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PANEL DISCUSSION ON LIPID METABOLISM IN CARDIOVASCULAR DISEASE*

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MODERATOR WILKINSON: At a preliminary meeting, we tried to reconcile our differences of opinion and found that, although we had many points of agreement, we also had many points of disagreement. Perhaps for this reason this particular panel was chosen.

We decided to ask each other questions, unless you have questions to ask us.

We shall start with a subject about which there has been much controversy—the vegetable sterols. There is a difference of opinion here. I shall ask Dr. Kinsell to tell his experience with vegetable sterols.

DR. KINSELL: We have used vegetable sterols only under experimental conditions in the metabolic ward and have not made any studies of them in the last two years. In the phase of the work in which we were trying to determine the common denominator in the cholesterol-lowering effect of a variety of vegetable fats, we gave huge amounts of vegetable sterols, including sitosterol, mixed soy sterols and other forms, up to 60 Gm., which is a great deal for persons on constant diets. In some instances, there were cholesterol-lowering effects, presumably attributable to interference with absorption of either endogenous or exogenous cholesterol, or both, but these effects were rarely of great magnitude. They were unpredictable, and for this reason, we have not continued work in this field.

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MODERATOR WILKINSON: Dr. Stare, would you care to speak on this question?

DR. STARE: No one in our laboratory has had first-hand experience with vegetable sterols.

MODERATOR WILKINSON: Dr. Pollak?

DR. POLLAK: I should like to speak on this question, because I started this whole business.

It is of value to try vegetable sterols. I cannot predict whether anyone will respond or not. Some reports are favorable, others not. From the records, those in favor have it, so far. I should like to ask whether there is anything better to reduce the blood cholesterol level, assuming that you believe it to be desirable.

MODERATOR WILKINSON: Dr. Keys?

DR. KEYS: Our own experience is quite limited. The change usually occurs following ingestion of a somewhat substantial amount of vegetable sterol—20 to 30 Gm. per day. There is usually a statistically significant lowering with an average daily ingestion of 15 Gm. of mixed sitosterols. This does not seem very interesting to us. We have stopped this work for the same reason as Dr. Kinsell.

MODERATOR WILKINSON: Dr. Epstein, have you had any experience with this?

DR. EPSTEIN: We have had no experience.

DR. STARE: Dr. Wilkinson, may I make a statement on that? Clinicians around Boston with whom I have talked are not enthusiastic about it. They tend to compare it with resin therapy—a form of treatment that was occasionally used in an attempt to lower the sodium level. You have to take 10, 12, or 15 Gm. of this material with each meal, and also if you have a snack in the afternoon or evening. In other words, it has to be taken every time you eat food. From a practical standpoint and in view of the uncertainty of results and the cost of medication, it is not practical for most patients.

MODERATOR WILKINSON: I might add that in our laboratory we tried every method of administration from mixing it thoroughly with an artificial diet to giving it fifteen, ten or five minutes before the meal. We also gave it in a wafer to be taken every hour while awake.

We had difficulty securing the ingestion of more than 20 or 25 Gm. per day. We found no predictable good results. In some people there seemed to be an initial drop in the cholesterol level that we could not sustain. None of the decreases differed from the cyclic variations seen during a three-year control period in these patients.

I agree with Dr. Stare that it is an impractical way to take medication. On the basis of our results, we believe that not only is it impractical, but not a justifiable way to reduce cholesterol concentration.

MODERATOR WILKINSON: Are there some questions from the audience, or shall we talk among ourselves?

SPEAKER: I should like to ask Dr. Keys whether he believes a deficiency of certain unsaturated essential fatty acids is as important in the pathogenesis of atherosclerosis as an excess of saturated fats?

DR. KEYS: I know of no way in which that question can be answered, at least not in the form in which it was posed.

I presume that we are talking about atherogenesis and not about cholesterol. As far as I know, there is no evidence for anything about atherogenesis in human beings that would be pertinent to that question.

With reference to blood cholesterol concentration, we know that some of the more unsaturated fatty acids are what might be called anticholesterol agents. This is in the sense that they do not induce the increases in cholesterol level that are associated with the ingestion of certain more saturated fats, but there is by no means a regular relationship to the degree of saturation. What this means in terms of atherogenesis in man, we do not know.

MODERATOR WILKINSON: We had agreed not to use the word "anticholesterol."

We should like to say, rather, that a hyper- or hypocholesterolemic effect is all that has been noticed with any of these agents. It does not imply a reduction in the endogenous manufacture of cholesterol.

Dr. Kinsell may be able to add something.

DR. KINSELL: The matter of the effect of different kinds of fats represents an area of great interest to us, both fundamentally and clinically. However, I should like to emphasize a statement made by other members of the panel, and which I am sure will be made again, to the effect that in the intact human being, unfortunately, we lack adequate means for short-term evaluation and even less than adequate means for long-term evaluation of what takes place within a blood vessel.

We can measure lipids and all sorts of things in the plasma. The general working hypothesis of almost everyone in this field is that, if one has a choice between a regimen that will produce a low cholesterol level in the blood and one that will produce a high cholesterol level, he takes the regimen that will produce a low level and hopes that this will be good in terms of prevention or progression of the lesion. Much time and work must be devoted to the problem before this is more than a hope.

With that as a baseline, one can say without hedging that the ingestion of a sufficient amount of essential fatty acids (meaning fatty acids of the linoleic or arachidonic acid series, the doubly and quadruply unsaturated fatty acids) under appropriate circumstances will be associated with a decrease in the concentration of blood cholesterol. Moreover, if given in sufficient amount and with appropriate other features in the diet, the decrease in the cholesterol level will be profound. We first noted this in 1951 and have had ample evidence of it since. It has been confirmed by many people. The mechanism is still unclear.

One of the important things for all of us to keep in mind is that cholesterol, which on occasion has been regarded as a very bad "boogy man," is found wherever there is animal life, and as such it undoubtedly has an important physiologic role. Therefore, when approaching this problem, one of the big jobs is not to determine how to get rid of cholesterol, but to determine the normal role of cholesterol and the rules of the game. Then we shall know what to do about the favorable modification of abnormal situations or, better still, the prevention of abnormal situations.

