Minority Report of the Committee on the Effect of Strain and Trauma on the Heart and Great Vessels

By J. C. Paterson, M.D.

Preamble

The report of the Committee on the Effect of Strain and Trauma on the Heart and Great Vessels was published in Circulation in October 1962, with a footnote stating that Dr. J. C. Paterson, the only dissenting member of the Committee, wished to present his viewpoint on one particular but important aspect of the subject. His Minority Report is here published to permit this in advance of the appearance of any later monograph planned to include both reports, details of some of the studies on which the reports were based, and the bibliography.

Dr. Paterson agrees with those who have stated that intimal hemorrhage "may be the critical secondary lesion" in acute and chronic coronary artery atherosclerotic disease, that such hemorrhages may be "caused by stress," and that "in certain circumstances some of them may have acute casualty-producing effects." And furthermore, the time relationships between stress and the effects thereof might thereby be prolonged beyond the limits considered likely by the majority of the Committee.

Such divergent views are incapable of proof at present, even though clearly possible from either standpoint. The immediate duty of the Committee, however, was to define criteria for, and to outline the probabilities of, causal relationships for the guidance of the medical and legal professions. The statistical evidence, admittedly lacking in perfect certitude, is strongly against stress as the primary or essential factor in coronary occlusion and in sudden death from obstructive coronary atherosclerotic disease, in which 60 per cent or more of victims show no recent occlusion from necropsy.

Since the legal process requires definite affirmative or negative decisions, the scientist’s "perhaps" can only be assessed by the weight of probability and the careful scrutiny of the evidence in every contested case. The Minority Report should be useful in supplementing the Majority Report in this respect. But inasmuch as coronary thrombosis, like a good many other diseases, is not primarily due to work but to other causes, it should be removed from litigation in the courts under the category of Workmen’s Compensation and taken care of by some form of health insurance.

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I HAVE HAD the advantage of reading the majority report of the Committee, as well as the submissions of individual members, which are appended below. With the greatest respect for all members of the Committee who have expressed a different view, I am of the opinion that the evidence at hand favors the verdict that unusual physical exertion or emotional stress (to be referred to hereafter as "stress") may be the precipitating factor, not only of acute coronary insufficiency (as is admitted in the majority report), but of acute coronary occlusion as well. I am also of the opinion that the mechanism by which stress precipitates acute coronary occlusion is through its ability to produce intimal hemorrhage. This lesion is sometimes referred to as "subintimal hemorrhage" or "intramural hemorrhage."

My worthy colleagues on the Committee have thrown doubt on the intimal hemorrhage hypothesis in the following sentences and paragraphs, which I have extracted from the majority report. They will serve as bases for my argument.

The theory most vigorously espoused which attributes acute coronary closure to increased cardiac activity (from stress) is that invoking subintimal hemorrhage in an atherosclerotic area of a coronary artery. The Committee does not deny that this may conceivably occur, but the finding of subintimal hemorrhages in 80-90% of all patients dying of atherosclerotic coronary artery disease makes it seem fully as likely that these hemorrhages are usually a part of the ordinary development of the degenerative process and not related to any particular stressful incident. It is felt that there is no pathological pattern pathognomonic of the influence of stress."

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gaged in usual or unusual effort. Some pathologists contend that such hemorrhage is usually found as a terminal process in the thickened intima of markedly narrowed vessels and that it does not materially contribute to the fatal outcome. Criteria for establishing a relationship of intimal hemorrhage to effort or emotion are not clear enough for the majority of the Committee to accept.

The sentences in these two paragraphs are the only references in the majority report to the subject of intimal hemorrhage. With respect, I submit that more emphasis than this should have been placed on a lesion concerning the significance of which “there has in recent years been a growing appreciation . . . in coronary disease.” This quotation is from a leading article on intimal hemorrhage in the British Medical Journal for April 11, 1959. Furthermore, I consider some of the views expressed to be of doubtful validity. For example, it seems illogical to argue that “the finding of subintimal hemorrhages in 80-90 per cent of all patients dying of atherosclerotic coronary disease makes it seem fully as likely that these hemorrhages are usually a part of the ordinary development of the degenerative process (of atherosclerosis) and not related to any particular stressful incident.” I would agree that intimal hemorrhages are intimately concerned in the progression of atherosclerosis, but this does not exclude the possibility (1) that they are caused by stress and (2) that in certain circumstances some of them may have acute casualty-producing effects. In this regard, it has been shown that fresh intimal hemorrhages are a common finding in the coronary arteries of adults who die suddenly of coronary artery disease, whereas they are absent in control subjects who die from extracardiac causes. Nor do I consider it proper to reject stress as a disease-producing entity simply because it has no “pathognomonic pathological pattern.” One might say the same thing about another well-known clinical syndrome—shock; but who would maintain that the physiological effects of shock are not very real? Evidence is also at hand about the physiological effects of stress, notably its influence on catecholamine formation and excretion, on blood pressure and coronary blood flow, and on capillary fragility. Some of these effects will be discussed later, but for the present I will merely suggest that they may be intimately concerned in the mechanism of production of intimal hemorrhage.

