5-1-1941

Anoxemia of the myocardium as the cause of angina pectoris

John J. McFee
University of Nebraska Medical Center

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ANOXEMIA OF THE MYOCARDIUM AS
THE CAUSE OF ANGINA PECTORIS

BY
JOHN L. MCFEE

SENIOR THESIS PRESENTED TO
THE COLLEGE OF MEDICINE
UNIVERSITY OF NEBRASKA
OMAHA, 1941
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I. Introduction And Definition

"The man stops suddenly. Carefully turns, goes slowly to the store window, and gazes into the case. He is not, however, seeing any of the articles on display. His face is drawn and anxious, his muscles rigid, his respirations shallow, and rather frightened. This attitude he maintains for a few moments. Then, takes a deep breath, and sighs, and proceeds deliberately on his way." (49)

Isn't this a peculiar way for a person to act? However, if the truth were known, our friend has just experienced an attack of angina pectoris. He may have suffered a severe pain over the precorcium, the epi-gastrium, the neck, or the left arm. On the other hand, it might have been simply a sense of constriction in the chest, of inability to breath adequately, a sinking sensation, a feeling of weakness, and impending death. The man knows without mistake, that something is wrong. In the past, his experience has taught him that activity or effort will prolong this agony. The peculiar nature of the symptoms, an appre-
hension of death, foretells against aggravating it. His self-consciousness naturally forces him to restrain from others so that they may not witness his discomfort.

At last, when the anginal attack has subsided, he again feels well and strong, and is capable of continuing as before. (49)

In Heberden's early description of angina pectoris are found the essential features of angina pectoris. It is in this description that the condition of angina pectoris rightfully belongs. It is characterized by (a) paroxysmal pain usually pectorial, provoked by an increase of the demands of the heart and relieved by a diminishing of the work of the heart, and (b) the likelihood of termination by sudden death. (23)

The answer to the cause of this phenomenon has been studied for a considerable time. According to the most present day observers in heart disease, the explanation concerns itself with the lack of nourishment or anoxemia of the heart muscle.

It is the desire of this thesis to prove the theory that the cause of pain of angina pectoris, either in the functional type, or when there is an...
organic basis as in coronary disease, is a cardiac ischemia or anoxemia—that is, a lack of sufficient supply of oxygen to the heart.

The consensus of opinion is that anoxemia of the myocardium is the cause of genuine angina; nevertheless, anoxemia of the myocardium may exist without causing angina, and it must be confessed at once that all factors determining whether or not angina pectoris will develop are not clear.
II. Historical

On the twenty-first of July, 1768, William Heberden (1710-1801) read before the Royal College of Physicians, London, his classical "Some Account of a Disorder of the Breast" which he called Angina Pectoris on account of the sensation of strangling and anxiety which accompanies it. (15) (31) (55) (62) (71) It was based on twenty cases, none of which had been examined after death; but very tentatively suggested "a strong cramp, or an ulcer, or possible both." The title, angina pectoris, proposed by Heberden is not without its drawbacks and interest. Angina has, like quinsy, been used for sore throat and tonsillitis, probably because a strangling or choking sensation was thought to be common to both. (16) (62)

Though Heberden's title of angina pectoris has long been firmly established and recently endorsed by Thomas Lewis' term "Heberden's Angina Pectoris, Angina of Effort," other names and forms of angina pectoris have been suggested and described. Parry in 1799, called it syncope enginosa, but preferred syncope angi gens, as he did not consider enginosa to be strictly Latin. (13)
Heath, insisting unwarrantably on the pulmonary symptoms, thought it necessary to rechristen angina pectoris and to call it "spasmodic asthma." (71) Similarly, Baumes, impressed by the intensity of the painful phenomenon, proposed a new name, "sternalgia," thus misjudging the true nature of angina pectoris. (62) (71) At last the reality of the newly-described morbid entity was recognized and the name proposed by Heberden became definite. (71)

