency have driven the blood glucose levels down below normal and the blood glucose has

not yet started to accumulate in excess, as would occur later should the condition continue to worsen.

Elevated blood lipids as the root cause of hyperinsulinemia fails to receive acceptance by the medical profession today, but hyperlipidemia is now generally recognized to be a factor of importance in cardiovascular disease. Cardiovascular disease looms as a special threat to the diabetic, causing deaths among diabetics at a rate far exceeding that for nondiabetics. An increase in carbohydrate intake and a lowering of fat intake would benefit the diabetic patient both in regard to improving his glucose tolerance and in reducing the cardiovascular disease process, but due to a mistaken notion--"carbohydrate induction of triglyderides"--the diabetic's carbohydrate intake is kept minimal. The fact is that only simple carbohydrates--not complex carbohydrates--raise blood lipids, as will be explained. Complex carbohydrates actually provide the most desirable fuel for the body's needs, whether the individual is normal, hypoglycemic or hyperglycemic, in that they break down slowly to form a steady stream of glucose. This obviates the need for the body to turn to alternative fuel sources such as free fatty acids, the oxidation of which can create ketosis.

A consensus view of factors important in the diabetic state would likely be that the disease, or a tendency to the disease, is inherited, and that pancreatic malfunction is at the basis of the abnormality. In this paper, identical twin studies are cited which show that heredity is not involved. In one of these studies with 96 twin sets, discordance for diabetes occurred in over half the pairs of twins. Pancreatic damage is ruled out as a likely cause of diabetes by another study in which children with damaged pancreases and substantially decreased insulin secretion still had normal glucose metabolism. Conversely, in studies with individuals with normal pancreases who had elevated lipid levels due to liver disease, a diabetic condition was found to exist. Elevated lipid levels, not decreased insulin secretion, seem incriminated.

The question may be asked: Why, if the Western diet we consume is so diabetogenic--being high in fat content (40+% of total

calories in fat)--aren't we all diabetic? The section entitled, On Becoming Diabetic, addresses itself to this interesting conjecture and concludes that we all are on our way to becoming diabetic! As is shown, many of us will test diabetic if the glucose tolerance test is made in the latter part of the day, when the gradually changing diurnal cycle creates the highest level of blood fats. However, most glucose tolerance testing is done early in the day when a threshold diabetic will test normal.

The gloomy prognosis for the diabetic--eventual blindness, high risk of early death, numerous neuropathies--and the bankruptcy of conventional therapies, create the diabetic crisis which faces us today. The solution, low fat diet, and a rationale supporting this solution, are strewn throughout the literature on diabetes. It has been my rewarding task to follow the trail from the earliest successes with this proven therapy to the latest research which substantiates this simple approach.

N.P.

12/10/73

I. A HISTORY OF DIABETES THERAPY

The hallmark of early diabetes treatment; carbohydrate limitation (and, at times, starvation, too).

The human race has been struggling with the diabetic state for thousands of years.(1) In 1500 B.C., the Ebers Papyrus, an Egyptian medical writing, listed at least four cures for diabetes--medicines "to drive away the passing of too much urine." A physician 1500 years later described diabetes as "a wonderful affection, not very frequent among men, being a melting down of the flesh and the limbs into urine." But it was not until 1796 that a treatment resembling recent-day practices appeared, when Dr. John Rollo began using a dietary approach which limited carbohydrates and was "to consist of animal foods principally."

The therapeutic rationale of limiting carbohydrates was based on the finding made a hundred years earlier that a diabetic's urine contains sugar. This led to the concept that sweet or sugar-containing foods should be avoided since the body seemed unable to absorb them. The opposite deduction was drawn by a Dr. Piorry in 1857, who fed his patients over a fourth of a pound of candy daily to make up for the sugar lost in the urine. But up to 1900 most diabetic diets not only followed the extreme restriction of carbohydrates, but in addition fasted the patients at frequent intervals.

The practice of fasting diabetic patients became popular. Some physicians became so enthusiastic about it that, in one case, a diabetic was fasted for 20 days to achieve a sugar-free urine. In addition to these emaciating programs, the practice of purging with harsh physics, alternating with fast days, kept the patients in a near skeletal condition.

From 1897 to 1914, the era of the Naunyn diet, diabetics of 25 years of age could expect to live two years. Naunyn, a German physician, used an almost carbohydrate-free diet. In the era of the Allen diet, from 1914 to 1922, the life span for the 25-year old diabetic increased to four years. Dr. Allen of the Rockefeller Institute for Medical Research and a leader in diabetic diet just

prior to the insulin era, developed a calorie- and carbohydrate-restricted regime so stringent that some of the patients actually died from starvation, but the risk was thought to be less than that due to diabetic coma.

Under the Allen program, the patient was first fasted for seven days, during which time he was permitted only indigestible bran and noncaloric liquid to provide some bulk. In the next nine days, his caloric intake was gradually increased, starting from 64 calories on the first day and building up to 504 calories on the ninth. The tenth day was a fast, on the 11th day the patient was permitted 151 calories, and caloric intake was thereafter gradually raised, so that on the 34th day, he was receiving 1031 calories.

This spartan regime was made more tolerable, perhaps, by special recipes concocted by Dr. Allen for his starving patients. One recipe, made deliberately indigestible with talcum powder, involved "making a batter with eggs, spices and impalpable talcum powder, and frying it crisp."

The advent of insulin therapy in 1922, with its first successful use on a diabetic patient, marked the end of the period when the diabetic's choice was death by starvation or by diabetic coma. The demonstration of the development of diabetes in a depancreatized dog and its recovery with insulin quickly convinced the world that: 1) diabetes was simply a disease caused by insufficient insulin, and 2) the cure had finally been found. Insulin was hailed as a miracle drug and the diabetic's problems were thought to be over.

Early use of insulin was in conjunction with the Allen diet. It was soon observed, however, that more calories could be consumed so long as glycosuria was prevented by increases doses of insulin. Diets were then increased in calories to maintain normal weight, though the restricted carbohydrate intake (with its concomitant high-fat content) was retained.

But even with increased caloric intake which restored the patients to their proper weight, the restricted carbohydrate diet and insulin regime did not restore mental or physical alertness. In an effort to find a diet formulation that would produce better

health, experiments were tried raising and lowering carbohydrates, fats, and protein--always adjusting the insulin to keep the patient free from sugar in the urine.

A radical new approach: the early experiences with high carbohydrate and limited fat.

First success achieved clinically by Sansum, experimentally by Sweeney

Dr. W.D. Sansum,[2] was one of the first to try a radical approach: high carbohydrate and reduced fat intake in the diabetic diet. A male patient, aged 51 years, of normal weight, had been discharged from the hospital after a three-week stay with sugar-free urine without insulin. He was given a diet of 67% fat. Six months later, he returned in a distressed state. Although both his blood and urine were normal and his weight remained constant, he felt mentally sluggish and generally unwell. Dr. Sansum lowered his carbohydrate ration further, raising the fat intake to 70% of total calories. When he became worse on this diet and his blood sugar rose above normal, it was decided to raise his carbohydrate intake.

Improvement in his condition was noted within a few days after the carbohydrate intake had been raised from 80 gms. to 119 gms. With the patient's permission, Dr. Sansum decided to raise the carbohydrate intake still higher to 278 gms., and to reduce the fat intake to 42% of total calories. In 24 hours the patient felt very much better and in another week he left the hospital and returned to work, having been away from his employment for nine months.

Was the typical high-fat diabetic diet responsible for the malaise observed in this and other diabetic patients? Dr. Sansum tried to find out. He recruited two of his lab workers, who were perfectly normal, and placed them on the typical high-fat diabetic diet. Within a few days, their complaints started: loss of mental and physical powers and acetone in the urine--the same problems that had beset the 51-year old patient. These symptoms did not completely disappear in the two lab workers even after they had abandoned the high-fat diet for some time.

Further testing by Dr. Sansum on his patients produced more surprises when the carbohydrate and fat rations were altered. One patient on a diet of 77 grams of carbohydrate and 182 grams of fat required about 70 units of insulin to stay in balance; the insulin requirement did not change when the diet was altered to increase carbohydrates to 179 grams and reduce fat to 85 grams. By previous concepts, the insulin requirement should have doubled; yet no more was required with the increased carbohydrate intake.

By 1926, Dr. Sansum had over 150 patients on the high-carbohydrate diet. Their insulin requirements had not had to be increased over the requirement on the old low-carbohydrate diets and the patients felt mentally and physically normal. These so-called high-carbohydrate diets, in actuality, were only high in carbohydrate with reference to the old diabetic diets, as they were really not much different from our conventional Western diets--14% protein, 42% fat and 44% carbohydrate.

Sansum's work was important in successfully breaking away from the high-fat starvation diets considered mandatory for diabetics up to that time; and also in its challenge to the foundations of the theory of the etiology of diabetes: the idea that a diseased pancreas in the diabetic patient produces insufficient insulin. According to that theory, the patient in insulin balance when on 77 grams of insulin should have required more than double the intake of insulin when the carbohydrates consumed were increased to 179 grams. Instead, the insulin requirement remained the same, as earlier noted.

The restricted-carbohydrate diet with its resultant high-fat intake should also have been questioned because of the work about that same time of another investigator, Dr. J.S. Sweeney, who explored the responses of different diets to glucose tolerance testing. Sweeney's interest in this experimentation was aroused by research such as that of Hamman and Hirschman,[3] who, in 1919 had shown that if two consecutive doses of glucose are ingested within a short period, the hyperglycemia produced by the second dose is lower than that produced by the first. (This phenomenon, now known as the Staub-Traugott effect, is discussed later.) It was thought

that the glucose somehow primes the beta cells, so that upon a later glucose stimulus more insulin is produced.

How would different diets, varying in their fat, carbohydrate and protein content, affect the glucose tolerance test response? In a series of tests performed in 1927, Sweeney sought the answers.[4] Four groups of medical students were put on dietary programs for 48 hours, then given glucose tolerance tests on the third morning. The following diets were tested:

1. Protein diet (only lean meat and egg whites)
2. Fat diet (only olive oil, butter, mayonnaise and 20% cream)
3. Carbohydrate diet (bread, potatoes, bananas, oats, rice, candy, syrup)
4. Starvation diet (no food)

The results, as shown below, indicated that only the carbohydrate diet group tested normal. An all-fat diet was found to turn normals into diabetics in just two days. The starvation diet and the protein diet both produced a blood fat environment similar to that created by a fatty diet; hence the glucose tolerance test responses were also similar, though not quite as abnormal as that obtained on the all-fat diet. In starvation, free fatty acids are drawn from the fat reserves after all the available glucose is metabolized, resulting in rapid elevation of the blood fats. The severe restriction of carbohydrates on the protein diet also caused an increase in free fatty acids, simulating a fatty diet.

GLUCOSE TOLERANCE TESTS ON FOUR DIFFERENT DIETARY GROUPS
(Results in ml. blood glucose/100 ml.)

Diet	Fasting	30 min.*	60 min.*	120 min.*
Fats	83	170	206	173
Starvation	67	145	188	184
Protein	69	143	167	145
Carbohydrate	84	118	113	96

*After glucose

The implications of these test results upset the established rationale for the universally employed carbohydrate-restricted, high-fat diabetic diet. These doubts reinforced those which were created by Sansum's successfully altering the carbohydrate-fat ratio in the diabetic diet.

The work of Sansum and Sweeney, significant though it was, failed to cause any reform to be made in the conventional diabetic diet; the old rationale was not to be easily displaced. Speaking in 1928, Dr. E.P. Joslin,[5] founder of one of the largest diabetic clinics in the United States, said: "one cannot treat diabetes successfully without increasing the quantity of fat...Even with the most modern ideas on treatment, the statement still holds that fat forms the bulk of the diabetic patient's diet."

A maverick in diabetic therapy: the important work of Rabinowitch

Despite the orthodox stance, extensive work with many hundreds of patients using the high-carbohydrate diabetic diet was continued by Dr. I.M. Rabinowitch of Montreal, who was one of the pioneers to bring insulin to wide clinical use in Canada, just as Sansum had done on the west coast of the United States.

When Rabinowitch used insulin in the early years (1923), it was in conjunction with the Allen-type diet; but after a few years of experience, he developed a high-carbohydrate, low-fat regime that was unique in North America. The diet, published in detail in 1930,[6] was an even more radical departure from the conventional diabetic diet than was Sansum's. He reduced Sansum's fat levels from 42% to 20%, kept the carbohydrates essentially all complex, and limited the cholesterol intake to 400 mg. per day. Total calories were calculated to keep the patient on the slightly lean side.

The results obtained on this regime convinced Rabinowitch that carbohydrate restriction in diabetic treatment was illogical, and he made efforts to convince medical audiences in Canada and the U.S. of the merits of the low-fat diabetic diet in writings and lectures. In 1932,[7] Rabinowitch published several detailed case histories of patients who had gone on this diet since 1930. Data

on these hundreds of patients were accumulated, trends were analyzed, and results were later published.

Although he considered his diets low calorie, Rabinowitch maintained his patients at a reasonable weight: for example, males 30-35 years old were held to 130 pounds if they were 5 feet tall, and 3 pounds were added for each additional inch of height. Thus, a 5'8" male weight was held below 154 pounds. Usually diets of under 2000 calories sufficed.

All types of diabetic cases benefited: juvenile, acute adult, secondary to gallbladder disease, associated with cirrhosis of the pancreas, complicated by infections, as well as cases of hyperglycemia created by thyroid or pituitary hyperactivity.

Close clinical observations disclosed new insights into the effect of diet on diabetes. Rabinowitch relates his discovery: "Since the diet consists of large amounts of carbohydrates, small amounts of fats and practically normal amounts of proteins,...the remaining temptation is, therefore, to take larger amounts of fat than prescribed...It is under these conditions that individuals who formerly have not required insulin must now make use of it and those who required it with the older forms of treatment (our comment: normal high-fat diet and limited carbohydrates) must take more."

Rabinowitch's work validated the findings of Sweeney's high-fat experiments, translating the concepts involved into clinical use with great success. Some of Rabinowitch's published cases are reported below.

(Hospital case #6000/19) - Adult male

Oct. 14, 1929 - Admitted with a 3-week history of acute polyuria, weakness and rapid weight loss, glycosuria, and blood sugar of 714 mg.%.

Oct. 30, 1929 - Discharged on 10 units of insulin per day, urine and blood normal. Diet: 125 gms. carbohydrate, 150 gms. fat, and 50 gms. protein.

Sept. 2, 1930 - Diet changed to 254 gms. carbohydrate, 45 gms. fat and 75 gms. protein. Taken off insulin. Cholesterol level 315 mg.%.

Sept. 18,1931 - All values normal. Cholesterol level 134 mg.%. Comment: Diet changed from 125 gms. carbohydrate to 254 gms. carbohydrate with less insulin and without impairment of carbohydrate metabolism. Taken off insulin.

(Hospital case #4461/31) - 64-year old male, diabetic for 3 years Admitted in precoma state; blood glucose 588 mg.%. Treatment: 50 units insulin followed by 20 units every 4 hours. Next day both urine and blood were normal. Brief history: 40 lb. weight loss in preceding 3 months; cardio-vascular renal disease.

Aug. 9, 1931 - 80 units insulin

Aug. 10, 1931 - 30 units insulin

Aug. 11, 1931 - 40 units insulin per day and high-carbohydrate diet was started; urine and blood glucose levels were normal.

Sept. 27, 1931- Blood and urine levels remained normal; discontinued insulin.

Oct. 7, 1931 - Discharged. Follow-up visits all normal on continuing high-carbohydrate diet.

(Hospital case #6236/30) - 27-year old male, very severe diabetic requiring 80 units of insulin per day to remain in balance.

Oct. 28, 1930 - Admitted to be changed from high-fat diet (140 gms.) to low-fat (45 gms.), high-carbohydrate diet (254 gms.).

Nov. 10, 1930 - Discharged; insulin reduced to 40 units per day.

Oct. , 1931 - Admitted for observation. Carbohydrate increased to 308 gms. per day and insulin reduced to 35 units per day. Normal urine and blood values. Comment: Severe diabetic increased carbohydrate from 125 grams per day to 308 grams per day, and yet decreased insulin requirements from 80 units to 35 units per day.

(Hospital case #3953/29) - 59-year old male, diabetic for 14 years, with severe angina. Diet consisted of 50 gms. carbohydrate, 150 gms. fat and 50 gms. protein. Cholesterol level between 400 mg.% and 577 mg.%.

Oct. 20, 1930 - Admitted; angina so severe he could hardly walk and was steadily worsening. Blood sugar 200 mg.%. Placed on diet 272 gms. carbohydrate, 56 gms. fat and 78 gms. protein.

Apr. 24, 1931 - Admitted for observation. Weight was unchanged, 164 lbs. He felt much better, walked greater distances with less nitroglycerin. Blood glucose 188 mg.%. EKG found normal in all respects. Comment: Patient increased carbohydrate from 50 gms. to 272 gms. per day without the use of insulin or increase in blood sugar. Low-fat diet improved angina condition.

(Hospital case #401/31) - 23-year old woman with a history of thirst and polyuria and rapid loss of weight.

Jan. 21, 1931 - Admitted and diagnosed diabetic. Glycosuria, fasting blood sugar, 250 mg.%. Treatment: high-carbohydrate diet, 236 gms.; 56 gms. fat; 72 gms. protein.

Feb. 2, 1931 - Discharged; urine and blood glucose normal. No insulin required.

May 2, 1931 - Admitted for observation. Blood sugar 333 mg.%. On intensive questioning, it was disclosed that she had been eating greater quantities of fat than permitted. She had thought that bacon was a "lean" meat and made it a daily part of her diet. Because of her general condition and lab data, it was decided to put her on 20 units of insulin per day and to strictly follow her high-carbohydrate diet.

July 2, 1931 - Admitted for observation. Urine and blood normal. Carbohydrate increased to 254 grams per day

and insulin reduced to 10 units. Comment: On May 2, after three months of eating bacon, her cholesterol level was 342 mg.%. On July 2, after only 60 days of bacon-free diet, it had dropped to 185 mg.%. The young woman was normal on the high-carbohydrate diet. In only three months, on a high-fat diet, she became diabetic and required 20 units of insulin per day. When her diet was modified to low-fat for only two months, her insulin requirement dropped to 10 units per day with the benefits of a lower cholesterol and blood sugar level.

Dr. Rabinowitch was elated over the results produced by the new diabetic diet: he had treated over 500 patients since 1930 and had had only 16 failures. And of the 16, 13 turned out to be due to not having followed the diet.

But he was puzzled: "The interesting question which arises is--'Why is this diet successful?' Experiences with it are incompatible with our present conception of the metabolism of diabetes. An explanation which suggested itself early in our experience was that the results were due to its low caloric value. Undernutrition does not, however, explain the fact frequently noted, that it is possible to change the diet of an individual from 50 gms. of carbohydrate, 150 gms. fat and 59 gms. protein to 250 gms. carbohydrate, 50 gms. fat and 75 gms. protein not only without the use of additional insulin but with less than required with the former diets; these diets are identical with respect to their caloric value."

A question aimed at the core of diabetic theory--implicit in the earlier work of Sansum and Sweeney--was raised even more urgently by Rabinowitch's extensive clinical experience. If diabetes is a disease characterized by an insufficiency or insensitivity of insulin, how can a diabetic cope with, say, 500% more carbohydrate (as an example, an increase from 50 gms. to 250 gms. daily) and yet require less insulin? Was the simultaneous reduction of fat (from 150 gms. to 50 gms. daily, in the example

given above) a factor of consequence? The significance of this relationship will be pursued at length later in this writing.

In Dr. Allen's famed animal experiments using partially depancreatized dogs, the conclusion was drawn that excess feeding of carbohydrates overstrained their pancreatic function, leading to hyperglycemia. Yet in Rabinowitch's patients, the high-carbohydrate diets not only did not produce hyperglycemia, but brought the patients back to normal.

Rabinowitch commented: "The view held generally at present is that, in diabetes, there is defective production of insulin. Much of our experimental data to date fail to support this view. Diabetes does not appear to be due to defective production of insulin but to interference with the action of a normal supply." (Our emphasis).

He further stated that in infection, hyperglycemia is attributed to defective insulin production. However, many cases do not respond to high doses of injected insulin, he noted, due to the presence of an unknown factor that prevents insulin from metabolizing glucose which is present in illness including diabetes. Since this factor is not known, Rabinowitch urged: "Until more is known of diabetes, our treatment must be largely dietetic. From our experience...in determining whether patients do or do not require insulin, our conclusion is that the great majority do not; diet in the majority of cases still remains the most important factor in the treatment of diabetes." As we have seen, that diet which Dr. Rabinowitch used with such outstanding results was the high-carbohydrate, low-fat diet.

By 1935,[8] Rabinowitch had had 5 years of experience with this diet. He had treated over 1000 patients in his clinic using this new dietary concept with miraculous results. At the Joint Meeting of the Ontario and Quebec (Canada) Dietetic Associations in 1935, he proudly revealed the results of his 5-year controlled experiment in which 100 diabetics, all on insulin, were divided into two groups for testing. Fifty had been placed on the conventional diabetic diet; the other 50 received the new low-fat diet. Every patient was carefully supervised throughout the five-

year period; in each case, at least 40 blood sugar and 25 plasma cholesterol determinations were made.

Rabinowitch's opening remarks at the meeting were prophetic: "These observations and subsequent experience make it necessary at least to modify the prevalent conception of the metabolism of diabetes mellitus...Suffice it to say that it now appears to be fairly well established (our note: on the basis of the evidence he presented) that (1) carbohydrates improve, whereas fats impair, carbohydrate tolerance; (2) and that carbohydrates increase, whereas fats decrease, the sensitivity of the individual, animal and man, to insulin."

The table below indicates the varying amounts of protein, fats and glucose ingested under each of the two diets used in Rabinowitch's test:

	Old Diet (High-Fat) (gms.)	New Diet (Low-Fat) (gms.)
Protein	55 (50-60)	55 (50-60)
Fats	145 (140-150) = 56%	43 (35-50) = 21%
Average total glucose	164 (100-200)	306 (260-340)

Carbohydrates were essentially all complex and were added not by increasing calories but by decreasing fats. In fact, calories were maintained on the lower side to avoid overfeeding and excess weight. As mentioned earlier, Dr. Rabinowitch considered his diet to be "low calorie" and attempted to hold weights to 5-10 pounds below the published height-weight charts of his time. An example of maximum weight of a 5'8" male, 35 years old, was 154 pounds.

The differences in insulin requirements in the two groups were marked: insulin dosages changed radically on the low-fat diets and almost not at all on the high-fat diets, as shown in the table below. Perhaps the most significant of the results was that 24% of those on the low-fat diet no longer required insulin and were normal as judged both by lab tests and clinical observation. The balance of the 38 low-fat patients were able to reduce their insulin dosage from 24.6 units to only 10.6 units daily.

INSULIN DOSAGE WITH HIGH- AND LOW-FAT DIETS OVER FIVE-YEAR PERIOD

	HIGH-FAT DIET			LOW-FAT DIET		
Insulin Units	Start No. of Patients	5 yrs later No. of Patients	%	Start No. of Patients	5 years later No. of Patients	%
under 10	3	0		9	13	
under 20	8	7		14	18	
over 20	39	39		27	7	
TOTAL	50	46		50	38	
off insulin		4	8%		12	24%
average insulin dose	32.2	31.8	-1%	24.6	10.6	-58%
cholesterol		229 mg.%			184 mg.%	

The results obtained with the patients on the high-fat diet provided a significant contrast with those obtained from the patients on the low-fat diet, in that there was no change in average insulin dose over the 5-year period for the entire group on the high-fat diet. At the start, 39 of the 50 patients on the high-fat diet were taking over 20 units per day; at the end of five years, 39 out of 50 were still using over 20 units per day.

There was no question as to the success of this program. At last there had been a demonstration that insulin-dependent diabetics could greatly improve their condition: one-fourth of those tested had been able to return to a normal life without insulin in the five-year period.

Dr. Rabinowitch observed that decreasing fat intake had still another benefit for diabetic patients: "...there has been a marked decrease in diabetic coma, and the chief reason, as I believe I shall show, is that with this diet the diabetic is deprived of that food which is the chief cause of coma, namely fat." And he said that in over 10,000 visits to his Diabetic Clinic, acetonuria had decreased from 9% when patients were on the high-fat diet (56% fat) to 1.8% when the low-fat diet (21% fat) became standard. Likewise, under the high-fat treatment, a total number of 32 precoma and coma cases were treated, but in 1934, during the low-fat period, only

two new cases of coma were treated and one of these was precipitated by an infection.

Not only did the low-fat diet benefit the patients in regard to their diabetes, but there were improvements also in relation to angina and atherosclerosis symptoms. Under the old standard diet and with good control of glucose in urine and blood, diabetics exhibited clinical symptoms of atherosclerosis in only five years; whereas the low-fat diet succeeded in delaying these symptoms or preventing them.

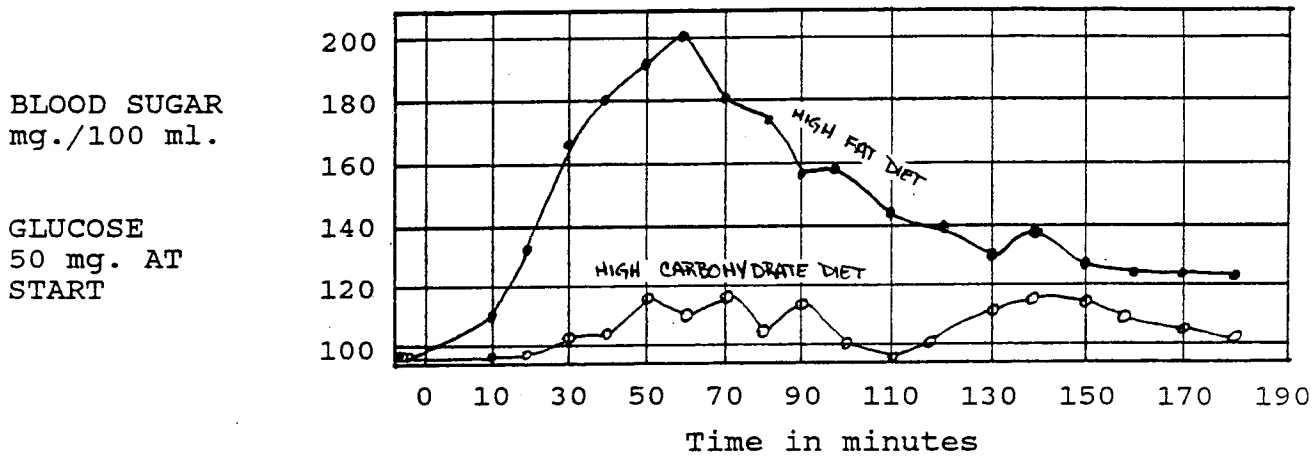
All of these results justified Dr. Rabinowitch's enthusiasm: "I believe that in the data presented here there is incontestible evidence that the high carbohydrate-low calorie diet is more effective in controlling diabetes than all other methods of treatment reported hitherto." It should be recalled that Dr. Rabinowitch was one of the first to use insulin (in 1922) and had tried the important diets and therapies current during this period. His evaluation of diabetic treatments was based on his work in a large clinic where over a thousand diabetic patients were added to those already in treatment in only the four-year period between 1930 and 1934.

A theoretical basis for success of low-fat diabetic diet is established

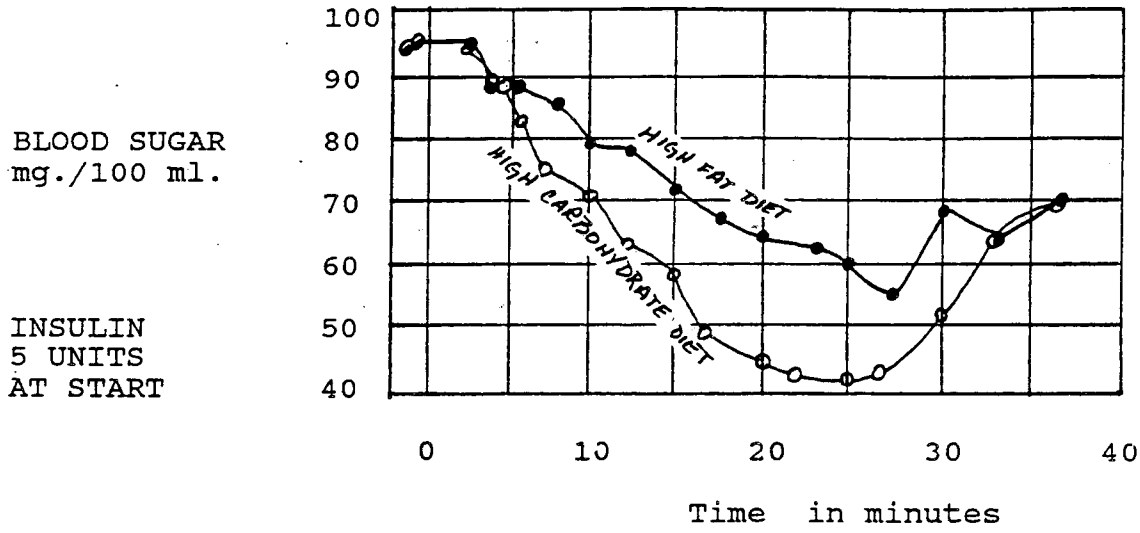
At about the same time, experimental evidence from England was confirming Rabinowitch's experiences.[9] Dr. H.P. Himsworth, in 1934, reported his research with healthy 20-year old men. He divided his subjects into two dietary categories, testing some on high-fat, low-carbohydrate diets and others on low-fat, high-carbohydrate diets, both diets being equal calorically and in protein intake. Each group remained on their respective diets for at least a week and were then challenged with 50 gms. of glucose. He found that those on the high-fat diet exhibited a diabetic glucose tolerance curve, while those on the high-carbohydrate diet tested as normals.

The groups switched diets after a lapse of time: the men on the high-fat diet went on the high-carbohydrate diet for at least a

week and vice versa. The results were the same--regardless of which individual was on the high-fat diet, those on this diet tested diabetic. This is illustrated by the two glucose tolerance curves reproduced below, both of the same subject. One was taken when he was on the high-fat diet, the other when he was on the high-carbohydrate diet of equal caloric value. As is noted on the graph, when on the fat diet, the curve met present-day criteria for diabetes: the peak was 200 mg.% and the two-hour value was 140 mg.%.



Tests for insulin sensitivity were performed on the same subject after the hyperglycemia of the glucose tolerance tests taken earlier had subsided. In these tests, 5 units of insulin were given the subject when he was on a fat diet, and again, on a carbohydrate diet. On the fat diet, the insulin was much less effective than when given on the carbohydrate diet, as noted in comparing the two curves below.

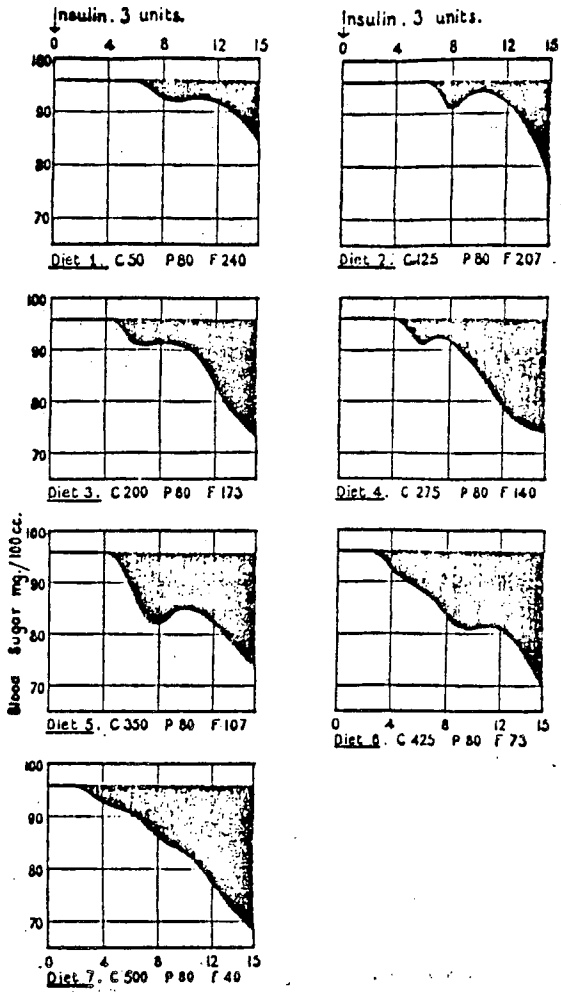


Himsworth was obliged on the basis of these experiments to conclude that the presence of fat in the blood above physiologically normal levels (as experienced on the high-fat diet) produces an ineffectiveness of insulin in its ability to facilitate the metabolism of glucose, thus creating the clinical picture of diabetes. His evidence demonstrated no lessening of secretion of insulin by the pancreas, but only a lessening of its efficiency.