In a chemical sense, there are 3 major lipid materials in the blood. There are other lipids, too, but we shall talk only about these 3. The first is triglyceride,

the glycerol molecule with 3 molecules of fatty acid attached. As far as we know, the make-up of the triglycerides probably varies under normal conditions and bears a significant relationship to the particular diet that is being consumed.

Our working hypothesis is as follows: Triglyceride probably serves as the major source of fuel that keeps the body running throughout the twenty-four hours. This means, then, that a great deal of fatty acid has to be moved around and that the transport of fatty acid is a high-priority situation. Therefore, in an economy noted for overlapping in terms of safety factors, there will be several ways of doing the same thing. The phospholipids also are part of the transport system for fatty acids. For reasons that we do not understand well as yet, one of these fatty acids normally is probably an essential fatty acid.

To run smoothly, the phospholipid must have one essential fatty acid and one nonessential fatty acid. It is the nonessential fatty acid that is constantly being burned and replaced. The essential fatty acid may well be associated with the way the phospholipid fits into certain enzyme systems. As the phospholipids are constantly being broken down and replaced, there has to be a refurbishing of the essential fatty acids, and possibly this is where cholesterol esters are introduced.

This means, then, that the essential fatty acids are just what the name implies. They are vitamins, *i.e.*, they are things that you either get in your diet or you don't get at all, because you cannot make them from other sources. The more saturated acids can be made from the less saturated acids but, once things get below the stage of linoleic acid, nothing can be made above that level. As you know, linoleic has two double bonds.

Since fat and water do not mix, and since fatty acid and these other lipids have to travel around in an essentially aqueous medium, there must be a variety of vehicles to prevent the formation of clumps of fat and consequent fat embolism. The main job of the lipoproteins is to make fat soluble.

MODERATOR WILKINSON: In fairness to our audience, we might point out that when Dr. Kinsell uses the word "essential," it does not imply unanimity of opinion among the investigators in the field. The amount of fat-soluble vitamins is smaller than the amount of fatty acid, saturated or unsaturated, that we are discussing. I do not mean to criticize the term "essential," but I want to point out that many people would prefer to use saturated versus unsaturated rather than essential versus nonessential.

I should like to ask Dr. Stare to talk about this question as he is the only man I know who is illogical enough to cure xanthoma by intravenous feeding of fat.

DR. STARE: Dr. Kinsell used the phrase "under appropriate conditions." This is an important phrase. Under such conditions, one can reduce the serum cholesterol level. These appropriate conditions are, tube feeding, which Dr. Kinsell frequently uses, or formula diets. Formula diets do not consist of meat, potatoes and string beans; they are mixtures of corn oil, sucrose and skimmed-milk powder. Three leaders in that field have been Kinsell, Bevredge in Canada, and Ahrens at the Hospital of the Rockefeller Institute. Under these "appropriate conditions"—the incorporation of large amounts of oil with an unsaturated

fatty acid—it is possible to reduce the concentration of serum cholesterol. Dr. Kinsell has now approached more realistic conditions, in that he has a modified feeding formula; that is, he has a certain type of breakfast and a certain regimented food program. The point I am leading up to is that I know of no evidence which indicates that an appreciable lowering of cholesterol concentration will result if we substitute rather generous amounts of corn or cottonseed oil for the usual amounts of butter, margarine, peanut butter, animal fat or mayonnaise, as an accompaniment of our customary diet of meat, beans, potatoes and grapefruit.

From an experimental point of view, here are some positive results. As Dr. Kinsell showed us this morning, it has been possible in some patients to reduce cholesterol concentration from around 400 mg. to about 270 mg. per 100 cc. In 1 patient, the value was around 260 mg. per 100 cc., and that is quite a reduction. However, I know of no evidence to indicate that, if you add these oils to an ordinary diet in any reasonable quantity, the same thing will take place.

MODERATOR WILKINSON: Is there another question from the audience at this point?

DR. JOLLIFFE: I should like to ask the panel whether there is any way to make a plasticized fat from corn oil, as is done in industry, without destroying its effect in lowering the blood cholesterol level. I know that a fat can be plasticized and remain unsaturated, but can it be plasticized without destroying its effect on the serum cholesterol level?

MODERATOR WILKINSON: I take that to mean, can one hydrogenate up to a point where it is a white fat and not a liquid one. Is that correct?

DR. JOLLIFFE: No. Do you have the *cis* forms and the *trans* forms, or can you leave the unsaturated bonds in these fatty acids, plasticize them, and have them remain almost as unsaturated as before? I have seen no evidence that these fats do not continue to elevate the serum cholesterol level, just as though they were hydrogenated.

MODERATOR WILKINSON: Dr. Stare, would you like to answer that?

DR. STARE: I obviously do not know much about it because I do not understand the term plasticize. The only thing I can say is that I have been told by manufacturers of shortening that they can control the degree of hydrogenation. Little is known about whether or not the isomers that are formed during hydrogenation affect the cholesterol content. As far as I know, the matter has to be limited largely to a discussion of the effect of linoleic acid, much less that of arachidonic acid. There are a few unpublished studies that show that the isomers formed in this reaction have no effect. Dr. Keys mentioned these to me, and perhaps he should tell you about them.

DR. KEYS: I would not want to say much about that question. This is a popular subject to talk about on the basis of no knowledge at all. To my knowledge, at present at least, no one has published or publicly produced evidence that there is any difference whatsoever in the effects of the *cis* and the *trans* forms. That can be stated flatly. Perhaps theoretically *cis* is better than *trans* or vice versa, if you happen to like those configurations but there is no evidence

as yet that these differences are biologically reflected in man. We want to investigate that problem.

I am interested, however, in the question as to whether we are talking about linoleic acid or unsaturation, because they are not necessarily the same thing. Some natural food fats contain considerable linoleic acid. Others have little and may still be more unsaturated than the first. Corn oil is an example of an unsaturated fat that has a fairly large amount of linoleic acid in it. We have made comparisons under rigidly controlled conditions. In the same subjects the regimen was changed from corn oil to sunflower-seed oil (which contains more linoleic acid and is much more unsaturated), or from corn oil to sardine oil (which contains no linoleic acid and little arachidonic acid, but is extremely unsaturated). Under controlled conditions, we invariably found that a change from corn oil to one of these fats caused a rise in the average serum cholesterol level. When people maintained on these fats change to corn oil, the cholesterol level falls.