A claim was made for Rougnon (61) by his loyal countrymen, Baumes in 1808, Jacquot in 1865, and Peter in 1883, who contended that he gave the earlier account of the disease, but omitted to name it, which Heberden did. (55) (62) (69) On the eighteenth of March, 1768, Rougnon wrote a letter to Anne Charles Lorry, "Docteur--Régent de la Faculte de medecine de Paris," a fashionable court physician of Paris. This printed pamphlet of fifty-five pages described the sudden death on the twenty-third of February, 1768, of a Captain Charles, fifty years old, formerly a cavalry officer, and recorded the necropsy. This report, therefore, preceded Heberden's delivery of his paper before the Royal College of Physicians of London on the twenty-first of July, 1768, by four months, and the
publication of the volume (1772) containing it by four years. (62)

There has, however, been general agreement that Morgagni in 1761 described an authentic case. (62)
(69) The report was that of a well-known Italian physician, Ferrianni, who died of angina pectoris and the postmortem was done by Morgagni. (69)

Huchard credits Drelingcourt (1700), (7) (69) Thebesius and Bellini, (1703) with making the first observations of coronary sclerosis. Others from then on, especially Morgagni, make frequent references to the formation of calcareous masses or stones in the aorta, and allude frequently to such changes in the coronary vessels. Neither Rougnon nor Heberden associated sclerosis of the vessels with production of anginal pain. This relationship was suspected by Dr. John Hunter, but more definitely stated by his pupil, Edward Jenner, after finding extensive sclerosis in the heart of Dr. John Hunter, who suffered with angina pectoris and died of coronary occlusion. Jenner communicated his impression to Parry, and they were the first to really advance the theory that sclerosis of the coronary artery is the cause of angina pectoris. Kreysig suggested that the pain is produced.
because of lessened blood flow through the coronary arteries, because of their constriction from sclerosis. Blackhall, Germain, See, and Huchard, because of finding an occasional heart in which there was no gross pathological lesion in the coronary arteries, suggested the possibility of spasm of the coronary artery to account for lessened blood flow to the myocardium. (67)
III. Organic Factors

A. Coronary Artery Disease

It seems probable, however, that John Hunter (1728-1793) already knew quite well that angina pectoris was associated with disease of the coronary arteries; for in 1775 John Fothergill (1712-1780) published a fatal case on which Hunter performed the necropsy in 1775, and had reported that "The coronary arteries from their origin to many of their ramifications upon the heart were become one piece of bone." Reference may now perhaps be made to an earlier necropsy made by John Hunter on a case of angina pectoris in 1772, on which he reported nothing more than small patches of ossification in the aorta, and did not mention the coronary arteries, but Jenner, who was present, wrote to Perry, "I can almost positively say that the coronary arteries were not examined." (62) (69)

As early as 1895, Osler believed the pain in angina pectoris was due to anemia of the myocardium produced by disease of the coronary arteries. (62) Schwertman states that the underlying cause is a temporary coronary insufficiency causing an anoxemia.
of the heart muscle. Several pathological conditions may give rise to angina pectoris, one of the most common of which is a partial or complete closure of one of the main coronary arteries, or a branch as a result of coronary thrombosis. Another condition often associated with the one just mentioned, is the narrowing of these vessels by sclerosis. The third important cause is the narrowing or closure of the mouths of the coronary arteries as a result of syphilitic disease of the aorta. (59) (62)

Bennett (1937) believes that 99 per cent of the cases of angina pectoris as a result of the narrowing of the lumen of the coronary artery, the amount of blood to the heart muscle is cut down and an ischemia results. (6)

Keefer and Resnik (1928) attribute the cardiac pain in the majority of cases to coronary disease. LeCount reported sixty cases in which death resulted from disturbance of coronary circulation or from lesions generally regarded as caused by such difficulty. Of 175 patients who died from heart disease, only those with coronary disease had had symptoms of angina pectoris. (42)
Danielopolu (1924) as well as Keefer and Resnik (1928) conclude that it is possible to say that all angina pectoris is the result of an inadequate coronary circulation, which may occur when the arteries are healthy, but it is more likely when they are in a state of sclerosis. (19) (42) This suggestion will account for the frequency of coronary disease in angina; anginal symptoms may, nevertheless, originate in a heart in which the coronary arteries are healthy, or be absent even when there is extensive sclerotic change. (19) (34) (48)

