Lipoproteins and Lipotropes in Atherosclerosis

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THE LIPOTROPIC substances are now recognized as one of the "legitimate" (if still experimental) treatments of atherosclerosis despite some dubious attitudes. For instance, Katz[1] now mentions lipotropic deficiency as one of the major contributing factors in the etiology of atherosclerosis.

In our considerations of atherosclerosis there are several pathologic processes which are frequently confused and considered as a single entity. It is questionable that the disease or lesion in a rabbit or any other experimental animal is comparable to the clinical entity which we term atherosclerosis in man.

Our experimental work in man is handicapped by the fact that we are forced to group our patients into two categories, the so-called "normals" and the "atherosclerotic individuals." There is no single test or even a group of tests which will allow us to divide our patients into two such categories.

One also frequently forgets the fact that a man may have a strategically located plaque and may die from coronary artery disease at the age of thirty-five years, while a person in whom atherosclerosis gradually develops may live to the age of seventy-five or eighty years and come to autopsy, at which time it is found that the cause of death is unrelated to the coronary artery disease.

Blumgart and Schlesinger[2] demonstrated by the injection technic that patients may have two coronary arteries completely occluded and still survive the ravages of coronary artery disease because adequate collateral circulation develops in them.

At times we get carried away in our enthusiasm and blame one factor alone for causing atherosclerosis. No one refutes this better than Katz in stressing the point that the disease, at least in man, is a multifaceted phenomenon, of which disturbed lipoprotein is only one factor.

The anatomy of the coronary tree is an extremely important factor, as proved by Enos.[3] The eddies and currents created by the tortuosity of the coronary tree are definitely a contributing factor. A second major question is: on what level do sex hormones act? We do not know whether it is on the level of permeability of the intima or of lipoprotein metabolism. Intravascular pressure is a third factor which must be considered and, in treatment and management of the disease, it must be properly controlled. Hypertension hastens the disease, probably as hypertension within the coronary system as well. All these factors must be kept in mind when we discuss the disease entity termed human atherosclerosis.

What do we have, consequently, as our therapeutic armamentarium against the human type of atherosclerosis? We cannot correct the anatomy of the coronary tree, just as we cannot, with any degree of great success, change our sex by administering hormones, even though they may be modified by their physiologic antagonists. This has been used experimentally by some investigators[4] but I do not think it offers hope of a practical treatment.

However, we can influence the lipoprotein metabolism. There are apparently few substances which can accomplish this. One of the classic substances is heparin, which hastens the production of the "clearing factor" (lipoprotein lipase). Treatment with heparin is impractical today for long term administration because of the cost and the inability to manufacture heparin for oral medication.

Lipotropic substances apparently do influence the lipoprotein metabolism. This may be

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proved with the aid of a modest test, the fasting-chylomicron index. This index can be affected by the administration of lipotropic substances. There is a definite group correlation, first reported by Zinn and Griffith[5] and which I later confirmed,[6] between the occurrence of clinically demonstrable coronary atherosclerosis and elevated levels of chylomicrons in the fasting state. Those levels can be lowered, as we reported in 1955.[7] This study has been repeated by Rawls[8] and confirmed.

Further interest was aroused recently by the unsaturated fatty acids. We studied the effect of unsaturated fatty acids in moderate doses (in comparison to the doses used by other investigators) because I questioned the advisability of administering large doses of either saturated or unsaturated fatty acids. I believe that we expose the intima to too much abuse if we administer large doses of even unsaturated fatty acids. Moderate doses of unsaturated fatty acids failed to lower cholesterol levels. There was a lowering in only six of twenty-five patients.

There was, however, a definite effect when those moderate doses of unsaturated fatty acids were combined with the lipotropic substances: beta lipoprotein was definitely and uniformly lowered by administration of a combination of the two.[9,10]

It is not known whether or not there is a true synergistic action between the unsaturated fatty acids and the lipotropic substances. Further studies, using similar technics, would be of great interest.

Although there is only one factor which we can apparently influence safely with a medicinal approach, the outlook as to the final outcome is optimistic. At this time 10 per cent of the total population has excellent collateral circulation. If we consider the human form of the disease as being an adaptive evolutionary phenomenon, then I believe the time element is important and through evolutionary processes our system of collateral circulation will eventually become 100 per cent effective.

SUMMARY

It is obvious that coronary atherosclerosis in the human being is an end result of a number of causative factors. In contrast, the laboratory-induced lesion in the animal is most often caused by a single experimental technic. Thus, there is no common ground for comparison. There is a distinct possibility that an absolute or relative lipotropic deficiency is behind the disturbed lipoprotein metabolism, one of the atherogenetic factors in the form of the disease found in man. It is possible to demonstrate objectively the effect of lipotropic substances on lipoprotein metabolism.

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DISCUSSION

Dr. Meyer Friedman (*San Francisco, California*): I do not consider atherosclerosis in the rabbit the

equivalent of human atherosclerosis. The answer must be collateral circulation or new arteries inserted surgically. I do not believe we will ever reach a point curatively where we will just diffuse something.

