EDITORIAL

Angina Without Coronary Disease (sic)

Since the establishment of coronary arteriography as a widely used method for studying patients with ischemic heart disease,1, 2 a puzzling group of individuals with chest pain has emerged in whom no arteriographic evidence of coronary disease can be demonstrated.3-5 They have most often been women at or near middle age, although examples from both sexes and at all ages have been described. A sort of aura has developed about these patients, and the purpose of this communication is to consider some of the pertinent facts of the situation. I will intentionally omit the differential consideration of pain due to esophageal disease, hiatal hernia, pericarditis, and musculoskeletal disorders of the chest and instead will focus on those patients in whom such considerations have reasonably been excluded. Similarly, I will exclude (for the sake of this discussion) complicating factors from real life, such as aortic and mitral valvular disease.

What are the etiologic possibilities which currently seem most plausible as explanations for angina without coronary disease? The diagnosis of angina pectoris due to ischemic heart disease is more easily and more accurately made with increasing experience of the physician, and it is neither unfair nor inappropriate to indicate that some alleged examples of angina without coronary disease are wrong diagnoses. For simplicity's sake let us consider only those examples in which the diagnosis of angina pectoris due to ischemic heart disease is correct, but the coronary arteriograms are interpreted as normal. In such patients three etiologic considerations are (1) that myocardial ischemia is due to an abnormal affinity of hemoglobin for oxygen, the so-called stingy hemoglobin concept; (2) that myocardial ischemia is due to occlusive disease of the small coronary arteries; and (3) that the technic of coronary arteriography does not permit a definitive exclusion of conventional forms of coronary disease. The last thought will naturally be considered sheer heresy in many centers.

The possibility that abnormal affinity of hemoglobin for oxygen may lead to symptomatic myocardial ischemia is an attractive thought, and there is little question that some subjects with angina pectoris have such abnormally behaving hemoglobin.5 However, patients with severe generalized anoxemia, like that which occurs in carbon monoxide poisoning or hemorrhagic shock, do not always exhibit angina pectoris whereas we must assume that they have degrees of myocardial ischemia at least as severe as that conceivably occurring in the presence of stingy hemoglobin. Similarly, patients with advanced degrees of chronic anemia but with unoccluded coronary arteries often are free of chest pain. The question of abnormal affinity for oxygen by hemoglobin of patients with coronary disease is an interesting new concept which deserves further investigation but presently seems unlikely as an explanation for...
most examples of angina without coronary disease.

In the past few years there has been an increasing interest in the pathology and pathophysiology of the small coronary arteries (0.1 to 1.0 mm in diameter). Some of the vessels in this size range include those supplying the sinus node, the A-V node, and the His bundle, most functionally important anastomoses, and perhaps most significant relative to angina pectoris, the terminal distribution of all the coronary arteries. The small coronary arteries are distinctly abnormal and their lumina are narrowed in a variety of disease states, but in many of these patients the large coronary arteries are not narrowed. Such patients do get episodes of chest pain, which sometimes are related to physical exertion or emotional stress and sometimes are not; the pain is usually relieved by nitroglycerin but sometimes is not. In these patients the production of myocardial ischemia is probably related to the gradual and progressive occlusion of small arteries in a relatively random fashion. Symptoms appear when enough small vessels in the same region are sufficiently narrowed, and this is only indirectly related to the patient's physical or emotional status at the time. Arrhythmias or conduction disturbances, which are a characteristic feature of the clinical course of patients with small coronary disease, may further contribute to the development or exacerbation of myocardial ischemic chest pain. Although some small coronary arteries can be visualized in optimal quality coronary arteriograms, even there the ones seen represent only a very small percentage of all such vessels. But in most coronary arteriograms it is not possible to make any interpretations at all concerning small coronary arteries. Despite the fact that chest pain does occur in patients with pathologic small coronary arteries and the fact that coronary arteriography does not permit any sort of quantitative assessment of the integrity of a significant number of such vessels, it is improbable that the majority of patients with angina and allegedly normal coronary arteriograms have abnormal small coronary arteries.

Exactly how many have has not yet been determined.

This brings us to the final consideration, which will be unfashionable and unpopular: namely, that patients with angina due to ischemic heart disease do in fact have abnormal large coronary arteries, but that the coronary arteriograms simply failed to show it. The great value of this new technic needs no defense, and nothing I can say will or should detract from its popularity as a diagnostic measure. At the same time it is worth remembering that all diagnostic methods have inherent limitations, not the least of which is human frailty. It is discouraging to me to see how many young investigators are keenly interested in learning how to perform coronary arteriograms but have not made even rudimentary attempts to learn the anatomic distribution of the coronary arteries. Some such knowledge will inevitably accrue as the coronary arteriograms are studied, but coronary arteriography is not the most suitable means for studying coronary anatomy per se. To my knowledge there is nothing magically different about the gross coronary anatomy of the living patient, compared to that in the postmortem heart. During life the vessels of course twist and bend, and blood is flowing through them (at speeds and in flow patterns which may or may not bear close resemblance to that of angiographic dye), but their anatomic distribution is the same before and after death.

In the past few years I have been invited to examine coronary arteriograms taken by a number of different investigators, particularly in cases of angina "without coronary disease." In a few of these I have been asked additionally to look at the coronary arteries post mortem. This experience has led me to the conclusion that the most frequent explanation for angina without coronary disease is an incorrect interpretation of the coronary arteriogram. In most subjects with ischemic heart disease, it is well known that there is not only a clearly visible abnormality of the coronary arteriogram, but more than one large coronary artery is usually involved. However,
patients with angina "without coronary disease" are by definition a selected group in whom it may be anticipated that situations other than the usual will prevail.

Some of the errors in interpretation of coronary arteriograms should be recounted here, although it must be added that the incidence of such errors is inversely related to the experience of the coronary angiographer. Occlusion of a major coronary branch is sometimes sufficiently close to its parent vessel so that little dye enters the unoccluded segment; this is particularly difficult to evaluate relative to diagonal branches of the left coronary artery. Complete occlusion of one of the three major coronary arteries is sometimes followed by development of radially distributed collateral branches just proximal to the site of occlusion; this "starburst" effect gives a striking and easily identified appearance when one is familiar with it, but it is sometimes misinterpreted as normal branching. The morphology of the luminal narrowing lesion is sometimes such that the radiographic image of contrast dye passing that point is wide while the volume of blood passing the same point is small; this error can be minimized by assessing the speed of filling of distal segments, the pattern of flow in cineangiograms, and by multiple projections, but the error still occurs in occasional instances. This is not the place to catalog all sources of possible errors in interpreting coronary arteriograms, and the examples above indicate only a few to illustrate the point.

Coronary arteriography has made us think more critically about the validity of a clinical diagnosis of ischemic heart disease. When the coronary arteriograms are interpreted as normal, the clinician must first carefully reexamine his evidence supporting the diagnosis. If, in his best judgment, the diagnosis is still valid, then the patient may have abnormal small coronary arteries or stingy hemoglobin. But, in my experience, the apparent paradox has most often been explained by the presence of abnormal large coronary arteries despite "normal" coronary arteriograms.

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References
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