MODERATOR WILKINSON: Dr. Kinsell, will you tell us what your experience has been?

DR. KINSELL: Going back to the matter of the term "unsaturated" versus "essential"—I personally do not use the term "essential" with any intent to indicate that we must have a pound of this a day, but rather to indicate that it is something which by definition one does not synthesize from other sources. You get it from your food, or you do not get it. It is different from oleic acid, for example, which is a single-bond acid that can be made from all sorts of things, but which is not in the "essential" category. Then there are other saturated or unsaturated substances which we know little about, as some of the other panelists have indicated, and which may not have the same effects as linoleic or arachidonic acid. This is an area where much work remains to be done.

As for relating the effects of an oil or a fat to its content of this so-called essential fat—specifically, linoleic acid—over the years we have carried out studies with safflower-seed oil, cottonseed oil, soybean oil, corn oil and a great variety of oils, and have found that safflower-seed oil per unit of volume will do more than will an equal volume or weight of corn oil. Roughly, this difference in effect is related to the difference in linoleic-acid content.

Recently, we carried out studies with ethyl esters of the fatty acid, that is, compounds with an ethyl radical attached to a simple fatty acid and free, or nearly free, of all other contaminants. In 1 instance, a batch of material of a very high degree of purity produced the same type of change. As far as the data go, these changes appear to be related to the amount of linoleic acid. This probably does not mean that there are not other things in oils which are of importance. In view of all of the interest in essential fatty acids and so forth, I should like to warn against any undue enthusiasm. You will recall that not long ago cholesterol was regarded as a poison to be kept out of the diet at any cost.

We do not wish to have anyone believe that we think that essential fatty acid is the entire answer to the problem of atherosclerosis or to lipid metabolism. That it is an important phase is beyond question.

MODERATOR WILKINSON: I might point out that there is relatively little linoleic acid in mother's milk. Is that not correct?

DR. KINSELL: It is correct that the amount varies with the intake.

MODERATOR WILKINSON: Dr. Keys.

DR. KEYS: In our comparison of 3 fats under rigidly controlled conditions and with metabolic balances, we observed changes in the concentration of serum cholesterol in 26 men. The differences between the levels in the groups fed corn oil, sardine oil and sunflower-seed oil were significant statistically, but whether they were biologically important or not is something else. When the corn oil in a diet was changed to the same amount of sardine oil, the serum cholesterol level rose. In terms of the degree of saturation, sardine oil is much more unsaturated (with a number of 186 in this particular case) than corn oil (with a number of 120).

Similarly, with sunflower-seed oil (our particular batch runs 61 per cent linoleic acid and has the number 140 or 141)—the cholesterol level rose in association with the increase in the intake of linoleic acid and fell with the decrease in intake which occurred in changing from sunflower-seed oil to corn oil.

In experiments with safflower-seed oil (78 per cent linoleic acid) we obtained similar results. If we replaced corn oil with safflower-seed oil, the cholesterol level did not fall. We have done this in both directions.

MODERATOR WILKINSON: I should like to point out that these changes are significant in the statistical sense but, at least as far as the moderator is concerned, they have little significance in the clinical sense.

DR. STARE: It might also be pointed out that the changes Dr. Keys mentioned took place in some 20 people when they were eating meat, potatoes, string beans and grapefruit. He could have shown, as Dr. Kinsell has shown for some years, that if you incorporate these oils into formula diets, or into tube-feeding diets, the changes are much more profound.

DR. KEYS: These diets involve 100 Gm. of experimental fat per day.

MODERATOR WILKINSON: Is there another question from the audience?

DR. KINSELL: With regard to Dr. Wilkinson's statement, may I say again that we would not regard the magnitude of these changes as being significant in a biologic sense.

DR. NATHANSON (from audience): I am a bit flustered. We have had a discussion of acids, and to me it seems that we are discussing something that is present. I, and maybe others, should like to know the opinions of the panelists as to what causes this hypercholesterolemia. We think of androgens and the metabolic activities in the various tissues of the body. However, it would interest us more to have a discussion of the biochemistry of lipid metabolism. I have a certain concept, which may not be totally accepted. I believe that altered lipid metabolism is based upon altered carbohydrate metabolism. As for the biochemistry—in the degradation involved in the transport system and the breakdown of lipids, eventually these compounds have to enter the acetoacetic-acid cycle. In the oxidative phase, there may be some alteration or delay, which accounts for the increased cholesterol content in the blood.

Another point that strikes me is the blanket use of the word cholesterol. Are we to disregard the S_f theory, the S_f-1020, and so forth?

MODERATOR WILKINSON: Yes, I think that we can disregard it.

DR. NATHANSON: We have been taught that theory so long that I should like to know the opinion of the panel today and to have some discussion concerning the chemical basis for hypercholesterolemia, so that we may plan an attack that way.

MODERATOR WILKINSON: I think Dr. Epstein can give us at least one basis for a high versus a low blood cholesterol level. Dr. Epstein.

DR. EPSTEIN: I think I can give at least one reason why serum cholesterol levels may become elevated and one reason why this would seem undesirable. May I also say a few words about atherosclerosis in general because it is this disease primarily rather than the serum cholesterol level, which we wish to control. The concentration of serum cholesterol is determined by multiple factors and so is atherosclerotic disease. In fact, all diseases, including the infectious ones, have multiple causes. As Dudley pointed out twenty years ago, these causes may vary in relative importance, according to space and time. This epidemiologic viewpoint is distinctly relevant to the current discussion. Our approach to this problem depends on the kind of population and the levels of dietary intake. I am convinced that if one compares populations that differ *widely* with regard to fat intake (and possibly in other dietary constituents), they will also differ widely with regard to serum cholesterol levels. The most important single determinant of the amount of atherosclerosis found in such a population may be the quantity of dietary fat. This is Dr. Key's basic theory. To my mind, this is established.

