Factors in the Production of Coronary Artery Disease

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The recent tendency to accept the syndromes of coronary artery disease as an indication of the presence or relative absence of coronary atherosclerosis in the living patient is open to serious objection. The production of these syndromes would appear to depend, not so much on the degree of coronary atherosclerosis, as on the presence of extraneous factors which precipitate occlusion. Of these factors, hemorrhage into atherosclerotic plaques is of major importance. The etiology of this lesion, and the manner in which it precipitates occlusion, are reviewed.

Much has been written during the past three years on the possible relationship between errors in lipid metabolism and the progression of atherosclerosis. Abnormalities in the cholesterol-phospholipid ratio and in the lipoprotein pattern of the blood have been incriminated, particularly, in the pathogenesis of the disease. The evidence obtained from cholesterol-fed rabbits has supported these claims, but it is extremely hard to obtain direct evidence in man. The stumbling block lies in the fact that an accurate assessment of the degree of human atherosclerosis can only be made on the autopsy table. This difficulty is well recognized; nevertheless, it has been the fashion in recent years to accept the syndromes of coronary artery disease as an indication of the presence or relative absence of coronary atherosclerosis in the living patient. When used in this way, these syndromes are open to serious objection.

It should be appreciated that coronary artery disease is not a pathologic entity; it is a clinical term for a number of symptom complexes which result from myocardial ischemia. Admittedly, at least 90 per cent of cases of myocardial ischemia are due to coronary sclerosis or its sequelae, but the qualification “or its sequelae” is important. Uncomplicated and progressive coronary atherosclerosis, resulting from the simple deposition of lipid materials over long periods, is not the common immediate cause of coronary artery disease. It is well known to pathologists that severe grades of coronary atherosclerosis are not incompatible with good health and normal heart action, while lesser grades of disease may be associated with occlusive phenomena. The classical studies of Blumgart and Schlesinger have shown that the gradual reduction of the coronary lumen to a pinpoint size does not necessarily result in symptoms since it is compensated for by the opening up of a collateral circulation which is adequate for the ordinary activities of life. If these ordinary activities are exceeded, the anginal syndrome or acute coronary insufficiency may of course result; but this is not the usual way in which coronary artery disease is produced. On the contrary, it is usually precipitated by structural changes in atherosclerotic plaques, changes which have no apparent relation to lipid metabolism at the time of the catastrophe, but are more concerned with extraneous factors like coronary pressure, coronary blood flow and capillary fragility. Thus, the difference between an individual with clinically-evident coronary artery disease and a so-called normal individual lies, not so much in his grade of coronary atherosclerosis, as in the presence of these extraneous factors which precipitate occlusion. These factors, and the occlusive lesions which result, will be described in this paper. They are not particularly

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new, having been recognized now for over 15 years, but they are reviewed again, here, as they seem to have been ignored or forgotten by many workers in the field of atherosclerosis.

**Morphologic Aspects of Coronary Sclerosis**

The structural alterations which lead to most of the complications of coronary atherosclerosis develop from changes in the blood supply to the arterial wall. The wall of a human artery, in health, obtains its nourishment from two sources. The adventitia and outer portion of the muscular coat are supplied with blood through the vasa vasorum which penetrate the arterial wall from without. The inner portion of the arterial wall, including the intima, is nourished in a different way, by the imbibition of nutrient materials from the blood circulating in the lumen of the artery. The intima of a normal human artery has therefore no true blood supply; but it develops one as the result of disease. Apparently by a compensatory mechanism, to supply the extra nutritional requirements of an abnormally thickened intima in the atherosclerotic process, capillaries grow into the intima and ramify within its substance.

These newly formed intimal capillaries are not derived from the usual vasa vasorum in the outer part of the arterial wall. They are abnormal structures and originate from the lumens of large arteries. Their direct origin from the arterial lumen was noted first in the aorta. They have been shown by serial section technic to arise in a similar fashion in atherosclerotic coronary arteries, and the full extent of their profuse ramifications in the inner parts of atheromatous plaques has been demonstrated by special injection methods. The microscopic appearance of the origin and extent of intimal vascularization is illustrated in figures 1 and 2.