The concept of the fat content of the diet versus insulin insensitivity was pursued in later experiments by Himsworth,[10] in which seven different diets varying in carbohydrate and fat content but constant calorically were tested. As in the previous experiments, the protein fraction of the diets remained constant as well.

Each group of young men followed one of the seven test diets for at least a week, then took glucose tolerance and insulin sensitivity tests before moving on to the next test diet, until at last all seven diets had been consumed by each of the groups. As the young men were confined to the University College Hospital in London for their meals, it was possible to exercise great care in regulating the diet of each of the test participants.

To test insulin sensitivity, three units of insulin I.V. were given after the glucose level returned to normal (below 100 mg.%), as shown by the glucose tolerance test. Two phenomena were noted: 1) the latent period, or the length of time after the injection before any drop in blood sugar can be detected (the less the time, the more sensitive the insulin response); and 2) area of insulin depression curve, or the area enclosed by the curve that depicts the relationship of the change in blood sugar vs. time elapsed in minutes after the I.V. insulin injection (the greater the drop in blood sugar, the larger the area--as shown in the graphs below).



SEVEN INSULIN DEPRESSION CURVES

(same subject)

(Time in minutes)

Composition of the seven diets with the latent periods and calculated areas of insulin depression are shown in the table:

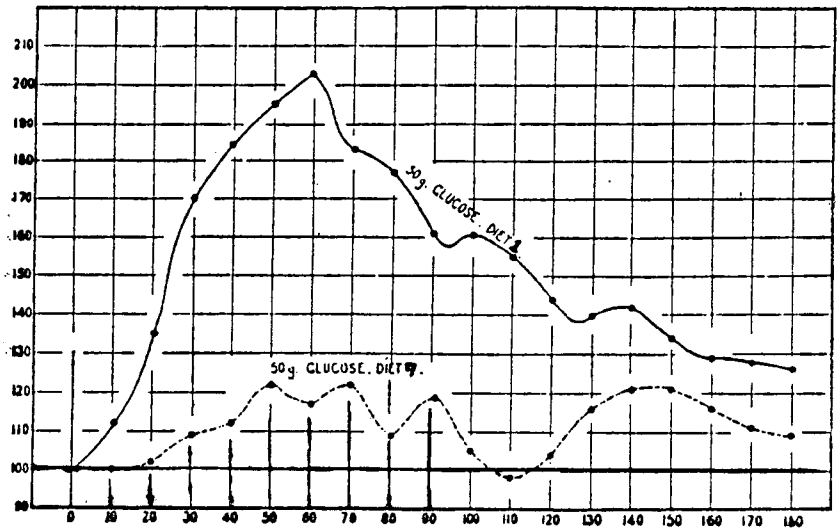
No.	Diet			Latent period	Area of insulin depression curve
	Carb.	Prot.	Fat	mins.	mg/mins.
1	*50*	80	240 *	7	30
2	*125*	80	207	6	54
3	*200*	80	173	4–5	97
4	*275*	80	140	4	119
5	*350*	80	107	3–4	130
6	*425*	80	73	2	152
7	*500*	80	40 **	2	154

* 80% fat content **13% fat content

It should be noted that as the fats decrease the latent period shortens. At 80% of total calories in fat, it took 7 minutes after the I.V. insulin injection for blood sugar to drop, whereas with

13% of total calories in fat, blood sugar dropped in only 2 minutes. All values between 80% and 13% were proportional. This relationship is very clear in the area of insulin depression curves. Area increased directly as the fat intake lessened, demonstrating clearly the relationship between the content of the diet and insulin sensitivity. In fact, the insulin sensitivity and glucose tolerance curves are practically identical: as the glucose tolerance decreases, insulin sensitivity decreased, and both do so as the fat level of the diet rises.

A graphic illustration of this interrelationship is shown in the following chart which depicts glucose tolerance curves in the same subject on the 13% fat diet and the 80% fat diet. As seen, on the 80% fat diet (diet #1), the curve is diabetic after only one week; on the 13% fat diet (diet #7), the curve remains perfectly normal.



Several other experiments were conducted to determine the relationships among endogenous insulin, glucose, and dietary factors. On the basis of all this testing, Himsworth concluded that the fat content of the diet was the factor involved in insensitizing both endogenous and exogenous insulin in its action towards glucose.

A history of the dietary practices of 131 diabetics and 118 normal subjects by Himsworth[11] indicated that diabetics showed a

preference for fatty foods in a high percentage of cases, as noted below.

COMPARISON OF DIETARY PREFERENCES OF DIABETIC AND NORMAL SUBJECTS

Group	% Of Subjects Taking: Excess Of Fat In Diet	Excess Of Butter, Cream & Drippings	Prefer Fat To Lean Meat	Excess Of Carbo-Hydrates
131 diabetics	76.3	70.2	46.0	20.0
118 normals	34.0	30.0	16.0	34.0

The consumption of a higher fat and lower carbohydrate diet by diabetics than by normals (as much as 250% more fat), indicated to Himsworth that these diabetic individuals had, in effect, created their own diabetic state. The insensitizing of their insulin due to the large amounts of fat consumed accomplished the same results observed in tests on his subjects on high-fat diets.

The promising low-fat diabetic dietary approach is put to rest

The work of Himsworth and Rabinowitch and others around the world whose research pointed in the same direction was published frequently and discussed at many medical meetings. Why, then, did their obvious successes fail to have a lasting effect on diabetic therapy?

Even Dr. E.P. Joslin,[12] one of the best-known diabetes specialists of the 1920 to 1930 era, whose diabetes clinic is one of the largest in the U.S. today, was caught up in the wave of enthusiasm for the low-fat diet. In a statement made in 1928, Joslin said: "Can it be that the prevalence of arteriosclerosis in diabetes is to be attributed to the high-fat diets we have prescribed and more especially to these diets having been rich in cholesterol? I suspect this may be the case. At any rate it is reasonable to maintain the cholesterol in the blood of our patients at a normal level and that I shall strive to do. This may result in the elimination of eggs, each one of which contains about .38 gms. of cholesterol...This therapeutic procedure is adaptable for

experimental investigation and should not require long for solution."

In 1931,[13] Dr. Joslin reconsidered, telling the nation's practitioners that since the standard methods using insulin and the high-fat diet were in his view quite satisfactory, there should be no haste to change from these established procedures. His influence and that of other highly regarded diabetitians put the low-fat concept into dormancy for the next 25 years. The tremendous inertia of old ways was not so readily overcome, and the work of Rabinowitch and Himsworth was shunted aside.

A choice of therapies--but which ones?

The advent of the oral hypoglycemic drugs provides another therapeutic choice

Diabetes research had meanwhile been intense in another area. Almost as soon as insulin was used commercially, the advantage of the oral "insulin" became apparent. As early as 1926, oral hypoglycemic drugs had been produced, though they were too toxic for continued use. The development of a drug in 1954[14] in Germany, called tolbutamide, ushered in a new era for the treatment of diabetes. Tolbutamide, which is a sulfonylurea, was put through one of the most extensive testing investigations to which a drug was ever subjected by the Upjohn Company, which introduced the drug into the United States.

The massive testing program, begun in February, 1956, after many months of animal testing, involved 3,000 physicians and 20,000 selected patients and lasted 16 months. Upjohn personally pursued 7,000 detailed case reports for a statistical analysis and evaluation. The results concerning the safety of the drug and absence of serious side effects were reassuring. As to its effectiveness, over half the diabetics were controlled better with the oral drug than with insulin. Both the Upjohn Company and the Food and Drug Administration were well-satisfied and tolbutamide, marketed as Orinase, was launched.

Meanwhile, other oral drugs (principally from the sulfonylurea and the biguanide groups) had undergone considerable testing and were deemed safe for clinical use; by 1964, 1,250,000 diabetics were being treated by one or another of these drugs. Since the oral drugs were able to control serum glucose levels so well preventing hyperglycemia, the diabetes diet that had constituted as standard therapy for so many years became much less important.

Controversy raged among physicians and researchers concerning the relative merits of the three available modes of treatment: diabetes diet, oral drugs, and insulin. While insulin had been considered the miracle breakthrough when first developed 50 years before, the visual and vascular complications associated with its use had tarnished its image. The convenience of the oral drugs and

their lack of apparent acute toxic effects were attractions, but not enough was known about the long-range degenerative problems developed by diabetics on this form of therapy as compared to those using insulin or the diabetes diet. Was it possible, as hoped, that in long-term use the oral drugs would lessen the complications of diabetes that develop from the degenerative problems associated with insulin and the progression of the disease? It is these complications that are responsible for most diabetes deaths--more than from the disease per se.

The University Group Diabetes Program seeks the answers

To resolve the question as to the best form of diabetes therapy, a large-scale clinical trial was begun in 1961, the University Group Diabetes Program (UGDP).[15] Funded by a federal grant, the study embraced 12 hospitals in the U.S. and Puerto Rico, and was conducted by 50 scientists. The 1027 diabetic subjects in the study were divided into five equal treatment groups, all receiving the same diet. The following forms of treatment were used:

Group I - Only diet was used. The conventional diabetes diet (20% protein and 40% fat), that had been used for years, was modified to 35% fat. Calorie control was stressed so as to maintain weight within 15% of the ideal.

Group II - This group was on the same diet as the other groups but also took Orinase (tolbutamide, a sulfonyluria).

Groups III and IV - Also on the same diet, these groups were given insulin in both fixed and variable doses.

A fifth group was added to the general program a year later. These patients followed the same diet and took the oral drug Phenoformin (a biguanide).

The study was double-blind among all groups except the insulin users. Group I patients, on diet alone, took a lactose placebo tablet or capsule which was identical in appearance to the Orinase tablet or the Phenformin capsule. Even the physicians in charge of treating the patients never knew which patients were on placebo and

which were receiving oral drugs until the first results were announced.

The study results, made known in 1970, were greeted with wild disbelief and dismay. Angry verbal exchanges among study physicians and many nonstudy physicians were reported in the media. But regardless of the opinions held, all were stunned by these results:

1. Orinase plus diet caused 250% more cardiovascular deaths than diet alone;
2. Phenformin plus diet caused 250% more cardiovascular deaths than diet alone;
3. Insulin, either in fixed or variable dose, was no better than diet alone;
4. The diabetics who were treated only with the diabetes diet still had a higher cardiovascular death rate than prevails in the normal population.

The study brought out some startling observations:

1. Control of hyperglycemia by drugs or insulin does not prevent or delay the appearance of vascular complications.
2. If none of the patients had ever been diagnosed and treated for diabetes, they would have fared at least as well.

The possibility that <u>any</u> treatment administered to a mature diabetic in the last 50 years was no better and oftentimes much worse than no treatment was indeed difficult to believe. But did these revelations come as a complete surprise to the medical profession as a result of the UGDP study? There had been warnings along the way. The researcher who was instrumental in making insulin available for general use by his methods of preparation and application, Dr. Somogyi,[16] said in 1949 that many diabetics were given such large doses of insulin that they were "actually victims of chronic insulin poisoning." He added that many of these diabetics could be treated by weight loss and diet alone, and predicted that oral hypoglycemics would eventually be discarded

because physicians would find them not only useless, but even harmful.

As a result of the UGDP findings, the Food and Drug Administration (FDA) issued a statement expressing agreement with the conclusions in which it proposed a ban on the oral drugs. The proposal infuriated physicians in the largest diabetes clinics. Forty of the nation's leading diabetologists, led by Joslin Clinic's medical director, called upon the FDA to rescind its recommendation. The head of the UGDP study retorted:[17] "There is no reason to use these agents until they have been shown to do more good than harm...Lowering blood sugar does not prevent the complications of diabetes. This is the core of the study."

Defending his product, the manufacturer of tolbutamide asserted firmly,[18] "There is no question of the effectiveness of tolbutamide in lowering the blood sugar of selected patients with diabetes." True enough; but no one had questioned that fact--this commercial spokesman merely neglected to mention that in addition to lowering blood sugar, the drug was also responsible for producing excess deaths!

English physicians were as reluctant to believe the results as were their American counterparts. Thus, when the shock wave hit the British Isles, an editorial[19] in a leading English medical journal commented with hollow reassurance: "What should be the decision in Britain? Here it is impossible to mount a study of similar structure: apart from the enormous cost, the delay in achieving figures of any significance could make it most unlikely that the results would be of any value. At this time it does not seem right to abandon this group of well-tried drugs; and the Committee on Safety of Drugs has said that at present it sees no need to change its attitude to tolbutamide and related drugs."

A year later a British retrospective study[20] of causes of death in 670 maturity-onset diabetics over a 12-year period was published. Their results: "Our findings seem to confirm the UGDP reports, which showed a higher frequency of cardiac deaths in diabetic patients treated with tolbutamide or phenformin compared

to a placebo group." The number of deaths caused by oral hypoglycemics was twice as high as for those using diet alone.

A sound statement did emerge from the usual conservative American Medical Association (AMA)[21] In reviewing the results of the study, an AMA spokesman said: "It should not be overlooked that the very best control of blood sugar by experts did not significantly benefit this group of diabetic patients...One might even raise the question of whether physicians should expend time and money to diagnose asymptomatic adult-onset diabetes, if its medical management leads to no significant benefit....If additional and highly regarded therapy for adult-onset diabetes has no scientific basis and results in no benefit to the patient, it will not be the first cherished therapy to be abandoned. One has only to reflect on the current attitude toward bed rest for the treatment of tuberculosis and to recall how many millions of dollars, staff effort, and patient years were wasted on bed rest therapy before comparative clinical trials showed it to be of no significant benefit."

One reason for the utter consternation over the UGDP implications was stated[22] by an editor of a widely circulated medical periodical: "Few if any drugs currently employed had such an exhaustive and lengthy study as did tolbutamide before it reached sanction for safety and efficacy by the Food and Drug Administration."

The careful and prolonged study of tolbutamide's effects did indeed confirm the fact that the short-term side effects were truly few; but the long-term effect of increased cardiovascular mortality was not predictable. Some insight into the mechanism by which tolbutamide and other sulfonylurea drugs injure the myocardium was reported[23] at the height of the UGDP furor in 1971, and later in 1972. These are the first studies to demonstrate a cardiac effect of sulfonylureas and should raise the flag of caution as to their general use.

Criticism of the UGDP[24] centered around the possible lack of comparability between treatment groups at the various centers participating in the study. It was maintained that this could have

biased the excess mortality associated with those on oral hypoglycaemics.

Most of these objections have been answered by Cornfield in 1971. Another rebuttal[25] to the critics of the UGDP was made by the Department of Medical Statistics, London School of Medicine, in 1973. In a reanalysis of the UGDP statistics, they considered all the criticism, attempting to eliminate potential bias by more stringent diagnostic criteria and the use of multiple diagnostic criteria as a basis for case selection. Their statistical reappraisal only confirmed even more strongly the original findings of the UGDP.

Sobering statistics, gloomy prospects: the crisis in the treatment of diabetics 50 years after the discovery of insulin

The UGDP served to focus attention on the facts concerning diabetic therapy and its consequences; but if that important study had never been conducted, the vital statistics would have warned that something was wrong. In the period from 1958 to 1973, encompassing the entire period of time that oral hypoglycemic drugs have been in use, there has been a world-wide increase in diabetes and related diabetic deaths.(26) Deaths from diabetes have doubled in Austria, Italy, Switzerland and Venezuela and almost tripled in Japan. Significant increases in the U.S. and Canada in diabetic mortality have also taken place. The UGDP revelations weren't necessary to tell us that we are in trouble with respect to a disease that was thought to have been "cured" 50 years ago with the discovery of insulin.

How little is understood even now and the gravity of the problem are underscored by recent public statements of leading diabeticians. The keynote speech given by the President of the American Diabetes Association, Dr. S.S. Fajans of the University of Michigan Medical School, in 1971 on the occasion of the 50th anniversary observance of the discovery of insulin, reveals how little has been accomplished in that large span of time to improve the diabetic's prospects.(27)

Dr. Fajans was brutally critical: "We do not understand why the beta cells of the islets of langerhans fail in the juvenile or adult onset type of diabetic patient. How can we prevent insulin deficiency if we do not understand its cause? If we could reproduce normal delivery of insulin in the diabetic patient (our note: by transplantation or bioengineering techniques), would we be able to prevent some of the complications of the disease? (All emphasis is from the original speech).

He continued: "We have a poor understanding of the factors which predispose the diabetic patient to premature atherosclerosis leading to...eye and kidney complications, blindness and death. How can we prevent these ravages of the diabetic state, until we learn their cause? Dr. Fajans sadly acknowledged the crisis:

"There is little doubt that premature vascular disease in the diabetic has reached 'epidemic' proportions and can be viewed as a major health problem. It is clear that present day therapy with diet, insulin or oral agents, as employed in routine clinical practice, has not prevented the occurrence of macroangiography, microangiography and neuropathy."

With these pessimistic statements, Dr. Fajans proceeded to discuss two unsolved problems[28] in diabetic care that demanded answers: 1) Is normalization of blood glucose a desirable goal in the treatment of the diabetic patient? Can the results of the UGDP be interpreted as indicating that "control" of blood glucose has no effect on prevention of vascular disease?; and 2) What constitutes the most beneficial diet for the diabetic patient?

The debate on high vs.low-fat diabetic diet re-emerges

Dr. Fajan's faith in the conventional diabetic diet had still not been shaken, despite the dismal state of affairs in diabetic care. What were the solutions he offered? For the first unsolved problem in diabetic care, Dr. Fajans proposed an electronic-mechanical device that would deliver insulin upon demand like a normal pancreas. For the second of the unsolved problems he discussed, he stated that there is no convincing evidence that would lead to a recommendation for changing the percent of fat or carbohydrate in the diabetic diet. All that is important, he asserts, is that normal weight should be maintained, so that total calories are important, though the amount of fat calories does not matter. To support this position, he cites a single study, Brunzell, et al[29] (1971), claiming that these "investigators have shown in the maturity onset type of diabetic patients that isocaloric substitution of carbohydrate for fat has not elevated fasting blood sugar levels or worsened glucose tolerance in response to a standard glucose load. However, these studies were carried out in obese diabetic patients with good insulin response and not in lean diabetic subjects. The studies were of short duration, and limited in the number of subjects studied."

Dr. Fajan's comment that the use of carbohydrates "has not elevated fasting blood sugar levels" could be interpreted to mean that they stayed at the same level, whereas the fact is that 100% of the 22 subjects, diabetic and nondiabetic, showed a decrease in their fasting blood sugar, and, in addition, glucose tolerance was improved. Dr. Fajans also thought the results were unimportant because the study was made with "obese diabetic patients". The data show that the average weight of 46% of the diabetics in the study was below 100% of ideal body weight.

Similar studies of long duration provide the answer to Dr. Fajan's criticism that the Brunzell study was of short duration. Rabinowitch's five-year high carbohydrate dietary trials in the 30's[31][32] using a thousand subjects came to the same conclusions reached by the Brunzell study published in 1971, yet the early work is forgotten and the later study is dismissed as unimportant.

An editorial in the New England Journal of Medicine[33] also commented on the Brunzell studies. "In the aftermath of the controversy ignited by the U.G.D.P. study, renewed enthusiasm for the various dietary approaches in the treatment of diabetes has surfaced. Just what is the ideal composition of a diabetic diet?", asked the Journal. "How much carbohydrate and fat should such diets contain? Brunzell and his colleagues, in this issue of the Journal, resurrect (our emphasis) the argument for a high carbohydrate diet in the treatment of certain patients...The improvement in glucose tolerance that follows the high carbohydrate diet occurs without alterations in total insulin secretion and brings to the fore the role of the sensitivity of peripheral tissue to insulin and the part that sensitivity plays in the pathogenesis of diabetes mellitus. Once again a controversial point is raised. Does the carbohydrate intolerance of the patient with mild adult onset diabetes result solely from a deficiency of insulin or is this in part due to an antagonism of peripheral tissues to insulin?"

What are the answers? How much carbohydrate and fat should the diet contain? Rabinowitch[34] and Himsworth[35-37] provided the answers 40 years ago. In the next section more data are

presented which confirm the work of these pioneers. As to the question of a possible role of insulin deficiency, this section will also offer an answer.

A bleak picture as to the unsolved problems in diabetic treatment has been painted by Dr. Fajans. It is the contention here that the picture is bleak only with regard to the present state of therapy and understanding, but that the answers to these problems are there. We will let the reader judge.

A HISTORY OF DIABETES THERAPY (SUMMARY)

1. Diabetes treatment from 1796 to 1922 consisted of a low-calorie, low-carbohydrate, high-fat diet.
2. After 1922, diabetics were permitted normal calorie high-fat diets, with insulin in variable amounts to prevent glycosuria.
3. Experimentation with normals and diabetics established these findings:
   a. High-fat diets can convert normal people into diabetics.
   b. Low-fat, high-complex carbohydrate diets restore diabetics to normal, even if they are insulin dependent.
   c. Insulin sensitivity is directly related to the fat content of the diet. The higher the fat content, the less the sensitivity, and the less the ability to metabolize glucose.
   d. Low-fat diets not only benefited diabetics, but also patients with angina and cardiovascular disease.
4. Oral hypoglycemic drugs in extensive testing demonstrate death rates 250% higher than controls on diet alone.
5. Control of hyperglycemia by insulin or oral drugs was found not to prevent or ameliorate visual and vascular damage in the diabetic.
6. Fifty years after the discovery of insulin, diabeticians proclaim their inability to treat diabetics successfully, and wonder if a change in diet--lowering the fat level--might help.
7. Because of the failure of present treatment, the low-fat diets of 40 years ago are being considered by some investigators.

II. CREATING THE DIABETIC STATE: FACTORS RAISING BLOOD LIPIDS

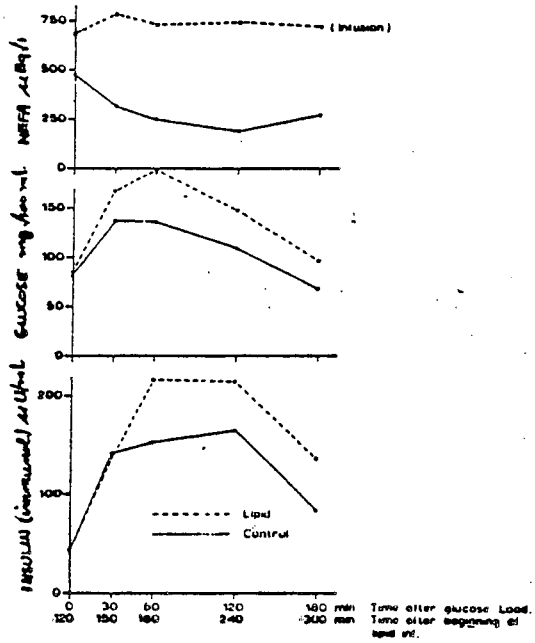
Experimental production of hyperglycemia by infusions raising and lowering blood lipid levels.

That elevated lipid levels brought about by Western-type diets (40% fat) create a hyperglycemic condition was well known by earlier investigators.[38-40] Hyperglycemia also results from elevated blood lipids caused by reasons other than diet. The following studies will show that the common etiology of hyperglycemia (severe enough to be classified as constituting the diabetic state) is elevated blood lipid levels, whatever their cause. Such levels may be created by strenuous exercising, fasting, cirrhosis, or diet. Further, it will be shown that when blood lipid levels are permitted to return to normal, the hyperglycemia disappears. Evidence will be presented demonstrating that a diabetic state, as confirmed by a glucose tolerance test, can be produced and reversed in normal people at will. The diabetic state can be induced in two hours by fat infusion,[41] two days by a high-fat diet,[42] and in periods varying from one to several weeks by many other regimens.

Thus, in a dramatic demonstration, hyperglycemia severe enough to be classified as diabetic was induced in two hours in a study[43] with 5 normal subjects. All subjects ingested 100 grams of glucose and tested normally after a 3-hour glucose tolerance test. A few days later, another glucose tolerance test was performed, but two hours before the glucose drink, a lipid infusion was started and continued until the end of the 3-hour test. Only enough lipid was infused to bring the free fatty acid level from the fasting value of 490 u Eq/1 to 700 u Eq/1, a level very similar to that found in many persons adhering to a Western diet (40+% calories in fats). This level of approximately 700 u Eq/1 was maintained throughout the 3-hour test.

Immediately before the glucose dose was taken, both the insulin and glucose values were identical with those noted in the previous glucose tolerance test without the fat infusion, but after the glucose was ingested following the raising of the free fatty acid level, the similarity disappeared. What followed can

well be described as some cases of instant diabetes! Blood glucose peaked at 190 mg.% and the two-hour value was 150 mg.%. Insulin (u U/ml.) rise was 50% higher. These results, as shown on the graph below, are those typically found in newly diagnosed diabetics.



Glucose tolerance test (oral). Repeated in the same 5 normal subjects with and without simultaneous infusion of a fat emulsion.

Unlike the diabetic, these five subjects were perfectly normal again in 24 hours, as soon as the fat infused was metabolized and the free fatty acid level return to normal.

The fact that the fasting levels of glucose and insulin were unchanged during the fat infusion poses some interesting questions challenging current theories regarding the etiology of diabetes. In the testing with raised levels of free fatty acids, only after the glucose dose were the hyperglycemia and hyperinsulinemia observed. What caused the hyperglycemia? The insensitivity of insulin could not have been due to some sudden defect in the pancreas. The investigator in this study suggests that it might be due to a block in the uptake of glucose completely independent of the effect of insulin. That block could be the newly introduced lipid in the blood that raised the

normal free fatty acid levels to abnormal heights. These abnormal heights, unfortunately, are commonplace in individuals on Western diets.

In a study[44] in which blood lipids were reduced by a two-hour infusion of B-pyridyl carbinol, the opposite effects were observed and the glucose tolerance test was improved. The infusion continued throughout the test with 100 gm. glucose (oral), and all of the subjects--six normals and a diabetic--showed a substantial lowering of glucose and insulin levels along with the drop in free fatty acid levels, as compared to results in patients tested without infusion of B-pyridyl carbinol. The reduction of free fatty acid with its attendant improvement of glucose tolerance and lowering of insulin level indicates that the problem lies not in the pancreas or in the insulin, but in the lipid levels of the plasma. It would be difficult to explain how the pancreas could, in a two-hour period, change the character of insulin produced from an insensitive to a sensitive type of insulin. What, then, did occur? As the plasma lipid levels became lowered, the insulin became more efficient in its ability to metabolize glucose; therefore, the glucose level dropped. The insulin level also dropped because the insulin sensitivity was no longer being impaired by the elevated lipids, and so less of it was required.

Thus, an elevation of blood lipid levels can decrease the sensitivity of insulin. If the lipid levels are high enough, a complete blockage of insulin action can occur. This was shown in a study in which four normal-weight subjects[45] diagnosed as diabetic were given increasingly high doses of insulin to reduce blood glucose levels, until the doses reached 300 units per day for several days. Even this sustained high insulin dosage had little effect. The blood test had demonstrated a high triglyceridemia, so treatment with hypolipidemic drugs such as clofibrate was used. This drove the blood lipids down sufficiently for the patients to be treated successfully with various diabetic drugs.

Exogenous and endogenous factors in the elevation of blood lipids.

Exercise and hyperglycemia

Whether the blood lipids are raised from exogenous or endogenous sources is not important; any sufficient increase of plasma lipids is associated with a raised level of plasma glucose. Elevated blood lipid levels, whether from lipid infusions, exercise, infectious diseases, diet, starvation, or whatever cause, will produce hyperglycemia.

Severe exercise, which acutely raises blood lipids, produces effects similar to those observed in the lipid infusion experiment described previously.(46) After strenuous and extended exercise, ketone bodies rise to a high level in the blood, producing a condition known as postexercise ketosis.(47) The ketone bodies are derived from the utilization of free fatty acid as a fuel. In extended continuous exercise, glucose tends to be depleted and the body uses free fatty acids from the adipose tissue, from which the ketone bodies are formed. The ketone bodies also serve as fuel and the plasma ketone level increases moderately during activity. As soon as exercise stops, however, free fatty acids rise and ketones continue to climb, causing the postexercise ketosis. This tendency is minimized in diets using complex carbohydrates as the major source of calories, as glucose storage is then at a maximum, and the use of free fatty acids as a fuel is less, thus reducing or eliminating the problem of ketosis.

In a study(48) demonstrating these effects from exercise, 21 normal subjects, averaging 20 years of age, none with regular athletic training, ran for 1-1/2 hours during which time they covered about 10 miles. The table below shows plasma changes following a 50 gm. oral glucose tolerance test given at the end of the run, compared with other runners who were not given the glucose at the end of the run (listed under the heading "No GTT"--no glucose tolerance test). Comparative glucose tolerance test results made on another day when the subjects were rested and not active are also shown.

	PLASMA FREE FATTY ACIDS (ueq./ml.)		BLOOD GLUCOSE LEVEL (mg.%)		KETONE BODIES (u mole/ml.)	
	GTT	No GTT	GTT	No GTT	GTT	No GTT
Peak Value Resting	.5	.5	130	130	.1	.1
Peak Value After run	1.3	2.0	160	80	.75	1.25

As shown on the table, the free fatty acids increased 400% as a result of the activity, from 0.5 to 2.0. The oral glucose ingested immediately after the run was able to return it to normal, but in two hours it had climbed to double the normal value. After the glucose tolerance test, blood glucose increased from a maximum of 130 mg. at rest to 160 mg. after the run, a 23% increase. After the run, ketone bodies increased 12 times over the resting level; two hours after the oral glucose test they were five times higher. Both the elevated free fatty acids and ketones are associated with hyperglycemia, apparently caused by lowering of the efficiency of the insulin.

Severe illness and hyperglycemia

Severe illness has been associated with glycosuria and most theories explaining this transient state blame stress on the pancreas for the syndrome. This condition poses a special problem for children as glycosuria is found in many childhood diseases;[49] in one study, 41% of the juvenile patients with acute infections had abnormal glucose tolerance tests. Since blood glucose values sometimes do not return to normal for months, some children in random examinations may test as diabetic and be started on insulin. Once started, many become confirmed diabetics.

The author knows personally of a 19-year old insulin-dependent diabetic who was started on insulin at the age of three, two weeks after she had become ill with an infectious disease. Even infants with acute infectious diarrhea have diabetic glucose tolerance tests. Acute tonsillitis and many other diseases also produce the abnormal glucose tolerance test results.

A recent study[50] explores the mechanism of abnormal glucose tolerance tests during illness. Ten healthy, nonobese men, ranging in age from 21 to 24 years, lived in a metabolic ward during the experiment. A 300-gram carbohydrate diet was started on the first day and repeated each day until the study terminated.

After three days on the diet a baseline I.V. glucose tolerance test was performed, and the following morning, seven of the men were inoculated with sandfly fever virus. The three control subjects were given uninfected plasma. I.V. glucose tolerance tests were taken at regular intervals and the results are summarized below.

TEST CONDITIONS	DAY -1	DAY +1	DAY +4	% INCREASE Over DAY -1
Glucose disappearance rate mean k value (serum)	2.69	2.38	1.23	-54%
Insulinogenic index insulin (IRI)	.61	.70	.87	+43
Plasma immunoreactive glucagon (IRG)	117 pg/ml.	112	130	+11
Serum free fatty acids (FFA)	285uEq/L	238	607	+210
Imunoreactive growth hormone (HGH)				
Base	1 mg./ml. (approx.)	1 (approx.)	7.3	+730
Max	9 (approx.)	6 (approx.)	23.2	+260
Rectal temperatures ^{o}F	98.2	98.1	101.8	+3.6^{o}F.
Urinary free cortisol excretion	90 ug/day		297.1	+330

One day (day +1) after contact with the virus, no changes appeared in the various tests as compared to tests made immediately before the virus was transmitted to them (day -1). But on the 4th day after inoculation, the seven viral-infected men tested with an abnormal glucose tolerance test. This is reflected in the 54% drop in the glucose disappearance rate.

Reasons for the hyperglycemic state all tie together. As shown in the table:

Human growth hormone	+730%
Cortisol excretion	+330%
Serum free fatty acids	+210%

As recalled in the lipid infusion study,[51] when sufficient lipid was infused into the blood to raise the level 50% from 500 Eq/L to 700 Eq/L, the subjects tested diabetic. Changes in the lipid and endocrine profile of these seven men were more

pronounced than occurred in the infusion test and provide the basis for understanding abnormal glucose metabolism tests during and after infectious disease.

Starvation and hyperglycemia

In fasting or starvation, the exhausted glucose stores produced under these conditions force the body to call on the fat reserves for fuel and the blood quickly becomes loaded with free fatty acids. Regardless of the source of the blood fat--endogenous or exogenous--the results are the same producing a diabetic glucose tolerance test. After two days of starvation,[52] six normal men aged 21 to 25 years, when tested for glucose tolerance, showed a diabetic response. The table below shows results on glucose tolerance test on the subjects with the two-day fat diet and on those on the two-day starvation regime.