The difficulty comes when we consider a country like the United States where, in general, everybody eats a high fat diet, has a fairly high blood cholesterol level, and has a considerable amount of atherosclerosis. Yet there is good evidence that, within this country, there are marked differences in the frequency of atherosclerosis and probably even differences in blood lipid levels among different population groups. The question arises whether factors other than lipid levels and diet come into play in these situations. In a study we carried out in New York City among clothing workers of Italian and Jewish extraction, we found that Jews had twice as much coronary heart disease, even though their diet differed relatively little from that of the Italians. We were also able to show that this could not be explained solely in terms of the lipid levels among these two groups; other population groups may behave differently.

In this context, it would seem important to decide upon one's aim, when considering dietary or other kind of management of lipid levels. It is becoming obvious that one can change these levels in a number of different ways, more or less successfully—but what magnitude of change would be necessary to affect the prevalence of atherosclerosis?

Let us take 2 population groups, one of which has an average serum cholesterol level of 230 mg., and the other a level of 200 mg. per 100 cc. It is fair to say that people with serum cholesterol levels habitually below 200 mg. per cc. do not have atherosclerosis as often as people with serum cholesterol levels

above 200 mg. It is also fair to say that American populations in general have mean serum cholesterol levels around 230 or 240 mg. per 100 cc. If we assume a standard deviation of 30 mg. per 100 cc., it is obvious that in the population in which the mean level is 230 mg., only 16 per cent of the population will have levels below 200 mg. Consequently, a large proportion (84 per cent) of the population will have potentially atherogenic levels. In a population in which the mean level is 200 mg., as much as half the population will have serum cholesterol levels below 200 mg. Thus, if the concentration of serum cholesterol were the only important determining factor, one might on that basis alone expect a profound difference in the prevalence of coronary heart disease among these 2 population groups whose serum cholesterol levels differ by only 30 mg. per 100 cc. This is the order of magnitude of the change that might be achieved by lowering the dietary fat intake.

Among American population segments whose mean serum cholesterol levels are between 230 and 240 mg. per 100 cc., it may be assumed that a change of 30 mg., or something of that order, will cause appreciable alteration in the prevalence of coronary heart disease. Future epidemiologic studies will solve this particular problem, rather than acute dietary experiments.

MODERATOR WILKINSON: I might summarize this, and then call upon Dr. Stare. It is more or less the consensus of the panel that in discussing changes in blood lipids, the alpha and beta lipoproteins and the concentration of beta-lipoproteins furnished by the S_f values, we are concerned with laboratory theoretic desirable or undesirable changes which will produce atherosclerosis if a diet or a regimen is modified to a considerable degree. Dr. Stare.

DR. STARE: In order to try to answer or comment on Dr. Nathanson's question, I have jotted down a few things which seem to be involved in the causation of atherosclerosis.

There are, certainly, genetic factors. I do not know what we can do about them except to recognize their existence. It has been well established that certain body types favor the development of coronary artery disease. It probably makes little difference how much atherosclerosis one has as long as he does not get a cerebral or coronary thrombosis. The structure of blood vessels has something to do with the development of plaques. As far as I know, this is something that may be on a genetic basis and we cannot do much about it. Let us say, therefore, that genetic factors are involved in this disease, as they probably are in many diseases.

Secondly, estrogens are involved. It has been shown that the level of circulating lipids in the blood stream can be influenced by estrogen therapy. Everyone is well aware that this disease is far more prevalent in the male than in the female, until five or ten years after the menopause when the incidence in the female increases. Experimentally, there are differences among animals. In many cases, the human sex difference is reversed. The female rabbit and the female rat are more susceptible to the experimental production of atherosclerosis than the male. Therefore, estrogens must have something to do with the things that we measure in the blood which supposedly are related to this disease.

The third is diet. Experimentally, half a dozen or more nutrients have been

shown to bear a relationship to the development of atherosclerosis. There also is the question of calories—not only the source, but the amount of calories, because of changes in body weight. In the field of nutrients, fat is being experimented with far more than other nutrients. However, I should like to mention a few of the others that have been studied experimentally.

In our laboratory, we have shown that diets high in sucrose favor the retention of cholesterol in the rat. In other words, there is not only the question of where the cholesterol is coming from and how much is coming, but how much cholesterol is being eliminated. We get rid of cholesterol by the excretion of bile acids. Dr. Portman in our laboratory showed two or three years ago that when the source of carbohydrate in rat diets was changed from sucrose to starch, the animals excreted more bile and got rid of more cholesterol during periods of high starch diets than during periods of high sucrose diets.

One of the usual differences between the diets of primitive groups of people, among whom this disease is relatively rare, and the diets of Americans is the source of carbohydrate. Primitive peoples tend to live off roots. Root vegetables furnish a diet high in starch and low in sucrose. American diets tend to be high in sucrose and lower in starch.

Pyridoxine came into the picture from the original or early studies wherein the late Dr. Reinhart produced a type of arteriosclerosis in monkeys with pyridoxine deficiency. The biochemists have shown that the conversion of linoleic acid to arachidonic acid requires pyridoxine.

In some unpublished studies that my colleague Dr. Waddell has been making at the Massachusetts General Hospital with substantial numbers of people (50 or 60), it was found that administration of huge doses of pyridoxine (about 100 mg. three times a day) caused a marked lowering in the serum cholesterol level. To some extent, this is similar to the report published a few months ago from the Mayo Clinic. They reported the same thing with the use of tremendous amounts of niacin.

Protein metabolism is clearly implicated in the development of atherosclerosis in the experimental animal. We have shown it in the monkey—an animal susceptible to increases in blood cholesterol concentration. If the protein in the diet of the monkey is what is called an "alpha-protein" (derived from soybeans) which is low in organic sulphur, methionine and cystine, and these sulphur compounds are added to the diet, the serum cholesterol level either is not raised or it tends to go down. We have shown the same thing in rats, as published a month ago in the *Journal of Experimental Medicine.* However, these observations on protein in 2 species of experimental animals are not in accord with the observations in man.