The peculiar position of these newly formed capillaries, in direct communication with the lumen of a major artery in which the pressure of blood is high, seems to be a major factor in determining their rupture. This point will be discussed later in this paper; but it is important to realize that intimal capillaries are exceedingly prone to rupture, and with their rupture disruptive hemorrhages within atherosclerotic plaques are produced. Serial section technic has proved that intimal hemorrhages are in fact intrinsic; they are not due to the reflux of blood through a break in the lining of the artery, as was previously thought. Examples of intimal hemorrhages are shown in figures 3, 4, 5, and 6. Winternitz and his colleagues have been so impressed with the frequency of hemorrhages in the intimal layer of arteries that they have suggested that they not only complicate the atherosclerotic process but may actually initiate it. Intimal hemorrhage cannot be accepted as a causative lesion in atherosclerosis (because the intima of normal human arteries is not vascularized), but as a complicating factor its importance is
FACTORS IN PRODUCTION OF CORONARY ARTERY DISEASE

beyond question. Depending on the size of an intimal hemorrhage, its position within a plaque, and on coronary blood flow past the point of injury, the following sequelae may be produced:

1. Coronary artery spasm. This possible effect is highly speculative, and the only reason it is mentioned is because it has been suggested by others. It has been postulated that, if a hemorrhage is sufficiently deep-seated and is close enough to the muscular coat, spasm of the artery may be initiated. An example of a deep-seated hemorrhage is shown in figure 4. If true, this mechanism may explain certain cases of sudden death which are otherwise obscure. But it must be an extremely rare phenomenon; in my series of many hundreds of intimal hemorrhages of the coronary arteries, there have been only two cases in which coronary occlusion might have been produced in this way.

2. Acceleration of the atherosclerotic process. Here, one is on safer ground. The addition of blood to an atherosclerotic plaque, like that illustrated in figure 5, must increase its bulk. Single hemorrhagic episodes, like this one, should produce little effect once the fluid portion of the blood is absorbed, but the gradual accumulation of the solid elements (such as cholesterol, blood pigment) from repeated hemorrhages into the same plaque should perceptibly increase its size. And in this regard it is to be noted that many atherosclerotic plaques contain blood elements in varying stages of dissolution, indicating the repetitive nature of intimal hemorrhages.

With a larger hemorrhage, like that shown in figure 6, there is a distinct possibility that the coronary lumen will be so reduced that the anginal syndrome might result. Symptoms which originate in this manner should be
transient, and one would expect them to disappear with the absorption of the hemorrhage.

3. Coronary occlusion from massive intimal hematoma. When hemorrhages are extremely large, the stenosis of the coronary lumen may be so marked that myocardial infarction, or acute coronary insufficiency with sudden death, occurs. This variety of coronary occlusion seems to be less common than has been reported in the literature. In my series of occlusions which have been studied recently. An intimal hemorrhage was noted in each case, but in none was it of large size. Indeed, the hemorrhages were indistinguishable in their bulk from those seen routinely in autopsies on patients who had not received anticoagulants. It would appear that the production of a massive intimal hematoma depends on factors other than blood coagulability.

serial section technic, the incidence of massive hematomata is less than 10 per cent. These large hemorrhages, however, have a clinical significance. It has been suggested that an ordinary hemorrhage which develops in a patient who is receiving anticoagulant therapy may progress to massive proportions because of abnormal blood coagulability. This danger appears to have been exaggerated. Eight patients in my series who succumbed from coronary artery disease at a time when they were receiving dicumarol have been studied

4. The initiation of coronary thrombi. This complication of intimal hemorrhage is the most important of all. Providing that suitable conditions of stasis and eddying of blood exist at the point of hemorrhage (and these may be supplied by the shape and size of an atherosclerotic plaque which projects into the arterial lumen), thromboplastic substances which are liberated from the area of tissue disruption may then become operative. Thrombus precipitation may occur in several ways, as has been described in detail elsewhere.4, 5.
6, 12 but, regardless of the exact mechanism, everyone who has worked intensively on the subject agrees that the usual precipitating lesion of thrombosis, not only in coronary arteries, but in other arteries as well, is hemorrhage into an atherosclerotic plaque. 4, 5, 6, 10, 12, 13, 14 Skepticism still exists, of course, in certain quarters.

