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Date	12/16/84

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CPD II Biological Studies of Radiation Effects
J. H. Lawrence - in charge
Project 48A-I

BIOPHYSICAL APPROACHES TO ATHEROSCLEROSIS

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By
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Atherosclerosis is the principal and really important form of arteriosclerosis.

The consequences of this particular form of arteriosclerosis result in the serious circulatory accidents in the coronary, cerebral and peripheral vessels which lead to so much death and disability in many areas of the world. There has been much debate and confusion about the nature of this disease, the exact sequence of pathogenetic events, and the role of certain dietary factors in its development and progress. Ever since lesions in the vessels have been shown to contain cholesterol, phospholipids and fatty acids there has been considerable interest in the problem of what might be the source of these lipid materials in atherosclerotic plaques. A reasonable suggestion made early was that possibly these lipid materials found their way into the blood vessel wall from the blood itself, since it has been known for years that such substances as cholesterol, phospholipids and fatty acids circulate in the blood stream. Whether these materials get into the blood stream directly from solution or suspension in blood, or whether they enter the blood vessel wall, as Leary suggests, via the macrophages which have migrated from the liver has been a subject of debate in the literature, with no definitive answers forthcoming. Two years ago our research group set out to attempt to answer certain questions concerning the pathogenesis of the atherosclerotic process and specifically the role of blood lipids in its development, and the possible

• The research upon which this report is based is the result of the efforts of a team of researchers at the Donner Laboratory of Medical Physics. The original team included Frank Lindgren, Harold Elliott and John Gofman and has been expanded with the inclusion of Doctor Hardin Jones, Doctor Thomas P. Lyon, William Manz, Beverly Strisower, John Hewitt, Virgil Herring and Doctor John Simonton. Even though the article is written by one of the group, the work involved represents the efforts of the entire group at one phase or another of the research.

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role of macrophage migration as suggested by Leary in the development of the pathological lesion.

With respect to macrophage migration from the liver, recent work in this laboratory by Doctor John Simonton and Doctor John Gofman (as yet unpublished) has been pointed toward a direct answer to this question. The technique has involved the labeling of macrophages of the liver, the spleen and bone marrow of the rabbit at the onset of the experimental period with ionium-containing colloids which localize in these cells. The rabbits whose macrophages had been labeled were then subjected to a long period of cholesterol feeding, during which time they developed atherosclerosis. If the macrophages which had received a dose of ionium-labeled colloids were functioning during the entire experiment, it was anticipated that one should expect a migration of the radioactive ionium colloid into the aortic atherosclerotic plaques. Demonstration that the ionium-labeled macrophages remained functional was provided by giving india ink at the last day of the feeding period, and by demonstrating that india ink was taken up by macrophages which showed a considerable radioactivity due to the ionium colloid. The results of these experiments, to be published in detail shortly, indicate that macrophage migration does not play a significant role in the development of atherosclerosis in the rabbit at least.

The role of blood lipids in the development of atherosclerosis has been investigated by a wholly different approach. As mentioned above, it has long been suspected that blood lipids might have something to do with atherosclerosis, even to the extent that the plaques might result from the infiltration of these lipids into the vessel wall. Anitschkow demonstrated many years ago that feeding rabbits diets high in cholesterol itself produced a hypercholesterolemia and atherosclerotic lesions in a feeding period of approximately 3 months. Thus, the concept that hypercholesterolemia might go hand in hand with the production of atherosclerosis was proposed. From this and other work there resulted a large volume of literature on study of human blood cholesterol in an effort to correlate blood cholesterol level with the presence

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or development of atherosclerosis. There is a relatively small group of people who develop atherosclerosis -- that is, a small percentage of the total group -- who do show definite and/or persistent hypercholesterolemia; this group includes patients with diabetes mellitus, nephrotic nephritis, myxedema and essential familial hypercholesterolemia. However, the summary result of many years of study of cholesterol levels on many thousands of people has been that the vast majority of individuals who suffer the consequences of atherosclerosis in general do not show an elevated blood cholesterol. This fact has led to much discrediting of the significance of cholesterol in the development of the disease and has led to an impasse as to the exact role that blood lipids might have in the development of the disease process.