In this country, where we have a great deal of coronary artery disease and atherosclerosis, we tend to have an abundance of good-quality protein in our diet. On the other hand, the people of South Africa, Guatemala, Nigeria, Italy and other places, who have a low incidence of this disease, generally have a far lower intake of protein than we do, and it tends to be more from vegetable sources than animal sources as compared with our diet.

Another thing that might be emphasized is that the production of infarction in experimental animals is rare. There are all kinds of reports about the experimental production of atherosclerosis, but relatively few about the production of infarction. In 3 or 4 reports in the literature, the authors claim to have found extensive infarcts in a few of their animals. In our paper in the current issue of the *Journal of Experimental Medicine*, we referred to 1 animal in which there was an extensive infarct; 1 animal among 50 or 60 is not many. I mention this in order to point out that one of the deficiencies of animal studies today is the lack of a procedure or technic to cause infarction.

We have shown in some acute studies in a few people that gaining or losing body weight is a factor that has something to do with the regulation of cholesterol metabolism. Dr. Keys, on the other hand, has shown in nonacute studies with large numbers of people that exercise is a relatively minor matter in regulating cholesterol metabolism. We both agree that it is a factor.

We end up with the fact that atherosclerosis is an important disease, particularly to the American public and to American males. It is a disease subject to experimental attack. It is being attacked, and there have been some advances in the last few years. Involved are the factors of genetics, sex hormones, and diet. An interesting question to ask is whether or not this disease can be prevented. The answer is yes, it can be prevented. What is the evidence? The evidence is the fact that there are millions of people in this world that do not have this disease, which means that it must be preventable!

MODERATOR WILKINSON: Are there any further questions from the floor?

SPEAKER: My question is, what about the thyroid? I should have included that when I mentioned estrogens.

DR. STARE: I should have said that the thyroid hormone has something to do with this, because you can affect the circulating lipid level by the administration of thyroxine, and the level tends to be high in people with hypothyroidism. Experimentally, you can also affect it to a slight degree by administering thyroid hormone.

MODERATOR WILKINSON: Thyroid is wonderful for conditions in which there is a lack of normal hormones. No good clinical evidence has been presented to show that an excess of thyroid is beneficial. Dr. Kinsell, would you like to speak on that?

DR. KINSELL: There is evidence that pharmacologic amounts of thyroid, or related material, will under appropriate circumstances produce a fall in the concentration of blood cholesterol, but I do not think that this is in any way synonymous with the thought that it is a good therapeutic measure, particularly in the group of people who have poor circulatory status initially. If one superimposes an iatrogenic hyperthyroidism, the cure is potentially worse than the disease.

MODERATOR WILKINSON: In 1947 or 1948 at the University of Michigan, we carried out an experiment wherein 6 people, one of whom was myself, became toxic on exogenous thyroid but maintained a normal weight. In none of the 6 persons studied was there a fall in blood cholesterol concentration.

My laboratory has also reported cases of hypercholesterolemia of the familial type, in which there was clinical hyperthyroidism showing no relation to the level of the blood cholesterol. It is true that if a person becomes very thyrotoxic and loses a great deal of weight, the cholesterol level will fall a little.

SPEAKER: I should like to hear the panelists discuss the statistics on blood cholesterol a bit more. For instance, Dr. Epstein noted that at levels of 230 and 200 mg. per 100 cc. or slightly below, there is a statistical difference between 2 population groups. If the difference, say, amounts only to a ratio of 1:2, that may be 100 per cent. What is the relationship when there is a difference of 400 per cent or 1000 per cent—as in Italy where the death rate from coronary artery disease is about one-fourth of ours, or as in Japan where the death rate is only one-tenth of ours. I should like to know more about the situation where there is a different relationship.

MODERATOR WILKINSON: Dr. Epstein, would you like to take that?

DR. EPSTEIN: If there were some way to reduce blood cholesterol levels in this country to the levels that are found, say, in Japan or in various other countries with a low incidence of atherosclerosis, the prevalence of atherosclerotic disease could probably be markedly lowered. As a matter of fact, looking at the data from the cooperative study on lipoproteins, it is evident that there is a marked difference in disease incidence between groups having high and low cholesterol levels. The only trouble in this country is that so few people have low levels.

I think that if there were some way to lower blood cholesterol levels significantly, it would make a striking difference.

DR. POLLAK: There is really no parallelism between high cholesterol levels and atherosclerosis. Let's not fool ourselves. We overemphasize the blood cholesterol level. There is a correlation in familial hypercholesterolemia—a condition in which there is a high incidence of atherosclerosis and complications of the disease, namely, coronary occlusions in young people. By and large, however, the correlation is not clear-cut.

I was happy that Dr. Stare brought up the question of other nutrients and pointed out not only the importance of quantity, but of quality. He mentioned unsaturated fatty acids, methionine, pyridoxine, and so on. I do not believe that everybody in this audience has a lack of unsaturated fatty acids, plant sterols, pyridoxine, nicotinic acid, tocopherol, or methionine. Still, almost every one of us has a considerable degree of atherogenesis, *i.e.*, plaques, in some of our arteries, and some of us here may have had a complication such as infarction. Maybe it is not only what we do *not* eat, but what we eat too much of, that matters. The ratio between unsaturated and saturated fatty acids in our diet may be wrong. A surplus of certain fatty acids may be just as bad as a lack of unsaturated fatty acids.

When we speak of the different factors causing atherosclerosis, we should not overlook the probability that this is not a disease of blood lipids and blood vessels alone, but a disease of the whole body. When a correlation is attempted, it becomes evident that there is an increase of clinically manifest atherosclerosis

with increasing age. There is enzymatic deficiency in aging, and there is liver dysfunction in aging. These may be within what we call physiologic limits, but possibly contributory to the deposit of lipids.

I am not sure that we should attempt to decrease blood cholesterol concentration. Maybe we can prevent the deposition of cholesterol in some other way. Maybe stabilization with albumin, phospholipids, or SH-compounds will provide the answer. It has been shown in experimental animals that the precipitation of lipoprotein molecules can be prevented.

MODERATOR WILKINSON: Dr. Stare has an engagement and must leave at a certain time so I should like to give him a chance to comment at this time.