Some pathologists will concede that an intimal hemorrhage may initiate thrombosis in certain cases, but they are not impressed with its frequency in this respect. Here again, some fairly exact data can be quoted. From a consideration of the figures given in table 1, it would appear that the incidence of intimal hemorrhage in any series of cases of coronary thrombosis will depend entirely upon the pains that are taken in searching for them. If thrombosed segments of arteries are sectioned serially at close intervals, the incidence of hemorrhage in relation to thrombus is as high as 90 per cent; but if only occasional random sections are studied through the thrombus (as in the series of Yater and co-workers18) the incidence falls to less than 20 per cent. The variation between these results can easily be explained. Intimal hemorrhages are often quite small, so small that they can only be demonstrated by serial sections at fairly close intervals. If they were usually large, and easily demonstrable by random sections, they would probably have been observed and described long before 1936.4

Perhaps the most impressive evidence of the relation of intimal hemorrhage to thrombus precipitation is obtained from a study of serial sections of coronary thrombi. When a throm-

![Fig. 6. Low power photomicrograph of an intimal hemorrhage of moderate size. The arterial lumen is shown on the left. The size of this atherosclerotic plaque must have been increased significantly by the hemorrhage. (Hematoxylin and eosin stain. × 15.)](image)
bus has been traced to its point of initial deposition, it will sometimes be found to occupy only part of the lumen, and here it is attached to the endothelium immediately adjacent to a point of hemorrhage. Examples of this close relationship of thrombus to hemorrhage are shown in figures 7 and 8.

**Fig. 7.** Low power photomicrograph of a thrombosed coronary artery. The thrombus occupies only part of the arterial lumen, shown on the upper left, and it is attached and suspended at a point where a small hemorrhage has occurred into an atherosclerotic plaque. (Heidenhain stain. × 10.)

**Factors Involved in the Rupture of Intimal Capillaries**

From the foregoing it appears certain that the rupture of intimal capillaries with the formation of intimal hemorrhages is the usual lesion in the production of the complications of coronary atherosclerosis. In the final analysis, then, the causes of capillary rupture in these locations are the usual causes of coronary artery disease. These causes are, admittedly, highly debatable. They will probably not be definitely established until they can be studied under controlled experimental conditions, and studies of this type must await the production of full-blown coronary atherosclerosis, with vascularized plaques, in susceptible animals. In the meantime, there are two schools of thought. First, there are those who regard capillary rupture as a purely fortuitous event in the course of atherosclerosis; who claim that it cannot be predicted, prevented or treated. The other school has a more optimistic outlook. It holds that capillaries in these locations rupture from definite causes, and that these should be sought for industriously. Certain hypothetic factors have already been suggested, but the subject deserves more attention than it has received in the past.

It is apparent that an intimal capillary, like that shown in figure 1, may rupture from three general causes, operating individually or in combination: (1) from abnormally high pres-
sure within its lumen; (2) from abnormal fragility of its wall; and (3) from lack of support from the adjacent tissues. Arguments which support each of these hypothetic factors have been given in detail elsewhere, but only two of them will be summarized here.