	Blood Glucose (mg./100 ml.)			
	Fasting	30 min.	60 min.	120 min.
Fat diet	80	155	184	196
Starvation	67	145	188	184

The benefits of weight reduction of obese diabetics can be understood in the light of these studies. An active exchange between adipose tissue and the blood constantly keeps the blood lipid levels elevated. Obese diabetics who reduced their weight into the normal range had a substantial drop in plasma lipids and a corresponding improvement in glucose tolerance, in many cases returning to normal. In a group of 39 diabetics, a positive correlation (P. 001) was observed between fasting insulin and the degree of obesity.[53]

The effects of starvation on the relationship of blood lipids and hyperglycemia have been explored in other studies with fasting subjects. During starvation, there is a shortage of carbohydrates and fuel requirements are mainly met by free fatty acids. In this switch of the body to a free fatty acid

substrate, ketone bodies are formed and accumulate in the blood. Ketosis can likewise occur on an adequate calorie diet low in carbohydrates.

Some of the runners in the study demonstrating ketosis resulting from exercise,[54] were put on a 72-hour fast to investigate this relationship. After 16 hours of fasting, their blood levels were in the normal range. After 72 hours of fasting, however, their free fatty acids (uEq./ml. blood) rose to 1.5, three times higher than normal, and the ketone bodies (u mole/ml. blood) rose to a 2.8, twenty-eight times normal levels. Their oral glucose tolerance test was hyperglycemic, with the blood glucose level 189 mg. after two hours. The elevated free fatty acids, 300% more than the base line value, mimics the elevated free fatty acid condition characteristic of postexercise ketosis. In both cases the glucose tolerance tests appear diabetic.

In another study, the relationship between free fatty acids and glucose tolerance during the continuing fasting period was examined. Twenty-year old normal subjects[55] were fasted for two, three, and four days; an oral glucose tolerance test was made at the end of each period. The following table summarizes the results on their tests.

		BLOOD GLUCOSE TOLERANCE TEST (100 GMS.)		
FAST PERIOD	AVERAGE FASTING FREE FATTY ACID (m Eq./l. blood)	PEAK (Mg.%)	3 HRS. (Mg.%)	4 HRS. (Mg.%)
24 hrs.	693			
48 hrs.	902	190	138	95
72 hrs.	898	170	143	120
96 hrs.	1,100 (est.)	190	160	158

Free fatty acids rose continuously as the fasting proceeded, and as this occurred, the glucose tolerance test worsened. At the end of the 96-hour period, the glucose level was plateauing above 150 mg., and this level was maintained up to even four hours afterwards. On the 5th day of the refeeding period, the glucose tolerance test still showed a peak of 190 mg. The

gradual deterioration of the glucose tolerance test can be seen day by day, as lipids rose.

Fasting produces elevated lipid levels in normals, and a glucose tolerance test taken after a fast (especially after a few days of fasting) produces a diabetic response to glucose tolerance testing. The same fast for a diabetic, however, produces very little change in a glucose tolerance test, since the diabetic's lipids are elevated before the fast.

This difference was demonstrated[56] in a group of eight young men, six normals and two diabetics, who fasted for eight days and were then given a glucose tolerance test. The table below contrasts plasma values before and after the fast between the diabetics and the normals. Values are given for the diabetics only and are reported in terms of percent variation from the normals. (Normals = 100%).

MINUTES AFTER GLUCOSE INFUSION	GLUCOSE LEVEL BEFORE FAST	GLUCOSE LEVEL AFTER FAST	FREE FATTY ACID LEVEL BEFORE FAST	FREE FATTY ACID LEVEL AFTER FAST
0	+35%	+0%	+40%	+0%
10	+10	+5	+80	+22
20	+23	+8	+100	+38
60	+95	+12	+100	+25
GLUCOSE DISAPPEARANCE Rate per minute	-75	-12		

After the fast there was no difference between either the glucose or free fatty acid levels of normals and diabetics, but the fasting glucose levels of the diabetics were 35% higher than the normals before the fast, and at all other time intervals the glucose levels carried out this trend. As the free fatty acid levels of the normal subjects rose to that of the diabetics', their glucose levels also rose until they were within 6% of reaching the level of the diabetics. By contrast, before the fast, their free fatty acid level was averaging 80% less and their glucose level 40% less than the diabetics'.

A comparison of the extraction rate of glucose of diabetics with that of normal subjects is also striking. While it was 25%

of that for normal subjects before the fast, after the fast it was 88%. This difference was due to the fact that the normal subjects approached the diabetic level, having first raised their free fatty acid level towards the level in diabetics--as there was no before and after rate difference for the diabetics.

Thus, by acute fasting which raised the plasma lipids sufficiently to inactivate the effect of insulin on glucose, six normals tested as diabetics after eight days. After their lipids were lowered by breaking the fast, the glucose levels returned to normal in a few weeks.

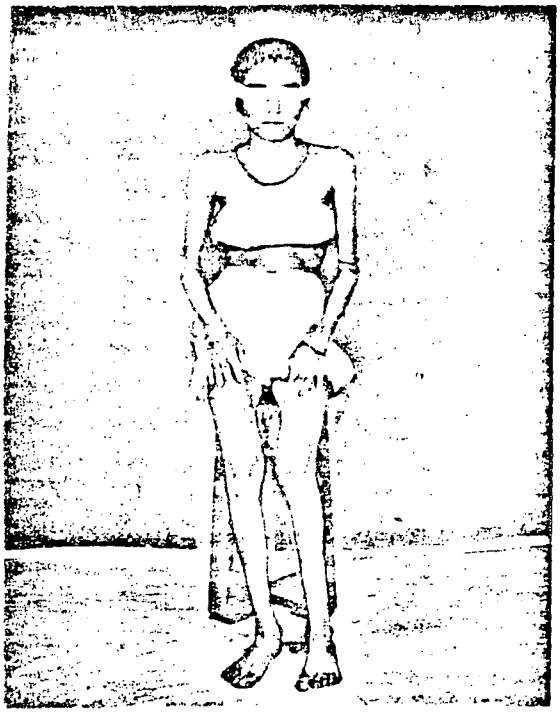
The results point to a common conclusion: higher lipids lead to elevated plasma glucose, and in a predictable period, to the hyperglycemia of diabetes. If this conclusion is indeed correct, we should be able to predict the occurrence of the diabetic state in particular subjects, using these concepts as guides.

We may ask, for example, if a person could be diabetic if he were in chronic mild starvation, ate only once every day, and subsisted on a diet consisting of grains, vegetables and practically no fat? To suppose this as a possibility goes counter to the common preconception of the diabetic as an obese person. In obesity, lipids are elevated as a direct consequence of diet and excess calories, but what could produce the diabetic state in our hypothetical subject?

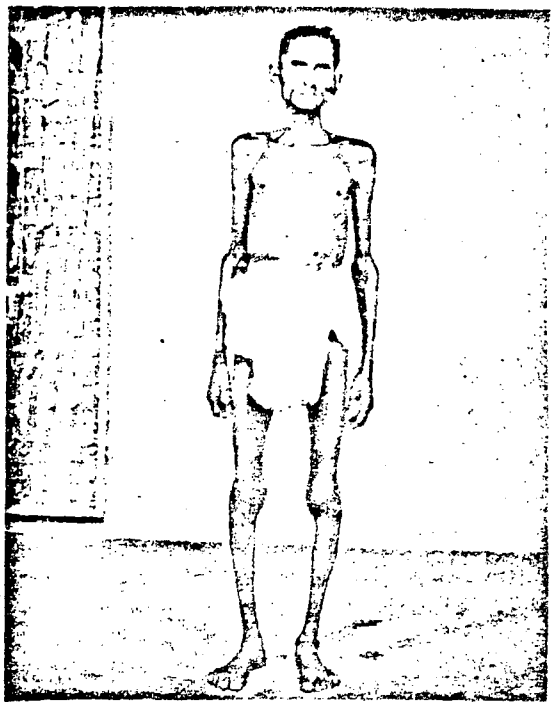
Applying our concepts, we could predict that the mild chronic starvation could raise the free fatty acid levels and therefore raise plasma glucose. The infrequent meals would force the body to reply on free fatty acids for most of the 24-hour period, adding to the free fatty acid total and further elevating the glucose level towards hyperglycemia. Since the subject is in mild starvation, the fat depots would gradually become exhausted. Thus, it could be predicted that one could become diabetic for reasons not explained by classical theories.

Diabetics corresponding to our hypothetical subject are found in India[57] in large numbers. In photographs, they resemble wasted concentration camp victims. Yet these individuals are not given food to cure their problem; they are

given insulin. As previous studies indicate, when adequate calories are consumed by subjects who have fasted, within a few weeks their diabetic glucose tolerance test becomes normal. It is tragic to maintain these individuals on insulin at a cost probably greater than that of the food which they require to return them to normal. Even when advanced kwashiorkor develops with pancreatic fibrosis, it is only a very few individuals who do not return to normal upon feeding.(58)



M.M., age 19, "J" type.



G.S., age 45, elderly-lean type.

<u>High fat diets and hyperglycemia</u>

Young children on a high-fat diet(59) present a blood picture very similar to that found in starvation. Ten children 1-6 years old were put on a diet of 80% fat for periods of up to one year. In only ten days, considerable increase in blood lipids occurred: total lipids increased 35%, cholesterol 140%, triglycerides 50% and ketones 800%. Although a glucose tolerance test was not reported, with these blood levels the response would probably be diabetic, with elevated insulin.

One girl, on the diet for nine months, showed rapidly rising lipid levels for the first month, and thereafter most levels stabilized. Total lipids doubled from 500 to 1000 mg.; cholesterol went from 150 to 400 mg.; and other lipids doubled with the exception of the free fatty acids, which did not change very much. Glucose was at the starvation level--65 mg.--and ketones rose to 40 mg./100 ml., a ten-time rise.

These children demonstrate on a condensed time scale the mechanism for producing elevated total lipids, including high cholesterol and triglyceride levels. What they have "accomplished" in weeks on an 80% fat diet, large numbers in our population "accomplish" in a period of years on a 40% fat diet. In terms of the blood picture, the end result is the same.

Just how potent fat in the diet can be in elevating blood lipids and producing hyperglycemia was demonstrated by another study(60) in which subjects went on a high-fat diet for only two days. Five normal men ranging from 21 to 26 years of age went on a diet eating only olive oil, butter, mayonnaise with egg yolk and 20% cream. After the two-day diet and an overnight fast, they were given a glucose tolerance test using approximately 100 gms. of oral glucose. In only two days these normal men tested diabetic. Later, on a two-day high-carbohydrate diet, the men tested normal.

A diet without carbohydrate, consisting of 60% fat and 40% protein, was found to produce ketosis in adults in three days.(61) An elevation of ten times the normal ketone level had occurred at the end of the three-day period. Cholesterol had increased by 15% on the fourth day. Other deleterious physiological effects were observed on this calorie-adequate but carbohydrate-free diet. The investigators interpreted their findings as indicating that ketosis represents carbohydrate deficiency, not starvation.

<u>The relative influence of dietary fat and simple carbohydrates on hyperglycemia</u>

To further demonstrate the effect upon blood glucose by fats in the diet, a particularly well-designed study compared the relative hyperglycemic contributions of a simple carbohydrate (glucose and sucrose) and fats in the diet.[62] A variety of diets were tested on normal men, 18 to 22 years old, within 15% of their ideal body weights, in the strict control of a metabolic ward where they lived and consumed their diet during the entire study. A control diet of solid food consisted of 3025 calories; 43% of this was fat, 17% protein, and 43% carbohydrate. This intake was divided into four daily meals. The four experimental diets were liquid and contained 15% of calories as protein (calcium caseinate) and totaled 3000 calories per day. Fats and carbohydrates made up the 85% balance and were as follows:

DIET	PROTEIN (caseinate)	FAT (corn oil)	CARBOHYDRATE (glucose)
65% fat	15%	65%	20%
45% fat	15%	45%	40%
25% fat	15%	25%	60%
5% fat	15%	5%	80%

Subjects were put on the control diet for four days, and the control glucose tolerance test was taken. They then started the 65% fat diet, continuing it for three weeks, after which another glucose tolerance test was done. The 45% fat, 25% fat and 5% fat diets were each followed for two weeks in succession, and a glucose tolerance test was taken after each diet period. The results are summarized.

ORAL GLUCOSE TOLERANCE TEST RESULTS
(CONTROL AND FOUR LIQUID DIETS)
Plasma glucose mg./100 ml.

% fat in diet	# of subjects	Minutes after glucose ingestion 0	30	60	90	120	150	180	% glucose in diet
Control-43%	4	89	133	143	117	116	101	78	
65% fat	4	91	155	186	183	184	149	122	20%
45% fat	4	88	154	188	200	183	146	105	40%
25% fat	4	88	150	170	162	127	112	76	60%
5% fat	3	89	134	132	125	116	99	68	80%

Fat clearly had the greatest hyperglycemic effect. Diets with 65% fat and 45% fat are in the diabetic range, while 80% glucose and 5% fat are well in the normal range. The power of fat unquestionably overshadows the glucose in its diabetogenic properties.

In another test series sucrose was substituted for glucose in a 65-day trial in which subjects ingesting 80% sucrose, 5% fat, and 15% protein. The average changes in glucose tolerance tests for all of the subjects for the entire period were in the normal range.

It should be noted that as the glucose content of the diet rose, the triglycerides increased significantly. Yet the glucose tolerance test improved despite the triglyceride rise. If the fat level is low enough--5%--the glucose or sucrose, even at 80%, does not create major problems over the short term.

One of the abnormalities generated by high sucrose diets is hyperinsulinemia, apparent on glucose tolerance testing. Some examples illustrate this.

A group of 19 young men went on a diet for only two weeks using sugar (sucrose) for 60% of their calories.[63] At the end of the period 1/3 of them developed hyperinsulinism and triglyceride levels were increased in all of them.

The same test was tried on two young people[64] for only one week during which time they each consumed 400 gm. of sugar (sucrose) daily as part of their diet. On the 8th day, they had a 50 gm. oral glucose tolerance test. The same test was repeated

14 days after the diet ended. The results appear in the table below.

EFFECTS OF HIGH-SUCROSE DIET ON
ORAL GLUCOSE TOLERANCE TEST RESULTS

Subject no.	Sex	Time-relation to high-sucrose diet	Glucose (mg. per 100 ml. (blood)				Insulin (uU. per ml. serum)			
			0 min.	30 min.	60 min.	120 min.	0 min.	30 min.	60 min.	120 min.
1	M	Before	83	130	102	80	14	30	39	22
		8th day	64	158	79	60	23	125	136	130
		22nd day	102	146	112	90	5	19	28	12
2	F	Before	74	108	100	85	17	51	62	19
		8th day	70	132	92	63	32	97	128	118
		22nd day	81	112	120	82	9	12	16	7

On the 8th day, each subject's fasting glucose level was lower than the prediet level; the young man's level was 23% less. This drop was probably due to the hyperinsulinemia that both subjects displayed. Their peak insulin levels rose from 39 to 136 in one case, and from 62 to 128 in the other. Although the peak glucose level was higher in 8 days, it was not diabetic, but approached hypoglycemia. Fourteen days after the diet, fasting glucose levels were raised as much as 23%, indicating a mechanism for an elevated fasting level and a prediabetic condition. The accompanying of hyperinsulinemia with normoglycemia suggests that the action of the insulin has become either less effective or has been impaired, or in some way is mimicking the diabetic state.

Simple vs. complex carbohydrates in the elevation of blood lipids

Differences in simple and complex carbohydrates show up in their effects on blood lipids, especially triglycerides. This is especially apparent when the protein and fat content of the diet is held constant, and only the type of carbohydrate is changed. In one study,[65] the diet consisted of 2,500 calories per day and the approximate distribution of calories was protein, 15%; fat, 25%; and carbohydrates, 60%. Two different diets were

formulated keeping the protein and fat content constant, and modifying the carbohydrates. One diet was based on simple carbohydrates primarily, 54% sucrose and 6% starch; the other reversed the proportions, and emphasized complex carbohydrates, with 54% starch and 6% sucrose.

Twelve patients tried each diet for 7-10 days. After each diet period, a glucose tolerance test was made. In the first and second hours after the glucose dose, it was observed that the 54% sucrose diet produced a 15% higher insulin level than the 54% starch diet. This study confirmed the tendency reported earlier[66][67] of high simple carbohydrate diets to produce hyperinsulinaemia.

By means of radioactive C^{14} (carbon 14) labeling of the sugar used in the glucose tolerance test, other data surfaced. On the 54% sucrose diet, the percentage of C^{14} test sugar converted to triglycerides was 200-500% greater than on the 54% starch diet. Probably the elevated insulin level was a factor in the increased formation of triglycerides. It was of interest that female patients on oral contraceptive, which in themselves raise plasma lipids, demonstrated an additional increase of as high as 200% more triglyceride formation on the 54% sucrose diet.

Although simple carbohydrates (e.g., sucrose) and complex carbohydrates (starch) provide the same amount of calories, only the simple carbohydrates abnormally raise blood lipids and especially the triglycerde fraction. To determine the relationship between simple and complex carbohydrates over a longer period,[68][69] a study was made to compare a sugar diet to a starch (bread) diet and also a Western (36% fat) diet. Fifteen normal people and one who had essential triglyceridemia were on one of the diets for a five-week period, before moving on immediately to the next diet for another five-week period.

The sugar diet included 230 gm. of sugar, and both the sugar and starch diets had 19% fat, 64% carbohydrate, and a protein content of 17%. At the end of each five-week diet an oral glucose tolerance test was given. The significant values for the

fasting and peak glucose levels on each of the three diets are seen on the table:

DIET	FASTING GLUCOSE	PEAK (30 min.) GLUCOSE
Western diet	88	149
Sugar diet	85	149
Starch diet	78	114

Both the cholesterol and triglyceride levels rose on the sugar and Western diets. On the starch diet these levels dropped. (Cholesterol level dropped at least 10% in all subjects on the starch diet.) In each case, the higher lipids were correlated with higher fasting glucose and peak glucose levels.

The importance of this study lies in its careful design: the entire group of subjects followed each diet for five weeks and the 30% higher glucose level reached on the sugar and Western diet as compared to the bread diet was demonstrated individually by <u>everyone</u> in the group. After the three diets were followed for the three consecutive five-week periods, all of the subjects went back to the Western diet, and their plasma levels again responded as they had to the earlier trial on the Western diet. By experiencing each of the three dietary variations in the tests, the subjects all acted as their own controls, and the cause and effect relationship of dietary intake and plasma changes was demonstrated by each subject.

If the glucose elevations experienced by the subjects of this study can be achieved in five weeks on an average Western diet, imagine the possibilities of consuming such a diet for 10 years, 20 years, or whatever time required to become diabetic on the typical American diet--the equivalent of the experimental Western diet in the study.

The test subject with the essential triglyceridemia, a 44-year old man, had a serum triglyceride level of 1200 mg. After five weeks on the starch (bread) diet, it fell to 400 mg. When he changed to the sugar diet, by the end of the fifth week it had risen to 840 mg. His glucose tolerance test mirrored the changes

in his triglycerides. Although his fasting glucose level was 80 mg. in both the sugar and starch diets, his peak glucose after the starch diet was 120 mg.; but after the sugar diet it rose to 200 mg.--a hyperglycemic and diabetic level. Even this subject, whose lipid levels were far in excess of the average diabetic's, was able to return to normal glucose tolerance test values in five weeks on a complex carbohydrate low-fat diet regime.

If a subject with lipid levels this high could test normal in a glucose tolerance test in five weeks, it would seem reasonable that the complex carbohydrate diet approach should be given wide trials. Unfortunately, there is insufficient interest in this nonpharmaceutical therapy at the present time.

The investigator in this study felt that the rapid increase of diabetes in Israel--where these tests were made--was due to dietary changes resulting from a decrease in the consumption of bread and an increased intake of sugar. A similar observation[70] was made among the Zulus in South Africa. Animal experiments also support this view linking simple carbohydrates and the tendency to diabetes.[71]

After reviewing the dangers of a diet in which a substantial part of the intake consists of a simple carbohydrate in the form of sucrose, it is shocking to note that one of the largest selling infant formulas (Similac)[72] has sucrose (sugar) as its sole source of carbohydrate comprising almost 50% of the total calories. This formula is highly recommended for children at least to the age of two--guaranteeing an increased incidence of diabetes (as well as of dental caries) among these young consumers.

Experiments with fat-free diets

Some diet studies have been made utilizing formula diets which contain no fat. These are not practical except on a short-term experimental basis, but the two studies reported do isolate the effect of fat in the blood.

In one of these studies,[73] a 34-year old man with a fasting glucose level of 500 mg. was first put on a control diet

of 40% fat for a week. His triglycerides rose to 5,500 mg. The fat level of the diet was reduced to zero for a week and his triglycerides dropped to 1,900 mg. Two days after resuming the 40% fat diet, the level rose to 7,500 mg. This example of dietary manipulation, repeated many times with similar results in other studies, illustrates how alteration of the lipid levels of diabetics through dietary modification is readily achieved.

Since the normal diabetic diet calls for 40% of calories in fat, it is clear why patients such as the man in this study maintain high lipid levels which typically are controlled with insulin, rather than diet. As this man's triglycerides were plateauing at 5,000+ mg., it would almost certainly be concluded that diet (standard diabetic diet of 40% fat) is ineffective in lowering the soaring lipids, and insulin therapy would be thought necessary.

In the case of the above subject, though his triglycerides were lowered remarkably after only one week on the fat-free diet, this was not considered a successful approach because one week was thought too long. It took the patient 34 years to raise his lipid values to their elevated levels, yet the dramatic drop in triglycerides in one week was not fast enough! Projecting from the one week response, six to twelve months on a low-fat diet conceivably would restore values of that level to normal.

In the other study[74] using a diet containing no fat, the purpose was to demonstrate the powerful effect of fat on glucose tolerance even when simple sugars (not including sucrose) were in the diet. Nine normal and 13 diabetic subjects participated. Half of each group was put on a special formula diet. The diet of one group consisted of 15% protein, 40% fat and 45% carbohydrate; the diet of the other group had 15% protein, 0% fat and 85% carbohydrate. The carbohydrates used were identical in each diet (Dextrimaltose). The diets were maintained for 8-10 days, after which the subjects fasted overnight and were given 100 gms. of glucose for glucose tolerance testing.

Both the normals and the diabetics on the high-carbohydrate diet improved to a greater extent than those on the 40%-fat diet:

fasting glucose levels on the high-carbohydrate diet dropped 8% compared to the 40%-fat diet. Fasting insulin levels decreased even more: a 16% drop occurred on the high-carbohydrate diet. During the glucose tolerance test, glucose peak values for the 0%-fat group were 160 mg.; the 40%-fat group's values for this test were 180 mg. Similar differences appeared in the insulin levels displayed: the 0% fat group peaked at 130 U/ml., while the 40% fat group's level was 180 U/ml.

Despite the short duration of this test and the disadvantage of not using complex carbohydrates, the results of the glucose tolerance tests clearly demonstrated the beneficial effects of the fat-free diet.

A dietary indictment: fats and simple carbohydrates and the creation of the diabetic state.

The principal role of dietary fat

Several studies have been analyzed here which, without exception, indicate that the principal nutritional factor which creates the environment conducive to diabetes is fat. We have shown evidence that fat can create diabetics in two hours (by fat infusion);[75] in two days (by fat meals);[76] or in three weeks (using a 65% corn oil diet).[77] In all three studies, there were no exceptions to the results: all subjects tested diabetic on glucose tolerance testing. With these subjects it was not necessary to check their histories for diabetic relatives--all that had to be noted was their fat intake.

Animals react to elevated fats in the diet with hyperglycemia, just as humans do. In a study with rabbits,[78] a diet with only 17% in fat was sufficient to bring the animals to a diabetic glucose tolerance test. The fat was primarily lecithin, derived from soy, so favored by many as a health supplement. Being a phospholipid, lecithin acts in the blood like any fat to create a diabetic hyperglycemia. This study will be further discussed later.

If a diet is low in carbohydrates and high in fats, the body is obliged to depend upon free fatty acid as its principal fuel,

as we have earlier noted. The continuous relatively high levels of free fatty acid and its oxidation products, ketone bodies, stimulate the pancreas to produce large quantities of insulin, which would depress the fasting glucose level.

Both ketones and free fatty acids stimulate the production of insulin. Some investigators[79] have found that by injecting ketones into the blood, the concentration of insulin increased 200%. Free fatty acids have been found to stimulate insulin secretion substantially. Injections of free fatty acids[80], in amounts sufficient to increase free fatty acid fasting level three times, induced over ten times increased insulin levels. Confirming evidence of this relationship is also noted in cirrhotics,[81] in whom the rise in free fatty acids correlates with hyperinsulinemia.

Although high fat diets eventually lead to hyperglycemia, the result of the initially evoked hyperinsulinemia is quite often hypoglycemia.[82] This is the condition found in low-carbohydrate diets and also in fasting, where free fatty acid is the primary fuel.

The important role of simple carbohydrates

Simple carbohydrates, such as sucrose, have been incriminated as etiological agents in hyperglycemia, but on the basis of these studies,[83] even an 80% sucrose diet for two months will not create a hyperglycemic condition. This last observation is not to be construed as a recommendation for a simple carbohydrate diet: as noted in other studies, simple carbohydrates raise triglyceride and insulin levels. These two factors are associated with both hypoglycemia and hyperglycemia.

Hypoglycemia is becomingly increasingly recognized as a somewhat disabling syndrome that is a basis for abnormal behavior patterns. The underlying etiology is hyperinsulinemia induced during the fasting state, on low-carbohydrate diets, as mentioned above, or by a meal of simple carbohydrates. In any case, the excess insulin drives the glucose level below that which the body can normally tolerate.

Hyperinsulinemia has multiple etiologies, but ingestion of sufficient quantities of simple carbohydrates will produce this state.[84][85] Current dietary treatment consists of high protein, restricted carbohydrate meals. Theoretically, only protein in a meal produces a flat, steady glucose level and so prevents the hypoglycemic periods; in practice, this approach actually worsens the condition. The following study demonstrates this.

Eight normal women ingested three different meals[86] on different days, after which both glucose and insulin levels were measured up to five hours after the meal. The meals were: 1) one pound of beefsteak; 2) 100 gms. glucose; 3) one pound of beefsteak plus 100 gms. glucose. Meal 3 contained 935 calories distributed as 27% protein, 31% fat, and 42% carbohydrate.

The effects of meals 1 and 2 in the glucose tolerance testing were predictable. The beefsteak meal (#1) produced a relatively flat plasma glucose and insulin response. The glucose meal (#2) produced a normal glucose tolerance test as would be expected in normal women. The results of meal #3, the beefsteak and glucose meal, came as a surprise. Its high-protein content (27%), almost twice a normal intake, and the percent of fats and carbohydrates it contained were not unlike the recommendations for hypoglycemic diets; yet the insulin reaction it produced was dangerously high. The insulin response on meal #3 was 400% higher than recorded on the beefsteak alone, and about 200% higher than on the glucose alone.

This reaction is not a phenomenon observed exclusively in adults but has also been demonstrated in premature infants.[87] In a study comparing their reaction to glucose, glucose plus amino acids, and amino acids alone, the following insulin responses were observed:

PREMATURE INFANT (wt. approx. 2200 gms.)
REACTION TO VARIOUS INFUSIONS

Infusion in 30 min.	Peak insulin level
1.25 gm. glucose	19 U/ml.
1.25 gm. amino acids	11 U/ml.
1.25 gm. glucose plus 1.25 gm. amino acids	75 U/ml.

Insulin increased 400% with the combined protein-carbohydrate infusion as compared to the responses with either of the other two infusions--very close to adult values.

This dilemma was noted in a review of hypoglycemic therapy:[88] "While the high protein, low carbohydrate diet is the standard recommendation for treatment for reactive hypoglycemia, this diet makes some of these patients distinctly worse...Patients develop an abnormal or diabetic glucose tolerance test when placed on a high protein, low carbohydrate diet...and one wonders if a potentially diabetogenic diet is the best physiological therapy for these disorders."

What is the proper diet for both hypoglycemia and hyperglycemia? One that furnishes a steady flow of glucose: in the average person, this is two calories per minute, day and night. This steady flow cannot be achieved with the ingestion of simple carbohydrates that enter the blood stream soon after ingestion and do not require a process of more prolonged digestion. The simple carbohydrates (sucrose, etc.) present the blood with not two calories per minute, but 20, 40, or 100, almost at once. The pancreas is stimulated to quickly raise its output of insulin, converting the excess glucose into triglycerides, or storing it in the fat reserves. Before the insulin level can return to normal, the glucose level may have dropped to hypoglycemic levels.

If, instead, complex carbohydrates are ingested, the breakdown into glucose would take place gradually over several hours, and the excessive stimulation of the pancreas with the subsequent adverse effects on glucose metabolism would not occur.

This is illustrated in the studies we have cited. Complex carbohydrate intakes promote low and steady insulin levels because the glucose derived from the slow digestion is entering the blood at a constant rate of approximately two calories per minute. With three main meals per day (largely complex carbohydrate) and a slice or two of bread between meals, cyclical plasma insulin and glucose variations may, for all practical purposes, be eliminated.

Under these conditions, hypoglycemia disappears because hyperinsulinemia is no longer created; and with a low-fat diet regime as detailed later in the section on Recommendations, hyperglycemia also disappears.

The dangers of simple carbohydrates are also pointed out by animal studies, as in an experiment with rats[89] which were fed diets constant in fat, protein, salt and vitamins but varying in type and amounts of carbohydrate. The animals fed sucrose diets developed diabetes in as little as three weeks. On a 67% sucrose diet, this development took 21-40 days; on a 40% sucrose diet, it took 40 days; on a 33% sucrose diet, it took 100 days. The animals in the study on starch diets remained normal, and diabetic rats switched to the starch diet became normal. Translated into human terms, on a 67% sucrose diet, diabetes could develop in two years; on a 40% sucrose diet, in four years; and on a 33% sucrose diet, it would take nine years to become diabetic.

Simple carbohydrates do their metabolic damage far more slowly than fat, which can create the diabetic glucose tolerance test in only two weeks in humans.[90] In this same study, 80% sucrose ingested for 65 days did not produce an abnormal glucose tolerance test.

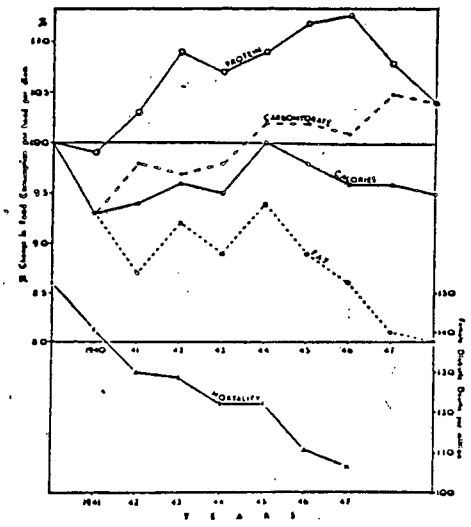
The results of this animal study confirm Rabinowitch's work with humans, which returned diabetics to a normal state on high complex carbohydrate dietary regimes.

Elevated lipids as an indicator in diabetes

The correlation of elevated total lipids with the hyperglycemia of diabetes is well established by many studies.[91-95] If elevated total lipids are a principal finding in the hyperglycemia of diabetes, diabetics should have elevated lipid levels; conversely, conditions conducive to reduced lipid levels should cause improvement in the diabetic condition.

A mass-scale study showing such improvement--a lowered mortality rate due to diabetes under conditions producing lowered lipid levels--is provided us by the war-time experiences in the British Isles, when strict food rationing limiting fats and cholesterol-containing foods was in effect. The graph below depicts the positive correlation in decline in diabetic deaths and fat consumption in England and Wales during the war years.

DIABETIC DEATHS (female) IN ENGLAND AND WALES



As can be seen from the graph, weight changes were not a factor in this lowered mortality rate, since the total caloric intake was not altered by more than 5%. Since rationing was still in effect in 1947 after the war, there was a continued decline in diabetic deaths, which followed the continuing state of lowered fat intake among the populace.

The association between elevated total lipids and diabetes is also demonstrated by many clinical investigations. In one

study,[96] 135 diabetic children 1-4 years old were tested for lipid levels prior to any treatment. Ninety percent had serum total lipids over 600 mg.%; 64% had levels over 750 mg.% and as high as 28,400 mg.%! Only 6% had serum cholesterol levels less than 150 mg.% and, at the other extreme, two were over 1,500 mg.%. In another study, a group of 35 diabetic children[97] were found to have all lipids elevated, with high lipid levels associated with high fasting glucose levels.

Several studies[98] have revealed the same findings with adult diabetics. In one group of 150 patients,[99] plasma free fatty acids were 909 mEq./L compared to controls of 548 mEq./L. Other lipid values were proportionately raised.

Even with mild glucose intolerance,[100] triglycerides and cholesterol levels are raised. In fact, the investigating group concluded that "hyperlipidemia may be a feature of established diabetes mellitus" because of the strong association.