The explanation appears to be as follows: The anginal attack arises from a disturbance of the balance between the work of the myocardium and its blood supply through the coronary arteries. (12) (19) (54) (69) (76) This disturbance may occur in the case of a healthy heart; but is more common if the coronary arteries are somewhat obstructed. It is conceivable that even healthy coronary arteries, faced by an excessive demand, may be unable to respond sufficiently to provide an adequate myocardial blood supply, and consequently, it is not out of the question that such a disturbance of balance may occur in a perfectly healthy heart. (12) (19) (40) (69) In this way can
be explained the anginal attacks occurring in young subjects following the rapid ascent of a mountain, or after cycling, or some other strained effort, when no coronary disease was found at the necropsy. Moreover, this suggestion explains those cases of coronary disease without anginal symptoms, where the slowness of growth, if obstruction in the coronary arteries has permitted the development of anastomotic channels, and the provision of a good supply. (12) (19) When an anginal attack occurs in a healthy heart after over-exertion, there is present a condition of coronary insufficiency without coronary disease; in case of extensive coronary obstruction without anginal attacks, there is present coronary disease without coronary insufficiency. (19)

While it was formerly believed that the coronary arteries were end arteries Blumgart has recently demonstrated that communications may exist between the coronary arteries. Watery solutions injected into one coronary artery are always found in the other coronary artery, demonstrating that even in the normal heart fine communications exist between the main coronary arteries. When, however, normal hearts were injected with colored lead agar mass Blumgart and his...
associates noticed that the passage of the mass from one coronary artery to the other side was unusual. Since the lead age suspension penetrates regularly only as far as arterioles forty microns in diameter, inner arterial collateral pathways of forty microns or more may be regarded as generally absent in normal hearts. Previous studies have demonstrated, however, that if narrowing of a coronary artery occurs, these larger collateral pathways develop and supply that area of the myocardium which would otherwise suffer from diminished blood flow. Vessels of the larger size are of major importance in obviating the effect of arterial narrowing and occlusions, on the other hand, the fine inner arterial communications of less than forty microns in diameter do not prevent infarctions following sudden thrombotic or embolic occlusions of a coronary artery clinically or after experimental ligation of an artery. (12)

In a series of 355 cases Blumgart (1941) found that there were 47 instances of angina pectoris. (12) In every case, examination of the clinical and pathological data suggested the existence of relative insufficiency of the coronary circulation. This coronary insufficiency, or reduced "coronary reserve,"
may be produced by factors which decrease the supply of blood or by factors which increase myocardial requirements. The chief factor decreasing the blood supply is mechanical obstruction to blood flow by arterial sclerotic narrowing or occlusion. (12)

Paterson (56) has studied intimal hemorrhage of the coronary arteries which are due apparently to rupture of the capillaries in the arterial wall. Such intimal hemorrhages are commonly found in recently thrombosed coronary arteries. His studies suggest that capillary rupture and intimal hemorrhages are closely concerned with the formation of most coronary thrombi. Thrombosis in the lumen of a coronary artery may be initiated by diffusion of blood from an intimal hemorrhage into the lumen, by necrosis of the intima or by retrograde capillary thrombosis. Paterson points out that during periods of physical stress a rise in pressure in the capillaries in the intima may occur, causing their rupture. (56) Complete closure of a coronary artery by thrombosis may occur hours or days after the original capillary hemorrhage. (13)

Winternitz (13) has demonstrated the rich capillary network that is found in arterial walls, part of which is found in the neighborhood of sclerotic areas.
He has found that hemmorhages into the intima are frequently the precipitating factors in arterial thrombosis.