DR. STARE: Some of our data which have not as yet been published, but which were recently accepted for publication in the *American Journal of Medicine*, show that there is a distinct difference between the cholesterol levels of young males who have infarctions and those who do not have infarctions. My comment on the question that someone raised about the effects of the cholesterol level is that I firmly believe that the level of serum total cholesterol does furnish a measurement of the degree of atherosclerosis. The reason is this: atherosclerosis has been produced experimentally in 6 or 7 species, including the monkey. The only way it has ever been produced is through some mechanism for elevating the concentration of serum lipids, including cholesterol. In the rat studies that we report this month in the *Journal of Experimental Medicine*, the cholesterol levels were in the range of 1000 mg. per 100 cc.—tremendous concentrations that we worked out by a dietary technic to produce atherosclerosis. Why? Because we wanted to do something in the hope that we could produce atherosclerosis. At such concentrations, there is no correlation between the degree of atherosclerosis and the serum cholesterol level, but we are working with levels of 800, 1000 and 1500 mg. per 100 cc.

We have found during the last year or so, in studies that are not yet published, that when we work at much lower cholesterol levels—150, 200 and 225 mg. per 100 cc. (modest elevations compared to the normal range in the rat of 70 to 90 mg. per 100 cc.)—there is clear-cut correlation between the degree of hypercholesterolemia and the extent of the atherosclerotic lesion at necropsy.

I am sure that others have published similar data, so I would say almost without a shadow of a doubt that measurement of the serum total cholesterol level today is the most important single laboratory determination we have for use in trying to evaluate whether a person has, or is developing atherosclerosis.

DR. POLLAK: Would you qualify that and say especially in the lower age group and much less in the older age group?

DR. STARE: Yes, I would.

MODERATOR WILKINSON: It is fair to point out that when Dr. Stare tends to say that this is an index of atherosclerosis, he does not mean in the patient sitting across the table from him. If you choose almost any level of blood cholesterol, or S_f molecules, or blood rhubarb, whichever you want to take, you will find that false positives will far exceed the cases you diagnose correctly.

It is pertinent to mention the long-term studies of Patterson and his group in Western Ontario. They did not find a correlation between the level of blood cholesterol and the degree of atherosclerosis present at necropsy.

It is also of interest that in young persons the average values for blood cholesterol concentration frequently include extremely high levels—as in xanthoma patients, who are much more likely to get atherosclerosis than the person with a modest elevation of cholesterol. Dr. Keys, you probably would like to say something here.

DR. KEYS: I am not quite sure whether we are agreeing or disagreeing about something, and whether this is what the audience wants us to discuss. I agree with Dr. Stare that at present most of us in the field think that determination of the blood cholesterol concentration is the best single measure we now have. If this measurement is carried out in large numbers of people, it can help us to make much better guesses regarding prognosis, as a statistical proposition. At the same time, I emphasize that we cannot make an accurate prognosis or diagnosis with any of these measurements at present.

One difficulty that should be stressed again and again is that we, the American public today, are in general a hypercholesterolemic population already afflicted with atherosclerosis. To try to decide *which* person will be the first to show clinical consequences of this basic fault is rather a foolish proposition, I believe.

MODERATOR WILKINSON: Dr. Kinsell?

DR. KINSELL: Amen, to the last comment and to most of those that preceded it. In masses, fine; but in individuals, we have no "Wassermann" that tells who is going to have a coronary thrombosis or when. May I now or later say something about estrogen?

MODERATOR WILKINSON: At this point, it might be wise to hold that to see if we have a question from the floor.

SPEAKER: As a practicing physician interested in keeping well, I should like to ask whether or not there is any value in such things as choline, methionine and so forth. These drugs are supposed to, and sometimes appear to, reduce the cholesterol level.

The second question is whether or not you can give us anything about the use of iodine in this connection.

MODERATOR WILKINSON: I shall call on the panelists in rotation for this, and take the prerogative of the moderator to say that in my laboratory we do not find choline, methionine or various mixtures of these to be effective. We see no logical reason for their use. We have not used iodides. Dr. Kinsell?

DR. KINSELL: My experience is the same as regards choline and the methionine group. As for the iodides, we have used them but have no idea how to evaluate them. It is our clinical impression that possibly there may be something interesting in this field that warrants careful investigation.

MODERATOR WILKINSON: Dr. Keys?

DR. KEYS: With regard to choline, methionine, and the like, we have observed no effect whatsoever in human beings with any of these drugs in their regular

form or with any of the preparations offered to us by pharmaceutical houses. We have not used iodine.

MODERATOR WILKINSON: Dr. Pollak?

DR. POLLAK: Some of these drugs—for instance, iodine—are mild vasodilators. Many aging people have fatty livers, and since the lipotropic substances remove neutral fat (not cholesterol) they may improve liver function and patients may feel better. I don't see much harm, nor any real good, as far as atherosclerosis is concerned. It may be like taking a stimulant.

MODERATOR WILKINSON: Dr. Stare?

DR. STARE: I would not add to any of the comments that have been made. I agree with them.

MODERATOR WILKINSON: Dr. Epstein?

DR. EPSTEIN: No further comment.

MODERATOR WILKINSON: Is there another question from the floor?

SPEAKER: I was interested in what Dr. Pollak said about enzymes. I wonder if a possible reason for an elevated serum cholesterol level might be a deficiency of the enzymes that ordinarily would make the precursors of cholesterol form some more useful compound, but when present in insufficient supply would permit these precursors to turn into cholesterol.

DR. POLLAK: That is my way of thinking about the whole thing. I think that basically there may be a deficiency of some enzyme. I have been hunting for that enzyme (cholesterase) for about fourteen years and I have not yet found it.

MODERATOR WILKINSON: Are there any other questions from the audience?

SPEAKER: I should like to ask the panelists if they know of any work that has been done, or if they have any ideas regarding the effects of environmental factors and perhaps endocrines on the level of cholesterol.

MODERATOR WILKINSON: I am not sure that we understood that, sir. Will you repeat it, please?

SPEAKER: I referred to the effect of strain. Has any work been done to show its effect on cholesterol concentration?

MODERATOR WILKINSON: I think Dr. Keys has a study in progress. I do not know whether he is ready to report on stress and strain at this point, but we shall ask him.