I think we may prevent, but I do not think we can cure—certainly, I am sure not by lecithin or anything like it. This observation is supported by post mortem studies on coronary arteries. Second, I want to stress again the multiple etiology of this disease.

We agree regarding the effect of emotional stress in the production (not just the changes in lipoprotein metabolism) of cardiovascular disease. The evidence is so overwhelming that it cannot be ignored. It is surprising and totally discouraging as far as therapeutics are concerned.

DR. LABECKI: I agree with Dr. Friedman's last remark. We deplore the methodology existing at this time and our inability to measure, gauge and determine the effects of such strain on the production of blood vessel disease in man.

Dr. Friedman used the term "lecithin," implying that one of these lipotropic factors can melt away calcific or fibrotic tissue. Studies have proved such a claim to be untrue. The only claim now made is that those substances do exert definite measurable influence on lipoprotein metabolism, always keeping in mind the other factors which we cannot influence.

Until quite recently some texts never mentioned lipotropic substances. Then we did our study on the alcoholic patients in Mississippi.* We did not melt away the cirrhotic tissues in any magic manner. What we accomplished was a high rate of diminution of fatty infiltration following high intake of lipotropic substances.

However, the rate of diminution of the fatty infiltration with a high protein diet is definitely slower, as proved by biopsy studies of the liver.

DR. W. STANLEY HARTROFT (*St. Louis, Missouri*): Dr. Labecki's report is of great interest. Taking choline out of an animal's diet and putting it back has been instructive. However, all of us are somewhat hesitant about transferring our studies to man at this point.

You stated that hypertension was associated with a higher incidence of coronary arteriosclerosis. We do not believe there is any evidence to support this concept that hypertension is a factor in the production of coronary arterial disease. My colleagues, Drs. R. M. O'Neal and W. Thomas, correlated the weights of the kidneys at autopsy with blood pressure levels. There is a distinct inverse correlation: the higher the blood pressure, the smaller the kidneys. If an increase in the levels of blood pressure was etiologically important in myocardial infarction, the weights of the kidneys in patients dying from recent myocardial infarcts should be smaller than in any control series. Results of the studies by Drs. O'Neal and Thomas show no significant difference in the weights of kidneys of patients dying from myocardial infarction and a control series of patients dying from other causes. Therefore, it is hard to believe that hypertension is a factor in producing myocardial infarction.

The incidence of myocardial infarction in Negroes living in St. Louis, in New Orleans and in Washington, D. C., is one-fifth to one-tenth of the incidence of myocardial infarction of white persons living in these same centers; yet the incidence of hypertension among Negroes in these same three cities is much higher than in white persons of the same age, and hypertension in Negroes develops earlier in their lives than in white persons. Therefore, more Negroes are subjected to these elevated blood pressure levels for longer periods of time and yet myocardial infarction occurs less in this group than in white persons.

DR. JULIUS POMERANZE (*New York, New York*): In this age of rapid pharmacologic advance I would like to think that we could find a treatment for arterial trauma other than surgery. We can only treat it too late, when the damage is already done. There must be some way of reaching it before this stage if we recognize the fact that man is naturally a sclerotic animal and that we must do something long before the irreversible vascular calcification develops.

We have to think in terms of what causes acute myocardial infarction. There is an ulcer and then a thrombus forms, or there is bleeding. Sometime in the future I hope we will be able to reverse this thrombus formation or stop the bleeding.

Recent releases indicated that Dr. Ross of Parker Hospital has activated plasminogen to dissolve the plaque, and a group in Boston achieved the same result experimentally. Whether or not this is therapeutically feasible is not known at present, but I cannot feel that this is as weak a picture as would appear from the discussion here.

DR. HARTROFT: I think the picture is more optimistic than yours, Dr. Pomeranze. We know that we could reduce the incidence of myocardial infarction in this country almost to zero right now. During the war the incidence of myocardial infarction in England dropped to one-half of what it was in the previous six months to a year. This occurred also in Denmark during the war.

DR. CAMILLO ARTOM (*Winston-Salem, North Carolina*): And in Norway.

DR. HARTROFT: During the siege of Stalingrad the incidence of myocardial infarction in that city before the siege came to an end fell to zero. This fact has been confirmed by autopsy reports. The incidence of myocardial infarction rose again as soon as food was restored.

I think we are in a period with regard to heart disease comparable to diabetes before insulin was used. Diabetes could be completely cured in that era by starving the patient. We could probably do the same thing

* LABECKI, T. D. and BUSBY, C. L. Medicinal management of fatty alcoholic livers. In: A. M. A. Scientific Exhibits, 1955, p. 371. New York, 1956. Grune & Stratton.

with myocardial infarction. Therefore, even if calcification is present (and that would have been true in the European populations) you can still reduce myocardial infarction.

DR. POMERANZE: I do not think you would even have to starve your patients. The picture looks promising, I think.