In general, the relationship of elevated lipids and insulin sensitivity has been well established. However, when attempting to correlate variations in insulin sensitivity with individual lipid levels, considerable disagreement exists and apparently contradictory findings have been reported. Some reports[101] indicate a relationship between elevated triglycerides and glucose intolerance. Others[102] have strongly urged that high levels of free fatty acids are the factor in hyperglycemia, though free fatty acids would not be totally reliable in determining the diabetic state since they have been found at normal levels at both extremes, as with ketonic children and in primitive populations on high-carbohydrate, low-fat diets. The effect of elevated ketone bodies upon glucose tolerance has been previously noted. And still other factors have been claimed as significant: in a well-designed study in Glasgow, Scotland,[103] it was found that elevated levels of cholesterol, but not of free fatty acids or triglycerides, are implicated.

Why the seeming contradictions? The problem is the difficulty in correlating a single lipid component with hyperglycemia in a nonsteady state. The total lipids of the body

are constantly undergoing fluctuation in the level of the individual components. In short term experiments, it is found that the individual lipid values are not constant. For example, if the subject's total lipids were decreasing due to temporary circumstances such as a weight reduction diet, the free fatty acids would be elevated during this period due to their being mobilized from the adipose tissue for fuel. Other factors, such as spacing between meals, transient variations in diet, emotional state, etc., influence levels of various lipids temporarily.[104]

Because levels of various components of the total lipids of the body fluctuate constantly, the closest approximation of the steady state is the total lipid value. It has the same advantage in accurate diagnosis that the continuous glucose infusion has over the single oral glucose dose in glucose tolerance testing, as will be later discussed. Total lipids would be raised if any of the lipid components were increased; whereas reliance upon a single lipid value might fail to correlate the hyperglycemia with an abnormal lipid profile. Unfortunately, few studies[105] have attempted to correlate elevated total lipids to hyperglycemia.

Although the relationship between elevated free fatty acids and reduced sensitivity of insulin has been noted in many studies, most all of the studies have confirmed this, and a better correlation could probably be made between total lipids and insulin sensitivity. As mentioned earlier, free fatty acids have been found in the normal range in young subjects with high total lipids.[106] These children were on 80%-fat diets with cholesterol levels at 400 mg.% and total lipids above 1000 mg.%, yet with free fatty acids at normal range. These young children very probably have tested diabetic.

In another study[107] 70 diabetics were analyzed for free fatty acids and glucose after an overnight fast. Plasma glucose ranged widely from 90 to 460 mg.%. Free fatty acids averaged .58 (± .18) uEq. per ml. for the entire group. Forty-two nondiabetics were matched for age, sex and weight and given similar tests. Their free fatty acids were 159 (± .20) Eq. per ml.

These studies demonstrate that although free fatty acids are frequently elevated in diabetics, they may not be. An explanation might be that circulating levels of free fatty acid do not always correlate with intracellular free fatty acid. As noted earlier, free fatty acid levels also are subject to considerable fluctuation.[108] For these reasons, the entire lipid spectrum must be analyzed to correlate elevated lipids to glucose tolerance.

Support for the concept of total lipids as a correlator is provided in a study[109] of 274 diabetics and their blood lipid levels as compared to a control group of normals. Total lipids were found to be significantly higher in the diabetics ($P < .005$) than in the normals. In a comparison between the male and female diabetics, total lipids constituted the only significant difference in the blood lipids of the sexes ($P < .005$). Four other blood lipid values demonstrated no significant differences.

Thus, total lipids become important as a diagnostic aid in both diabetics and normals.

THE NONDIABETOGENIC DIET

Diabetes is not found in populations on a low-fat diet

Much light is shed on the problem of understanding the role of diet in relation to diabetes by turning to another source of data: observations of primitive populations who subsist on nourishment consisting of foods found in nature--primarily complex carbohydrate foods. These natural diets comprised of leaves, roots, fruits, and small amounts of meat or fish, contain no artificially created foods, such as oils, butter, sugar, cheeses, or meat from animals fed to develop extensive tissue marbling.

Most of these populations have very similar blood values, all low in lipids. The blood values in these populations closely correlate as to reaction to sugar and fat clearance. (The lower the lipid values initially, the faster the glucose or fat clearance.)

One group of New Guinea natives[110] eats a diet of sweet potatoes and their leaves as their major calorie source. Ninety-four percent of these calories are in complex carbohydrates, with only 3% in protein. Yet upon testing 777 natives over 15 years of age, not one case of diabetes could be found. Moreover, blood pressure did not rise with age and fasting glucose levels stayed low during their entire lives.

Another primitive group in Africa was studied;[111] these were nomadic bushmen subsisting on a diet made up mostly of leaves, roots and fruits, and also low in fat from animal sources. The lipid levels of these bushmen were found to be subnormal by our standard. Some of their levels were probably half what we consider low normal: cholesterol, 80 mg.; triglycerides, 50 mg.; phospholipids, 107 mg. Free fatty acids and insulin were in the normal range.

Bantu children on a diet very high in cereals, with very little animal protein, fats or sugar show the typical response to sugar and fat clearance expected with these diets. Eighty children,[112] 10 to 12 years old, were found to have a glucose fasting level of 43 mg. This would be considered hypoglycemic for subjects on a Western diet. When these children ingested 50 gms. of glucose (well over 1 gm. of glucose per kg. of weight), the one hour glucose level was only 54 mg., half the value that would be found in Western children. Their handling of fats was just as efficient. Fasting levels of triglycerides were 48 mg. With a load of 56 gm. of butter, the triglycerides rose in 3 hours to only 78 mg. This would be considered a good fasting level for Western children. The ability of these children to handle large loads of sugar or fat and efficiently remove them from the blood is not found in subjects on Western diets. Bantus over 60 years respond to fat and sugar clearance as do the Bantu children.

It has been said that the reason for the Bantus' low lipid levels must be genetic,[113] perhaps racial differences, or due to a variety of other causes--except diet. Bantus, however,

respond to dietary changes as quickly as any Western white person.

This response to dietary change by Bantus was demonstrated in a study of South African white and Bantu long-term prisoners. The prisoners, aged 21 to 54 years, free of any disease, were tested on different diets. On a basal diet of 15% fat and 70% carbohydrate, both groups had triglyceride levels that were not significantly different. When the diets were changed to 40% fat, but with the same total calorie level, each group showed a substantial increase in the triglyceride level. There was no racial difference in this response.

Further evidence demonstrates that the Bantu's freedom from diabetes does not have a hereditary basis. Bantus who live in the large cities and adopt the standard dietary practices existing there become diabetic just as often as the whites. In a survey[114] done in Cape Town, the incidence of diabetes for those over 15 years of age was 3.2% for the whites and 3.6% for the Bantus. Another study made in Johannesburg[115] found a substantial diabetic population not only among the Bantu, but also among the Zulu and several other African tribal groups. These diabetics, many of them skilled workers, most of whom had lived in the city for at least 20 years, had long since adopted the characteristic diet of urban dwellers.

Lipid levels are controlled by diet--age, sex and race are inconsequential. Although a primitive diet may not appeal to Western tastes, the dietary direction in which we must proceed is clear, if hyperglycemia and diabetes are to be eliminated. High-complex carbohydrate, low-fat diets are antidiabetogenic; Western diets of high fats and simple carbohydrates make the diabetic state inevitable.

The failure of the American Diabetes Association diet

A renewed interest in diet as a treatment method for diabetes has developed among many physicians in the last few years because of the discouraging results obtained with the popular diabetic drugs, especially after the outcome of the

University Group Diabetes Program Study became known in 1970. Commenting on the conclusions of this massive test, Dr. Prout,[116] co-author of the study, said: "The results from the U.G.D.P. have given little hope that the degenerative complications of diabetes are preventable by the simple control of blood glucose. In the maturity-onset diabetic, neither insulin nor oral hypoglycemic agents gave better protection against these complications than diet alone."

While hope for successful diabetic therapy with drugs is fading in the official view, any hope for successful diabetic therapy with diet will lead only to further discouragement--unless there are changes in the nature of the dietary recommendations of the American Diabetes Association.

When the ADA dietary approach is analyzed, it is easy to understand why it has not succeeded. This diet, recommended by the majority of clinicians, is a high-protein, high-fat, moderate-carbohydrate diet, not unlike the typical Western diet.

Limiting carbohydrate intake in the diabetic diet was a goal of most prominent diabetologists through the years. The commitment to this dietary orientation was early expressed in remarks by Dr. Russell Wilder, noted diabetes authority in charge of the Mayo Clinic Diabetic Department from 1919 until his retirement, in his last public speech before his death in 1959. Dr. Wilder's bias was stated in the context of words of praise for his head dietitian:[117] "To Mrs. Smith, again, should go some credit for a method of treatment which was effective. This was dietetic. It consisted of limiting as much as possible the carbohydrate in the diet and replacing it with calories derived from protein and fat."

Unfortunately, this goal is still reflected in the current ADA recommendations for the diabetic diet. In an official statement (1971),[118] the ADA's dietary committee gave a broad outline on diet which concluded that 45% or even more of total calories in carbohydrate in the the diet could be acceptable to diabetics. However, in a later guide to the diabetic diet appearing in the Sept.-Oct. 1972 issue of the official American

Diabetes Association publication Forecast, a model meal plan was published in the Diet Therapy Section, which called for 18% protein, 40% carbohydrate and 42% fat. Despite the liberalization in carbohydrate intake suggested by the official statement, in practice, the old rule persists.

We have now gone full circle: high-fat and low-carbohydrate intake create the diabetic condition and the official recommendation is to continue this diet or to "liberalize" it to normal Western standards. However, as long as a diet of 40% fat is eaten, there will be no letup from the diabetes epidemic.

The role of excess dietary fat has been established as the major etiology of hyperglycemia in the studies cited and in many others. Protein alone[119] has been studied in glucose tolerance tests: it was found that the ingestion of protein alone produces a flat response both in glucose and insulin tests. However, the combination of simple carbohydrates and protein gave unexpected results, producing hyperinsulinemia, with levels reaching twice those attained by the ingesting of glucose alone, and four times those attained by the ingestion of protein alone. (An example of a common food consisting of pure protein and simple sugar is jello.)

The widespread notion that substantial amounts of fat in the diet are essential to good health resulted in one investigator[120] abandoning an experimental low-fat diet for diabetic patients which was obtaining very good results. Sixty diabetics--33 of whom were on insulin--were placed on a diet of potatoes, rice and fruit for 18 days. After one or two days on the diet, glucose levels dropped in both the plasma and the urine; in fact, 22 subjects became completely free of glucose in the urine. Azoturia, which had been present in 10 patients, subsided. In addition, improvement in patients with gangrenous extremities was observed. The favorable effects were noticed on diabetics of all ages.

Yet after the 18-day period, 40 gm. of oil was added to the diet. This slight amount, only 360 calories, raised the glucose levels in the plasma and urine. Why did the investigator add the

oil? "Continuous treatment with a fat-free diet is not advisable because the organism needs the supply of unsaturated fatty acids", he asserted.

This view is widely held among clinicians, although it has little basis in fact. Experimental diets given to both children[121] and adults for many months have been very successful even though the fat content has been below 11%. Connors[122] has had excellent results with a diet of 49 gm. fat instead of the conventional 100 gm., using 358 gm. of carbohydrate instead of the recommended 220 gm. He noted that in addition to good blood glucose control, both the cholesterol and triglycerides dropped significantly. This is of importance because of the higher than normal death rate from coronary heart disease in diabetics.

Connors' institution, the University of Iowa Medical School, stands almost alone in its efforts to encourage reform in diet. Their publication "A Low Cholesterol Diet Manual" prepared by their Internal Medicine Department, offers some 30 pages of recipes developed by their dietitians that are based on 18% protein, 20% fat and 62% carbohydrate. This diet has been used by many diabetics they have counselled since its inception 14 years ago. Such a diet, followed from childhood on, would reduce the incidence of diabetes to an insignificant figure.

Diabetes is a Western disease; it is not found where populations consume high complex carbohydrate, low-fat diets. There is nothing inherently "normal" about the high-fat, low-carbohydrate Western diet. The normal diet must be one which does not create disease states such as diabetes.

CREATING THE DIABETIC STATE:
FACTORS RAISING BLOOD LIPIDS (SUMMARY)

1. Diabetes on demand:
   a. Normals become diabetic in two hours by raising their blood lipids.
   b. Diabetics become normal in two hours by lowering their blood lipids.
   c. If blood lipid levels are high enough, insulin becomes completely ineffective.
2. The diabetic state is created by elevated blood lipids. Etiologies that produce this degree of elevation temporarily are: strenuous exercise for the untrained, illness, starvation, and infrequent feedings. A chronic diabetic state can be produced by Western-type diets (40+% calories in fat), and an excess of simple carbohydrates.
3. Excess dietary intake of fat and/or simple carbohydrates can produce the diabetic state; however, fat is far more rapid in its action.
4. Diabetics are found to have higher blood lipid levels than normals.
5. Populations on low-fat diets are free from diabetes.
6. The American Diabetes Association diet is doomed to failure because the fat levels are diabetogenic.
7. The University of Iowa Medical School offers the best "official" diet for diabetes today--20% of total calories in fat.

III. NEW LIGHT ON THE DIABETIC STATE

An evaluation of standard methods of determining the presence of diabetes.

The single load oral glucose test: is it valid?

The observations and conclusions drawn from many of the studies we have been discussing necessitate a reexamination of the classical concept of the disease diabetes mellitus. Generally, it has been believed to be associated with inadequate production or insensitivity of insulin. A recent medical dictionary definition concurs with an older one: in 1956, it was defined[123] as "an inheritable, constitutional disease of unknown cause, characterized by the failure of the body tissues to oxidize carbohydrates at a normal rate. The metabolic disturbance...has as its most important factor a deficiency of insulin." The more recent definition (1968)[124] states: "Basic cause is still unknown but direct cause is failure of beta cells of the pancreas to secrete an adequate quantity of insulin."

With such a premise, the emphasis in treatment has been to provide the body with drugs that increase the supply or efficiency of its insulin so as to reduce the level of glucose in the blood; or, if these drugs do not prove effective, to inject insulin into the body to form a supplementary source to the endogenous insulin to help in metabolizing glucose. The key to the treatment in either case is to lower the blood glucose level so that the hyperglycemic state returns to normal fasting levels.

The development of the immunoassay test of insulin reported[125] in 1960 made it possible to accurately measure insulin concentrations. Using this technique, various studies suggest that diabetics can have insulin levels exceeding those of normals. In fact, Rabinowitch demonstrated[126] in 1932 that insulin-dependent diabetics who were stable on a particular insulin dosage were able to increase their carbohydrate intake from 50 gms. per day to 250 gms. per day--500% more carbohydrate--and still require less insulin on an isocaloric diet. This does not suggest either an inadequate production or insensitivity of insulin even in

an insulin-dependent diabetic. Yet such revelations did not alter the authoritative position regarding the nature of the body defect in diabetes mellitus.

The determination of the possible presence of diabetes is made on the basis of the patient's response to the single load glucose tolerance test. In this test, the patient ingests 50-100 grams of glucose just before the test is performed, having previously taken orally at least 150 grams of carbohydrate each day for three days prior to the test. Glucose values are measured at fixed time intervals; if the values exceed certain accepted limits, the patient is considered to have diabetes. Most values taken today are related to the plasma content of glucose, but many of the older and some recent studies report in blood glucose. If the blood glucose level rises above 170 mg.% at any time and fails to return to fasting levels (below 110 mg.%) by the end of the third hour, the diagnosis of diabetes is made. A fasting level of 110 to 120 mg.% is regarded by some authorities as sufficient for a diagnosis of diabetes.

If insulin levels are measured in conjunction with the single load glucose tolerance test, the response of diabetics is usually a low and delayed insulin level. Thus, in a typical glucose tolerance test made with a group of untreated diabetics and controls,(127) the diabetics--all nonobese maturity-onset diabetic patients--had a fasting level of insulin that started from 10 microunits and peaked at 35 microunits after 30 minutes. By contrast, the normals in the same test started with 8 microunits and peaked at 216 microunits at only two minutes. The test would seem to show that normals had six to seven times the quantity of insulin that the diabetics had. This study is typical of many that have been done whose results reinforced the widely held belief that an insufficient level of insulin is the principal cause of diabetes.

The almost exclusive reliance upon the single-load glucose tolerance test for determination of the diabetic state makes it critically important that this test be truly valid. The reliance upon this diagnostic procedure was stated by a prominent diabetes

spokesman in an address to a 1969 nutritional conference:[128] "Before we talk about the treatment of diabetes, dietary and otherwise, we should reflect on exactly what diabetes is. It is a disorder diagnosed by a glucose tolerance test which determines the speed at which an individual's blood sugar elevation falls back to normal after administration of a standard level of glucose."

Dependence upon the single load glucose tolerance test as the basic diagnostic test in diabetes does not provide sufficient information to assess the subject's condition, however. That this is the case will be shown now on the basis of various studies that were designed to investigate the body's response to glucose. These studies examined this body response under different circumstances, when glucose was administered orally, intravenously, in large doses, in small continuous amounts, and in diverse planned time sequences.

The Straub-Traugott effect raises questions

In one group of studies, an interesting phenomenon, dubbed the Straub-Traugott effect, has been found when subjects are given successive oral glucose tests repeated within 1/2 to three hours. Different values are obtained for both glucose and insulin for each glucose load, the differences being more pronounced in diabetics than in normals. A second glucose load will produce a decrease in glucose peak and an increase in insulin output; a third load will produce a lower glucose peak and a higher insulin output than that obtained in the second load. If the patient's diet preceding the test[129] is very high in fat, it may require as many as 8 or 10 successive glucose loads before the peak glucose starts to drop; whereas if the diet has been moderate in fat, it will drop at once on repeated glucose loads.

The Straub-Traugott effect was studied with 18 subjects without a history of diabetes.[130] All received three intravenous glucose loads of 30 grams each at hourly intervals, following an overnight fast. Based on their hyperglycemic responses, a number of the subjects were classified as diabetic after the first load. These newly diagnosed diabetics also displayed a typical diabetic

insulin response with maximum insulin levels that were only 1/4 of the normals.

If the test had been concluded at this point, the diagnosis would have been insufficient insulin. However, a second glucose load given these newly diagnosed diabetics one hour later evoked very different results: the insulin output was now 50% of normal. The third glucose load, given one hour after the second, produced an insulin response almost equal to that of the normal subjects. If the diagnosis were now to be made, after these additional tests, the conclusion would be normal--sufficient insulin.

The response of the insulin-producing beta cells in these consecutive tests refutes the classical view of diabetes that assumes that the beta cells are unable to produce sufficient insulin. For if this were the case, as might be suggested by the meager response to the first load, the second load one hour later should have been even more meager, and the third load should have had the smallest insulin response of all. But the data indicate that the beta cells were capable of performing adequately, even though the first glucose loading elicited a subnormal response. The investigators in this study concluded that their findings supported the view that the subnormal response of insulin to a single glucose load was functional rather than structural.

To further explore the Straub-Traugott effect,[131] the interval of time between glucose loads was changed from one hour to three, four, and six hours. In addition, human growth hormone response was noted, a factor of interest because this substance stimulates the release of free fatty acids. The free fatty acids have been reported[132] to reduce the sensitivity of insulin to glucose. The effect, theoretically, would be to require a larger output of insulin to act against the same quantity of glucose. (In fact, a higher level of free fatty acids is a common finding in diabetics. In the previous study,[133] for example, free fatty acids were found to be higher in the diabetics by 15%.)

The eight normal subjects in this subsequent study were given an oral dose of 100 grams of glucose after an overnight fast, followed after three hours by another 100 gram oral dose. The same

procedure was repeated on other days, with the intervals extended to four and six hours. The results are summarized below.

(100 gms. glucose for each glucose load)

MAX. LEVEL REACHED	THREE HOUR INTERVAL 1st GTT	THREE HOUR INTERVAL 2nd GTT	FOUR HOUR INTERVAL 1st GTT	FOUR HOUR INTERVAL 2nd GTT	SIX HOUR INTERVAL 1st GTT	SIX HOUR INTERVAL 2nd GTT
glucose	130 mg.%	100 mg.%	140 mg.%	180 mg.%	140 mg.%	180 mg.%
insulin	80	70	160	130	140	220
HGH	2	2	2	15	2	13
hrs. to reach HGH after 1st GTT				4 hrs.		4-5 hrs.

In the three-hour interval test, there was definite improvement in the second glucose load, even though the insulin output was less--a clear demonstration of the Straub-Traugott effect. Human growth hormone was unchanged throughout the period. This was probably explained by the fact that 100 grams of glucose--over 400 calories--was apparently adequate for three hours of metabolism and the body did not need to call upon free fatty acids as additional fuel.

During the four-hour interval test, however, human growth hormone started to rise before the end of the interval and reached 7.5 times its initial value. Although free fatty acid levels were not noted, the rising human growth hormone would imply some free fatty acid metabolic usage. Even if free fatty acid rise was nominal, the insulin effectiveness would be somewhat lessened. In comparison with the three-hour interval test, glucose tolerance worsened, although the insulin output remained relatively the same.

In the six-hour interval test, human growth hormone rose 6.5 times its initial value, this time rising early enough to permit a probably substantial increase in free fatty acid, as the peak human growth hormone level occurred almost two hours before the second glucose load was given. Compared with the three-hour interval test, glucose tolerance again worsened (to the same degree of deterioration as occurred in the four-hour test), but insulin output was three times as high.

This series of tests indicates that there is a critical period which occurs as the interval between glucose loads increases; plasma lipids start to rise and insulin begins to lose its sensitivity toward glucose during this period. An attempt to discover the control of lipolysis pointed to the sympathetic nervous system as the sensitive center responding to the hyperglycemic state by mediating the release of free fatty acids.

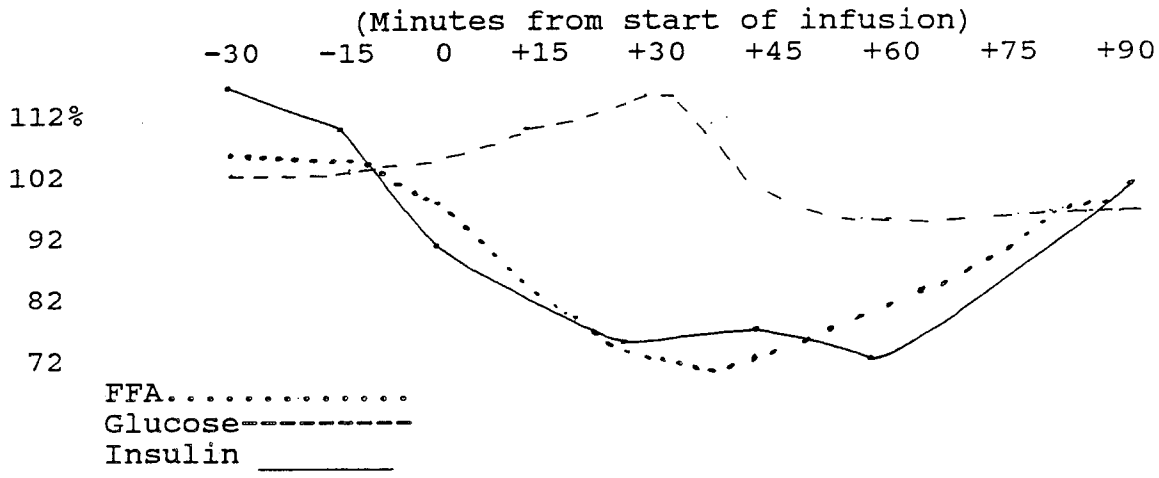
The tests[134] also threw further doubt upon the validity of the single load glucose tolerance test inasmuch as the response of the same individual varied significantly under different circumstances. Thus, the same individual in different tests and with the identical glucose load could show normal glucose tolerance or a diabetic glucose tolerance. This individual could also demonstrate high insulin levels with high glucose peaks or low insulin levels and low glucose peaks. If the rationale of the glucose tolerance test is correct, as insulin levels rise, glucose levels should become depressed; conversely, as insulin levels decrease, glucose levels should increase. The findings, however, did not follow this pattern, indicating that other controls independent of insulin secretion operate in the regulation of glucose level.

Investigating glucose metabolism in the diabetic.

Interrelationships of glucose, insulin and free fatty acids

Studies were now devised to detect the nature of these controls. These studies sought to discern the most subtle changes in blood levels through the infusion of small, continuous quantities of glucose instead of the large volume oral glucose intake. Thirty-nine nondiabetics participated in tests[135] using low level infusion of glucose at rates of 20 mg. to 100 mg. per minute for 30-minute periods. As little as 20 mg./min. was found to produce a significant fall in free fatty acids. However, on a second challenge only 30 minutes later, free fatty acids rose instead of falling. This procedure was repeated with diabetics and with normals, using 100 mg./min.

Insulin level was stable during these low level glucose-infusion tests, with no apparent rise at each glucose infusion, in contrast to the response in tests using large glucose doses. In the tests using the large glucose doses, the free fatty acids are kept depressed by some mechanism, possibly the rise in insulin secretion; whereas with low levels of glucose, the control of free fatty acids by insulin does not appear to occur. The following graph shows the relationship between free fatty acids, glucose, and insulin over a two-hour period.



An interesting relationship was noticed after a 100 mg./min. glucose infusion for 30 minutes in normals. Glucose level was seen to be inversely proportional to that of free fatty acids, and free fatty acids and insulin were directly proportional to each other. This suggests that an unexpected relationship exists among free fatty acid, glucose, and insulin when they are at these levels: as glucose level rises, free fatty acid drops, indicating the switch to a glucose substrate; as the free fatty acid level drops, insulin becomes more sensitive, therefore lessening its secretion. The drop in insulin secretion continues as long as the free fatty acid level drops, with the low point occurring between 30 and 45 minutes.

As the glucose level drops and the metabolic substrate leans towards free fatty acids, the latter rise. Even though the glucose level is dropping, insulin is now rising because the higher free

fatty acid level is inhibiting the sensitivity of the insulin. Thus the paradox: glucose dropping, insulin rising--reversing the relative positions of less than an hour before.

It should be noted that the peak glucose level coincided with the minimum insulin level, whereas in classical diabetic theory it should have been associated with the maximum insulin rise (at the 30 minute mark). Classical diabetic theory would predict this sequence: Glucose load comes in ----> plasma become hyperglycemic ----> insulin is stimulated to secrete ----> increased insulin limits glucose rise ----> glucose returns to normal ----> insulin returns to normal. The theory may have to be revised.

These studies indicate that a single load (oral) glucose test inherently limits the understanding of glucose in the body. Various circumstances may enter into this, one possible factor being the raising of the insulin level before the glucose has left the stomach, due to the action of gastrointestinal hormones.(136) It has been shown(137) also that the continuous infusion of glucose into the blood under steady state conditions provides better control of variables. Under more controlled circumstances insulin concentration is directly related to the secretion of insulin into the general circulation and can be used as a direct measure of insulin output.

Diabetics handle glucose normally in test situations

The revealing technique of continuous glucose infusion has clarified other basic questions concerning diabetes. Because of the excess blood glucose during hyperglycemia, the question as to whether the diabetic is sensitive to glucose in the same manner as the normal required an answer. There seems to be sufficient time for the glucose in the blood to be utilized between meals, and especially so for an overnight period. Further, insulin secretion is stimulated during a meal readily enough when confronted by new glucose, yet the excess glucose already in the blood seems to be unaffected by the insulin present at the time in the diabetic individual. Is it possible that the diabetic is stimulated by glucose in a delayed manner?

A study[138] was designed to test the minimum quantity of glucose under constant infusion that would produce some insulin response. Three groups of subjects were tested: normals, obese normals, and diabetics. Results obtained show that 60-100 mg. of glucose per minute is the minimum quantity that will produce a significant raising of the insulin level. This occurred at 60 mg./minute in four out of eleven diabetics, one out of seven obese subjects, and two out of ten normals. Both the absolute and relative plasma glucose increases were almost identical in all three groups.

Another experiment[139] tested the amount of glucose used when injecting subjects with glucose UC-14, a radioactive glucose, and monitoring its disappearance rate with frequent blood samples for four hours. Results of plasma glucose loss were similar in normals and diabetics amounting to 1.36 mg. per kilogram of body weight per minute with a variation of only ± 14% for all subjects. Since the tests were carried out in a steady state and patients with glycosuria were not used, glucose irreversibly removed from plasma must have equaled glucose irreversibly taken up by tissues metabolizing glucose. There was a wider range of fasting glucose and insulin concentrations, yet glucose usage was similar in all subjects as demonstrated.

These tests were repeated after three weeks using different diets. A high-fat diet (68% of total calories), high-carbohydrate diet (85% of total calories), and the normal control diet (42% of total calories in fat) did not produce a difference in the results.

When enough glucose is infused for a long enough period to produce a steady state of glucose and insulin levels, a more accurate description of the relationship between these levels can be obtained. To avoid the exaggerated response obtained in a glucose tolerance test when the subject has not had sufficient carbohydrate intake beforehand, all patients, normal and diabetic, were hospitalized and placed on an 85%-carbohydrate diet for two weeks.[140] After this period, they were infused with 6 mg. per kg. body weight per minute for 3 hours--a rate that would supply a 50 kg. subject with about 2,000 calories daily.

Tests were started after an overnight fast, and within 90 minutes, glucose values stabilized. Since glucose concentration remained stable for the succeeding 90 to 180 minute period, it must be assumed that the glucose uptake was equal to the infusion during this time. The equal uptake of glucose was in contrast to the wide variation of insulin output. Both normals and diabetics were disposing of identical glucose loads.

Thus, in a variety of test situations, diabetics were shown to use glucose very much as normals do, both in speed of utilization and in ability to metabolize total caloric requirement using only glucose. The sensitivity of response was demonstrated to be at least as effective in the diabetic as in the normal.

A quantitative deficiency of insulin is not found in diabetics

If glucose handling seems to be normal, the question next to be asked is whether the diabetic's problem is due to a deficiency of insulin. If a deficiency of insulin is demonstrable, it can logically be argued that a corresponding rise in glucose would take place, which, in time, would produce the hyperglycemic state. The introduction of the immunoassay method[141] of insulin determination in 1960 made possible much progress in research in this area, inasmuch as plasma insulin levels accurately reflect insulin secretion under steady state conditions.[142]

The steady state glucose infusion test described earlier,[143] infusing 100 mg. glucose per minute, was utilized in making insulin determinations in normals, mild diabetics, and severe diabetics. The benefits of the infusion technique have been mentioned: the elimination of variables associated with oral glucose intake--including the action of gastrointestinal hormones--and the advantages of the steady state which reflects the chronic balance rather than an acute and constantly shifting series of variables. Careful controls to produce maximum accuracy in results also included placing the subjects on an 85%-carbohydrate diet for two weeks prior to the test and hospitalizing them during the test so their food intake could be completely regulated.

The following table summarizes the test results.

MEAN STEADY STATE GLUCOSE AND INSULIN RESPONSES

	Plasma Glucose (mg./100 ml.)		Plasma Insulin (U.ml.)		
GROUP	FASTING	STEADY STATE	FASTING	STEADY STATE	UNIT INCREASE
Normal	81	159	19	55	35
Mild diabetic	100	222	34	125	90
Severe diabetic	201	372	35	68	30

Mild diabetics had almost three times the increase of insulin that the normals had (90 to 35). Even severe diabetics with fasting glucose levels of 200 mg. had a total insulin rise no different from normals. Under these conditions, diabetics were found not only to have sufficient insulin, but to have amounts considerably in excess of normals. There were no differences related to age or degree of obesity in the results observed in the three groups.

Other studies[144] confirm these results. One study[145] compared 20 normals to 11 diabetics for glucose and insulin responses to oral glucose, intravenous glucose, and intravenous tolbulamide. Diabetics and normals in the test were closely matched for adiposity, age and sex. Results of all the tests were in agreement: plasma insulin concentration in diabetics was equal to or greater than those in the control subjects at every period of time during the tests, and insulin response was as prompt as in any of the normal controls. Even though the insulin level was consistently higher in the diabetics, the plasma glucose was also higher at every point on the tests.

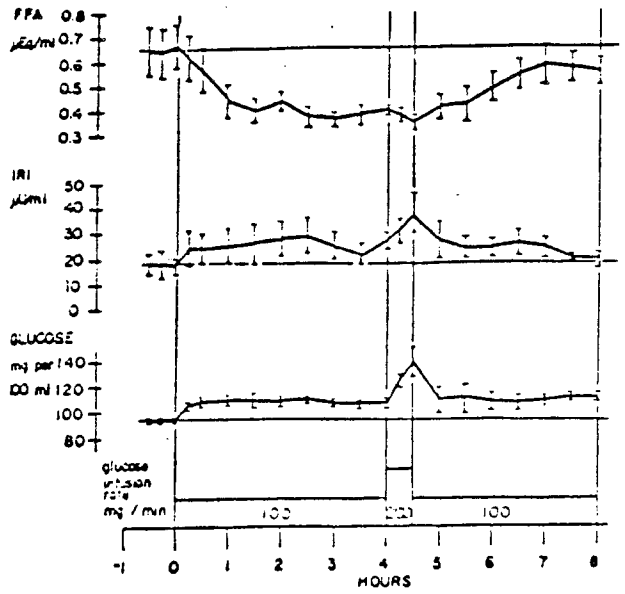
These results were compared to similar tests made by several other investigators and it was concluded that "our results are consistent with a large body of previous information which states that the quantitative insulin response of patients with minimum abnormalities of glucose tolerance is as prompt and as great as it is in normal subjects."