In Donner Laboratory we began the study of the problem of the blood lipids from the point of view that possibly the quantity of cholesterol or other lipids in the blood as measured by the usual analytic techniques might be of little importance in the pathogenesis of the disease when compared with the nature of the giant molecules in the blood in which cholesterol and other lipids are carried. At the time our experiments were begun Pedersen had published some results concerning a so-called "X-protein" which exists in human serum and on which he had done ultracentrifugal studies. He reported that this molecule was apparently a labile lipoprotein which would dissociate into its constituent parts by several varied manipulations of serum, including a reduction of the total protein concentration or certain changes in serum salt concentration. Upon attempting to reproduce Pedersen's study with human serum we found similar variability in the apparent concentration of "X-protein" and ease of losing this molecule during our manipulations. There were certain features of this ultracentrifugal pattern, however, that did not seem reasonable on the basis that the "X-protein" and albumin were two separate sedimenting peaks in the ultracentrifugal diagram. (See figure 1). As a result of several experiments in this direction we proposed the theory that the observed peaks which gave the appearance of two sedimenting components -- the albumin and "X-protein" -- were really not such peaks, but rather that the "X-protein", being a lipoprotein of low density (that is, of a density close to that of the medium in which

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it was sedimenting) was actually piling up in the region of the albumin concentration gradient which exists at the albumin boundary. This type of piling up of the lipoprotein at the albumin boundary gave rise, for the lipoprotein alone, to a biphasic curve on the Schlieren diagrams obtained in analytical ultracentrifugation. The pile-up superimposed upon a normal albumin peak would give rise to a composite peak which could be mistaken for two separate downward sedimenting peaks, when in reality it represented a pile-up of one protein in the region of a boundary due to another. (Figure 2 demonstrates the expected individual peaks for such a phenomenon and how the composite peaks might appear).

The reason for the pile-up phenomenon is that the lipoprotein changes in its rate of sedimentation and in some cases even its direction in the vicinity of the albumin boundary. If the solution containing albumin is more dense than the lipoprotein itself, whereas the solution without albumin is less dense, then all the lipoprotein in the solution will pile up in the vicinity of the albumin-concentration gradient during the course of an ultracentrifugal run. Also, if the lipoproteins migrate more rapidly than does albumin in the supernatant solution, whereas they migrate more slowly than albumin, but in the same direction in albumin-containing solution, the net result is a progressive sweeping of the lipoprotein into a pile-up on the albumin boundary. Thus, the ultracentrifuge diagrams that had been seen by workers previous to Gofman, Lindgren and Elliott were those representing a pile-up of lipoprotein on the albumin-concentration gradient rather than two sedimenting peaks -- the albumin boundary and the "X-protein". It was then shown by Gofman, Lindgren and Elliott that the "X-protein", or lipoprotein, was not the unstable molecule which Pedersen had thought it to be, but was quite stable to such maneuvers as dilution with salt solution or lowering of the protein content. The reason for the apparent disappearance of the "X-protein" in Pedersen's runs is that he had inadvertently adjusted the experimental conditions such that pile-up no longer occurred. Once these facts were clarified, it became possible to think in terms of a suitable method for studying the lipoproteins in serum in order to determine something of their physical chemistry and diversity.

It was predicted and then observed by Gofman, Lindgren and Elliott that if the density of the solution were raised to a point such that all regions of the solution

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would have a higher density than that of the lipoprotein (or lipoproteins) one should observe these molecules floating against the centrifugal field as inverted peaks on the Schlieren sedimentation diagram. This experiment has been repeated thousands of times and in the hands of the present workers has become a standard technique for studying the lipoproteins of serum directly or for studying isolated low density components. Numerous human sera and the sera of animals were investigated by this technique in an effort to characterize the low-density molecules which had previously been lumped together under the name of the Beta₁ lipoprotein or the "X-protein". It was soon found that a rich diversity of components existed from serum to serum and, in fact, a single serum might have from one to five separate components present. /

There is present in nearly all human sera a lipid aggregate which in a solution of density 1.0625 at 27° Centigrade (our standard conditions) migrates with a rate of between 35 and 70 Svedberg units. This component can readily be shown to be greatly influenced by the relationship between the time and character of the last meal and the time of drawing the blood sample. In other words, it represents a part, at least, of the alimentary lipemia. In addition, components have been seen with migration rates of the group from 20 to 30 Svedbergs, 10 to 20 Svedbergs, and 3 to 10 Svedbergs. In every one of some 2500 individual sera examined there was found at least one molecule of the low-density class (density approximately 1.03 to 1.04 grams per cc) which migrated with a rate of between 3 and 8 Svedberg units. This component is a lipoprotein of approximately 25% protein and 75% lipid by weight. It is approximately 30% cholesterol -- free cholesterol and cholesterol esters being lumped together in this estimate. In some individuals this component of 3 to 8 Svedberg units exists as a doublet of components whereas in others a single, apparently homogeneous, component is seen. The significance of the singlet or doublet of components is now under study. Further, there are quite definite differences in this group of components from one individual to another. For example, if one person possesses a 4 S_f component and another a 7 S_f component, the mixing of these two sera shows the presence of both components rather than either one or the other, thus obviating the possibility that the difference in migration rates might have