DR. FRIEDMAN: I did not mean to be unduly pessimistic. I believe if the artery is left you can do a lot, and if there is infiltration you may be able to remove it. However, I do not agree with Dr. Hartroft about these countries. He has to explain why the incidence of hypertension diminished and why the suicide rate in Great Britain during its greatest siege increased.

I want to know what other things happened during the siege besides the lowering of the fat ration. Low intake of fat is not the only factor in these blockaded countries, unless you want to say that hypertension is due to a high fat intake.

DR. GEORGE F. WILGRAM (*Toronto, Canada*): In view of our own work, Dr. Lucas' statements and Dr. Hartroft's work, I feel fairly safe in stating that, to the best of my knowledge, there is not too much convincing evidence that lipotropic deficiency has something to do with human atherosclerosis.

There have been several reports in the literature to that effect. However, they either have been disproved or disclaimed. The work done by Dr. Hartroft and which I later continued indicates that the lipotropic deficiency observed in animals does not have any resemblance to the atherosclerosis of man.

How do you reconcile your findings with those presented here, namely, that a deficiency of lipotropic factors tends to decrease all classes of blood vessel disease and on the readministration of choline a rise to normal occurs.

I realize that Dr. Labecki is dealing with a different situation, giving choline to persons who already have enough choline. Yet, on physiologic grounds, it is hard to see on the basis of our findings how those two things go together. Would you mind elaborating on this point?

DR. LABECKI: I will be glad to. The curves shown given today were those of laboratory animals. I do not believe the metabolism of choline and the fate of lipotropic substances in human beings and in experimental animals is the same. There is a lot of evidence to support this.

DR. WILGRAM: There is a preponderance of evidence that many different species, including the monkey, are fairly close to the human being, and exhibit similar patterns. From a biologic viewpoint it is hard to understand why man should be so very different.

DR. LABECKI: By stating that lipotropic therapy is a recognized form of treatment of atherosclerosis I meant that it is recognized as a form of therapy for one of the contributing factors. You cannot disprove or disclaim records such as electrophoretic strips. That is how we determined the levels of beta-lipoprotein. The chylomicron index was lowered, but not in all the cases; one does not expect 100 per cent success. Dr. Rawls, who used exactly the same technic, confirmed our study and published his results about a year ago.

We are dealing here with group correlation which exists between the high cholesterol levels and coronary atherosclerosis and between the higher beta-lipoprotein levels and coronary atherosclerosis. Anything which would influence such elevated levels should be considered as a preventive rather than a therapeutic measure. Dr. Katz' studies on chicks on methionine-deficient diets are indeed very convincing.

DR. WILGRAM: You are dealing with choline and not with methionine. The methionine-deficient chick is so drastically different from a human being given extra choline that comparison or a common ground is not possible. A methionine-deficient chick is different even from a chick that has enough choline in the food and is given extra choline.

DR. LABECKI: Admittedly, the individual lipotropic substances administered are less effective. There is apparently some synergism which at this time we are unable to explain, probably because of the methodology.

DR. W. E. CORNATZER (*Grand Forks, North Dakota*): In reference to Dr. Wilgram's question about similarity in the rat and man, there is a similarity in the phospholipid synthesis as shown by giving a single dose of choline or methionine. They both stimulate phospholipid synthesis in the plasma following a given dose. The methionine can be given orally or intravenously. Chaikoff's studies with dogs gave identical results. Therefore, we can say that there is a similarity between man, the rat and the dog, in that phospholipid synthesis is affected by choline and methionine.

DR. LOUIS FREEDMAN (*New York, New York*): Dr. Wilgram, in reference to your interpretation of the resemblance of lesions in animals to those of man, are you referring to the application of some method of overcoming these lesions or is it an interpretation of the anatomic factors?

In your paper read at the New York Academy of Sciences (April 11, 1958) you referred to the vascular lesions in animals as the Mönckeberg type but stated that they have no direct or immediate clinical application.

However, you said they were useful in providing us with the know-how for the development of other methods to produce cardiovascular changes in rats. These newly-developed methods yield lesions that are indeed an appropriate experimental counterpart to atherosclerotic heart disease in man.

DR. WILGRAM: What I meant to say is that the lesions developed by choline-deficiency trained us in learning, understanding and know-how for the development of lesions by other methods. These "other" methods are definitely different from anything that has to do with choline deficiency.

The method described and used has many things in common with the approach that Dr. Hartroft has developed using a diet very rich in choline and other ingre-

dients which induces hyperlipemia and vascular anemia. Animals on a choline-deficient diet with cardiovascular disease have the opposite, namely, decreased blood lipid, as has been shown here by different and independent investigations.

The connection between choline deficiency and those coronary infarcts described is a personal one in our laboratory.

DR. COLIN C. LUCAS (*Montreal, Canada*): In other words, you wish to say that choline is good for curing choline-deficiency but not for curing other things?

DR. WILGRAM: That is my definite conclusion.