These anatomic studies suggest how unusual exertion may bring about arterial occlusion, hence, angina pectoris. With physical effort there is a sudden alteration of arterial pressure, cardiac action is increased, rupture of one of the capillaries or sinusoids in the arterial wall may occur, or a softened atheromatous plaque may rupture into the arterial lumen. If the hemmorrhage is large, there may be almost immediate occlusion of the coronary artery; if the hemmorrhage is small or slow, or if it is followed by a gradually growing mural thrombosis, the occlusion may develop slowly or remain incomplete. Thus, the concept of coronary occlusion or of angina pectoris induced by physical exertion may be explained. (13)

Boas (1939) reported fourteen cases of angina pectoris immediately following a non-penetrating injury to the precordium or unusual bodily effort. Eleven additional similar cases have been observed and further cases have been reported in the literature. (13) Undoubtedly the explanation given for such may be that cited by Paterson as stated previously.

14.
However, the complete acceptance of the coronary theory has two objections. Hubble (1930) recognized that many cases which were found at post mortem examinations to have extensive coronary disease, even with obstruction, had no history of attacks of angina pectoris. (34) Investigation into the coronary circulation has done away with this first objection. It is now known that anastamoses between the various branches of the coronary system are often very extensive, and sometimes, even in an acute obstruction, so free that the supply of the blood through the myocardium is not seriously jeopardised and no anginal pain develops. The second objection is not so easily dismissed. Cases of angina pectoris in which there are no demonstrable lesions of the coronary arteries have frequently been described in the literature. These cases have been examined very critically by many authors and the conclusion is inevitable: Angina pectoris can occur in the absence of any coronary lesion.

To account for the cases of angina pectoris present in the absence of any lesion of the coronary arteries an ingenious and attractive idea of a spasmodic constriction of the coronary arteries was hypo-
thesized. This however, is only a hypothesis which is not very susceptible of proof and if the myocardial anoxemic theory is accepted, it seems to do away with the need for any coronary spasm. (42) Keefer and Resnik (42) oppose this further development of the coronary theory on other and more debatable grounds. First, they say that it "is difficult to understand how vasoconstrictors could affect a coronary artery which was already altered by coronary sclerosis."

No one, today, postulates vasoconstriction in a calcareous artery. It is enough for the production of angina pectoris that when the myocardium calls for a productional blood supply, the diseased artery fails to dilate. Again they say: "One would expect, if coronary spasm were the actual cause of angina pectoris to find fairly frequent examples of myocardial infarct without organic obstruction of the coronary arteries. This seems an unreasoning argument. Is it rational to expect a temporary and relative diminution in the blood supply of the myocardium to result in the production of a myocardial infarct? It has been previously proved that a permanent and absolute occlusion of a branch of the coronary circulation may not result in an infarction owing to an adequate
coronary anastomosis. In the third objection to the theory of coronary spasm, it seems likely that they are on surer ground. Keefer and Resnik (42) quote the animal experiments of Anrep and Segall which prove that vasoconstriction of the coronary arteries is due to vagal action. Thus stimulation of the vagus is always accompanied by a slowing of the heart rate and they quite rightly point out that there is no characteristic alteration of the pulse-rate in angina, and certainly no constant deceleration. (34)

It is impossible to accept the theory of coronary disease as a complete explanation for all cases of angina pectoris, and that the occurrence of coronary-arterial spasm as a factor in the causation of angina pectoris is by no means improved. Coronary spasm is only a hypothesis unless there is proved to be no condition present which is capable of producing an anoxemia of the myocardium. (34)
B. Aortic Insufficiency

Since Heberden's classical description of angina pectoris in 1768 there has been lively debate as to the etiology of angina pectoris. Allbut believed aortic lesions were responsible for this syndrome. While MacKenzie, on the other hand, held that coronary artery disease leading to myocardial exhaustion was found in practically all of these cases and, hence, was the cause. (16)

Keefer and Resnik (1928) observed in thirteen cases coming to necropsy, five had coronary disease alone, five had aortic insufficiency alone, and three had combined coronary disease and aortic insufficiency. (42)

Nothnogel, Neusser, Frainkel, Osler, Gallavarden, Longoscope, MacKenzie, and others (42) noted aortic insufficiency is accompanied by angina. Lord stated that in five of his six cases of angina occurring in syphilitic patients, there was aortic insufficiency. Gallavarden found that of his cases of angina with aortic insufficiency, 87 per cent were of syphilitic origin.