Thus, diabetics are hyperglycemic in spite of a sufficient and even excessive insulin response.[146] The failure to correct fasting hyperglycemia was unexplained, since there is adequate time between meals to bring blood glucose to normal.

In the study[147] which used normals, obese normals, and diabetics to determine the minimum quantity of glucose under constant infusion capable of producing some insulin response, it was observed that the minimal glucose dose producing a significant insulin rise was approximately the same in all three groups. After the glucose stimulus, the insulin dropped back to its preexisting fasting level. In the diabetics, the glucose level was still hyperglycemic, yet there seemed to be no effort on the part of the beta cells to maintain the insulin level high enough to bring the glucose down to normal.

These results seem to indicate that the control of insulin secretion is regulated by increased concentrations of glucose over the fasting level. Fasting glucose, no matter how high, can maintain itself because of an equilibrium between glucose, insulin, and undefined blood components, possibly total lipids.

An artificial hyperglycemia was created in this study using normals who were given a constant infusion of glucose for eight hours. Glucose levels rose from 95 to 110 mg.% and remained constant for the period. Insulin rose and fluctuated inversely to free fatty acids, as shown in the graph on the next page.



At the end of the first four-hour period, glucose infusion was increased from 100 to 200 mg./minute for 30 minutes. The immediate response was a similar rise in both glucose and insulin. After the 30-minute period, glucose infusion returned to 100 mg./minute. Plasma glucose dropped to its previously elevated value, but now plasma insulin was dropping below its previously elevated value, inversely following the rise of free fatty acids.

Why did the insulin level drop in the face of the hyperglycemia? The beta cells were instantly responsive to a change of glucose level at the end of the four-hour period, so insulin was immediately available. Yet at the end of the eight-hour period, the insulin level had dropped back to fasting levels. The investigator speculated: "it is possible that the failure of the beta cells to attempt normalization of the blood sugar in the hyperglycemic diabetic or in the glucose infused normal individual may reflect the operation of controls geared to other cellular fuels".

Whatever the control mechanism, it is clear that in hyperglycemic diabetics insulin response is not delayed with a glucose challenge; insulin secretion in response to newly ingested glucose is as great or even greater than in normals.

Insulin sensitivity is found to be impaired

If a quantitative deficiency of insulin cannot be demonstrated, can a decrease in insulin sensitivity be involved? In the study of insulin responses[148] among normals, obese normals, and diabetics using the smallest effective glucose stimulus (a glucose infusion of 100 mg. per minute for 30 minutes), it was found that the glucose level in all groups rose about 10% above control values. The insulin levels also rose and were about 25% over control values in all groups. While the rate of rise in the normals started earlier, the total average secretion was similar. In all groups, when the glucose stimulus was stopped, the insulin returned to control levels.

A relationship between glucose and insulin levels for both normals and diabetics in the fasting state was also found in the previously cited test[149] using glucose UC-14. It was determined that the greater the degree of hyperglycemia, the less efficient was the removal of glucose from the plasma; the higher the insulin concentration, the less efficient the removal of glucose. Diabetics with both elevated glucose and insulin had the most severely impaired rate of glucose removal. This fact cannot be correlated with a decrease in insulin; but only with a decrease in the efficiency of insulin.

Himsworth's findings[150] demonstrate the cause for decreased sensitivity or efficiency of insulin during hyperglycemia: elevated blood lipid levels.

Although obesity is associated with higher insulin levels, several studies have demonstrated this association with nonobese normals on high fat diets.[151-153]

A revised definition of diabetes

What is diabetes? In the light of the observations drawn from the studies we have cited, a revised definition of this disease state would read significantly differently from the definitions quoted earlier from medical dictionaries of 1956 and 1968. To take into account these observations, it would read this way: Diabetes is a transient abnormality, characterized by the failure of insulin

to metabolize glucose normally in the presence of an elevated plasma lipid level. When the lipid levels return to normal, the insulin-glucose relationship becomes normal.

This revised definition becomes better understood if the following data are provided: Normal lipid values--total lipids < 575 mg.; cholesterol < 160 mg.; triglycerices < 80 mg. The rationale for these seemingly arbitrary value ceilings is developed further in various sections of these writings.

It may be argued that this revised view of diabetes has been built on selected studies on the mechanisms of carbohydrate metabolism which support the clinical experiences of Rabinowitch, Himsworth and others who reached like conclusions; and that the many studies which oppose them have been ignored. In answer, it must be said that the number of studies upholding a position is not the crucial question. The fatal flaw in a large number of studies opposing those we have cited is usually the failure to distinguish between simple and complex carbohydrates and their effect upon insulin, glucose, free fatty acids, and carbohydrate metabolism generally.

Even investigators of the University of Iowa Medical School, who have as much understanding now (1973) as most as to the role of simple carbohydrates in raising blood lipids, in 1963 said:(154) "We know of no evidence which suggests that mixed carbohydrates per se are hypocholesterolemic".

Confusion over the effects of simple and complex carbohydrates.

An error takes root: the concept of carbohydrate induction of triglycerides

The evolution of the erroneous concept of carbohydrate induction of triglycerides is a matter of importance: it has been perpetuated and disseminated throughout the medical world extensively, doing a grave disservice to efforts to research the mechanisms of carbohydrate metabolism. This mistaken notion has its basis in the misreading of a rice-fruit diet study for hypertension by National Institutes of Health investigators.(155) Dr. D.S. Fredrickson, the Director (1970) and a key decision-maker

at the National Institutes of Health has popularized the concept of "carbohydrate induction of triglycerides" to such an extent that it is accepted almost without question, worldwide.

The basis for the confusion in Dr. Fredrickson's thinking is revealed in his writings (see "Familial Hyperlipoproteinaemia" by Fredrickson and Lees in the text Abnormal Lipid Metabolism). In a section entitled "Possible Biochemical Defects in Type III", the co-authors discuss a phenomenon called "carbohydrate induction of hyperlipemia". "Type III" is one of five main types of hyperlipidemias in a classification devised by Dr. Fredrickson. According to Dr. Fredrickson, Types III, IV and V are all related in that carbohydrates will raise the pre-B-lipoprotein level in these groups of individuals.

Citing examples of "carbohydrate induction of hyperlipemia", the co-authors say: "An important effect of diet on plasma triglycerides was first noted in 1950 when Watkin et al found that a high-carbohydrate, fat-free diet increased the average serum glyceride concentration in a group of hypertensive patients on a rice and fruit diet. In 1955 Hatch et al extended these observations, showing that one-third of a similar group of hypertensive patients with no obvious defect in lipid metabolism became grossly hyperlipedemic on a rice and fruit diet and rapidly reverted to normal on the resubstitution of fat for carbohydrate in the diet..." Fredrickson and Lees conclude: "Carbohydrate induction is therefore a mechanism common to all men and perhaps many other species. It becomes pathological when it occurs on ordinary diets." (Our emphasis).

As we will show, the authors' conclusions are based on some misconceptions concerning the effects of simple and complex carbohydrates in relation to blood triglycerides. The only carbohydrates referred to by Fredrickson and Lees in their discussion (rice and fruit) are complex carbohydrates. These, however, can only have the effect of lowering the triglycerides. It is only the simple carbohydrates (e.g., sucrose and fructose) which can raise the triglycerides--there are no exceptions. Yudkin[156][157] has been raising triglycerides for 10 years using

sucrose on old and young, male and female. The effect of sucrose on the raising of triglycerides is documented in many studies.[158-165]

A comparison of the effects of sucrose--a simple carbohydrate, versus starch--a complex carbohydrate--on hypertriglyceridemia,[166][167] was demonstrated in striking fashion in the case of a 44-year old man with a triglyceride level of 1,200 mg. percent. When placed on a 64% carbohydrate, 19% fat diet for five weeks, in which all of the carbohydrate was starch, his triglyceride level dropped to 400 mg. When his diet was changed by replacing 230 gms. of bread with sugar (sucrose), with the sugar providing about 30% of his caloric intake, his triglycerides rose to 840 mg. percent after another five-week period.

Fredrickson should have hesitated about concluding that a complex carbohydrate food such as rice can raise lipids if only because 700,000,000 Chinese, among other peoples, whose diet uses rice as a staple, dispute this! Could this influential investigator's erroneous conclusion about the effect of complex carbohydrates on lipid levels been due to a careless reading of his references? Watkins et al used a diet of rice and fruit and sugar! Sucrose actually provided 47% of total calories in the Watkins diet. Or, perhaps, Fredrickson thought the sugar was not significant because he regarded it as no different from other carbohydrates. Or--a third possibility--could he have ignored its significance on the grounds that this much sugar, or more, occurs in "ordinary diets"?

That this last possibility may actually have been the case is suggested by another study in which Fredrickson participated[168] which was designed to test the question of "carbohydrate induction"--raising of the triglycerides by elevation of the carbohydrate level. In this study with 107 patients, a reference is cited in support of the carbohydrate induction hypothesis[169] in which a diet of 88% of total calories was comprised of carbohydrates, primarily sucrose. It is not surprising that in Fredrickson's study, the carbohydrates of the diet, making up 80% of total calories, were lumped together indiscriminately in this

catch-all manner, viz: "the carbohydrates consisted of simple sugars, complex sugars and starch." No percentages, no further descriptions of the sugars. It is obvious that he considers this mix as normal. As he states in the study: "There is a similar lack of firm data supporting a predictable and sustained effect of substitution of one carbohydrate for another." Without reading the results of this study, the conclusions could be predicted: carbohydrates (his to mix) induce lipid elevation.

In a continuing tradition of failure to distinguish the nature of the carbohydrates used, most investigations of carbohydrate intolerance draw no distinctions, despite the vast amount of evidence that only simple carbohydrates raise triglycerides and that complex carbohydrates actually lower them.(170-177)

Imbedded in the investigations of many of today's competent researchers, the complex carbohydrate confusion continues apace. Thus, in the October 7th issue of the New England Journal of Medicine, an editorial appeared calling attention to a study(178) by Dr. David Kipnis, a well-established and respected investigator associated at the time with the Washington University School of Medicine. After summarizing Kipnis' study, the editorial stated: "Hyperinsulinemia is thought to result from dietary factors--in particular increased ingestion of carbohydrate." This important journal, with its widespread influence, was caught in the carbohydrate confusion, in an unfortunate throwback to Dr. Allen's 1917 views.

Another unfortunate ramification of the Kipnis study was an English investigation(179) with 200 diabetics in which carbohydrate restriction was used in an effort to control their hyperglycemia. One justification cited for the test was Kipnis' work of 1971.

A close look at Kipnis' study finds no mention of the carbohydrates used in any of the three diets tried: 1) low carbohydrate (25% of total calories); 2) high carbohydrate (62% of total calories); 3(high carbohydrate (liquid-72% of total calories). In a communication with Dr. Kipnis, it was revealed that he never knew the composition of the carbohydrate ingested--he simply left it up to the hospital dietitian. The conclusion of the

entire study becomes invalid because it ignores the different relationships of simple and complex carbohydrates to blood lipids.

Dr. Kipnis cannot be blamed for this critical oversight. He, like most investigators, would hardly believe that the esteemed National Institutes of Health investigators inadvertently misled much of the medical world with their erroneous "carbohydrate induction of triglycerides."[180] Starting with an incorrect basic premise, many carbohydrate intolerance studies failed to arrive at valid conclusions.

<u>If diabetes is inherited, simple vs. complex carbohydrate controversy becomes irrelevant</u>

The conviction that diabetes is an inherited condition underlies the attitude on the part of some clinicians which dismisses controversy on carbohydrate metabolism as a mere academic question; after all, they reason, since diabetes is an inherited disease, we are powerless to prevent it or to alter its prognosis.

The assumption that diabetes is inherited is a slender reed. Studies cited earlier in this writing have demonstrated the absolute relationship between fat intake and abnormal glucose tolerance, and the ability to produce a diabetic glucose tolerance on demand.

Nor do studies of diabetes in identical (monozygotic) twins lend credence to the inheritance concept. As of November, 1972, only five studies[181] of identical twins have been reported, the earliest appearing in 1938. These five studies cover 323 pairs of twins in which one of the twins tested as a diabetic. In the latest study of 96 twin sets, the investigator states his case: "In an attempt to elucidate the role of both genetic and environmental factors in the etiology of diabetes, we have studied the condition in identical (monozygotic) twins. If all identical twins are concordant for diabetes (i.e., if both twins are diabetic), the cause of the diabetes may be either genetic or environmental, but if they are sometimes discordant (i.e., if one twin is diabetic but the other is not), then <u>the difference between them must be due to</u>

environmental factors, and, in these pairs at least, diabetes cannot be inherited. (Investigator's emphasis).

The investigator said further: "Twins might be discordant because there has been insufficient time for diabetes to develop in the second twin. But this is not what we found; over half the pairs have been discordant for more than ten years and in six the second twin is still not diabetic, clinically or chemically, after more than 20 years." In fact, the study disclosed that the longest duration of discordance in the twin subjects was 30 years, and the unaffected twins tested normal, with no trend even towards prediabetes.

He added: "It is often assumed that diabetes is certain to develop in the identical twin of a diabetic. If this were so it would strongly suggest that the cause of diabetes was solely genetic. Our results seem to refute this proposition."

Elevated lipid levels in liver disease: more light on diabetes etiology.

The pancreas is normal in liver disease, but elevated lipids produce hyperglycemia

The position that elevated blood lipids create chemical diabetes and that lowering blood lipids will return the glucose tolerance test to normal may appear to be an oversimplification of an exceedingly complex problem, but that position is borne out by the studies earlier cited. Evidence that chemical diabetes may appear when the pancreas is completely normal comes from still another type of study, in which individuals with cirrhosis were tested.

Twenty-five normal subjects and 25 cirrhotics were investigated[182] in a study designed to test the relationship between elevated lipids and insulin insensitivity. In cirrhosis, lipids are elevated and xanthomas are frequent, but the pancreas is unaffected as demonstrated in several function tests.

Although each subject had clinical, lab and biopsy evidence of cirrhosis, serum bilirubin was normal and in no case was there any previous evidence of diabetes. To prepare for the glucose

tolerance test, a high carbohydrate alcohol-free diet was given the subjects for five days. Following an overnight fast, each subject then took an oral dose of 75 grams of glucose. The results of the test are shown in the table below.

	(Hours after oral glucose)							
	0		1/2		1		2	
Plasma conc.	Norm.	Cirr.	Norm.	Cirr.	Norm.	Cirr.	Norm.	Cirr.
FFA (uEq./l.)	477	781	423	653	365	539	376	462
Glucose (mg.%)	81	84	126	160	114	190	95	148
Insulin (u units/ml.)	9	29	43	100	51	152	38	163

In the patients in this study, the pancreas was normal, ruling out the possibility of any demonstrated hyperglycemia being due to pancreatic abnormality, inability to produce sufficient insulin, damaged beta cells, or any other pancreas-related cause. The high lipid levels observed in these patients was due to their cirrhosis. Based on conclusions derived from studies cited earlier in these writings, hyperinsulinemia and/or hyperglycemia could be predicted from the elevated lipids of these cirrhotic patients.

This is indeed what was found. The glucose fasting level was only slightly higher in the cirrhotics, but free fatty acid levels were 50% higher and insulin was three times as high. Two hours after the glucose intake, the normals' glucose was 95, while the cirrhotics' was 148--in the diabetic range. The insulin was very elevated in the cirrhotic subjects: four times as high at the two hour point. Even in the cirrhotics with normal glucose tolerance tests, hyperinsulinemia, with values 300% higher than normals, and elevated free fatty acid levels were noted.

Other studies[183] of liver disease report the same abnormal carbohydrate metabolism. In 28 patients whose liver disease was confirmed by biopsy, 57% had abnormal glucose tolerance tests, but all of them had abnormally high insulin levels. In these adult patients the gradual evolution of an abnormal carbohydrate metabolism as observed in the obese children later cited[184] was also seen. The investigator stated her findings:[185] "We suggest

that initially there is in liver disease a compensatory, exaggerated increase in insulin secretion in response to hyperglycemic stimulus and that this maintains apparently normal glucose tolerance. Later compensatory insulin hypersecretion is no longer adequate to maintain normal glucose tolerance and a stage of impaired glucose tolerance is reached." (Emphasis is from original.) We might add, and so the diabetic condition is reached!

How a fatty liver is formed and its effects

Hyperglycemia in liver disease is associated with fatty invasion of the liver, especially in alcoholic cirrhosis,[186] but also in obesity, toxicity from solvents and anesthesia.[187] Insufficient circulation to the liver and blockage of bile ducts are also known as causes producing a diabetic hyperglycemia.[188]

The role of dietary factors in causing a fatty liver is clarified by animal studies. In a study already cited with rats,[189] sucrose-fed animals not only tested with a diabetic hyperglycemia, but had 90% more fat in their livers than those on starch, who tested with a normal glucose tolerance test. In another study,[190] rats were fed ad lib rations as follows: 1) high in fat; 2) a grain diet; 3) a diet similar in composition to the grain diet (#2), but with a simple carbohydrate, sucrose, instead of the complex carbohydrate. It was found that obesity developed in the rats on the high fat and the sucrose diets, but not on the grain diet. In fact, when rats made obese by diets #1 and #3 were then placed on the grain diet of complex carbohydrates, they lost weight.

In a subsequent study,[191] the ad lib diets were further explored to compare the effect of grain rations (complex carbohydrate) with rations containing the same proportion of nutrients, but with simple carbohydrates such as sucrose or fructose being substituted for the complex carbohydrates. Diets using simple carbohydrates in the rations all increased the fat deposition in the organs greatly as compared to the diet using grain. Fat in the kidney was lowest in the grain-fed rats. In the fat depots of the inguinal, genital and perirenal-retroperitoneal

areas, the sucrose-fed rats had a 300% higher amount of fat deposition than the grain-fed rats. In the liver, the simple carbohydrate-fed animals had lipid accumulations 50% to 200% higher than the complex carbohydrate grain-fed rats.

There is a crucial difference in the effect of simple carbohydrates versus complex carbohydrates in the diet. Simple carbohydrates (sucrose, fructose, etc.) can produce hyperglycemia in two ways: 1) by increasing the lipid content of the liver which by itself can produce a diabetic glucose tolerance test, as can be noted in subjects with liver disease; and 2) by increasing blood lipids, which, as shown in many studies earlier cited, can also independently produce a diabetic glucose tolerance test. These two mechanisms combined--fatty liver and elevated blood lipids--can guarantee success in creating diabetics.

Insulin deficiency with normal liver and blood lipids

In the Western culture the only population group not likely to have elevated blood lipids is comprised of the children, since they haven't consumed the typical diet long enough. With low blood lipids, in previous studies cited of Bantu children, there is extremely efficient action of insulin on glucose. With a normal liver and low blood lipids, even in circumstances causing a subnormal production of insulin, diabetes does not result in children.

This was noted with six children,[192] four to eleven years of age, who had suffered injuries to the pancreas, and as a result, had significant reduction in insulin secretion. They were tested by various methods to determine the consequences of such a deficiency--oral glucose tolerance tests were given and also intravenous tolbulamide and glucogen tests. None of the test procedures gave any suggestion that the children had become diabetic or that carbohydrate metabolism was impaired.

If deficiency of insulin is a cause of diabetes, it was not demonstrated in these children.

NEW LIGHT ON THE DIABETIC STATE (SUMMARY)

1. Theories of diabetes etiology focus on concepts of inadequate production or insensitivity of insulin. In line with this thinking, if repeated glucose doses are ingested, each succeeding load should further stress a diabetic pancreas until exhaustion, and less and less insulin should be secreted. In practice, each additional glucose load elicits successively greater insulin secretions (Straub-Traugott effect).
2. Insulin loses its sensitivity to glucose as free fatty acids rise.
3. Diabetics are found to react as rapidly as normals in:
   a. Disposing of large glucose loads;
   b. Secreting sufficient insulin to metabolize a glucose load;
   c. Elevating insulin levels in immediate response to even very low glucose intake.
4. A new definition of diabetes, based on studies discussed:
   A transient abnormality, characterized by the failure of insulin to metabolize glucose normally in the presence of an elevated plasma lipid level. When the lipids drop to normal, the "diabetes" disappears.
5. "Carbohydrate induction of triglycerides"--only happens with simple carbohydrates. Complex carbohydrates lower triglycerides.
6. Heredity as a basic etiology of diabetes is not supported by twin (monozygotic) studies.
7. Elevated blood lipids as the primary etiology of diabetes is demonstrated in fatty liver diseases, where the pancreas is completely normal. Livers can become fatty by diets of simple carbohydrates, high fats and alcohol.
8. Insufficiency of insulin due to trauma to pancreas did not produce a diabetic condition in children.

IV. ON BECOMING DIABETIC

Why aren't we all diabetic if the Western diet is so diabetogenic?

Criticism of the view that the diet recommended by the American Diabetes Association is diabetogenic has been made on the basis that it is not much different from the normal Western diet (40% of total calories in fat) that all of us consume. Why, then, aren't we all diabetic?

One factor was pointed out in a study(193) by Himsworth, earlier discussed. While the average dietary intake in the population is 40% of total calories in fat, the diabetics in the study were found to ingest 45-50% total calories in fat, while the normals ingested 30-35% of total calories in fat. There are many factors that determine whether or not one will become hyperglycemic, but on the Western diet it is inevitable. The only question is: how soon?

To avoid having most of the older population (around 60 years and older) test diabetic, the "normal" values are shifted. By the standards applied to 40-year olds, these older individuals would test diabetic; but by the relaxed standards for the older population, they fall into the high normal range. On the Western diet, much of the population which tests normal at 7 a.m. would test diabetic at 7 p.m. due to the diurnal variation in blood lipid levels. This should not come as a surprise. Ophthalmologists have found that patients who are normal in a test for glaucoma(194) during certain hours of the day test positive at other hours, when intraocular pressures approach the maximum.

A study with 13 healthy nonobese normal males(195) aged 17 to 42 illustrates this diurnal swing from normal to diabetic. Glucose tolerance tests were taken after a ten-hour fast at 7 a.m., and on another day at 7 p.m. On the day when the test was performed at 7 p.m. they ate a light meal at 8 a.m., and at 9 a.m. ingested 100 grams of glucose. For ten hours, only water was permitted. No smoking was allowed. Up to 3 p.m., they were permitted to sit or walk in the hospital, but after that they were confined to their beds until the test at 7 p.m. In addition to blood glucose values,

plasma free fatty acids, insulin and human growth hormone were also recorded on both test days over the three-hour testing period.

During the 7 a.m. testing, all the men tested normal in all values; but at the 7 p.m. tests, all tested diabetic. A look at the following graph explains the reason. As seen, fasting glucose and insulin values were the same for both the 7 a.m. and 7 p.m. tests. The critical difference was the free fatty acid level, which was almost 40% higher in the 7 p.m. test than in the 7 a.m. test.

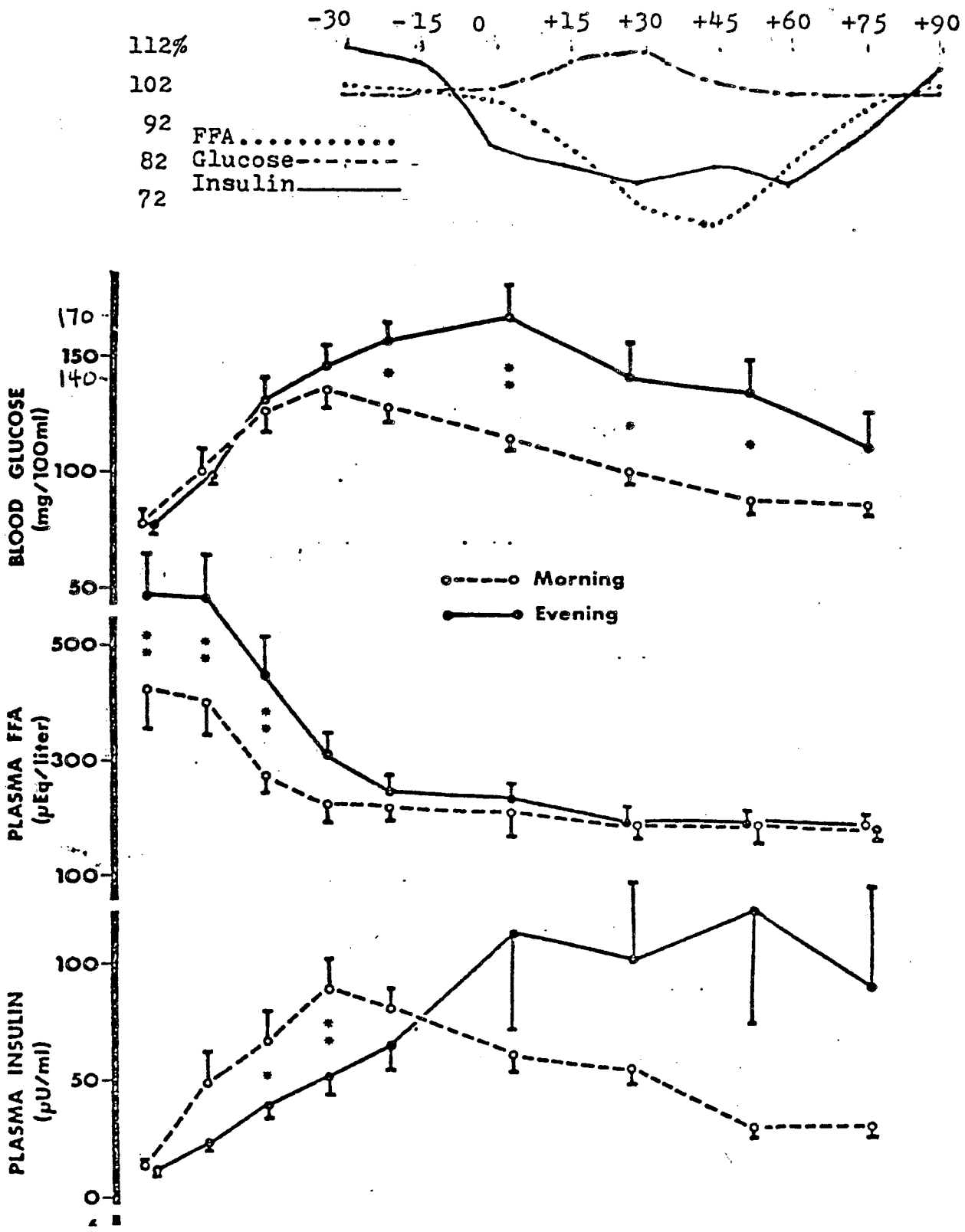
Almost identical conditions to those found in this study were present in the earlier cited lipid infusion study in which the glucose tolerance test was normal before the fatty infusion; but after the fat infusion (which raised the free fatty acid level to about the same level as was found in the 7 p.m. readings of these 13 male subjects), the glucose tolerance test was diabetic. Exactly the same process!

In the study comparing blood glucose values at 7 a.m. and 7 p.m., these were found to peak at 170-190 mg.% at 7 p.m., and the two-hour postglucose level was 140-160 mg.%. Definitely diabetic, yet the subjects would not have been revealed as diabetics had they been tested at usual times.

An example familiar to all of us of the effect of the diurnal swing on body functions concerns body temperature. Thus, a person with a slight fever may start the day with a normal temperature reading (when the diurnal cycle is at its low register), but as the day proceeds and the diurnal cycle produces a temperature rise, a later reading may indicate the presence of a fever.

Glucose tolerance testing of many of us in the latter part of the day would, likewise, reveal a diabetic condition.

Western diets make us all diabetic in time.


Minutes from start of infusion
-30
-15
0
+15
+30
+45
+60
+75
+90
112%
102
92
82
72
FFA
Glucose
Insulin
BLOOD GLUCOSE (mg/100ml)
170
150
140
100
50
Morning
Evening
PLASMA FFA (μEq/liter)
500
300
100
PLASMA INSULIN (μU/ml)
100
50
0

Carbohydrate metabolism abnormalities develop gradually in everyone on the Western diet.

Abnormal carbohydrate metabolism starts with an elevated insulin level. This can come about through illness,[196] liver disease,[197] and other diverse factors; but the observations and studies presented demonstrate that most of the problem originates from diet.

A normal weight subject can elevate his insulin level by a diet high in lipids[198] or simple carbohydrates.[199][200] Obesity is associated with hyperinsulinemia, the insulin being elevated in proportion to the degree of obesity.[201] A possible reason for hyperinsulinemia directly related to obesity is that insulin is required for the deposition of fat. Since the fat depots undergo constant resynthesis, a supply of insulin proportionate to the size of the fat depots is necessary. In the obese hyperinsulinemic individual, an important reason for the elevated insulin level is probably due to the excessive ingestion of fats and simple carbohydrates as part of the excess calories that brought on the excess weight. With the elevated blood lipid levels these would produce, the insulin becomes reduced in sensitivity and must rise.

Childhood obesity provides some insight into the gradual development of carbohydrate abnormalities. Seventy-two children with an average age of 10.9 years were studied[202] for their glucose and insulin values. Of these, 30 were normal-weight children and the balance were obese, averaging 46.7% higher than normal weight. The glucose tolerance tests for the normal children were all normal with fasting insulin levels of 6u U/ml. and peak values of 50 u U/ml. In the obese children, only the youngest did not have elevated insulin levels, and the oldest members of the group (12 children) tested as diabetic. The comparison of plasma glucose and insulin levels for the normal and obese children is shown in the table below.

PLASMA GLUCOSE AND INSULIN LEVELS OF
NORMAL AND OBESE CHILDREN

SUBJECTS	AGE (yrs.)	Glucose (mg./100 ml.) FASTING	Glucose (mg./100 ml.) PEAK	Insulin (u U/ml.) FASTING	Insulin (u U/ml.) PEAK
Normal (30)	8.7	78	114	6	50
Obese (30) Normal	10.3	84	122	16	103
Obese (12) Diabetic	12.3	92	192	21	208

None of the children had any clinical disease symptoms or were on drugs. The deterioration in carbohydrate tolerance appeared to be related to the degree of obesity and the length of time the obesity existed. There were no clearly definable levels of elevated insulin in the obese children; just a gradually increasing insulin level with a gradually decreasing carbohydrate tolerance--from normal to abnormal.

As seen in the table, obese normal children had a 260% higher fasting insulin level than normals, and obese diabetics, a 350% higher level. Of note is the very elevated insulin peak that was found in the obese diabetics--416% higher than in the normals.

Adult studies have reported much lower peak insulin levels, but there is no way to determine how long the adults had been diabetic. In the case of the children, the abnormal carbohydrate metabolism can be seen in many stages of development, but possibly after they reach adulthood, they may also have much lower insulin peaks.

It should be noted that all these juvenile subjects demonstrated a normal fasting glucose value. The evolution from normal to abnormal glucose tolerance test and insulin levels was gradual. Diabetes was not seen in these children at ages younger than 9 years.

The gradual processes observed in these children may very well be the prototype for adult diabetes. As earlier indicated, in normal weight subjects, elevated insulin levels can lead to hyperglycemia.(203)(204) The hyperglycemia becomes inevitable in time as the rising blood lipid levels, which cause a loss in

insulin insensitivity, force insulin levels ever higher. Such normal weight subjects may then test diabetic in glucose tolerance tests.

Once one is diabetic, what lies ahead?

The problems faced by the diabetic

Some physicians have contended that even if dietary changes (drastic fat reduction and increase of carbohydrates) would eliminate diabetes, no one would follow such a diet. Too restrictive, too bland for sophisticated tastes. Better to find some pharmaceutical means to control diabetes which would enable one to follow a normal or almost normal Western diet.

The question to be asked is whether good health is worth giving up a habit. The Western way of eating is a widespread habit associated with our particular culture. It is a habit just as smoking or the taking of heroin are habits. Thousands of physicians abandoned smoking when they realized the association with lung cancer. The evidence linking the high-fat Western diet and diabetes (and other degenerative diseases) is far stronger than that linking cigarettes and lung cancer. When the association of diet and diabetes becomes better understood, our present dietary habits will undergo the necessary changes.

The serious problems which plague the diabetic should act as a potent prod to make the necessary changes in dietary lifestyles in order to avoid becoming diabetic.

The prognosis for diabetics is indeed sobering, even when they are under the finest medical care. Many studies have been made; all tell a very grim story. An analysis[205] over a ten-year period of 370 male diabetic Du Pont Corporation employees showed that the death rate of the diabetics was 260% higher than for the controls. Most of these deaths were due to coronary heart disease, a finding that has been repeated in many other studies.