DR. KEYS: As you know, Dr. Wilkinson, some of us have been trying to get at this question of stress and strain for a long time. We have brought psychiatrists, psychosomatists, psychologists, and sociologists in to work with us. The net result is a big zero—mainly, I think, because of lack of good methods. We have no way of measuring it. Thus, the answer is simply that we know nothing about the question of stress and strain. It is unmeasured and unmeasurable at present.

We can say that if modern civilization, telephones, radios, and being run over by automobiles be stressful, we can find plenty of places where these things happen and yet the residents do not have much coronary heart disease. We can also find places where these environmental factors are not operating (as I found last summer and early fall in Finland, a country in which people live simply and

perform much hard physical labor) but where the frequency of coronary heart disease is at least as high as in this country. Therefore, I would say at present that there is no evidence to support the idea that there is a relationship between stress and atherosclerosis, and that on the other hand, there is no definite evidence against it. We are talking in a vacuum most of the time.

MODERATOR WILKINSON: We might at this point ask Dr. Keys whether or not, in Finland, the suicide rate is as high as generally reported throughout the Scandinavian countries. If it is, this might indicate some stress not measured by the simple life.

DR. KEYS: Dr. Wilkinson, we have tried to use various things such as suicide rates and the frequency of diagnosis of neurosis and psychosis, and have found no relationship. Everybody says those things do not have to do with stress and strain.

The highest suicide rate in the world at present is reported to be in Japan, followed by Denmark. What that means, I do not know.

MODERATOR WILKINSON: Are there any other questions?

SPEAKER: My question is about a specific product—Cytellin of Lilly. Can you tell me its value? How does it work, and does it effectively control the level of cholesterol?

MODERATOR WILKINSON: We discussed this question in opening the panel. We thought it better not to name specific products, but we have covered all of the vegetable sterols in rather meager fashion. I think no member of the panel really recommends or uses the material. If I am wrong, I should like the panelists to speak up.

DR. KEYS: Dr. Wilkinson, could we add the point that some of the vegetable sterols, in contradiction to the statements in textbooks, are absorbed and some of them do not appear as cholesterol in the ordinary measurement. Thus, one may have a false sense of security through having a low blood level of cholesterol but a high level of plant sterols. Finally, there is evidence that these materials can appear in the atherosclerotic lesion. Therefore, I do not see where we are getting with this question.

MODERATOR WILKINSON: We might also point out that a week ago last Sunday it was reported by one of the groups at Goldwater Hospital that it is possible to have dihydrocholesterol gallstones in animals fed these substances. Gallstones have not been produced by sitosterol, as far as I know, but by similar substances. I think the subject is far more complex than we have time to go into now, but I do not believe that many laboratories are still enthusiastic about the use of these vegetable sterols. Dr. Pollak, do you want to add something?

DR. POLLAK: The only thing I would like to say is that Cytellin is a sitosterol product. You spoke of the necessity for large doses. If the fat in the diet were restricted to, let us say, 50 per cent and combined with a smaller (50 per cent) dose of sitosterol, perhaps a compromise could be made.

In the first set of patients I reported, I mentioned a case of gallstones in discussion. We do not always have one specific drug for any disease. If nothing else helps to reduce the blood cholesterol level, maybe sitosterol will. It is a question

of trying. If it works, it is all right; if it doesn't, nothing has been lost. As we have seen today, we have nothing much better to offer. Essential fatty acids work in some patients and in others they do not. Nicotinic acid and pyridoxine go down the same drain.

MODERATOR WILKINSON: Have you actually seen sitosterol work in a patient still taking the drug? That is more or less the sense of the question.

Has any of us given his patients sitosterol or the vegetable sterols other than during experimental periods? Is that the question you wanted answered?

SPEAKER: Yes, that is right. I saw it work effectively in hypercholesterolemia, but its effect is wearing off. I wondered if that was your experience, or whether it is a matter of the diet?

MODERATOR WILKINSON: We have had no good results, so we do not use sitosterol in our laboratory any more. Dr. Pollak, how long has any of your patients been taking sitosterol?

DR. POLLAK: The longest is eighteen months.

MODERATOR WILKINSON: Is he still receiving it?

DR. POLLAK: No. I discontinued it. I am not convinced that we have to reduce the blood cholesterol level. Dr. Stare spoke of elevated blood cholesterol levels in younger people with infarction; but what are we trying to diagnose, infarction or atherosclerosis? Some of you may have read 2 papers of mine published not long ago in the *Journal of the American Geriatrics Society*, in which I raised that question. Are we justified in dividing people into goats and sheep according to whether they have had a coronary infarction or not?

MODERATOR WILKINSON: Someone had a question.

SPEAKER: Do the panelists know whether the young Oriental who comes to America and eats an American type of diet has atherosclerosis in later life?

MODERATOR WILKINSON: Dr. Kinsell, you see many young Orientals.

DR. KINSELL: We have quite a few data on young Orientals, most of them second generation. We also have a few data on fairly young Orientals who have recently come to this country and consume something approaching our diet—not identical, because they do not like our diet. There is a significant change in their plasma lipid levels, particularly with reference to cholesterol.

SPEAKER: Thank you.

DR. KEYS: With regard to the Japanese at least, it is evident that a major difference exists between the Japanese in Japan and their relatives from the same part of Japan living in the Hawaiian Islands. During the last two months, we have been able to carry out a cholesterol study on Japanese living in Los Angeles, although there we do not have the necropsy material that we had in Japan and Hawaii.

The average cholesterol concentration for 52 men selected as representative of the business class was compared with that for a Caucasian group at the same time. The 52 Japanese, aged 40 to 49 years, had an average serum cholesterol level of 246.2 mg. per 100 cc. In that community, according to the vital statistics and the records of the Japanese Hospital in Los Angeles, coronary heart disease is the most important and most frequent single cause of death.

MODERATOR WILKINSON: Is there another question?

SPEAKER: I have heard that, in the initial stages of starvation, the blood cholesterol level will often rise. I wonder if that is due to the fact that bile probably was not secreted and cholesterol was therefore retained. Is there any comment on that?