MacKenzie (42) observed angina pectoris in ninety patients with aortic insufficiency, 23 per cent of the 18.
total number of cases reported. It is not clear how many of his cases were due to syphilitic aortitis. In some, in which postmorten records were available, the coronary arteries were normal, in others, some degree of obstruction of the coronary arteries was present, either by narrowing of the orifices or sclerosis of the vessels. Resnik and Keefer (1928) reported in their cases of angina, seven cases occurred in patients with syphilitic aortic insufficiency. Of these latter patients, five came to necropsy, and in two there was partial occlusion of the coronary arteries. Among other authors who mention the occurrence of angina in cases of syphilitic aortitis and aortic insufficiency may be mentioned—Longoscope, five cases, and Lamb, ten cases. (42)

When angina pectoris develops in a patient with aortic insufficiency, the valvular lesion is usually of syphilitic origin. Angina pectoris is also seen in instances of rheumatic aortic insufficiency. Resnik and Keefer observed four patients with this type of valvular disease who suffered from seizures of angina pectoris; in the one case in which necropsy was performed, the coronary arteries were patent. In a group of thirty-three cases of aortic insufficiency 19.
in young person, in which the history of rheumatic infection was positive in 87 per cent. Clark found that many of the patients suffered from attacks of angina pectoris. (42)

Angina has also appeared in rare cases of rupture of the aortic valve. (42)

Various hypotheses have been advanced to explain the occurrence of angina pectoris in cases of aortic insufficiency. (42)

Lewis and Drury (42) first demonstrated that the circulatory changes taking place in arteriovenous fistula were similar to those seen in aortic regurgitation, namely, low diastolic pressure, high pulse pressure, water-hammer pulse, collapsing pulse, and etc. They presented evidence to show that these signs were dependent on a leak of blood from the arterial stream and suggested that the same was true in case of aortic reflux. Since the coronary blood supply pressure is dependent, for the most part, on the height of the diastolic blood pressure, and since in aortic insufficiency the diastolic blood pressure is characteristically decreased, it was reasonable to suppose that a diminished coronary flow was present in cases of aortic insufficiency. (42) (18) However, it remained for Smith,
Miller and Graber to demonstrate that the coronary flow was actually decreased in experimental aortic insufficiency in dogs, and that this decrease was caused by the lowering of the diastolic level. Resnik and Keefer believe they have definite proof that in aortic insufficiency there is a diminished blood supply to the heart muscle, satisfactory grounds for assuming that anoxemia of the myocardium may ensue. (42)

They state it is possible to show that practically all patients with angina pectoris do have a diminished blood supply to the heart, since practically all patients with angina pectoris have either coronary disease or aortic insufficiency. In the one case, the decreased flow is due to anatomic alterations in the coronary vessels, in the other, it is due to physiological changes resulting from the valvular lesion. The end-result in both conditions is the same, anoxemia of the myocardium. It is no longer necessary to assume that spasm of the coronaries takes place in angina, a hypothesis which rests in uncertain evidence and to which there are weighty objections. (34) (42)

Keefer and Resnik compare the occurrence of angina
pectoris in aortic insufficiency caused by syphilis and those cases produced by rheumatic aortic insufficiency. In syphilitic aortic insufficiency, the valvular lesion is "pure," it is uncomplicated by the presence of aortic stenosis. In rheumatic aortic insufficiency, however, there is likely to be associated a more or less marked degree of stenosis, which tends to counter-balance the effects of the insufficiency. The result is that usually the insufficiency is more marked in syphilitic cases as evidenced by the greater lowering of diastolic blood pressure, the higher pulse pressure, etc. In the second place, and probably of great importance, is the fact that many of the patients with syphilitic aortic insufficiency have, in addition to this lesion, narrowing or complete occlusion of the orifices of one or both coronary arteries. As either one of these lesions may lead to a certain amount of diminution of coronary flow, the combined effect of the two tends to cause a greater disturbance than is likely to occur in the average case of rheumatic aortic insufficiency. (42)