I also submit that some of the remarks about intimal hemorrhage, quoted above, do not agree entirely with the facts. In the first place, I believe it is incorrect to refer to intimal hemorrhage as a “terminal process.” Many of these lesions, in fact the great majority of them, show histochemical evidence of having been present for some time (i.e., they contain hemosiderin and ceroid pigments). Secondly, it is wrong to state that intimal hemorrhages usually occur in “markedly narrowed vessels.” I have in my own collection numerous examples of hemorrhages into relatively small plaques; indeed, evidence is at hand that they occur even in fatty streaks, the earliest and smallest of atherosclerotic lesions. Thirdly, the claim that intimal hemorrhages are of “very common occurrence in patients at rest,” and that they cannot therefore be due to stress, implies that a person in bed is always in a state of utter tranquility. I submit that the stress which results from a nightmare (for example) may be just as severe as that due to unusual physical exertion. It is to be regretted that the emotional origin of stress has been completely neglected in the majority report.

Turning now to the facts about intimal hemorrhage, I find them unambiguous and plain for all to see. The original description of the lesion, and of its origin, have been amply confirmed by independent workers. The latest confirmation was made by members of the Pathology Study Group of the Committee who, in the minutes of a meeting held June 21, 1960, are quoted as saying that their material “has demonstrated the importance of intimal hemorrhage in acute (and in chronic) coronary artery pathology. Indeed it is our working hypothesis that this may be the critical secondary lesion.”
The facts about intimal hemorrhage that are not disputed are as follows:

1. Intimal hemorrhage is the extravasation of blood into an atherosclerotic plaque. It is an intrinsic lesion within the thickened intima, not merely the result of reflux of blood through a defect in the lining of the vessel.

2. Intimal hemorrhage is caused by the rupture of capillaries that ramify in the substance of atherosclerotic plaques. These capillaries are derived in part from the lumen of the main artery, in part from the orifices of branch arteries, and in part from the usual vasa vasorum in the outer coats of the vessels.

3. Both recent hemorrhage and the products of old hemorrhage (hemosiderin, ceroid) may be observed in the same plaque, indicating the repetitive nature of the extravasations.

4. Intimal hemorrhage may occur both with and without associated thrombosis of the adjacent arterial lumen. A high level of association between recent intimal hemorrhage and recent coronary thrombosis (80 to 90 per cent) has been reported by all workers who have used adequate methods in studying the problem.7-8

These are the pathologic findings which are not disputed, or should not be disputed. The interpretation of these findings, however, has varied between different observers. The major points of conflict are to be found in three questions: (1) whether a fresh intimal hemorrhage of large size may, because of its space-occupying qualities, stenose the lumen of a coronary artery to the point that coronary insufficiency results; (2) whether a fresh intimal hemorrhage may, by virtue of its tissue-disrupting qualities, liberate thromboplastic substances and thus initiate coronary thrombosis; and (3) whether stress may be responsible for the rupture of intimal capillaries with the production of fresh intimal hemorrhage, and of the sequelae of hemorrhage itemized in (1) and (2) above.

It may be inferred from some of the references to intimal hemorrhage in the majority report, which are quoted previously, that most of the Committee have answered each of these three questions in the negative. With respect, I find myself unable to agree with this verdict for reasons which I will outline in the succeeding paragraphs.