But increased death rates only record statistics at the end of the journey. What is the quality of life in the years before death? The diabetic under current treatment has little to look

forward to, except progressive loss of function, including loss of sight.

This pessimistic view is disputed by some clinicians, who believe that, under proper treatment and direction, diabetics have the prospect of a life not much different than normals. This is not the opinion of Dr. Keo Krall,[206] of the famed Joslin Clinic in Boston, who said: "The oft-repeated platitude that the diabetic should be able to lead a normal life is nonsense." Nor is it the view of Dr. Harold Cole,[207] Department of Pediatrics, New York Medical College, who spoke of problems he encounters in his adolescent diabetic patients: "They resent having to follow a different daily routine--insulin injections, urine testing, diet. In addition, they may feel despair because they have a reduced life expectancy...It is most important to remember that suicidal attempts are much more common among adolescent diabetics than in association with <u>any other cause</u>." (Our emphasis).

And what about the happy adult diabetics on hemodialysis? Publicity in the lay press often shows photos of smiling victims with their new equipment, sometimes in a newly constructed hospital department, or even in a camper with a build-in unit so that they can enjoy traveling around the country with their mate. But the truth is revealed in a recent study[208] of nine patients with diabetic nephropathy treated by hemodialysis. At the end of the first year, 78% had died. All suffered continued visual deterioration. The ages of these diabetics ranged from 25 to 49 years, and the average duration of their diabetic condition was 21 years. The clinician appraising the results of the study commented: "Rehabilitation to a level better than the predialysis state was negligible or transient...There is little prospect of improving the quality of life for patients with diabetic nephropathy and renal failure, and that survival is likely to be short. For some, we only prolong the misery."

When the mother is diabetic, problems begin before birth. In a study of the medical records of 1,200 children,[209] congenital abnormalities were found in 38% of newborns of mothers who were diabetic before age 25, compared to 3% for newborns of nondiabetic

mothers. A recent study[210] found that 75% of the mothers of children with Down's Syndrome had hyperglycemia. Another study of 500 "prediabetic" and diabetic cases during pregnancy found that 87% had suffered loss of the babies. Many of the mothers were of normal weight.

If a child is born normal, the manufacturers of infant "milks" try hard to push the child towards diabetes. One of the largest selling[211] of the infant "milks" (Similac) is advertising its new improved formula which contains almost 50% of its calories in sucrose, a simple carbohydrate. Considerable evidence[212] implicates sucrose in the development of diabetes in children.

During the early use of insulin on children, substantial reduction in growth and sexual development was noted. With the absence of controlled studies, it was thought after 1935 that this "diabetic dwarfism" disappeared.

A recent study (Nov. 1973)[213] documents its continued existence. Ninety-six pairs of identical twins (monozygotic) were studied to detect growth differences in the 'teen years due to diabetes. It was found that a child diagnosed as diabetic before his 13th birthday (this age was selected to coincide with puberty) would lose 1.8" to 2.9" of height by the time he became an adult. If he became diabetic after puberty, there was essentially no loss of height.

All diabetics in this study were on insulin and on a restricted carbohydrate diet.

When one twin was diagnosed as diabetic before puberty, height measurements of the diabetic and nondiabetic twin were made. The diabetic twin was then placed on insulin and carbohydrate restriction. After adulthood, they were both measured, and the 2" to 3" difference in height was noted in 11 out of 12 twin pairs.

This loss in stature is one price paid by children for the diabetic state.

Juvenile diabetics in another study[214] were found to exhibit impaired sensory perception involving touch, hearing, taste and vision. The impairment was discovered so early in the disease it was thought to have preceded it. The cause--damaged nerve

conduction velocities resulting in a neuropathy--was thought to occur only in adult diabetics who had had the disease many years.

An interesting drug test points up the role of compromised circulation in the capillaries in the creation of neuropathies. Such compromised circulation[215] in the capillaries is caused by blockage due to blood cell sludging and rouleaux formation and chylomicra, and is brought about by a high-fat diet or a diet that maintains a high lipid level. In the double-blind drug test[216] using clofibrate, a lipid-lowering drug, over a 12-month period, 78% of those receiving the drug improved and had disappearance of pain and numbness, as well as a return of deep tendon reflexes and an increase in muscle strength. Sixteen percent of the controls on placebo were improved, but 50% of the controls developed gangrene and required leg amputations. There were no vascular complications or amputations in the drug group.

Diabetic microangiopathy[217] is due primarily to compromised capillary circulation. Bell's Palsy, which affects the facial nerve, is thought to be due to a decrease of blood to the nerve caused by insufficient capillary circulation. Such a decrease in blood supply would result in edema, which would compress and degenerate the nerve. The facial nerve is encased in a rigid bony canal, and any increase of pressure would produce great compression on the nerve.

It was noted in 200 cases of Bell's Palsy patients that a "remarkably high" incidence of diabetics was found, even though 90% of these cases did not know they were diabetic. Thus, in the 10-19 year old group, 45% were diabetic, and the percentage rose until it was 100% in the 70-79 year old group. The high plasma lipid levels of diabetes produce the microangiopathy responsible for neuropathies such as Bell's Palsy.

The neuropathies extend in many directions. A random survey[218] of 200 diabetic men found 59% to be impotent. It was thought they might be lacking in testosterone, but they were not. The key was in the fact that 82% were neuropathic, again probably due to circulation problems. Diabetic impotence[219] occurs whether the patient is on insulin or oral drugs. In a group of 175

male diabetics with an average age of 53 years, 49% were impotent, yet they had had diabetes for an average of only six years.

Gall bladder abnormalities[220] including gallstones are frequent in diabetics. In the case of enlarged gall bladder, it is thought that it could be due to a neuropathy--"diabetic neurogenic gallbladder". In a group of 100 randomly chosen patients who had gall bladder x-rays, the mean gall bladder area in 32 diabetics was significantly larger than in 43 nondiabetics.

High-fat and high-cholesterol diets can produce gallstones as well as producing hyperglycemia. In group of 61 patients[221] with gallstones, this correlation was discovered. The relationship between gallstones and hyperglycemia, elevated free fatty acids and elevated cholesterol were all statistically significant in this group.

One of the most tragic consequences of diabetes is diabetic retinopathy. Before insulin, diabetes as a cause of blindness was less than 1%. From 1930 to 1960, it increased from 1% to 15% and it is rapidly becoming the leading cause of blindness in the U.S. Reports from British Diabetes Association[222] indicate that diabetics there are 20 times more likely to become blind than normals. Even worse, many investigators have found no relationship between control of blood glucose and retinopathy. The standard treatment for diabetics, tragically, does not allay the problem.

By illustration, we offer the reported results[223] of Dr. Knowles of the University of Cincinnati in a study with 60 patients treated with the classic measured diabetic diet (40% fat, 20% protein, 40% carbohydrate) and 167 who were on a less restricted diet. The study began in 1945, when the subjects were teen-agers. Twenty-five years later, when the oldest subject was just 43 years old, both diet groups revealed equally depressing outcomes--34% blindness at 30 years' disease duration and 20% mortality at 25 years' disease duration.

What is to be done? Suggestions that the problems of retinopathy could be lessened by lowering the blood lipids constantly appear, but are neglectfully ignored. Regression of exudative lesions in the retina in response to a low-fat diet was

reported in 1959. Lipid-lowering drugs such as clofibrate produced[224] a highly significant decrease in the waxy hard exudates in retinal lesions ($P < .0001$) over a three-year period--another encouraging indication of the benefits of lowering of the blood lipid levels on retinopathy. Other tests with clofibrate[225] have indicated that the visual deterioration can be stopped, though the damage is not reversible.

The diabetic condition is implicated in another visual disorder. In 16 patients with a condition called Asteroid Hyalitis,[226] in which cholesterol crystals become deposited in the lens, six were found to be diabetic and five others had borderline hyperglycemia. It is of interest that moderately elevated cholesterol levels (326 mg.%) will cause this deposition--a point that receives insufficient recognition.

Dietary control would seem to be a simple and logical answer to detering diabetic retinopathy, based on the indications that a lowering of blood lipid levels has caused regression of retinopathic symptoms. However, some clinicians prefer draconian measures,[227] such as a mutilating procedure that destroys the pituitary gland (a hypophysectomy). The rationale for this is that limiting the peaks of human growth hormone, regulated by the pituitary gland, causes the lowering of free fatty acid. While there is an immediate reduction of retinal edema and some vitreous clearing occurs as a result, the retinopathy continues, nevertheless.

Meanwhile, the prognosis for diabetics with respect to the prospect of blindness using methods of current therapy is 17.4 years.[228]

Coronary heart disease is responsible for most deaths in diabetes. A contributing factor in the development of atherosclerosis in diabetics probably is hyperinsulinism, common in the diabetic condition. It has been found in animal studies[229][230] that high insulin levels can stimulate cholesterol synthesis directly in arterial walls, independent of the plasma cholesterol. Vascular lesions can thus be formed regardless of the level of plasma lipids, and have been produced on

normal diets when the plasma cholesterol is in the normal range. Thus, this mechanism can be additive to the usual method of plaque formation in the intima of the arteries due to elevated cholesterol and/or fat levels. In this way, the diabetic or prediabetic can have an accelerated atherosclerosis.

These, then, are the dismal prospects facing diabetics on current forms of diabetic therapy. The situation becomes even more depressing when the diabetic is bombarded with the point of view that treatment is lifelong and there is no other way. One of the large pharmaceutical houses producing diabetic drugs distributes through physicians free copies of a popular paperback,[231] How to Live with Diabetes. It is good pharmaceutical business for the diabetic to take drugs throughout his lifetime, and it is good public relations to help him to learn to "live" with the "few" problems he may encounter.

Though in use since the early 1920's, when its discoverers received worldwide acclaim for their work, insulin still has many problems associated with its use.

Insulin is a complete protein,[232] and as an active antigen which induces an antibody response, it produces allergic reactions within a few months or sooner after its use is begun. This reaction is of particular importance to the diabetic who starts insulin therapy, as it initiates a destructive process. Within a short period, the antibodies (or some mechanism associated with the foreign protein insulin) begin a destructive action affecting the Islets of Langerhans, and, in particular, the beta cells. This destruction proceeds for years until, finally, no further activity in the beta cells can be detected.

Insulin therapy has another effect: the circulating antibodies, which are formed in an allergic response to the foreign insulin protein, bind and inactivate large amounts of endogenous insulin,[233] forcing the body to progressively greater dependence upon insulin injections. The dual action of injected insulin in binding and inactivating body insulin and gradually destroying the ability of the body to produce insulin is the reason why insulin

treatment, once begun, if continued long enough, must be lifelong. In the case of insulin therapy, the cure guarantees the disease.

How insulin damages the pancreas is conjectural. Certain facts are known[234] that help us to understand the destructive mechanism, however. If cows are injected with insulin derived from other cows or other species, they develop gross lymphocytic invasion and scarring of the Islets of Langerhans. In sheep also, there is a similar pathological response to injection of insulin from other sheep or from pigs. Apparently, whether from the same or another species is not important; exogenous insulin seems always to act as a foreign protein. Similar observations have been made with pigs, guinea pigs, and other species as well.

In humans, pancreas loss can be produced[235] by injection of insulin in normals. The loss can be great enough to cause normals to become diabetic. No determination of lymphocytic infiltration was made in this test because of the ethical problems of removing a section of pancreas in a nondisease state.

The antibodies seem only to exist in response to exogenous insulin. Thus, efforts[236] to detect the damaging antibodies in newly diagnosed juvenile diabetics who are candidates for insulin treatment, using a variety of sensitive procedures, have proved negative.

Insulin shock treatment has been implicated in impairment of the ability of the body to handle glucose, and even creating the diabetic state. Insulin shock treatment (IST) for certain mental conditions became very popular several decades ago. The treatment consisted of giving insulin until a hypoglycemic coma was reached, and adjusting the flow so as to maintain the coma for up to an hour. Patients were brought back to consciousness by infusion of sugar. One course of IST could induce 20 to 50 comas. Over a period of two to three months, insulin was used in hundreds and even thousands of units at a time for a single patient. (Contrast this dosage with the normal doses taken by diabetics of 10-40 units per day.) During the comas, the brain dependency on glucose was ignored and permanent brain damage was not infrequent. (A curious way to "alleviate" mental disturbances!) In addition, great risks

were taken in courting cardiovascular disease. A recent study[237] using 10-year death rates on mortality vs. insulin intake indicates the magnitude of this risk. Diabetics with a daily dose of 40+ units had a death rate 570% greater than normals. The diabetics on diet or oral drugs showed death rates 217% greater than normals. The findings on cardiovascular death confirmed the UGDP results.

In one study involving an IST group of 31 patients, all residing in the same mental hospital, 16% were found to have diabetes, as against 5% in a control group not subjected to insulin shock treatments. A young man became acutely diabetic only one month after a treatment schedule that included 53 comas and 7 seizure fits due to insulin shock. In a comparison of the glucose tolerance tests between the insulin treated patients and the controls, the insulin group had significantly higher glucose values at 60 minutes, 90 minutes and 120 minutes. Whether they were diabetic or not, there was definite impairment of glucose handling. In addition, insulin binding antibodies were found in the treated group, but were absent in the controls.

Currently favored therapeutic approaches in diabetes

Reviewing the currently employed treatment for diabetics, we find the following dismal picture:

Oral hypoglycemics - 250% more coronary heart disease than diet alone (American Diabetes Association diet containing 40% of total calories in fat).

Insulin - destruction of endogenous insulin leading to life-long dependency on exogenous insulin.

Diet - Standard diet (American Diabetes Association diet containing 40% of total calories in fat) initiates and perpetuates the diabetic state.

In desperation, research is taking bizarre forms, like the artificial pancreas implanted in the body to dispense insulin automatically in response to blood sugar levels.[238] Or Islets transplants![239] The rats in which the transplants were made were not cured of their diabetes (chemically produced), but the investigator was not devoid of hope for this line of inquiry.

Antibody problems due to exogenous insulin are apparently unimportant to these researchers.

Why is it that low-fat, low-cholesterol diets are not seriously considered by physicians? Ansel Keys[240] has studied 25-30 populations all over the world and is impressed by the direct relationship between dietary fat and degenerative disease. No population living on a low-fat diet (below 15-20% fat) has been found which has a high incidence of degenerative disease such as atherosclerosis or diabetes.

Aside from the long range effects of high-fat diets in producing diabetes and other degenerative conditions, these diets often cannot be tolerated for even short periods without ill effect. Studies[241] in Germany and Japan have indicated an increased incidence of human acute pancreatitis after the Second World War, coinciding with increased fats in the diet. Even dogs, far better equipped constitutionally than man to handle high-fat diets, cannot be maintained on such diets without injury. Dogs on high-fat diets had a much higher incidence of severe pancreatitis after mild trauma to the pancreas than dogs on other diets.

The fundamental role of diet in diabetes as the major etiological factor as well as the best prophylactic and therapeutic tool available is poorly understood. Lacking this appreciation, there is a sense of futility as to how to go about the prevention and treatment of diabetes. Thus, we heard these remarks[242] from a 1971 Nobel Prize winner in Medicine, Dr. Earl W. Sutherland: "I am not sure that any of our discoveries (author's note: on hyperglycemia and diabetes), and especially any of my own thinking, will ever be useful in the treatment or prevention of disease. For example, a bright practicing physician asked me a few weeks ago how I would treat a middle-aged patient who was severely diabetic, whose history he described. Fortunately for all concerned, he was bright enough to realize that I could not tell him anything worthwhile. Most of the thinking time that I have given to the subject of human diabetes mellitus has been spent trying to guess what basic genetic defect or defects might be carried by man, and

whether experiments with bacteria and viruses will ever help us cure the disease if we do identify the genetic defect."

This talented and respected scientist who has spent his last thirty years in medical research is still thinking of bacteria, viruses or genetics--all unsubstantiated hypotheses--as a solution to the problem of diabetes, when so much tangible evidence exists pointing to diet for the origin, prevention and cure of the disease.

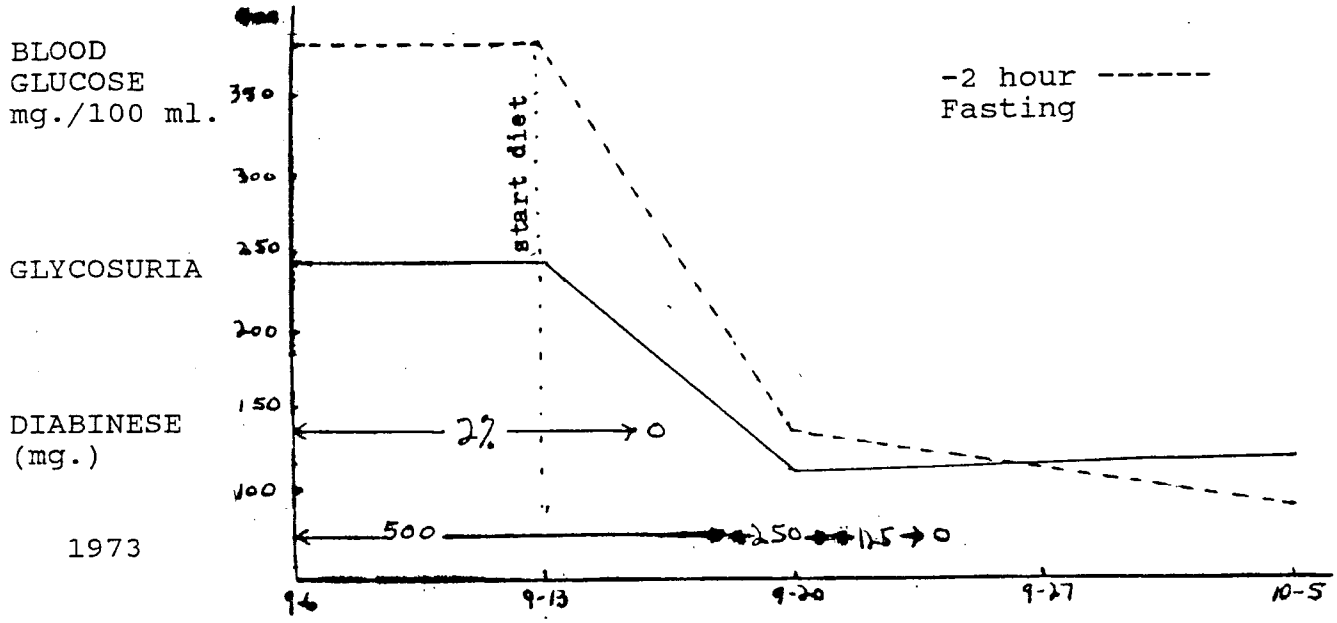
The potential for successful treatment of diabetes with low-fat diet, earlier demonstrated on a mass scale by the Canadian Rabinowitch, was again underscored by the incredibly rapid response to this approach of a 26-year-old male diabetic in a program undertaken this year ('73). J.F., a schoolteacher in Santa Barbara, California, was on oral diabetic drugs for three years. When his blood glucose failed to be controlled by the potent diabinese, he was scheduled to go on insulin within days.

At this juncture, he started on a diet and activity program under the writer's supervision. Within three days, spilling of sugar in the urine had ceased. Blood tests taken one week after the diet and activity program had commenced showed normal glucose tolerance response. Subsequent glucose tests taken two weeks after the first tests confirmed his normality. The diabinese was slowly phased out as the carbohydrate metabolism returned to normal, and the subject was no longer on drugs after 10 days on the diet and activity program. The table and graph on the following page document this one week transition from a diabetic to a nondiabetic state in a patient unsuccessfully treated for his diabetic condition for three years by conventional therapy.

CHRONICLE OF RESPONSES OF A DIABETIC TO LOW-FAT DIET AND ACTIVITY PROGRAM
(J.F., male, age 26, 6'0", 157 lbs.)

1970	Feb. -	Diagnosed diabetic; started on 6 tablets daily of Orinase (Tolbutamide).
1973	Jan. -	Started to spill heavily (2% glycosuria, lost 10 lbs.)
	Aug. 20-	Changed to diabinese (Chlorpropamide), 2 tablets daily. Still out of control (2% glycosuria).
	Sept. 6 -	Blood tests: fasting glucose 240 mg.%; 2 hr. 377 mg.%.
	a.m. 14 -	Still out of control; scheduled for insulin on Sept. 17. (Weight 161 lb.).
	8 a.m. 14 -	Started on diet and activity program.
	16 -	Aglycosuria. (Weight 158 lb.)
	18 -	Drop from 2 to 1 diabinese tablet per day.
	20 -	Blood tests; fasting glucose 119 mg.%; 2 hr. 141 mg.%.
	21 -	Drop from 1 to 1/2 diabinese tablet per day.
	23 -	Drop to 0 diabinese tablet per day. (Weight 157 lb.).
	Oct. 5 -	Blood test: fasting glucose 125 mg.%; 2 hr. 94 mg.% (Weight 158 lb.).

BLOOD GLUCOSE CONTROL OF DIABETIC (J.F.) ON LOW FAT DIET AND ACTIVITY PROGRAM



The quick turnabout from a chronic diabetic condition to a normal state in this individual (J.F.) was neither a miracle nor an aberration; it merely reflected the rapid response of endogenous insulin to a lowering of blood lipid levels brought about by a suitable dietary regime.

At a recent Diabetes Symposium (November 27, 1972),[243] the urgency of the problem of diabetes became even more apparent. On the one hand, one of the speakers discussing lipid metabolism was able to say: "No clear-cut evidence is available to explain elevated lipids in man." (The conclusions of the studies cited in these pages linking dietary fats and simple carbohydrates to elevated lipid levels seem clear-cut enough!) On the other hand, other speakers were deploring the failure of current diabetic therapy: "The resounding message from this study (University Group Diabetes Program) is that we are not treating diabetes mellitus effectively by any means." (Our emphasis).

It is the contention of this writer than an effective means for the treating of diabetes mellitus stands waiting. It is a dietary therapy based on high-carbohydrate and low-fat intake; it

has been mass-tested clinically and substantiated by dozens of studies and is simple, healthful and inexpensive. The answer to the diabetes dilemma exists; tragically, it has been overlooked.

ON BECOMING DIABETIC (SUMMARY)

1. Virtually everyone on a Western diet (40+% calories in fat) is or will become diabetic.
2. Those who test normally in morning glucose tolerance tests probably would test diabetic if this same test is performed in the evening.
3. Abnormal carbohydrate metabolism (diabetic) starts with hyperinsulinemia.
4. Hyperinsulinemia is created by diets of high fat and/or simple carbohydrates, illnesses, liver disease, obesity, etc.
5. Hyperinsulinemia encourages the synthesis of cholesterol crystals in the intima, independent of plasma cholesterol levels.
6. Prognosis for diabetics is visual and vascular damage and premature death.
7. Diabetic mothers have a high incidence of defective children.
8. Neuropathies characterize diabetics, young and old. These appear as impaired sensory perception, impotence and general loss of function.
9. Exogenous insulin is a foreign protein and produces antibodies which can inactivate endogenous insulin and damage beta cells. This is evident in insulin shock treatments, where normals become diabetic as the result of the insulin injected.
10. A proven regime which will prevent or cure diabetes is based on a low-fat diet. The appendix presents recommendations for a dietary and exercise program designed to free the individual from diabetes or the threat of diabetes and to maintain good health in general.

DIABETES REFERENCES

1. Dolger, H., Seeman, B. How to live with diabetes. Pyramid Books, N.Y.C., 1967.

2. Sansum, W.D., et al. The use of high carbohydrate diets in the treatment of diabetes mellitus. JAMA 86: 178-181, 1926.

3. Himsworth, H.P. High carbohydrate diets and insulin efficiency, Brit. Med. J., J2: 57-60, 1934.

4. Sweeney, J.S. Dietary factors that influence the dextrose tolerance test. Arch. Int. Med. 40: 818-30, 1927.

5. Rabinowitch, I.M. Experiences with a high carbohydrate-low calorie diet for the treatment of diabetes mellitus. Canad. Med. Assn. J. 23: 489-98, 1930.

6. Ibid.

7. Rabinowitch, I.M. The present status of the high carbohydrate-low calorie diets for the treatment of diabetes. Canad. Med. Assn. J. 26: 141-8, 1932.

8. Rabinowitch, I.M. Effects of the high carbohydrate-low calorie diet upon carbohydrate tolerance in diabetes mellitus. Canad. Med. Assn. J. 33: 136-44, 1935.

9. Himsworth, H.P. High carbohydrate diets and insulin efficiency. Brit. Med. J. J2: 57-60, 1934.

10. Himsworth, H.P. The dietetic factor determining the glucose tolerance and sensititvity to insulin of healthy men. Clin. Sc. 2: 67-94, 1935.

11. Himsworth, H.P. The diet of diabetics prior to the onset of the disease. Clin. Sci. 2: 96-115, 1935.

12. Joslin, E.P. The treatment of diabetes mellitus. Fourth Edition, Philadelphia, Lea and Febiger,1928.

13. Joslin, E.P. JAMA 95: 595, 1931.

14. Op. Cit. Reference 1.

15. University Group Diabetes Program. Supplement II. Diabetes. Vol 19, 1970.

16. Pioneer in Study of Insulin Diet at Age of 88. JAMA. 218: 25,1971.

17. Diabetes Study Head Assails Critics. Medical Tribune. 1-6-72.

18. FDA and 2 Groups Concur on Curb of Tolbutamide. Medical Tribune. 11-70.

19. The Tolbutamide Evidence. Lancet 171-2, 1-23-71.

20. Hadden, D.R., Montgomery, D.A.D., and Weaver, J.A. Myocardial infarction in maturity onset diabetics. Lancet 335-9, 2-12-1972.

21. Barclay, W.R. Tolbutamide: More questions than answers. JAMA, 215: 108-9, 1971.

22. Gubner, R. Treatment of diabetes: effect on cardiovascular disease. Medical Tribune, p. 13, 9-7-70.

23. Tolbutamide and the Heart. JAMA 222; 1179-80, 1972.

24. Gray, R.H. The influence of diagnostic criteria on the mortality findings in the University Group Diabetic Programme Study of Diabetic Therapy. Med. J. Aust 1: 594-6,1973.

25. Ibid.

26. Diabetes Up World Wide. Medical Tribune, 7-18-73.

27. Address of the President. Diabetes 21: 918-9, 1972.

28. Fajans, S.S. Current unsolved problems in diabetes management. Diabetes 21 (Suppl. 2): 678-84, 1972.

29. Brunzell, J.D., et al. Improved glucose tolerancwe with high carbohydrate feeding in mild diabetes. New Eng. J. Med. 284: 521-24,1971.

30. Op. Cit. Reference 5.

31. Op. Cit. Reference 7.

32. Treating, Eating, and Impeding. New Eng. J. Med. 284: 553-4, 1971.

33. Op. Cit. Reference 8.

34. Op. Cit. Reference 8.

35. Op. Cit. Reference 9.

36. Op. Cit. Reference 10.

37. Op. Cit. Reference 11.

38. Op. Cit. Reference 4.

39. Op. Cit. Reference 5.

40. Op. Cit. Reference 9.

41. Felber, J.P. and Vannotti, A. Effects of fat infusion on glucose tolerance and insulin plasma levels. Med. Exp. 10 Basel: 153-6,1964.

42. Op. Cit. Reference 4.

43. Op. Cit. Reference 41.

44. Buber, V. Improvement of oral glucose tolerance by acute drug induced lowring of plasma free fatty acids. Schweiz Med. W. Schr. 98: 711-2, 1968.

45. Vogelberg, K.H., et al. Clinical picture and treatment of insulin resistance in primary hyperlipoproteinemia. Dtsch. Med. Wochenschr. 98: 1751-8,1973.

46. Op. Cit. Reference 41.

47. Johnson, R.H., et al. Metabolic fuels during and after severe exercise in athletes and nonathletes. Lancet 2: 452-5, 8-30-69.

48. Johnson, R.H., et al. Post-exercise ketosis. Lancet 2; 1383-5, 12-17-69.

49. Williams, J.L., and Dick, G.F. Decreased dextrose tolerance in acute infectious diseases. Arch. Int. Med. 50: 801-18, 1932.

50. Rayfield, E.J., et al. Impaired carbohydrate metabolism during a mild viral illness. N. Eng. J. Med. Sept. 20, 1973.

51. Op. Cit. Reference 41.

52. Op. Cit. Reference 4.

53. Op. Cit. Reference 33.

54. Op. Cit. Reference 48.

55. Anderson, J.W., and Herman, R.H. Effect of fasting, caloric restriction and refeeding on glucose tolerance of normal men. Amer. J. Clin. Nutr. 25: 41-52, 1972.

56. Cahill, G.F., et al. Hormone-fuel interrelationships during fasting. J. Clin. Invest. 45: 1751-69, 1966.

57. Tripathy, B.B., and Kar, B.C. Observations on clinical patterns of diabetes mellitus in India. Diabetes 14: 404-12, 1965.

58. Pitchumoni, C.S. Pancreas in primary malnutrition disorders. Amer. J. Clin. Nutrition 26: 374-79, 1973.

59. Dekaban, A., and Mizel, D. Plasma lipids, glucose and ketones in young children on a high fat diet. Amer. J. Clin. Nutr. 15: 358-64, 1964.

60. Op. Cit. Reference 4.

61. The Role of Carbohydrates in the Diet. Nutrition Reviews 22: 102-5, 1964.

62. Anderson, J.W., et al. Effect of high glucose and high sucrose diets on glucose tolerance of normal men. Amer. J. Clin. Nutrition 26: 600-7, 1973.

63. Yudkin, J. Sucrose and heart disease. Nutrition Today. 16-20, Spring, 1969.

64. Szanto, S. Hyperinsulinemia and high sucrose intake. Lancet 2: 260-1, 7-29-67.

65. Sugar and The Pill Make Fat Faster Apart From Calories. Brookhaven Bulletin. Brookhaven Labs., Upton, N.Y. 1-2, 8-12-71.

66. Op. Cit. Reference 63.

67. Op. Cit. Reference 64.

68. Groen, et al. Effect of interchanging bread and sucrose as main source of carbohydrate in a low fat diet on the serum cholesterol levels of healthy volunteer subjects. Amer. J. Clin. Nutr. 19: 46-58, 1966.

69. Cohen, A.M., et al. Effect of interchanging bread and sucrose as main source of carbohydrate in a low fat diet on the glucose tolerance curve of healthy volunteer subjects. Amer. J. Clin. Nutr. 19: 69-62, 1966.

70. Campbell, G.D. Diabetes in Asians and Africans in and around Durban. South Africa M.J. 37: 1195, 1963.

71. Ingle, D.J. The production of experimental glycosuria in the rat. Recent Progr. Hormone Res., 2: 229, 1948.

72. Similac Advertisement. Medical Tribune 7-7-1971.

73. Bagdade, J.D., Porte, D., and Bierman, E.L. Diabetic Lipemia, New Eng. J. Med. 276: 427-33, 1967.

74. Op. Cit. Reference 29.

75. Op. Cit. Reference 41.

76. Op. Cit. Reference 4.

77. Op. Cit. Reference 62.

78. Himsworth, H.D. Dietetic factors influencing the glucose tolerance and the activity of insulin. J. Physiol. 81: 29-48, 1934.

79. Madison, L.L., et al. The hypoglycemic action of ketones. J. Clin. Invest. 43: 408, 1964.

80. Free Fatty Acids May Affect pancreas, Spur Insulin Output. Medical Tribune, p. 8, 10-6-1969.

81. Berkowitz, D. Glucose tolerance, free fatty acid, and serum insulin responses in patients with cirrhosis. Amer. J. Digest. Dis. 14: 691-9.

82. Wales, J.K., et al. The effect of hydrocholorothiazide in normal subjects receiving high fat or high carbohydrate diets. Amer. J. Med. Sci. p. 499-505, Oct. 1967.

83. Op. Cit. Reference 62.

84. Op. Cit. Reference 63.

85. Op. Cit. Reference 64.

86. Rabinowitz, D., et al. Patterns of hormonal release after glucose, protein and glucose plus protein. Lancet 2: 454-457, 8-29-66.

87. Grasso, S., et al. Insulin secretion in the premature infant. Diabetes 22: 349-53, 1973.

88. Anderson, J.W., and Herman, R.H. Classification of reactive hypoglycemia. Amer. J. Clin. Nutrition 22: 646-50, 1969.

89. Cohen, A.M., and Teitelbaum, A. Effect of dietary sucrose and starch on oral glucose tolerance and insulin-like activity. Am. J. Physiol. 206: 105-8, 1964.

90. Op. Cit. Reference 62.

91. Op. Cit. Reference 3.

92. Op. Cit. Reference 4.

93. Op. Cit. Reference 5.

94. Op. Cit. Reference 9.

95. Op. Cit. Reference 10.

96. Chance, G.W., Albutt, E.C., and Edkins, S.M. Serum lipids and lipoproteins in untreated diabetic children. Lancet 1: 1126-8, 6-7-69.