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been due to differences of conditions in preparing solutions or in making the ultra-centrifugal runs. The group of low-density components of 10 to 30 S_f units of flotation are contrasted with the major lipoprotein components by virtue of their greater migration rates and also by virtue of the fact that they are of even lower density than are the major components of the 1.03 to 1.04 density class. There appear to be several components in the S_f 10 to 30 category, at least one of which (whose flotation rate is 10 to 15 S_f units) contains protein, but less than the 25% protein of the major components; others contain little or no protein and hence the term "free lipids" probably should be applied to these.

Investigating the sera of normal rabbits in parallel with the human sera, the identical situation with respect to pile-up of low-density molecules on the albumin-concentration gradient was observed. Utilising the techniques described above, it was possible to adjust the conditions of flotation such that the low-density components could be observed migrating inward toward the axis of rotation in a solution of adequately high density. A low-density component which is a lipoprotein of density approximately 1.03 -- containing approximately 30% cholesterol and 25% protein by weight -- is found in varying concentration in all rabbits.

Having this basic picture of the major cholesterol-bearing components of human and rabbit serum, it was possible to go ahead with studies of atherosclerosis and its possible relationships to the blood lipids. Rabbits developing atherosclerosis as a result of cholesterol feeding were investigated. It was found and reported by us that all rabbits receiving cholesterol (3 gms/week) developed in the course of this feeding period an increase, first, of the low-density lipoprotein of density 1.03 up to a certain point. Some of the rabbits never showed any further changes of serum beyond this increase in the concentration of the normally existing lipoprotein. However, after 4 to 8 weeks the majority of rabbits developed new components in appreciable concentration these components being first in the 10 to 20 S_f class and subsequently appreciable concentrations even of some in the 20 to 30 and higher flotation rate classes. Almost all of the increment in serum cholesterol which occurs in the course of cholesterol

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feeding goes into these new components after the build-up of the lipoprotein of the 3 to 8 S_f class. Autopsy of fifteen animals following a 15 week feeding period demonstrated that atherosclerosis had developed paralleling roughly in severity the final concentration of molecules of the S_f 10 and higher class; rabbits developing very low concentrations of these molecules in the serum showed minimal or no gross atherosclerosis. At present there are 50 or more animals becoming hypercholesterolemic and from which further correlations of the occurrence and severity of atherosclerosis with the presence of these components will be available. At the present time all that can be said from the existence of these components of the S_f 10 to 30 class in the serum is that they are a reflection in the blood of the tendency to develop atherosclerosis. However, these facts do not prove that these molecules themselves are actually the ones which deposit to form atheromatous plaques, or, on the other hand, if all the low-density lipids and lipoproteins deposit, that those of the S_f 10 to 30 class are the molecules that remain behind. Direct evidence on this point is now being obtained by the labeling of the lipids and lipoproteins of this class in donor rabbits which are hypercholesterolemic by use of P³²-labeling of phospholipid and tritium-labeling of cholesterol. The isolated components, with the label incorporated, are re-injected into other rabbits developing atherosclerosis. From an examination of the radioactivity of the atheromatous plaques it should be possible to determine whether these molecules which correlate with the presence of atherosclerosis are actually the ones which deposit in plaques. At the same time these experiments are giving us some idea of the rate of production and destruction of the various ultracentrifugal components of rabbit serum.

The discovery that cholesterolemia in the rabbit was by no means a simple increase in one component but a very special type of increase with distinct type of molecules appearing suggested immediately that a search should be made in the human for components of similar type and for relations between such components and the development of human atherosclerosis. In the human most studies of atherosclerosis for a long time have centered around an effort to show that possibly the total level of cholesterol in the serum might be increased in those people who suffered the consequences of athero-

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Accession No.	434-94-0309
File Code No.	14-5-22
Carton No.	3
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sclerosis in one part of the vascular bed or another. Although there exists a group of disease states characterized by hypercholesterolemia and premature atherosclerosis, this is a very small fraction of the total group of humans who show atherosclerosis. The vast majority of persons developing atherosclerosis do so with a cholesterol level in the blood within the presently accepted normal range (100 to 300 milligrams percent). The use of the analytical cholesterol value has been rather fruitless in the effort to demonstrate its relationship to the development of atherosclerosis. With the view that possibly the cholesterol level itself might not be important but that the nature of the molecules transporting cholesterol might be, we set about to investigate the low-density lipids and lipoproteins which carry cholesterol in human serum.