Contralto (16) (1937) states that aortic insufficiency, syphilitic in origin, is rarely associated
with angina pectoris except in those cases in which the coronary orifices are narrowed. He states that, although associated with aortic valvular disease, it is due to the insufficiency of the valve rather than to the stenosis. The explanation that is offered for this association is that coronary flow takes place during diastole, and with a low diastolic pressure that accompanies aortic insufficiency there is inadequate flow through the coronary system with resultant relative myocardial anoxemia. (18) (34) (42)

Harrison (18) confirms there are two important points about angina pectoris and aortic stenosis; (1) that there is no evidence of anything which can decrease the circulation of the heart in these cases, and (2) that in such patients there is much less relationship of the pain to exercise than in ordinary coronary angina. In cases without aortic stenosis Contralto (18) found, as a rule, at autopsy either coronary arterial sclerosis, luetic narrowing of the coronary orifice, or a well-marked aortic insufficiency, with a low diastolic pressure during life. The low diastolic pressure produces angina pectoris causing interference with the blood supply to the heart during diastole. In persons with aortic stenosis.
typical anginal seizures may occur in the absence of any of these factors, the aortic insufficiency either not being present at all or in many cases of such mild degree as to cause no lowering of diastolic pressure. In such cases the pathological evidence does not point toward diminution of coronary flow, and the enlarged coronary arteries suggest that the flow during life was actually greater than normal. However, this does not mean that the mechanism of angina is any different in such cases as that occurring in other patients.

The coronary flow has to be looked upon as not per se but from the standpoint of its relationship to the need for blood; the latter, of course, depends upon the oxygen consumption of the heart, which in time depends largely on the work done by the heart. The latter depends on three factors (1) the amount of blood expelled per unit of time, (2) the pressure against which this blood is expelled, and (3) the energy expended in imparting the velocity of this blood. (18)

The pressure within the ventricle during systole is probably enormously increased and this, of course, tends to increase the cardiac work. The velocity factor is under certain conditions, a relatively small 24.
fraction of the cardiac work. However, it may become the greatest factor in aortic stenosis, where, with a markedly narrowed orifice, the rate of flow must be enormously greater during systole. It is possible, and indeed quite likely, that the velocity factor is more than fifty percent of the cardiac work in a case of marked aortic stenosis. Therefore, even though the coronary flow increases, say threefold, it is quite likely that the cardiac work may be increased fourfold, and this would, of course, tend to produce angina pectoris through the usual mechanism of myocardial anoxemia. (42)

Cantelo (18) offers another explanation which depends on the likeness of the aorta and the coronary system to a common faucet suction pump. The water flowing through the larger orifice causes a suction on the smaller orifice which enters at right angles. The amount of suction is somewhat dependent upon the velocity of the flow through the larger orifice. He states that it seems reasonable to assume that in the normal heart with "paper thin" aortic valves, during systole these leaflets are fairly close to the coronary ostia preventing any such suction action. In cases of aortic stenosis with rigid, calcified,
immovable aortic valves, and markedly increased velocity of blood flow, it is possible that this suction may even draw blood out of the coronary arteries and lead to relative myocardial ischemia. (18)

LePlace (44) in a series of cases of angina pectoris found that angina occurred in 8.3 per cent of the cases in which the diastolic pressure was eighty mm. mercury, or above, 33.3 per cent in 16.7 per cent of the cases in which it was below forty mm. mercury. The fact that this syndrome did not occur most frequently in the latter group he concluded that a low diastolic pressure is of relatively slight importance in the pathogenesis of angina pectoris. The incidence of congestive failure was also studied, but its increase at low diastolic levels was insufficient to account for the relatively greater decrease in the incidence of angina pectoris in the same group. (46)

These observations by LePlace and others indicate that the appearance of angina pectoris in cases of aortic regurgitation cannot be attributed to an insufficiency of the coronary perfusion pressure during diastole. They support the view of Hochrein that the work of the heart is the most important factor in determining the volume of the coronary blood flow, and
that the myocardial circulation is relatively little affected by alteration in the diastolic pressure level. (44)
C. Aortitis

The aortitis of angina pectoris has special features which were observed as early as the end of the eighteenth century by Jenner, rediscovered in 1816 by Kreysig and confirmed by various contemporary authors. (71)