97. Wolff, Salt. Serum lipids in diabetic children. Lancet 1: 707, 1958.

98. Braunsteiner, H., et al. Hyperlipemia and latent diabetes mellitus. Klin. W. Schr. 43: 715-7,1965.

99. Khachadurian, A.K. Plasma lipids in diabetes mellitus. J. Med. Liban. 24: 1-11, 1971.

100. Danowski, T.S. Serum cholesterol and triglycerides during mild glucose intolerance. Amer. J. Clin. Nutr. 24: 855-8, 1971.

101. Albrenk, M.J., and Davidson, P.C. J. Lab Clin. Med. 67: 573,1966.

102. Randle, P.J., et al. The glucose fatty-acid cycle. Lancet 1: 785, 1963.

103. Jackson, I.M.D., et al. The glucose fatty-acid cycle. Lancet 1: 785, 1963.

104. Toggart, P., and Carruthers, M. Endogenous hyperlipemia induced by emotional stress of racing driving. Lancet i: 363-6, 2-20-71.

105. Pfeifer, U.,and Linke, E. Zum verhalten einiger parameter des fettstoffwechsels beim diabetes mellitus (about some parameters of fat metabolism in diabetes mellitus). Zeitschrift fur innere medizin 27 (3): 95-100, 1972.

106. Op. Cit. Reference 69.

107. Goodner, C.J., Conway, M.J., and Chee, P.C. Regulation of lipolysis in the presence of hyperglycemia. Amer. Soc. Clin. Invest. 46: 1061, 1967.

108. The Glucose Fatty-Acid Cycle. Lancet 2: 479, 8-28-71.

109. Op. Cit. Reference 105.

110. Primitive Life Keeps Tribesmen's Hearts Strong. JAMA 210: 1687, 1969.

111. Serum Lipids In Bushmen. Lancet 2: 395, 8-17-68.

112. Glucose and Fat Tolerances in Bantu Children. Lancet 2: 51-2, 7-4-70.

113. Antones, A., and Bersohn, M.B. The influence of diet on serum-triglycerides. Lancet 1: 3, 1961.

114. Jackson, W.P.U., et al. Prevalence of diabetes, glucosuria and related variables among a white population in Cape Town. S. Africa. Med. J. 43: 1496-9, 1970.

115. Seftel, H.C., and Schyltz, E. Diabetes mellitus in the urbanized Johannesburg African. S. African Med. J. 35: 66-70,1961.

116. Late-Onset Diabetes: Study Group Urges More Stress on Diet. Medical Tribune, 9-71.

117. Wilder, R. Adventures among the Islands of Langerhans. J. Amer. Diet. Assn. 36: 309-12, 1960.

118. Forecast-A Publication of the A.D.A. Sept.-Oct., 1972.

119. Op. Cit. Reference 86.

120. Wolf, H.J., and Priess, H. Experiences with fat free diet in diabetes mellitus. Deutsche Med. W. Chrnschr. 81: 514-5, 1956.

121. McKeon, C.M. Growth of phenylketonuric children on chemically defined diets. Lancet 1: 149, 1-17-70.

122. Present Knowledge of Nutrition in Relation to Diabetes Mellitus. Nutrition Reviews. 24: 257-60, 1966.

123. Blakeston's New Gould Medical Dictionary, New York, McGraw Hill Book Co., Inc., p. 337, 1956.

124. Taber's Cyclopedic Medical Dictionary, Philadelphia, Pa., F.A. Davis Co., p. D-20, 1968.

125. Yalow, R.S., and Berson, S.A. Immunoassay of endogenous plasma insulin in man. J. Clin. Invest. 39: 1157-75, 1960.

126. Op. Cit. Reference 7.

127. N. Varsano-Aharon, et al. Early responses to glucose and to tolbutamide in maturity-onset diabetes. Metabolism 19: 409-417, 1970.

128. Streeten, D. Diabetes mellitus--medical and dietary treatment. Recent advances in nutrition. Syracuse U., Syracuse, N.Y., p. 16, 1969.

129. Op. Cit. Reference 78.

130. Metz, R., and Friedenberg, R. Effects of repetitive glucose loads on plasma concentrations of glucose, insulin and free fatty acis. J. Clin. Endocr. 30: 602, 1970.

131. Yalow, R.S., Goldsmith, S.J., and Berson, S.A. Influence of physiologic fluctuations in plasma growth hormone on glucose tolerance. Diabetes 18: 402-408,1969.

132. Szabo, A.J., et al. Diabetes 18: 732, 1969.

133. Op. Cit. Reference 130.

134. Op. Cit. Reference 131.

135. Goodner, C.J., et al. Studies of substrate regulation in fasting. Diabetes 16: 576-89, 1067.

136. Elreck, H., et al. Plasma insulin response to oral and intravenous glucose administration. J. Clin. Endocr. Metab. 24: 1070-82, 1964.

137. Stern, M.P., et al. Insulin delivery rate into plasma of normal and diabetic subjects. J. Clin. Invest. 47: 1947, 1968.

138. Gooner, C.J., Conway, M.J., and Werrbach, J.H. Control of insulin secretion during fasting hyperglycemia in adult diabetics and in nondiabetic subjects during infusion of glucose. J. Clin. Invest. 48: 1878-87, 1969.

139. Reaven, G.M., et al. Study of the relationship between plasma insulin concentration and efficiency of glucose uptake in normal and mildly diabetic subjects. Diabetes 19: 571-78, 1970.

140. Reaven, G.M., and Farquhar, J.W. Steady state plasma insulin response to continuous glucose infusion in normal and diabetic subjects. Diabetes 18: 273-79, 1969.

141. Op. Cit. Reference 125.

142. Op. Cit. Reference 137.

143. Op. Cit. Reference 140.

144. Chiles, R., and Tzagournis, M. Excessive serum insulin response to oral glucose in obesity and mild diabetes. Diabetes 19: 458-64, 1970.

145. Reaven, G.M., et al. Is there a delay in the plasma insulin response of patients with chemical diabetes mellitus? Diabetes 20: 416-23, 1971.

146. Op. Cit. Reference 140.

147. Op. Cit. Reference 138.

148. Op. Cit. Reference 138.

149. Op. Cit. Reference 139.

150. Op. Cit. Reference 10.

151. Op. Cit. Reference 138.

152. Op. Cit. Reference 125.

153. Op. Cit. Reference 135.

154. Stone, D.B., and Conner. W.E. The prolonged effects of a low cholesterol, high carbohydrate diet upon the serum lipids in diabetic patients. Diabetes 12: 127-32, 1963.

155. Glueck, C.J., et al. Immunoreactive insulin, glucose tolerance, and carbohydrate inducibility in types II, III, IV and V hyperlipoproteinemia. Diabetes 18: 739, 1969.

156. Op. Cit. Reference 63.

157. Op. Cit. Reference 64.

158. Op. Cit. Reference 29.

159. Op. Cit. Reference 63.

160. Op. Cit. Reference 64.

161. Op. Cit. Reference 65.

162. Op. Cit. Reference 68.

163. Op. Cit. Reference 69.

164. Op. Cit. Reference 70.

165. Op. Cit. Reference 71.

166. Op. Cit. Reference 68.

167. Op. Cit. Reference 69.

168. Op. Cit. Reference 155.

169. Ford, S.F., et al. Interactions of obesity and glucose and insulin levels in hypertriglyceridemia. Amer. J. Clin. Nutr. 21: 904, 1968.

170. Op. Cit. Reference 29.

171. Op. Cit. Reference 63.

172. Op. Cit. Reference 64.

173. Op. Cit. Reference 65.

174. Op. Cit. Reference 68.

175. Op. Cit. Reference 69.

176. Op. Cit. Reference 70.

177. Op. Cit. Reference 71.

178. Grey, N., and Kipnis, D.M. Effect of diet composition on the hyperinsulinemia of obesity. N. Eng. J. Med. 285: 827-31, 1971.

179. Wall, J.R., et al. Effect of carbohydrate restriction in obese diabetics: relationship of control to weight loss. Brit. Med. J. 1: 577-8, 1973.

180. Op. Cit. Reference 155.

181. Tattersall, R.B., and Pyke, D.A. Diabetes in identical twins. Lancet 2: 1120-5, 1972.

182. Op. Cit. Reference 81.

183. Megyesi, C., Et al. Glucose tolerance and diabetes in chronic liver disease. Lancet 2: 1051-5, 1967.

184. Martin, M.M., and Martin, A.L.A. Obesity, hyperinsulinism and diabetes mellitus in childhood. J. Pediatrics 82: 192-201, 1973.

185. Op. Cit. Reference 183.

186. Rehfeld, J.F., et al. Carbohydrate metabolism in alcohol induced fatty liver. Gastroenterology 64: 445-451, 1973.

187. Althausen, J.L., and Thoenes, E. Arch. Int. Med. 50: 257, 1932.

188. Himsworth, H.P. The physiological activation of insulin. Clin. Sci. 1: 1-38, 1933.

189. Op. Cit. Reference 89.

190. Schemmel, R., et al. Fed. Proc. Abst. 26: 473, 1967.

191. Winnie, G., Schemmel, R., Rand, E., Mickelson, O., and Leveille, G.A. Effects of high carbohydrate diets on lipid accumulation in the rat. Mich. State U., East Lansing, Mich. 48823 (1973).

192. Grabner, W., et al. Insulin reserves in children with and without pancreatic injuries. Dtsch. Med. Wochenschr. 98: 1499-1501, 1973.

193. Op. Cit. Reference 11.

194. Lennon, R.G., and Turnbull, C.D. Diurnal intraocular pressure variation in a glaucoma screening program. Arch. Ophthal. 80: 714-7, 1968.

195. Carroll, K.F., et al. Diurnal variation in glucose tolerance and in insulin secretion in man. Diabetes 22: 333-48, 1973.

196. Op. Cit. Reference 50.

197. Op. Cit. Reference 183.

198. Op. Cit. Reference 4.

199. Op. Cit. Reference 63.

200. Op. Cit. Reference 64.

201. Bagdade, J.D., et al. The significance of basal insulin levels in the evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. J. Clin. Invest. 46: 1549-57, 1967.

202. Op. Cit. Reference 184.

203. Op. Cit. Reference 63.

204. Op. Cit. Reference 64.

205. Pell, S., and D'Alonzo, C.A. Factors associated with long-term survival of diabetics. JAMA 214: 1833-40, 1970.

206. Krall, L.P. Platitude that diabetic should lead normal life is held to be nonsense. Med. Trib. 10-24-73.

207. Cole, H.S. What's new and important in diabetic therapy? Med. Trib. 9-12-73.

208. Ghavamian, M., et al. The sad truth about hemodialysis in diabetic nephropathy. JAMA 222: 1386-9, 1972.

209. Comess, L.J., et al. Congenital anomalies and diabetes in Pima Indians of Arizona. Diabetes 18: 471-7, 1969.

210. Emanuel, I., et al. Accelerated aging in young mothers of children with Down's Syndrome. Lancet 2: 361-3, 1972.

211. Op. Cit. Reference 72.

212. Yudkin, J. Infant feeding and diabetes. Lancet 2: 1424, 1972.

213. Tattersall, R.B., and Pyke, D.A. Growth in diabetic children. Lancet 2: 1105-9, 1973.

214. Cochenov, R.H. Early sense impairment seen in juvenile cases. Medical Trib., p. 1, 7-7-71.

215. Swank, R.L. A biochemical basis of multiple sclerosis. C.C. Thomas, Publisher, Springfield, Ill., 1961.

216. Berenyi, R., et al. Treatment of diabetic neuropathy with clofibrate. J. Am. Geriatr. Soc. 19: 763-72, 1971.

217. Korczyn, A.D. Bell's Palsy and diabetes mellitus. Lancet 1: 108-10, 1-17-71.

218. Ellenberg, M. Impotence in diabetes: neurologic factor. Ann. Intern. Med. 75: 213-19, 1971.

219. Barnett, D.M. Diabetic impotence unrelated to treatment. Med. Trib. 10-3-73.

220. Getelson, S., et al. Size of gallbladder in patients with diabetes mellitus. Diabetes 18: 493-8, 1969.

221. Kremer, G.J., et al. Early diabetic metabolic anomalies and bioptically established fatty infiltration of the liver in gallstone subjects. Schweiz Med. Wscher. 98: 110-3, 1968.

222. Diabetic Retinopathy. Lancet 2: 1073, 11-21-70.

223. Knowles, H.C. Measured diet may not lower diabetic death. Med. Trib. p. 3, 8-1971.

224. Duncan, L.J.P., et al. Three year trial of atromid therapy in exudative diabetic retinopathy. Diabetes 17: 458-67, 1968.

225. Clarke, B.F., et al. Diabetic retinopathy. Lancet 2: 1255, 12-12-70.

226. Smith, J.L. Asteroid hyalitis. JAMA 168: 891-3, 1958.

227. Pituitary Destruction for Diabetic Retinopathy. Lancet 2: 415-6, 8-23-69.

228. Daughaday, W., and Boniu, I. Diabetic retinopathy. JAMA 214: 1867-72, 1970.

229. Stout, R.W. Insulin stimulation of cholesterol synthesis by arterial tissue. Lancet 2: 467-8, 8-30-69.

230. Stout, R.W. Development of vascular lesions in insulin treated animals fed normal diet. Brit. Med. J. 3: 685-686, 1970.

231. Op. Cit. Reference 1.

232. Coleman, W.P., et al. Insulin allergy. Ann. Allergy 29: 383-8, 1971.

233. Grodsky, G.M. Production of autoantibodies to insulin in man and rabbits. Diabetes 14: 396-403, 1965.

234. Renold, A.E., et al. Metabolic regulation in herogenous systems: some new questions about diabetes mellitus. Fed. Proc. 25: 827-31, 1966.

235. Hunter, R., et al. Impaired glucose tolerance: a late effect of insulin shock treatment. British Med. J. 1: 465-8, 1970.

236. Parker, M.F., et al. Juvenile diabetes mellitus, a deficiency in insulin. Diabetes 17: 27-32, 1968.

237. Op. Cit. Reference 205.

238. Bessman, S.P. Breakthrough made in fight against diabetes. Santa Barbara News Press. 4-24-71.

239. Ballinger, W.F. Islet transplants--hope for diabetics. JAMA 219: 1282-3, 1972.

240. Keys, A. Atherosclerosis. JAMA 5: 290-4, 1957.

241. Medical Tribune, 4-9-70.

242. Sutherland, E.W. On the biological role of cyclic AMP. JAMA 214: 1281-8, 1970.

243. The Obese Diabetic--A Symposium On New Developments. Calif. Med. 119: 14-48, 1973.

APPENDIX: Recommendations for a Healthful Lifestyle

I. RECOMMENDED DIETARY COMPOSITION

Protein intake

Total protein intake should not exceed 10% of total calories. Most of this should be in the form of grains, roots, and other vegetables. In order to restrict cholesterol intake to < 100 mg. per day, animal protein should be limited to about 3 oz. per day. Corn and millet should be eaten in moderation since these grains can cause pellagra if they are the sole or principal protein source.(1)

There has been much concern in the U.S. about "complete" proteins and adequate levels of intake to avoid protein malnutrition. These concepts grew popular in the 1940's when rats on low-protein diets developed fatty livers which eventually became fibrotic. However, what is true for rats, in this instance, was found to be untrue for primates, including man.(2) Low-protein diets not only do not produce fibrosis or cirrhosis, but actually produce an environment not conducive to cellular regeneration or fibrous tissue proliferation. Several populations whose protein intake varies from 3% to 9% total caloric intake have been discussed in other sections of this book and these groups are free of degenerative diseases even though most of their meager protein intake derives from plant sources (not a "complete" protein).

Dangers of high protein intakes are cited throughout this writing: loss of bone matrix, risk of cancer, producing conditions conducive to hyperinsulinemia, elevated uric acid levels, etc. In one study with men over a 55-day period, it was found that the amount of calcium loss was directly related to the quantity of protein in the diet(3) as shown in the following table:

Amount of protein	Calcium gain or loss (daily)
high	-85 mg.
medium	+ 1 mg.
low	+12 mg.

The men consumed the same amount of calcium per day. The high-protein intake was equivalent to about a pound of meat daily, far less than consumed on the currently popular high-protein reducing diets.

In underdeveloped countries and especially in India, it has generally been believed that the growth retardation and the extensive malnutrition in childhood was due to a "protein gap" in their diets.[4] A PCM syndrome (protein calorie malnutrition) is commonly referred to with reference to these children. The results of an in-depth study of the diet of undernourished children in poor communities in India is instructive on the matter of protein nutrition.

This study, conducted by the National Institute of Nutrition in Hyderabad, India, surveyed a total of 415 children from 1 to 5 years of age in nine villages in the environs of Hyderabad. A detailed analysis of their diet found, surprisingly, that their protein intake was 1.1 gm. per kilogram, which exceeded the recommended allowance of 1 gm. per kilogram of body weight. Their caloric intake was low, so a program of supplementary feeding was started of 300 calories per day. This was added to the 700 calories per day they were receiving and was continued for 276 days. During that period the growth and height gain of the children receiving the supplementary feeding exceeded by 15% for the 4-5 year olds and 50% for the 1-2 year olds that of a control group of children who did not receive supplementary nourishment. The supplementary rations contained only 4% protein, making extra protein an insignificant dietary contribution.

The investigators, all members of the Indian Council of Medical Research, concluded: "The immediate practical approach towards combating malnutrition in children living in poor rural Asian communities would seem to lie in educating these communities in bridging the calorie gap with the present dietaries after such improvement, rather than in distributing elaborately processed 'protein-rich formulations,' which are unnecessary and expensive."

As is typified by these Indian children, the problems ascribed to "low protein" diets are mostly due to inadequate caloric intake.

Another common concern, the protein adequacy of vegetarian diets, was the object of another significant study[5] involving young adults on a purely vegetarian diet yielding 0.5 to 0.6 gm. protein per kilogram of body weight. Seven men and women between 23 and 30 years of age ate all their meals in a laboratory environment for 60 days, where their metabolic wastes were collected for daily nitrogen balance tests. These were positive in all cases irrespective of the kinds of vegetables eaten in a variety of combinations tested. (Wheat comprised 50% of the diet; the other 50% was beans and corn; beans and rice; beans and milk; corn and milk; rice and milk; beans, corn and milk.) Positive nitrogen balance was not significantly different in any of these food combinations.

This diet was adequate, generally, and for protein intake, specifically, despite the fact that the wheat flour used in the study was not of the highest nutritional quality, being a commercially bleached and enriched flour. (In most underdeveloped nations, the flour is usually whole grain, with all the wheat germ and natural vitamins.) Ironically, they are too poor to afford the refined flours easily available in more advanced nations!

The investigators in this study cited other research using similar protein intake which also resulted in positive nitrogen balance.

There is no danger to Americans from protein malnourishment on a diet of less than 10% of total calories in protein and from "inferior" vegetable proteins! If Tarahumara Indians[6] can run up to 200 miles continuously for two days playing their kickball game on a "low" protein (mostly vegetable) diet, loss of strength on such a reduced protein intake cannot be a problem.

Carbohydrate intake

Carbohydrates are contained in every grown food, but in sparse amounts in a few animal foods. Natural carbohydrates are principally polysaccharides--complex carbohydrates--although they contain simple carbohydrates as well.

Simple carbohydrates that have been isolated by the ingenuity of food manufacturing processes should be avoided. This includes common sugar (sucrose), honey, molasses, glucose, fructose, lactose, etc. Simple carbohydrates raise triglyceride levels and generally produce adverse metabolic changes. Complex carbohydrates act in an opposite manner: they lower triglyceride levels and produce the steady state supply of calories over the 24-hour period that is most beneficial to the body. The complex carbohydrates should provide 80% of the total caloric intake of your diet.

Starches are a main component of many of these foods and are one of the most important sources of energy. They do not promote weight gain and, in fact, because they provide much bulk for the same amount of calories, they have a greater satiety effect. If starches are laced with fatty sauces or fried in oils or blended with simple carbohydrates, weight gain becomes easier, as there will be more calories for less bulk. This is not understood by many in the U.S. who are overweight and hold a 100 calorie potato tuber responsible, but ignore the 300 calories of butter or sour cream that goes over it.

Fat intake

Adjusting the fat intake to a healthful level presents the greatest change for those on the Western diet--along with reducing simple carbohydrate consumption. Fats and simple carbohydrates are present in abundance in the bulk of our food delicacies--whether popular junk food fare or gourmet preparations. Unfortunately, a little modification in fat intake is not enough: it must be a drastic change--10% should be maximum. This low level can readily be achieved by avoiding the use of any fats or oils in the preparation and serving of foods and by restricting high-fat animal foods. Natural foods are mostly under 10% fat and many are under 5%.

The question may be asked: is this amount of fat adequate to meet all the body's needs? A relevant study[7] described a synthetic diet containing a total fat content of <1% which kept both children and adults in good health for months and even years.

In nature, it is essentially impossible to select a menu in which the level of fat is not above 1%. Even lettuce has a fat content from 9-15% depending upon the variety (although being so low in total calories, the fat consumed eating lettuce is negligible).

On the diet recommended in this book, most of the fats will be of vegetable origin, so there will be no problem getting the body's daily requirement of 1.5 gms. of linoleic acid.

Mineral intake

All the minerals the body requires can come from a diet of 80% complex carbohydrates. From time to time, pressure is put on the public to increase consumption of one or another mineral. Supplements are suggested to "protect" against deficits produced on ordinary diets. These promotional campaigns, in the writer's opinion, are not in the public interest, but are largely designed for the seller's profits.

Calcium

One example is calcium. Requirements for calcium are controversial. The average recommended intake in the U.S. is 100 mg. per day. Yet the World Health Organization in their report on calcium requirements[8] states: "No frank signs of calcium deficiency have ever been described in any part of the world, even in populations with an habitually low calcium intake." Many population groups subsist on intakes of 200 mg. per day and show no signs of calcium deficiency.

One such group is the Bantu population in Africa.[9] They not only get along well, but have great bone density. They also enjoy freedom from caries, rickets, osteomalacia (adult rickets), and osteoporosis, and have good healing of fractures. Children subsist completely on mother's milk for six months and during that time grow as rapidly as Caucasian babies (even though as adults they do not reach Caucasian stature). Low calcium intake is no disadvantage to this population group.

What happens with high intakes of calcium? In farm animals, high intakes of calcium have produced deficiencies of iron, zinc,

and magnesium and have, in addition, resulted in impaired utilization of protein and fat.

Iron

Another mineral that is big business is iron ("tired blood"). In underdeveloped countries, a serious problem exists with parasites. Hookworm infection involves over 450,000,000 people[10] and can drain 250 ml. of blood daily; other parasites, too, drain blood from millions of people. It is very clear how anemia and debilitation can be caused under these circumstances. These conditions do not exist in the United States, and it is questionable whether there is any reason for the constant pressure for iron supplementation for infants, menstruating females, and anyone whose hemoglobin levels drop below the arbitrary standard of 10.5 grams per 100 ml., the usually accepted minimum level.

Most clinicians have seen asymptomatic patients with hemoglobin levels down to 6 gms./100 ml., and even lower.[11] To prescribe iron for those patients with values of 9-10.5 gms./100 ml., a range where much anemia falls, may be of no value, as is indicated by a study in which correlation of anemia and symptoms of fatigue, weakness, pallor, etc. was attempted.

Hemoglobin and hematocrit were tested for 295 patients aged 15 to 74 years, of both sexes, who had complained of symptoms which would make them suspect of having deficiency anemia. Average hemoglobin values were surprisingly high: 14.8 gms. for the men and 13.0 gms. for the women. Only 2% of the men and 10% of the women had hemoglobin values below 11.4 gms.

A group of women from the 295 subjects was given iron to ascertain whether raising of the hemoglobin levels with iron would alleviate the symptoms of fatigue, etc., typically associated with anemia. The hemoglobin and hematocrit levels increased, but there were no changes in the symptoms. Bringing the blood values into the "normal" range may make the physician feel better, but not necessarily the patient.

Other much broader-based studies have failed to find correlation between blood values and work performance.[12]

One reason for this lack of correlation might be the practice of relating the hemoglobin concentration to 100 ml. of blood, rather than hemoglobin in grams to kilograms of body weight. The latter would be a far more reliable basis for comparison because the amount of hemoglobin would not be affected by fluctuations in plasma volume. Using this more reliable criterion, 114 pregnant women whose hemoglobin levels varied from 8.6 to 14.2 gms. per 100 ml. were all found to be normal in terms of hemoglobin per kilogram of body weight. This was confirmed by their blood films, normal serum iron and iron-binding capacity, folate levels, and absence of reticulocytosis on iron and folate therapy.

Iron deficient anemia--except in definite cases of blood loss--is rare enough in the U.S. to be of no consequence. The taking of iron, especially for males, is dangerous because of the possibility of iron overload. Because iron ingestion will raise the hemoglobin level doesn't mean that the higher level is more beneficial: it may be deleterious.

Vitamins

All the vitamins required by the body will come from the diet recommended in this book; none need to be added by supplements. This statement may be difficult to accept because of the tremendous pressure from both commercial interests and well-meaning individuals exhorting us to take large amounts of various vitamins.

While a detailed analysis of all the vitamins is beyond the scope of this book, we will go into the facts concerning vitamin requirements for those vitamins for which supplementation is most publicized.

Vitamins can arbitrarily be divided into two categories: fat- and water-soluble. The fat-soluble vitamins include A, D, E and K. These fat-soluble vitamins are capable of long-time storage in the body, ranging from months to several years--an attribute that has led to many cases of toxicity due to overdose.

Vitamin toxicity due to overdosing

Numerous cases of vitamins A and D toxicity have been reported. In some instances, this was related to prescribed acne treatment; in others, it was associated with efforts to improve night vision. Much of the toxicity was achieved in less than a year.

In one report, Vitamin A intoxication produced hypercalcemia with increased bone resorption.[13] Bone and nerve lesions caused a halt in growth and this was followed by destruction of the bone cartilage,[14] a consequence of dissolution of the cartilage lysosomes, whose enzymes then destroyed the cartilage. A list of additional symptoms associated with hypervitaminosis A includes bone or joint pain, fatigue, severe headaches, night sweats, loss of hair and exophthalmus.

A recent finding in animals fed a high-fat diet with sub-toxic levels of vitamin A is quite disturbing.[15] Cholesterol was deposited in the tissues which accumulate vitamin A, and the deposition of cholesterol increased as more vitamin A was stored. In time, a very large amount of cholesterol was distributed in the tissues, apparently stimulated by the vitamin A.

In Ghana, where this observation was made, the native population generally consumes this same type of diet, and there is suspicion that the animal findings could explain similar pathological observations in the natives.

Vitamin D toxicity is well-known, ranging in effects from deposition of calcium in the heart, lungs, blood vessels and various soft tissues,[16] to the raising of the cholesterol level in man, even in "normal" supplemental doses.[17] Any supplemental dose at all is quite unnecessary, unless one is a cave-dweller, since one's vitamin D requirements are amply met by a few minutes of exposure to sunlight each day--without risking toxicity.

Water-soluble vitamins, such as vitamin C and the various B vitamins, are reputed to be without danger in high dosage, the theory being that any excess is simply excreted. This is by no means confirmed and enough studies have been done to question alleged benefits of this type of therapy.

Years ago vitamin B_{12} was given routinely for fatigue, poor appetite, etc. When large doses were given under controlled conditions, they were found to be of no value.[18] While the use of vitamin B_{12} in pernicious anemia is well-established, its extensive use for conditions of debilitation is an unfortunate deception.

Folic acid in pharmacological doses of 15 mg. daily produced toxic symptoms in normal healthy volunteers in only 30 days.[19] Niacin has been used to treat chronic schizophrenia, but in a controlled test large amounts were found to produce a worsening of the patients' condition.[20]

Animal studies[21] indicate a possible basis for niacin toxicity. Rats fed a diet comparable to the Western diet (40% of total calories in fat) were found to have fatty livers produced by niacin supplements of 0.1%. The niacin-fed rats had 50% more fat in their livers than the rats not fed niacin. Yet this is only 1/20 the mount of niacin given to humans in the treatment of hypercholesterolemia. It is not a surprise that liver dysfunction has been reported as a side effect of this treatment.

The advocacy of daily dosing with B vitamins is not supported by the evidence. Vitamin B_{12} can be stored in the body for more than five years.[22] Even on a total fast of 10 days, no deficiency symptoms associated with vitamins B_1, B_2 and B_6 were observed.[23] In fact, during World War II, vitamin deficiencies were rarely clinically evident among the victims of starvation. There is no daily emergency to make sure you have had your vitamin B ration; the diet recommended in this book will amply meet your requirements.

Meeting the requirements for vitamin A

How much vitamin A does the body require? Is the required amount readily available on the average diet?

Studies with 16 adults placed on essentially vitamin A-free diets showed a deficiency in night vision developing in only three subjects. Some of these individuals maintained this diet for almost two years without symptoms.[24] As demonstrated by this

study, it is apparent that vitamin A does not have to be ingested daily; the body stores in these subjects sufficed for many months.

In India, where young children are generally malnourished and have a chronically low level of vitamin A, some telling studies have been made.[25] In one of these, 32 children between 2 and 6 years of age--all undernourished and some with obvious optic signs of vitamin A deficiency--were given daily servings of 40 grams (1-1/3 oz.) of amaranth (one of the most commonly used green leafy vegetables in India), in addition to their normal diet. Over half the children had below normal vitamin A serum levels (15 ug%); but after only 15 days of ingesting the small quantity of green leaves, all the children were brought into the normal range (28 ug%): their serum level almost doubled on this simple regime.

Forty grams of leaves, added to the daily diet, provided these children with 1200 ug% of B-carotene, sufficient to bring them into the normal range in only 15 days; 40 grams of carrots would have provided enough vitamin A for four days at the same rate; and three medium-sized carrots could provide their entire vitamin A requirement for one month by this calculation. (Absorption of carotene from the amaranth leaves averaged 75% for the children, about the same as reported for normal adults.)

Thus, in young children on impoverished diets, under great metabolic stress, no problems are encountered in the rapid absorption of enough carotene, to cure their deficiency condition easily.

Some reports claim a low-fat diet would inhibit vitamin A absorption,[26] but the results of the study with the Indian children dispute this. The diet of these children averaged only 6 gms. of fat per day (about 5% of total calories), but vitamin A absorption was not impeded.

Factors associated with vitamin absorption and depression of vitamin levels have been related to a variety of circumstances. A high blood level of unsaturated fats due to addition of these fats to the diet[27] has been shown to depress vitamin E levels, increase erythrocyte hydrogen peroxide hemolysis, and decrease erythrocyte survival. High intake of vitamin C and iron also

depress vitamin E levels[28] so that current trends to encourage large doses of these supplements can have the effect of reducing the protective action of vitamin E as an antioxidant. Vitamin A levels have been found to become depressed due to high dosage of vitamins C or E, both of which inhibit vitamin A absorption. Other adverse effects due to high dosage of vitamin C have been reported.[29]

Meeting the requirements for vitamin C

How much vitamin C does the body actually require? Is daily or even weekly ingestion necessary?

Two critical factors to consider are these: the average daily maintenance intake of vitamin C is so low that only with great difficulty would anyone in the U.S. achieve a deficiency state, whatever his particular diet; the second factor concerns the relatively long storage of vitamin C in the body--at least a month or two is required before any signs of deficiencies appear. In some studies of experimental scurvy, one of which is described below, the body stores protected against scurvy for 5-6 months.[30]

In one of these studies, six healthy men ranging in age from 26 to 52 years were put on a vitamin C-free diet until some scurvy symptoms appeared.[31] After three months, they were all permitted various amounts of vitamin C to restore their levels to normal. Two of the group were given 6.5 mg. per day for a period of over three months and were closely monitored.[32] It was found that they were using a maintenance quantity of 3.5 mg. per day, and were retaining the balance of 3 mg. in body storage. Theoretically, it would have been possible to saturate their tissues with vitamin C if this dosage were continued for an adequate period of time, after which their intake could be reduced and their maintenance needs met from their storage supplies.

While reducing the vitamin C intake to a maintenance level of 3.5 mg. per day is not advocated here on the basis of this study, it should be noted that a medium-sized orange possessing 45 calories will provide enough vitamin C for 20 days at this maintenance level. In other studies, a maintenance level of only 1-3 mg. per day[33] has been suggested.

In an effort to determine how much vitamin C is required to completely saturate the body stores, a study was undertaken using 19 healthy volunteers between 16 and 45 years of age. The subjects were dosed with 500 mg. of vitamin C each day until their leukocytes became saturated with the vitamin. (Leukocyte levels of vitamin C are generally accepted as reflecting tissue levels.) After saturation was reached, vitamin C intake was then reduced to 10-12 mg. per day. At this reduced level, it was found over a 30-90 day period of checking that adequate though not saturated levels were maintained in eight subjects, and that seven maintained saturation throughout the 30-90 day period on the 10-12 mg. of vitamin C per day.