As mentioned above, all humans show at least one lipoprotein of the density class 1.03 to 1.04 which contains cholesterol. However, early studies revealed that only certain humans showed the presence of the even lower density components of the 10 to 20 and 20 to 30 S_f classes which are also important cholesterol-bearers of serum. A systematic study was then initiated, using various groups of supposedly normal individuals and groups of individuals with known atherosclerotic disease in an effort to determine whether the presence of certain of these components could be correlated with the presence of atherosclerosis. The preliminary findings in this regard were published by the present author and his colleagues in SCIENCE, February 17, 1950. Many other studies have been made since that time, and have served to confirm and extend the original observations. In Figure 5 is given a histogram with the essential details of the findings, which indicate a definite relation of molecules of the S_f 10 to 20 class to human atherosclerosis.

Concerning living individuals, no absolute direct evidence can be obtained that atherosclerosis exists, but the indirect evidence is essentially certain. For example, patients with a proven myocardial infarction will in at least 97 of 100 cases have had such an infarction on the basis of atherosclerosis. It is seen from the histogram that approximately 95 percent of patients on ad libitum feeding with myocardial infarction show the presence of molecules of the S_f 10 to 20 class in their serum.

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in variable concentrations. This represents almost universal occurrence of such molecules in those individuals who have atherosclerosis. By contrast, it is seen that in young women from 20 to 40 years of age the occurrence of such molecules in serum is relatively rare. In females there is a striking increase in the frequency of occurrence of such molecules in the serum as the 40 year age mark is passed. In young men the occurrence of such molecules is much more frequent than in young women. Diabetics show a higher frequency of occurrence of such molecules than do normal individuals of the corresponding age groups. Three patients with the nephrotic syndrome were studied and showed exceedingly high levels of molecules of the S_f 10 to 20 group. Of 15 patients with clinical hypothyroidism, 14 showed the presence of such molecules. All of the above described observations are consistent with the known data concerning the occurrence and the complications of atherosclerosis in the various groups studied. Here as in the rabbit the existence of these molecules of the S_f 10 to 20 class in the serum of individuals with atherosclerosis does not prove that these molecules actually deposit to form plaques, but does show that they are at least a reflection of the metabolic disturbance which results in atherosclerosis. It may be possible in the near future by tracer techniques in the human as well as in the rabbit to demonstrate directly whether or not the low-density molecules of the S_f 10 to 20 class actually do form the atherosclerotic plaques. The striking rarity of such components in the serum of young women and the loss in the apparent protection in women following the menopausal years strongly suggests that some metabolic feature of the premenopausal women is involved in the control of the lipid and lipoprotein metabolism in a way such as to prevent the appearance of these molecules in serum. The effect of the thyroid gland in the control of these molecules is strongly suggested both by studies of experimental atherosclerosis prior to those of the present workers and by our own finding of high concentrations of such molecules in the serum of patients with thyroid deficiency. Studies currently in progress are directed toward an understanding of how the estrogenic and thyroid hormones are related to this problem.

As to exact mechanisms of pathogenesis of the lesion, assuming the molecules of the S_f 10 to 20 class might be directly involved, it is too early to offer any

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concrete explanation. However, it is tempting to speculate that possibly the less well proteinized molecule of the lower density group may serve in some way as a stimulant to phagocytosis by phagocytic elements in the arterial wall whereas the fully proteinized molecule of the 1.03 to 1.04 density classes does not. Studies are now in progress with tissue culture technique in an effort to determine whether or not there is a difference in phagocytosis of the various components by phagocytic cells, of the types that might presumably be present in the arterial wall.