I would like to address myself first to the hypothetical stenosing effect of fresh intimal hemorrhage, particularly of a hemorrhage of large size. Although not specifically mentioned in the majority report, stenosis, or occlusion, or both, by a lesion of this type are apparently not admitted, since it is stated that "such hemorrhage . . . does not materially contribute to the fatal outcome." In my opinion this statement is incorrect. A large body of expert opinion exists in the literature4, 6, 7, 8 to the effect that intimal hemorrhage may stenose the coronary artery lumen to the degree that acute coronary insufficiency and sudden death result. Indeed, I have had difficulty in finding a valid authority for the contrary view. It may be that the supporters of the majority report are referring to a recent article by Crawford10 who states that "while intimal hemorrhages are of frequent occurrence, the evidence that they . . . are themselves the cause of occlusion is quite inconclusive." Crawford supports his claim by showing a photomicrograph (fig. 10 in his paper) of "large recent hemorrhages in the intima . . . (which) have not affected the narrowed lumen." I consider this kind of evidence to be fallacious and inapplicable to the lesion under discussion. The hemorrhages shown in the photomicrograph are not intimal hemorrhages: they have not occurred into an atherosclerotic plaque, an essential precursor of true intimal hemorrhage by definition. What is shown instead is a healed recanalized thrombus with many dilated and congested blood channels from which blood has seeped into the adjacent loose tissues. Any of these channels, and not merely the one referred to as the "narrowed lumen," could have been compressed by the hemorrhages.

An affirmative answer to the question may also be obtained by applying to it simple logic and principles of basic pathology. The addition of blood to an atherosclerotic plaque must
increase its bulk, in exactly the same way that recent hemorrhage causes swelling when it occurs into a semi-enclosed space elsewhere in the body (e.g., the hemorrhage which precedes black eye, cauliflower ear, etc.). Intimal hemorrhage is thus a space-occupying lesion within the arterial wall, and the increase in bulk must be reflected in one direction or another. It is doubtful if displacement outward can occur to any significant degree because of the great tensile strength of the adventitia. Sideways displacement, or diffusion, is obviously not a factor, since the lesions are quite circumscribed on gross and microscopic examination. By a process of elimination, then, an intimal hemorrhage must exert its space-occupying effect by inward displacement, thus narrowing the arterial lumen. Extravasations of small size will probably have no significant clinical effects; those of moderate size may conceivably result in angina pectoris; while large ones may cause acute coronary occlusion with sudden death or myocardial infarction. The chairman of the Pathology Study Group of the Committee reports that large occluding hematomas are a good deal more common than was previously suspected.

The second point of conflict is concerned with the thrombogenic potentiality of intimal hemorrhage. Ever since a relationship between intimal hemorrhage and coronary thrombosis was first suggested, wide variations in the frequency of association of the two lesions have been reported by different investigators. The matter has now been clarified; and I feel quite confident in stating, categorically, that recent intimal hemorrhages can be demonstrated in close association with recent coronary thrombi in 80 to 90 per cent of the cases, providing a thorough examination of the occluded segment of artery is made. Such an examination, to be thorough, must be done either by complete serial section at short intervals or by clearing techniques followed by serial section. The question is still debated as to whether this high level of association between the lesions is coincidental, whether the hemorrhage is the result of thrombosis, or whether the hemorrhage causes thrombosis. The majority report of the Committee does not include any specific mention of the causes of coronary thrombosis; nevertheless, I infer from the statement that intimal hemorrhage "does not materially contribute to the fatal outcome" that most of the Committee members feel that such a mechanism is not acceptable. With respect, I take the opposite view. The high frequency of association between intimal hemorrhage and coronary thrombosis has been demonstrated in so many cases, and by so many different investigators, that the factor of coincidence is improbable. I suggest that intimal hemorrhage is not the result of thrombosis simply because so many hemorrhages can be demonstrated without thrombosis. By a process of elimination, therefore, it may be deduced that intimal hemorrhage, in certain circumstances, actually causes thrombosis and that it does so probably because it disrupts tissue and liberates thromboplastic substances. The fact that all intimal hemorrhages do not produce secondary thrombosis has been used by some investigators as an argument against the thrombogenic potentialities of these lesions. In my opinion, this argument does not conform to general pathologic principles. All patients who take sulfonamides do not develop polyarteritis nodosa; nevertheless there is a striking cause and effect relationship between the two. All fresh myocardial infarcts do not go on to rupture of the heart; but who would deny that cardiac rupture is usually the direct result of myomalacia cordis? Only 1 per cent of hydatidiform moles terminate in choriocarcinoma; but it is agreed that there is a cause and effect relationship between the two diseases in 50 per cent of the cases. I submit, therefore, that it is wrong to exclude intimal hemorrhage as a cause of coronary thrombosis just because it does not cause thrombosis in every instance. Other factors undoubtedly are concerned in the process, and of these the change in blood flow produced by an atherosclerotic plaque at the point of disruption of tissue by hemorrhage is probably an important feature. Nevertheless, this secondary
factor should not operate in the absence of the primary injury, which is intimal hemorrhage.