Intracapillary pressure appears to play a major role in the rupture of intimal capillaries. These capillaries are peculiar in that they lie in direct communication with the lumen of a large artery in which the pressure of blood is normally high, and this high pressure will be transmitted, to a degree, into the capillaries themselves. If persistent hypertension is present, intracapillary pressure should be correspondingly increased, and there should be imminent danger of capillary dilatation and rupture. Intimal hemorrhages should therefore be more numerous in individuals with persistent hypertension that in those with normal blood pressures. This is, in fact, the case, as has been reported elsewhere; and it may therefore be deduced that the transient elevations in blood pressure which accompany excessive exertion or emotion will have a similar effect in producing intimal hemorrhages.

The role of capillary fragility also deserves some comment. Many factors may increase the fragility of these small vessels. Some of these cannot be corrected, but those which are due to nutritional disturbances can. Possible deficiencies in vitamin C therefore deserve consideration, and recently it has been claimed that abnormal capillary fragility, in general, can be corrected by the administration of rutin. It has been stated that this material will protect the capillaries of the eye in hypertensive retinopathy, and the capillaries of the brain in hypertensive encephalopathy. If true, rutin should be equally effective in protecting capillaries in atherosclerotic plaques. Obviously, carefully conducted and well-controlled clinical trials are needed to assess the validity of these claims and assumptions.

**COMMENT**

The evidence reviewed in this paper suggests strongly that other factors besides atherosclerosis play a major part in the production of coronary artery disease. All of these extraneous factors have probably not yet been elucidated, but an important one has: the rupture of capillaries within atherosclerotic plaques seems to play a major role in determining whether or not an individual with coronary sclerosis will present signs and symptoms of myocardial ischemia. It follows that these signs and symptoms cannot be accepted as a measure of the severity of the atherosclerotic process, per se, in the coronary circulation. This conclusion has an important application to current investigations on the relation of errors in lipid metabolism to atherosclerosis. To use coronary artery disease as a criterion in these studies means that one is measuring not only atherosclerosis but these extraneous factors as well. Obviously, a more critical method of assessment is needed in this field of research. In my opinion, this can be done only by comparing serial blood lipid levels obtained during life with an accurate estimate of the severity of atherosclerosis as revealed at autopsy. In carrying out an assessment of this type, two points must be borne in mind. Since atherosclerosis is a disease which may take years to develop, and may persist for some time after the causative agent has ceased to act, the serial determinations of the blood lipids should be made over long periods. And it would be helpful if techniques could be devised for estimating the severity of the disease at autopsy which are more accurate than the crude methods of grading in use today.

However, future research on atherosclerosis should not be confined to the chemistry of the blood lipids. It should include studies on arteries—on the tissues which are actually affected by the disease. In this regard, the causes of capillary rupture in atherosclerotic plaques demand attention. Statistical studies carried out recently by Morris suggest that the incidence of coronary occlusion in England has increased during the past 40 years while the over-all severity of coronary atherosclerosis for the same period has declined. If one accepts the thesis that coronary occlusion is usually the result of extraneous factors which lead to the rupture of capillaries in the walls of arteries, and is not usually due to coronary
sclerosis, per se, there is no inconsistency in this interesting report from England. Indeed, until atherosclerosis is completely eradicated from the human race, or is so inhibited that it reaches no more than slight proportions, the complications which have been described in this paper will remain with us: atherosclerotic plaques of any size will continue to become vascularized, intimal capillaries will continue to rupture, and the sequelae of intimal hemorrhage will continue to occur. In the circumstances, it seems reasonable to suggest that the causes of capillary rupture in these locations deserve more attention than has been given them in the past.

SUMMARY AND CONCLUSIONS

Evidence is reviewed to show that the signs and symptoms of coronary artery disease cannot be accepted as a measure of the degree of coronary atherosclerosis in the living patient. The production of these symptom complexes is a reflection, not necessarily of the degree of coronary sclerosis, but of certain extraneous factors which result in the rupture of intimal capillaries, the formation of disruptive hemorrhagic lesions within atherosclerotic plaques, and in the production of occlusive lesions. The urgency in elucidating the causes of capillary rupture in these locations is stressed.

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