The question arises immediately as to the relationship of the S_f 10 to 20 class of molecules to the total analytical serum cholesterol level. The lack of a relationship except in certain groups has been shown by us to exist and may well help explain the impasse to which analytical cholesterol determinations had led. For example, at a serum cholesterol level of 200 mg % there are approximately as many persons of the normal group who will show molecules of this S_f 10 to 20 class in the blood at a measurable concentration as ones who will not. Below this cholesterol level there are fewer persons showing these molecules, but still a fair percentage will be positive with respect to the presence of these molecules in the serum. It is not rare to find molecules of the S_f 10 to 20 class in the serum of individuals whose total serum cholesterol are as low as 120 mg. %. Above a serum cholesterol of 300 mg % we have not yet found any persons who do not show appreciable concentrations of the S_f 10 to 20 molecules in their serum. All these observations taken together help us understand why atherosclerosis may well be related to blood lipid transport when evaluated in this new light, since there does exist a feature common to hypercholesterolemic individuals who show more than usual atherosclerosis and individuals having normal cholesterol levels who may have atherosclerosis, namely, the presence in the serum of molecules of the S_f 10 to 20 class. From these statements it is evident that if the presence of the S_f 10 to 20 molecules in the serum is a necessary finding in the serum as an index to active atherosclerosis, then the determination of analytical cholesterol values is essentially a meaningless criterion for the same purpose, a fact which has actually been evident for a long period of time, with the exception of the group of individuals of

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the frankly hypercholesterolemic class.

The research on this subject by us to date has demonstrated the almost universal occurrence of molecules of this S_f 10 to 20 class in the serum of individuals with proven atherosclerosis. The existence of the same molecules in the sera of a large number of presumably normal individuals may infer that these are precisely the individuals in the population at large who are developing atherosclerosis. This can be proven beyond doubt positively or negatively by studying the blood of a large number of persons in the susceptible age categories with respect to the presence of these molecules, then observing the incidence of atherosclerotic manifestations in these persons. The first 2000 of the 30,000-person screening procedure is now completed. It will be only after complete study of these people has been done that the possible value of this test for the presence of such molecules in the blood as a diagnostic procedure can be determined. Pending this study and for fundamental physiological information, as well as for possible thoughts along the lines of prevention and therapeutics of atherosclerosis, it was of great interest to us to determine whether the level of such molecules in the blood could be altered by dietary or other manipulation. The rationale for the possibility that dietary factors might be involved rests on several observations. First, rabbits develop these molecules in the blood and develop atherosclerosis only if they are fed diets rich in cholesterol; the same is true in dogs, provided their thyroid function is depressed. Secondly, in other areas of the world where diets are low in cholesterol and fats, a low incidence of atherosclerosis has been reported. It was an obvious step, therefore, to determine whether dietary restriction of cholesterol (and necessarily certain fats) would result in a lowering in concentration of molecules of the S_f 10 to 20 class in those persons whose serum showed them initially. This experiment is now in progress in a long-term way. It is already evident that if persons showing such molecules in their serum are placed on diets restricted in cholesterol and fats the concentration of molecules in the S_f 10 to 20 class can be reduced or brought down below resolution limits within a period of one to eight weeks in over ___ % of ___ cases studied. This is true for young and old individuals alike - for normals, diabetics, and coronary patients.

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Vegetable fats contain no cholesterol but in our preliminary studies vegetable fats as well as animal fats have been moderately restricted, especially in view of the fact that experimental work suggests that vegetable fats may facilitate absorption of cholesterol. The extent of restriction of cholesterol and fats of either vegetable or animal origin which may be necessary to keep the blood cleared of such molecules over long periods of time can be determined only by long-term studies, and will undoubtedly be variable from individual to individual. An interesting question which then arises is: will the clearing of such molecules from the blood be of any prophylactic or therapeutic value with respect to atherosclerosis? Obviously, this cannot be answered at the present time. If the molecules being present in the blood of atherosclerotic individuals represent only a reflection in the blood of the disordered metabolism which gives rise to atherosclerosis, clearing the blood may prove of no value. On the other hand, if the pathogenesis of the disease involves actual deposition of such molecules in the arterial intima to form atheroma, it may conceivably be of great importance from the prophylactic and therapeutic point of view to clear the blood of such molecules by dietary or other means which may prove effective. Parallel with basic studies of the pathogenesis of the disease by labelling techniques, a series of persons with or without proven atherosclerosis is being followed closely, these individuals being on such regimens that do reduce the blood level of these molecules. The incidence of primary or recurrent complications of atherosclerosis in these individuals will give us the answer as to the value of such blood alteration. In any event, we have available for the first time an objective criterion to follow in evaluating the effect of diet in this disease, no matter what the final result may be.

Obviously the research to date is preliminary, the answers already available having served to raise an entire new host of questions. In the next few years it may be that the real significance of these molecules in atherosclerosis may be evaluated as one approach to the understanding of a very common, important and baffling disease.

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