Finally, I would like to discuss a point which, in my opinion, is the crux of the matter—the question as to whether stress is a factor in the rupture of intimal capillaries with the production of intimal hemorrhage and acute coronary occlusion. If this question could be answered in the affirmative, the association between a stressful incident and a bout of coronary occlusion would take on more significance than is admitted by most of the Committee members in the majority report. Admittedly, the evidence in favor of this association is indirect and theoretical; but this should not preclude it from consideration. Forensic pathology, as well as pathology in general, is replete with examples of acceptable decisions having been made on indirect and theoretical evidence. Indeed, pathology has been defined as "the theory of disease." The evidence that stress may be instrumental in rupturing intimal capillaries is as follows:

Because intimal hemorrhages are significantly more numerous in persons with persistent hypertension than in normotensive subjects, it has been deduced very properly that the transient elevations in blood pressure that occur with stress will also tend to rupture intimal capillaries and produce hemorrhages. Two explanations for the actual rupture of capillaries in these circumstances have been suggested. The first, which is the one I prefer, is that the high arterial pressure is reflected into those capillaries that arise directly from the arterial lumen, causing them to dilate and rupture. In this regard, there are two references in the literature in which, by the application of Bernoulli's principle, it is shown how the increased coronary blood flow and coronary pressure that occur with stress may result in higher pressures within intimal capillaries than within the main arterial lumen. The second explanation relates the cause of intimal capillary rupture to the mechanical, shearing effect of the increased arterial pulse wave in hypertension, whether the hypertension be of the persistent variety or transient due to stress.

Stress may favor the rupture of intimal capillaries in quite a different fashion: it has been shown that stress of any type results in a marked increase in capillary fragility in the rat; capillaries rupture at lower pressures than in unstressed animals. These findings have been partially confirmed in experiments on animals that are given anticoagulant drugs. Spontaneous hemorrhage rarely occurs from the anticoagulant itself, but it can be produced almost at will when stress is superimposed. I do not wish to imply that increased capillary fragility results only from stress; other factors may also play a part, notably the increased fragility that occurs with aging, with nutritional deficiencies, and from a variety of chemical substances.

The clinical evidence that links acute coronary occlusion to stress is circumstantial—but quite impressive. Persons who are chronically addicted to lives of stress have been found to be seven times more prone to coronary occlusion with myocardial infarction than are those with converse behavior patterns. The criteria for "addiction to stress" are that a person must manifest an intense, sustained drive for achievement and that he be continually involved in competition and deadlines, both at work and at play. There were no claims in this clinical report that the coronary occlusions were, or were not, the direct result of intimal hemorrhages; nevertheless, it may be deduced from other studies, which have been referred to previously, that this is a frequent mechanism.

This is the evidence, then, that stress may be an important factor in the production of capillary rupture, intimal hemorrhage, and acute coronary occlusion. One of the terms of reference of the Committee was to "Bring what knowledge we do have to the attention of the medical and legal professions, insurance companies, industrial management, labor and the public at large." I respectfully submit that the way in which the intimal hemorrhage hypothesis has been treated in the majority

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report does not conform to this instruction. An attempt has therefore been made here to repair what, in my opinion, is a major deficiency.

References

Principles of Research
The supreme task of the physicist is to arrive at those universal elementary laws from which the cosmos can be built up by pure deduction. There is no logical path to these laws; only intuition, resting on sympathetic understanding of experience, can reach them. In this methodological uncertainty, one might suppose that there were any number of possible systems of theoretical physics all with an equal amount to be said for them; and this opinion is no doubt correct, theoretically. But evolution has shown that at any given moment, out of all conceivable constructions, a single one has always proved itself absolutely superior to all the rest.—Albert Einstein. Essays in Science. New York, Philosophical Library, Inc., 1934, p. 4.
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