The eight whose levels dropped below saturation were now given an additional 10 mg. of vitamin C daily; the small addition was found sufficient to saturate their stores once again. Thus, a range from 10 to 22 mg. of vitamin C taken daily was capable of maintaining saturation of this vitamin in the body tissue.

During the study, six of the subjects had minor infections such as colds and upper respiratory infections. This did not produce any significant changes in the vitamin C levels in the leukocytes indicating that these minor stresses did not require utilization of extra vitamin C. This observation leads to the subject of proper therapeutic dosage of vitamin C.

It is an axiom that the therapeutic dosage is larger than the maintenance dosage in a deficiency state. Therapeutic dosages as low as 6.5 mg. per day have been demonstrated,[34] yet some scientists are recommending daily doses of 1000 times this quantity. Some reasons given for these recommended high doses is that they enhance one's sense of well-being, working capacity, and even athletic performance.

To determine the validity of these claims, a study[35] was made using 20 smokers and 20 nonsmokers, all males averaging 24.5 years of age. These men were more active than the average since they were students in physical education, all of whom had had experience with the method of testing, running on a treadmill. During the test periods, which varied in length of time,

measurements were taken of oxygen utilization and efficiency, heart recovery rates, maximum oxygen intake, etc.

Following these tests for a five-day period, the 40 subjects were divided into two groups. One group received tablets containing 2 grams of vitamin C; the other was given a placebo. Neither subjects nor investigators knew who was taking which tablet, since the test was designed to be double-blind, but each of the two groups had an equal number of smokers and nonsmokers. After the five days, blood tests indicated that the 20 subjects on vitamin C had doubled their plasma levels of this vitamin, while those on the placebo tablets were unchanged.

The treadmill tests were rerun and the results compared with the previous values. The investigators concluded: "The results of the various analyses performed on all parameters in all levels revealed no significant differences between the mean response of subjects given vitamin C and those given the placebo, whether they were smokers or nonsmokers...daily supplementation of two grams of vitamin C had no effect on respiratory adjustment and oxygen utilization before, during, and after exercise in smoking and nonsmoking subjects."

One authority, whose views regarding the role of vitamins in improving physical performance are based on much experience is Dr. D.L. Cooper,[36] who was intimately associated with the Olympics (1972) as a physician. Dr. Cooper commented: "vitamins need to be mentioned as another subject of the 'great drug myths.' We must remember that vitamins act primarily as catalytic agents and are not metabolized. If a person eats a balanced diet of fresh, well-prepared food, he is getting all the vitamins has body can use. There are many salesmen in this country and many gullible people are victimized financially by vitamin 'pushers'. Americans excrete the most expensive urine in the world because it is loaded with so many vitamins."

The growing vitamin C cult is based on the conviction that it can be taken in massive doses without ill-effect. Even those who are somewhat skeptical about the alleged benefits of heavy dosing with vitamin C, tend to regard this practice as innocuous, whether

effectual or not. However, many new facts are indicating that large doses of vitamin C may be detrimental.

In 1971, a physician experimenting with vitamin C[37] discovered that when she took 1 gram a day, her cholesterol level rose from 140 mg. percent to as high as 230 mg. percent. Intrigued by this ability to vary her cholesterol level at will in this manner, she repeated the experiment giving 1 gram of vitamin C daily for 6 weeks to 58 volunteers. While none of the subjects had clinical signs of illness, she found that 25 among them with atherosclerosis had the greatest rise in cholesterol level: from 242 mg. percent to 261 mg. percent whereas the subjects who were healthy and under 25 years of age had drops from 194 mg. percent to 177 mg. percent.

These data inspired a large double-blind study[38] in a geriatric unit involving 538 patients. Half were given 200 mg. of vitamin C per day and the other half were given placebos. At the end of a six-month period on this regime, 30 coronary episodes had taken place: 19 involved subjects who had been taking vitamin C, but only 11 had occurred in the placebo group. While the size of the groups may not be large enough to be statistically significant, there was a greater tendency for thrombotic episodes among those who took vitamin C.

One case showing how vitamin C in large dosages creates a thrombotic condition is of special interest: this involved a 70-year old woman who was on Warfarin (an anticoagulant).[39] She was treated for acute thrombophlebitis and was discharged, having been controlled by 5 mg. daily of the Warfarin. Six weeks later she was back with an acute fulminating thromphlebitis, with much pain and tenderness in the lower abdominal area. In trying to control her prothrombin time, it was found that the Warfarin dose had to be increased from 5 mg. to .25 mg. daily. Upon questioning, it turned out that the woman had been taking 16 grams of vitamin C daily for the previous several weeks, having been influenced by a popular magazine. Taken off the vitamin, her prothrombin was controlled at 10 mg. of Warfarin when she left the hospital.

In this case, and possibly in the geriatric unit cases, vitamin C played a role in initiating adverse changes in the clotting system. Vitamin C in therapeutic doses bears close watching.

Vitamins and placebos

Vitamins are frequently given to patients as placebos. The physician upon examination can only find a nonspecific malaise: he may sometimes be tempted to suggest vitamins. This is unfortunate, since it may start a life-long habit of supplements, with unknown side effects. Some people become psychologically addicted to vitamins: if they stop taking them, they feel deprived and this adverse mental state may even cause susceptibility to periods of suboptimal health.

Just how powerful the placebo effect may be was demonstrated to a second-year class of medical students in the following study.[40] Volunteers among them participated in a study of sedative and stimulant drugs in which the 56 subjects were divided into four groups taking capsules as follows: 1. one pink capsule; 2. two pink capsules; 3. one blue capsule; 4. two blue capsules. No one was told that the number and color of capsules differed for the other groups. After an hour, they were asked to fill out questionnaires to evaluate the drug effects. Sixty-six percent had a drop of pulse rate; 71% had a drop of blood pressure; 32% developed various adverse effects. Two of the subjects were so affected by dizziness, abdominal discomfort, tingling, watery eyes and headaches that they sought reassurance from faculty members, fearing major drug effects.

Sixty-six percent of the subjects taking the blue capsules reported sedative effects, whereas 73% of the subjects taking the pink capsules felt stimulated. Those taking two capsules reported more symptoms than those taking only one of the same color.

Two weeks later, the results were tabulated and presented to the class who then learned that all of the capsules were placebos. No one was angry, but a number felt humiliated. It was a good lesson for future doctors--and for all patients.

II. PRACTICAL GUIDELINES FOR YOUR NEW DIET

(for keeping young until a ripe old age)

No placebos are given in these recommendations: the reader is expected to have the courage of the convictions gained from exposure to the facts and to live without magic potions and unsupported or harmful dietary rituals.

Here is a summary of the recommended diet:

Total protein - 10% of total calories: Protein to be derived mainly from vegetable sources such as grains; animal protein in the form of meat or fish to be limited to a maximum of 3 oz. daily; cholesterol limited to 100 mg. daily (omit high cholesterol foods such as egg yolks, liver and other organ meats, etc.)

Total carbohydrates - 80% of total calories: Complex carbohydrates predominantly (e.g., rice and other grains, pasta, bread, potatoes and other vegetables)--simple carbohydrates (such as sugar, honey, molasses, etc.) are to be avoided.

Total fats - 5 to 10% of total calories: No fats may be used at any stage of cooking, preparation or serving of food (such as cooking oils or shortening, margarine, butter, mayonnaise, etc.); processed foods containing fats are to be omitted (e.g., ice cream, sherbet, almost all cheeses) as are natural foods that are high in fats, such as nuts, olives, avocados.

Liquids: No soft or hard (alcoholic) drinks. No caffeine beverages, (decaffeinated beverages o.k.) Nonfat milk to be used in place of whole milk. Fruit juices to be restricted to 8 oz. per day. Water is really the best drink.

Supplements and salt: No salt is to be used in preparation of food or at the table (--there will be a minimum of salt coming from any canned and frozen vegetables you may use). No vitamins or mineral supplements to be taken.

Some Suggestions on Following the Diet:

1. Total calories

The diet is self-regulating and does not have to be closely monitored, as much of the food intake has a high bulk and satiety to calorie ratio so that hunger becomes appeased before excess calories create a problem. If additional weight gain or loss is desired after the diet has been followed for a period of time, an adjustment to higher or lower calorie foods can be simply made, as will be discussed.

2. Spacing of meals

Proper spacing of meals is important to the proper functioning of the body. At least three meals a day should be eaten, and the caloric content of each should be no less than 25% of the total day's intake.

Those that eat a skimpy breakfast, skip lunch and eat a large dinner are inviting hypoglycemia and elevated lipid levels; the same intake divided into more frequent and balanced meals would avoid these problems. Eating one large meal a day is also conducive to stomach distress and ulcer formation.

A method that has been used successfully by the writer in quickly curing ulcers suggests that meal-spacing and ulcer-producing physiological mechanisms are related. This method has been used with individuals exhibiting pre-ulcer burning or distress as well as with others with established ulcers where blood is evident in the stools. A simple nonmedical technique is used, as follows: bread or crackers in 10 calorie amounts are consumed at half-hour intervals. (They may be easily carried wherever one goes, so that the "treatment" is most convenient.) The bread or crackers should preferably be made of whole grain flour and water, without addition of fats, sugar and, if possible, salt. Within 48 hours most of the ulcer pain will have disappeared, and within a week or so in almost every case there will be complete freedom from symptoms. If the pre-ulcer uneasy abdominal feeling reoccurs, the bread or cracker regime should be immediately begun again, until symptoms disappear. (This occurs much sooner this time;

within 24 hours generally.) After the symptoms are gone, gradual weaning from the bread or crackers over 3-4 days is helpful. A simple method with no adverse side effects due to drugs or special ulcer diets! (The famous Sippy ulcer diet has been shown in large studies to cause a marked increase in coronary heart disease deaths due to the required high intake of such foods as cream, butter, eggs and cheese--all of which raise cholesterol and triglyceride levels.)

3. Keeping your bowels happy

Considerable evidence points to insufficient roughage or fiber in the diet[41] as the cause of diverticular disease of the colon and the general "irritable" bowel syndrome (bowel pain and alternating constipation and diarrhea). Eating the unadulterated grain and other foods with high roughage content (potato tubers, other vegetables) furnishes the necessary fiber for roughage which encourages a fast transit time, yet discourages constipation and diarrhea. Bowel control becomes automatic and bowel syndromes practically nonexistent.

4. Planning your menu

At least 6-8 oz. of a green salad is a daily must. This should preferably be made with romaine, butter leaf, or other deep-green lettuces.

Fresh fruit should be eaten in moderate amounts, 2-5 pieces per day, but not to exceed 20% of total calories. One of the daily fruits should be citrus, if possible. Fruits that have not been altered by cooking or fine crushing are much preferred.

Grains may be considerably altered and damaged in processing. Conversion of whole grains, such as wheat, rice, etc. to the commercial product is responsible for loss of most of the bran, fiber, and vitamins. Unless grains are cold stone ground where nothing is lost, they should not be used as a flour.

A summary of food to eat and to avoid as well as a sample day's menu follow. A recipe book that parallels rather closely the

rules we have proposed is the Low Cholesterol Cook Book, published by the University of Iowa Medical School, Iowa City, Iowa ($2.50). The several hundred recipes it contains are designed to limit the daily intake of meat or fish to 3 oz. and the cholesterol intake to < 100 mg. It will be necessary, however, to delete from some of the recipes proscribed ingredients such as sugar, syrups, salt, oils and fats in order to omit fat, simple carbohydrate and salt.

SAMPLE MENU FOR A DAY

Will provide 1500 to 3000 calories a day,
depending on lunch and dinner portions.

BREAKFAST (approximately 770 calories)

1 Orange
Whole Rolled Oatmeal (5 oz.) fills an 8 oz. measuring cup
8 oz. water
1/2 to 1 banana sliced in oatmeal
Cook for 2-3 minutes, constantly stirring

LUNCH

Salad - (dark green leaves preferred) - Romaine or other lettuce, plus celery, carrots, tomatoes, etc.
If trying to lose weight, let the salad fill a large soup bowl, and eat with a few slices of bread.

If trying to maintain present weight, eat half of the portion of salad, and choose from following:

Rice & Beans
Sandwiches using sliced hoop cheese (skim milk cottage cheese pressed into a brick).

DINNER

Main Course - Maximum 3 oz. Meat or Fish (< 100 mg. cholesterol)

(Meat or Fish may be served by diffusing it in a loaf, stew, etc. in order to "stretch" it further.)

Cooked Vegetables
Soup
Bread
Salad if desired
Potatoes, baked, or sweet >either or both
Brown Rice

Beverages - Decaffeinated Coffee
Nonfat Milk
Water

SNACKS BETWEEN MEALS - Bread, sour dough, rye, whole wheat
Crackers - any whole grain and water, as rye, rice, wheat

	Use	Avoid
MEAT FISH BEANS NUTS EGGS	Chicken, turkey, veal, fish, beef (lean), lean hamburgers Trim all visible fat before cooking. Bake, broil, roast or stew Dried beans and peas Eggs--whites only	Lamb, pork, ham, duck, goose Shellfish, shrimps Marbled and fatty meats--spare ribs, mutton, frankfurters, sausages, fatty hamburgers, bacon, luncheon meats Organ meats--liver, kidney, heart, sweetbreads Eggs--no yolks Nuts--none
VEGETABLES FRUITS	All fruits and vegetables raw, baked, boiled Limit dried fruit as raisins to 1 oz./day, prunes to 2 oz./day	Olives, avocados Dried fruits as figs, dates
BREADS CEREALS	Sour dough bread, any other without shortening or sugar Rice, pasta, noodles (except egg noodles) Spaghetti Any cold cereal without shortening or sugar, as shredded wheat Any hot cereal without shortening or sugar, as oatmeal	Any baked goods with shortening and/or sugar as cakes, crackers, donuts, sweet rolls, commercial mixes with dried eggs & whole milk
MILK PRODUCTS	Milk, skim (nonfat) Cheese made from skim (nonfat) milk, as farmer's, baker's, or hoop cheese	Milk chocolate, canned whole milk, powdered whole milk, creams, yogurt, nondairy cream substitutes Cheeses--all cheeses except hoop (nonfat) cheese
FATS & OILS	None	Butter, lard, meat fat, margarine, all oils
DESSERTS BEVERAGES SNACKS CONDI- MENTS	Fresh fruit Canned fruit (not in syrup) Limit fruit to 4 pieces per day or 15-20% of total calories Bread or rolls without shortening or sugar Limit fruit juices to 4 0z. daily Decaffeinated Coffee	Puddings, ice cream, sherbets Canned fruit in syrup Gelatin desserts Fried foods, as potato chips All bakery items containing shortening and sugar Candy Salt (do not add to food) Soft drinks (especially cola) Coffee Tea

III. NEXT COMES EXERCISE

Start walking, at any age, at least 15 minutes without stopping, every day. If time permits, walk for longer periods; an hour is ideal. (This can be divided into half or quarter-hour walks.)

If you are not accustomed to prolonged walks, start at a moderate pace for the first weeks, gradually increasing your speed as the muscles restore their tone. It is important that the walks be uninterrupted, since a great part of the value depends upon achieving a sustained elevation of your heart rate.

If you are capable of walking for an hour at a vigorous pace and feel you can be more active, start running--but slowly. At the start, run at as slow a pace as is comfortable for 30 seconds of each 5-minute walking period. If this exertion is too exhausting, reduce the running time to 20 seconds, or even 10 seconds, until there is little exertion required. After you have achieved this comfortably, you can start to increase the length of the running interval in each five-minute walking period, though still running at a slow pace. As the amount of running time per walking period grows longer, the run will gradually become continuous.

One who has never run or who has not run for many years should run about 5-6 miles per hour--a mile in 10 or so minutes. To make sure you are within your physiological boundaries, your heart rate (pulse) should be monitored. Exactly 60 seconds after you stop, count your pulse for exactly 30 seconds: if the count is more than 65, you are beyond safe limits--take more time to achieve your goal.

Fifteen minutes is a minimum time for a continuous run, if it is done at least three times weekly. This will maintain you in good condition. As the body becomes trained, you will automatically increase your running tempo, or if you are walking, you will walk at a brisker pace.

These exercise recommendations are intended specifically for improving cardiovascular capability. Other activities--game-playing of all kinds, swimming, stretching, etc.--are all good

methods for maintaining muscle tone and are desirable but are not a substitute. Walking or running in a sustained manner as described are specific for achieving or maintaining cardiovascular health and should be part of every health program.

IV. BLOOD TEST STANDARDS THAT REFLECT GOOD HEALTH

Blood tests can be deceptive if proper standards are not used. Unfortunately, current medical practice ascribes permissable standard levels that are too high to be safe, in most instances. The following table gives the writer's recommended values for several important tests. The recommended standards have been selected from the findings in population studies where cardiovascular disease, diabetes, and other degenerative states are essentially nonexistent.

BLOOD TESTS: CRITERIA OF ABNORMALITY

Test	Recommended standard	Present standard
Total Lipids	< 575 mg./100 ml.	< 800 mg./100 ml.
Cholesterol	< 160 mg./100 ml.	< 260 mg./100 ml.
Triglycerides	< 80 mg./100 ml.	< 135 mg./100 ml.
Uric acid	< 6 mg./100 ml.	< 7 mg./100 ml.
Hemoglobin (M)	> 10.5 gm./100 ml.	> 12 gm./100 ml.
Hemoglobin (F)	> 9 gm./100 ml.	> 11 gm./100 ml.

APPENDIX REFERENCES

1. Mehta, S.K., et al. Small Intestinal Deficit In Pellagra. Amer. J. Clin. Nutrition 25: 545-9, 1972.

2. Editorial - Nutrition & Liver Disease - Lancet p. 1132, 11-25-72.

3. Linkswiler, H.M., et al. High Protein Diet Causes Calcium Loss. Med. Trib. 3-14-73.

4. Gopolan, C., et al. Effect of Calorie Supplementation on Growth of Undernourished Children. Amer. J. Clin. Nutrition 26: 563-66, 1973.

5. Clark, H.E., et al. Nitrogen Balances of Adult Human Subjects Fed Combination of Wheat, Beans, Corn, Milk & Rice. Amer. J. Clin. Nutrition 26: 702-706, 1973.

6. Casdorph, H.R., & Connor, W.E. Nutrition For Endurance Competition. JAMA 222: 1062, 1972.

7. Winitz, M., et al. Studies in Metabolic Nutrition Employing Chemically Defined Diets. AMer. J. Clin. Nutrition 23: 525-45, 1970.

8. Calcium Requirements - Report of an FAO/WHO Expert Group. Bulletin #230 - World Health Organization - Geneva, 1962.

9. Walker, A.R.P. The Human Requirement of Calcium: Should Low Intakes Be Supplemented? Amer. J. Clin. Nutrition 25: 518-30, 1972.

10. Patwardhan, V.N. Nutritional Anemias. Amer. J. Clin. Nutrition 22: 496-517, 1969.

11. Symptoms of Iron Deficiency Anemia. Nutrition Reviews 25: 86-7, 1967.

12. Elwood, P.C. Proc. R. Soc. Med. 63: 1230, 1970.

13. Wieland, R.C., et al. Hypervitaminosis With Hypercalcemia. Lancet p. 698, 4-3-71.

14. Roels, O.A. Present Knowledge of Vitamin A. Nutrition Rev. 24: 129-32, 1966.

15. Kordylas, J.M. Vitamin A & Fat Combination in Cholesterol Biosynthesis & Atherosclerosis. Lancet p. 606, 9-16-72.

16. Goodhart, R.S. The Vitamins - Modern Nutrition in Health & Disease. p. 213-322 - Lea & Febiger - Phila. 1968.

17. Fleishman, A.I. Caution Given on Rise Found in Cholesterol. Med. Trib. 12-8-69.

18. Friend, D.G. Cyanocobalamin (Vit. B12) Injections for Nonspecific Debilitation - No Value. JAMA 214: 604, 1970.

19. Hunter, R., et al. Toxicity of Folic Acid Given In Pharmacological Doses To Healthy Volunteers. Lancet p. 61-64, 1-10-70.

20. Meltzer, H.Y. Large Niacin Use in Schizophrenia May Be a Danger. Med. Trib. 3-16-1970.

21. Rikans, L.L., et al. Fatty Livers Produced in Albino Rats by Excess Niacin in High Fat Diets. J. Nutrition 82: 83-87, 1964.

22. Op. Cit. Reference 16.

23. Consolazio, C.F. Thiamin, Riboflavin, & Pyridoxine Excretion During Acute Starvation & Calorie Restriction. Amer. J. Clin. Nutrition 24: 1060-7, 1971.

24. Op. Cit. Reference 16.

25. Lala, V.R., and Reddy, V. Absorption of B-Carotene From Green Leafy Vegetables In Undernourished Children. Amer. J. Clin. Nutrition 23: 110-113, 1970.

26. Op. Cit. Reference 14.

27. Op. Cit. Reference 16.

28. Stocks, J., et al. Increased Susceptibility of Red Blood Cell Lipids To Autoxidation In Hemolytic States. Lancet p. 266-8, 2-6-71.

29. Bieri, J.G. Effect of Excessive Vitamins C & E on Vitamin A Status. Amer. J. Clin. Nutrition 26: 382-3, 1973.

30. Hodges, R.E., et al. Clinical Manifestations of Ascorbic Acid Deficiency in Man. Amer. J. Clin. Nutrition 24: 432-43, 1971.

31. Ibid.

32. Baker, E.M., et al. Metabolism of ^{14}C & ^{3}H - Labeled L - Ascorbic Acid In Human Scurvy. Amer. J. Clin. Nutrition 24: 444-54, 1971.

33. Strikantia, S.G., et al. Human Requirements of Ascorbic Acid. Amer. J. Clin. Nutrition 23: 59-62, 1970.

34. Op. Cit. Reference 30.

35. Bailey, D.A., et al. Vitamin C Supplementation Related To Physiological Response to Exercise In Smoking & Non-Smoking Subjects. Amer. J. Clin. Nutrition 23: 905-12, 1970.

36. Cooper, D.L. Drugs & The Athlete. JAMA 221: 1007-11, 1972.

37. Spittle, C.R. Atherosclerosis & Vitamin C. Lancet, ii, 1280, 1971.

38. Andrews, C.T., and Wilson, T.S. Vitamin C & Thrombotic Episodes. Lancet, ii, 39, 1973.

39. Smith, E.C., et al. Interaction of Ascorbic Acid & Warfarin. JAMA 221: 1166, 1972.

40. Blackwell, B., et al. Demonstration To Medical Students of Placebo Responses & Non-Drug Factors. Lancet p. 1279-82, 6-10-72.

41. Wolf, S., and Wolff, H.C. Human Gastric Function. Oxford University Press N.Y.C. 1943.

42. Harvey, R.F., et al. Effects of Increased Dietary Fibre on Intestinal Transit. Lancet p. 1278-80, 6-9-1973.

AFTERWORD: A WORLD WITHOUT DEGENERATIVE DISEASES?

An imposing body of evidence underlies the thesis that the common degenerative diseases originate with and are nurtured by the destructive high-fat, high-cholesterol, high-in-simple-carbohydrates Western diet, and that they regress when this harmful diet is withdrawn and supplanted by a healthful one. In these chapters we have discussed many of the hundreds of important studies that together substantiate this position.

This view of the common origins and therapy for the degenerative diseases leads inexorably to a novel but fully reasonable concept concerning their nature: diseases such as atherosclerosis, coronary heart disease, hypertension, gout, gallstones, diabetes, glaucoma, and some forms of arthritis and cancer--are not separate disease states, but are diverse syndromes associated with the same etiology. (In an analogous manner, symptoms associated with the common cold may variously involve the throat, nose, ears, sinuses, lungs, etc.). We have given the name "lipotoxemia" to this new master disease. It describes a condition of body poisoning due to chronic high blood lipid levels that is capable of expression in a wide range of degenerative disease symptoms.

While both fats and cholesterol are used by the body, at abnormally high levels they become a reservoir of toxins, as indeed even water can become when present in the body in excess for extended periods. When this toxic reservoir of fats and cholesterol recedes, there is regression of disease symptoms; when it rises, the symptoms increase and are exacerbated. The particular degenerative disease syndrome that develops with elevated blood lipids is influenced by a variety of factors, including the particular blood lipids involved, the degree of their elevation, and the length of time at abnormal levels. In many cases, the symptoms of several degenerative diseases are present simultaneously in various degrees in the same individual.

Lipotoxemia, with all its varied manifestations--hypertension, gout, diabetes, coronary heart disease, etc.--can be prevented or

alleviated by dietary reform substantially reducing fat, cholesterol, and simple carbohydrate intake. Such a simple solution to the problem of the common degenerative diseases could be easily implemented if the desire existed, but official sanction and public acceptance of this approach are not in the near offing, despite the formidable body of evidence that exists. The inertia springing from tradition and habits, and the active opposition from vested interests, among other obstacles, stands in the way, even if those with contrary viewpoints who wish to be objective could be educated overnight to an acceptance of the concepts we have propounded.

Like utopian dreamers, however, we find pleasure and inspiration in speculating about the kind of world we would have without degenerative diseases, and the life-enhancing possibilities it would open to individuals and whole societies. The likelihood for reaching the full potential of our natural life-span would mean that death before 100 years of age would be considered foreshortened and be mourned, while a span of life reaching 120 to 150 years would not be infrequent.

Not only would it be common to live out the full natural life-span, but the later years would no longer be vexed by painful and debilitating symptoms that accompany many of the degenerative diseases and often appear even in early middle age. An extended life-span in which good health and vigor would not diminish with age would offer greatly expanded opportunities for life enrichment through a diversity of experiences--study, work, travel, human relationships, creative endeavors, etc. For the many whose decline now begins in early middle life, another fifty years of good health would be tantamount to a second life.

Dramatic social changes would appear due to ramifications of the decline in degenerative diseases and the new dietary habits. The medical world in its vast complexity would become transformed: the human, financial and physical research facilities, the hospitals and care facilities, as well as the pharmaceutical industry, would no longer need to concentrate on the havoc wrought by the degenerative diseases. Medical care would largely focus on

other health problems, such as treating infectious diseases, mechanical repairs of the body due to accidents or congenital defects (would we still have a doctor shortage?); medical research would be freed to press forward the frontiers of unsolved problems and challenges in other areas--involving genetic or psychosomatic factors, or probing the mystery of cell mortality, which holds the answer to a life-span even beyond the apparent natural limits.

The food industry and the manufacturers and dispensers of magic potions and pills would feel the impact greatly: food modification, food supplements, and all of the associated deceptions would find very few takers. In its place, a vast new industry would arise aimed at producing and distributing wholesome, healthful foods to satisfy a huge market of enlightened consumers.

Closer to nature in food consumption patterns, aspiring confidently to a longer and richer life, man could be helped to find more peace within himself and in all his human relationships as the benefits of a longer, healthier life begin to alter his existence.

Unfortunately, the profound changes projected in this visionary picture, which would occur as masses of individuals, broad institutions, and whole industries reoriented to the diet reforms and their social impact, are not likely to be fully realized in our society, even in decades to come. Such a basic restructuring will not come easily, desirable though it may be.

Some of the resistance to these changes comes, of course, from the medical profession itself. A major theme which pervades these pages has been overt and implied criticism of the majority of the medical profession for its failure to utilize the knowledge well-established by decades of field, clinical, and laboratory studies that ties the degenerative disease epidemic to our Western diet.

One reason so much confusion exists in the medical profession on how to treat degenerative diseases is that it is basically a nutritional problem. Physicians, unfortunately, are not trained in nutrition, and on that ground cannot be entirely blamed. At the 1969 White House Conference on Food, Nutrition, and Health[1] in Washington, D.C., the nutrition experts stated, "the teaching of

nutrition in schools of medicine is most inadequate at the present time; in some schools it is almost nonexistent."

Nonetheless, the responsibility resides with the medical community to protect our health. Fundamentally, fault is not found with treatment for a particular degenerative disease, or a certain drug, or any minor aspects of therapeutic practice. Our criticism is more sweeping. The position we take is that if the entire medical practice of elaborate diagnostic techniques and methods of management of the various degenerative diseases were destroyed and all knowledge of these were lost, the advanced nations would be far more healthy than they are today--if instead they were to follow the diet and exercise recommendations in this book.

Before the reader smiles at this statement, reflect upon the "cures" of the past when physicians were just as confident that the therapy they practiced was serving their patients' best interests: Pneumonia treatments for 2000 years[2] have almost without exception hastened the death of those unfortunate enough to be able to afford a physician.

In 230 A.D., Galen advised blood letting and the practice continued until modern times. In 1835, it was formally demonstrated that the practice of bleeding was of no benefit, but this ritualistic procedure persisted for almost another 100 years and even today is recommended in two leading American medical textbooks. How much precious life's blood was spilled over hundreds of years, and in every case, the treatment had to worsen the prognosis.

Other treatments have included the inhalation of chloroform; subcutaneous injections of gold, silver, and platinum solutions; orally administered preparations of mercury, quinine, and digitalis; and countless other damaging regimes from harsh physics to harsh whiskey. These treatments were abandoned over the years when their inefficacy became apparent. In the case of digitalis, which was routinely used to "support the circulation", it was shown by a controlled study in 1930 that the death rates were greater when it was used.

If the reader believes that science is too advanced today for such absolutely mistaken judgment, one need only remember thalidomide--the innocent sleeping pill--and its creation of thousands of deformed children.

Although many of the teachings set forth in this book are advocated by a group of leading physicians, most medical professionals are unaware of the supporting studies they cite, or are unconcerned by the arguments. This despite the fact that those supporting the basic dietary approach have long argued their case before their colleagues in talks and addresses at medical meetings and in their published studies and statements.

Dr. Will Connors of the University of Iowa Medical School has for years been a spokesman for this point of view. Dr. Jeremiah Stamler of Chicago, another advocate, stated: "If one takes the two alternatives...in dealing with a coronary epidemic that is killing 650,000 persons a year--to leave the American diet as it is or to make changes--then it is my best medical judgment that we must make changes. We have waited too long already."(3) Dr. Ancel Keys said, "In all populations and situations, serum cholesterol and blood pressure are major factors in etiology. Unless there are sudden and unexpected changes in the picture, there is no prospect that a quarter century of epidemiological work will have produced a dent in the frequency of heart attacks and coronary deaths."(4)

Dr. Keys,(5) in analyzing various prospective studies, concluded that as cholesterol rises, so does coronary heart disease, and that there is no critical bottom level where the benefit stops. "In regard to serum cholesterol concentration, the lower the better. Since there is no penalty from other disease or other disadvantage associated with cholesterol levels lower than the current average in the United States, the inference is that a large fraction of the whole American population should be candidates for serum control if safe and otherwise acceptable means are available."

The safe means without unknown side effects can only be diet. Other nations have started to move in this direction.

On May 3, 1968, an official recommendation[6] on diet changes was issued in the Scandinavian countries. Their principal changes were: 1. Reduction of total calories in fat from 40% to 30%. 2. Reduction of sugar and simple carbohydrates. 3. Increase of complex carbohydrates. 4. Reduction of saturated fats.

In 1972, the East German government[7] announced changes to be completely in effect by 1975. These included: 1. Reduction of total calories of fat to 30%. 2. Reduction of sugar and simple carbohydrates. 3. Reduction of saturated fats. 4. General changes to reduce cholesterol levels.

And in the United States,[8] Dr. Paul Dudley White, at 86-years of age, hasn't given up. He has abandoned hope of changing the parents and is starting on the children. A year's course, "Prescription for Life" was given to 310 eighth graders in New York. After the lecture on diet and heart disease, one child exclaimed; "My mother is killing me, making me eat two eggs and bacon and toast and butter for breakfast."

People in advanced countries cannot wait a hundred years for the education and gradual evolution of the dietary changes that must come to stop the epidemic. As individuals, we need not be helplessly bound by the constraints that impede social change; we can choose today to make those reforms in our daily lives which will bring us extended lives, better health, and greater happiness. As a society, the millenium may never be reached, but whether lay people or medical professionals, we are free to reach for it in our own lives. The purpose of this book is to make the information you need available to you. You can start today with the changes!

AFTERWORD REFERENCES

1. Frankle, R.T., et al. Nutrition Education in the Medical School: Experience With an Elective Course for First Year Medical Students. Amer. J. Clin. Nutr. 25: 709-19, 1972.

2. Dowling, H.F. Frustration & Foundation. JAMA 220: 1341-5, 1972.

3. Deutsch, R. Family Guide to Better Food & Health - Meredith, 1971.

4. Keys, A. Bleak View Given of Progress in Preventing Heart Disease. Med. Trib. 12-4-69.

5. Keys, A. Minnesota Symposium on Prevention in Cardiology. Minn. Med. 52: 63-67, 1969.

6. Official Collective Recommendation on Diet In The Scandinavian Countries. Nutrition Rev. 26: 259-63, 1968.

7. Noack, R.E. Germany Plans to Make Changes in National Diet. Med. Trib. 6-21-72.

8. Editorial - Stop Ma - You're Killing Me. Med. Trib. 6-28-72.