MODERATOR WILKINSON: Dr. Keys wrote a two-volume book on starvation, so I will give it to him.

DR. KEYS: It is not true. In the initial stages of starvation and in total fasting the cholesterol level frequently rises. Our interpretation is that this is associated with the mobilization and transport of lipid for metabolic purposes from the body depots. So far as I know, it has no particular relation to the production, secretion or reabsorption of bile. If you are going to live on the fat of your own body, you still have to try to transport it around as lipid protein and you have to do that by combining it with cholesterol. The liver will make all the cholesterol you want, at any time, or even more than you want.

MODERATOR WILKINSON: Another question?

SPEAKER: I should like to ask Dr. Keys if there are any pathologic changes in the blood vessels of people who are starving. If so, I presume that the lesion would not be the usual atherosclerosis.

DR. KEYS: We have not carried our experiments that far, but we have had the experience of examining material from concentration camps and others have studied material from concentration and prisoner-of-war camps. There is complete unanimity of opinion as to a striking absence of atherosclerosis or any other abnormality that I know of in the blood vessels.

DR. KINSELL: Do you think this would speak for possible reversibility, assuming that a reasonable number of these people might have had atherosclerosis before they got into the starving state?

DR. KEYS: I think, Dr. Kinsell, that that is the only reasonable interpretation you can place upon this observation. We know that under normal circumstances a sizable number of persons have atherosclerosis. The fact that these starved people were uniformly found to be virtually free of atherosclerosis, suggests either that all those who had atherosclerosis were the first ones to die in the prisons, or that there had been some reversal.

DR. POLLAK: May I add one thing. Yesterday afternoon I talked to a pathologist from Germany. He told me about necropsies on prisoners who came from Russian camps. He remarked on the absence of atherosclerosis. Of course, we do not all talk the same language. He added one comment. None of these men had a body weight over 90 pounds.

MODERATOR WILKINSON: It looks as if we can be starved and have reasonable assurance that we won't have atherosclerosis.

DR. KINSELL: May I say one word, Dr. Wilkinson, with regard to a previous statement by Dr. Pollak to the effect that the same kind of variability in results applies to the use of essential fatty acids as applies to the use of sitosterols. I doubt that you meant this. If you did, perhaps you were misinformed. As far

as we know, given a sufficient amount (which may vary with different persons and may be very large) of essential fatty acid such as one of the high linoleic acid-containing fats, any person can have his blood cholesterol level brought within the normal range.

DR. POLLAK: I respect your opinion, but I read the literature and I know that some people disagree with you.

DR. KINSELL: I mean in terms of our own experience over the past six years, which includes controlled and semicontrolled studies in several hundred people.

MODERATOR WILKINSON: This is a matter of how much, not whether. Are there any other questions from the floor?

SPEAKER: Do you have any diet, on the basis of present data, that you would care to recommend to the practicing physician?

MODERATOR WILKINSON: We think that the heterozygous hyperlipemic person is not uncommon, and that, if his fat intake is spaced so that he is able to clear it before he has the next fat load, his blood lipid level can be kept within a theoretically normal range. We also think that there is a real possibility that a person may not be able to clear the fat load from the bloodstream as he grows older. We, more or less arbitrarily, would advise people between 45 and 50 years of age to eat a fat-free breakfast, and anything they want for lunch and dinner. Dr. Kinsell?

DR. KINSELL: We are using 3 diets at present. I think Dr. Wilkinson at this meeting last year made a remark to the effect that there were 2 procedures for lowering the blood cholesterol level. One was caponization by the administration of estrogen and the other was the consumption of some of Kinsell's horrible diets. He implied that he would prefer to have a coronary thrombosis and, in terms of the formula diets and of caponization, we might be inclined to agree.

We have diets now which approach reasonable palatability. The composition of these diets together with our observations will be published in the near future in the *Journal of the American Geriatrics Society*.

MODERATOR WILKINSON: Dr. Keys, have you a diet?

DR. KEYS: The easiest way to get a diet of this sort is to go to some place where the diet is specialized and developed for an entire population. That is why I am sorry that I am not going to be in Italy this spring for the first time in five years.

MODERATOR WILKINSON: Dr. Pollak, have you any diets?

DR. POLLAK: I have no suggestion to make. I agree with what has been said.

MODERATOR WILKINSON: Dr. Epstein?

DR. EPSTEIN: Even though the pathogenesis of the disease is very complex, a cure may be relatively simple. If one could reduce the fat content of the diet in this country, one might make an appreciable dent in the frequency of the condition.

MODERATOR WILKINSON: That is Dr. Epstein's opinion.

SPEAKER: Nothing has been said about the soybean with reference to the Oriental and his diet. I should like to be brought up to date on that.

MODERATOR WILKINSON: The soybean products used in the Oriental diet contain largely protein and practically no fat. The soy meal available to us also contains little fat. I believe Dr. Keys will bear me out in this.

DR. KEYS: That is right; the consumption of soy oil is negligible in Japan. The main form of eating soybeans is soy "curd," which is substantially a fat-free protein.

SPEAKER: Should we recommend soybean for use in America?

DR. KEYS: Not I, after much experience trying to put this across as a war measure in the feeding of soldiers.

SPEAKER: Can you say anything about lecithin and phospholipids in this connection?

MODERATOR WILKINSON: The experience in our laboratory with lecithin has been about the same as that with choline and methionine.

SPEAKER: I should like to ask whether or not any studies have been made comparing any sizable group of vegetarians in this country with ordinary people on ordinary diets?

MODERATOR WILKINSON: Dr. Keys?

DR. KEYS: There are not many true vegetarians. Dr. Stare has worked with vegetarians in this country. I think most of them consume milk and milk products and otherwise are not proper vegetarians. There has been a study here in the United States and another in the Netherlands, but I think they are not in full agreement.

MODERATOR WILKINSON: There is quite a group in Southern California in a Medical School—the College of Medical Evangelists. The whole principle of the Seventh Day Adventists is vegetarianism, but it has been implied that there are degrees of vegetarianism.

DR. KINSELL: I had a classmate in medical school who was a vegetarian, but this meant only to the exclusion of rare beefsteak.

MODERATOR WILKINSON: Thank you.