Brooks (1924) states angina pectoris is found in many instances in which, at post mortem, extensive disease of the aorta is present. (15) As a rule, those cases of aortitis which develop angina pectoris are such as show the disease changes most extensive in the first part of the ascending aorta, in or about the sinuses of Valsalva. It will be recalled that it is from this point that the coronary arteries take their origin, and in many such instances Brooks (15) has observed the degenerative or inflammatory process to be very marked at the openings into the coronaries. Here a small tumulus of tissue may in part obstruct the lumen of the coronaries. It is easy to assume that lesions similar to these may produce at times circulatory conditions precisely similar to those mentioned above as appearing in coronary endarteritis or coronary spasm, and the assumed mechanism may be
precisely identical. This is, however, not invariably the case, for in some instances no apparent lesions of this character exist. At least there can be no question that there is a frequent association of aortitis, occasionally without associated coronary disease, with angina. Angina pectoris is not always present even in very advanced instances of aortitis. (15)

Vaquez (71) (1924) attributes the principal role in the pathogenesis of angina pectoris to a stenosis of the coronary arteries produced by aortitis. He states that the stenosis is situated either at the very beginning of the artery, especially the left, or along its course. In a case reported by Potain, there were only two small plaques of aortitis situated exactly around the orifice of the coronaries, the orifices of which they obstructed. The rest of the aorta was remarkably healthy. (71)

Allbutt and Vaquez, and, recently, Wenkebach (42) strongly support the theory that many cases of angina pectoris have involvement of the aorta because all patients with angina pectoris have either arteriosclerosis or syphilitic aortitis.

Keefer and Resnik (42) (1928) discussed the
relation of aortitis to angina pectoris. They reported twenty-six cases of uncomplicated syphilitic aortitis, proved by autopsy, and in not one instance was there a history of angina pectoris.

They state in every case in which detailed information is given, either aortic insufficiency or coronary disease, or a combination of the two, is present in cases of angina pectoris associated with syphilitic aortitis. This is apparently true, too, in case of angina associated with aneurysm. Frankel called attention to the fact that angina occurred in patients with aneurysm, particularly when there was arteriosclerotic changes in the region of the coronary vessels. (42)

Allbutt's view was that the pain of angina was due to tension of the first part of the aorta, which was invariably the seat of an inflammatory lesion. Sudden death occurring in angina was, in his opinion, due to vagal inhibition of the heart's action. The main support for this theory rests on the finding of an aortic lesion in most cases of angina pectoris, and it is undoubtedly true that the post mortem records of patients who have suffered from angina pectoris during life show, as a rule, either aortic atheroma 30.
or syphilitic aortitis. The relevant objections to this theory may be briefly stated:

(a) Many cases of angina pectoris have been recorded in which no disease of the aorta was demonstrated after death. Allbutt confessed, for example, that he was unable to account for the occurrence of angina aortic regurgitation of rheumatic origin. (15) (42) (34)

(b) Aortic lesions occur very frequently without anginal symptoms, for instance on this theory, it is difficult to account for the variety of angina pectoris in aneurysm of the aorta. (34) (42)

(c) The average age incidence of syphilitic aortitis is a decade earlier than the average age incidence of angina pectoris. (34)

(d) The theory of death from vagal inhibition is inadequate. (34) (42) Lewis writes: "To accuse the vagus when unexpected syncope terminates life, in the absence of clear evidence of its responsibility, is unjustifiable. It is probable that sudden death in angina pectoris results from ventricular fibrillation and there is no experimental evidence to show that fibrillation of the ventricle is dependent on the vagal stimulation. Again there is no evidence that
the vagus is stimulated during an attack of angina pectoris, there is neither slowing of the heart rate nor any evidence of auriculo-ventricular block." (33)

(e) The high rate of incidence of aortic changes accompanying angina pectoris is well explained by an alteration in the coronary circulation. Aortic atheroma is often accompanied by coronary atheroma and in syphilitic aortitis the mouths of the coronary arteries are often obstructed. It has also been recently suggested by East and Bain that advanced atheroma of the aorta results in a diminished elasticity which impairs the head of pressure regulating the coronary circulation. (34)

Resnik and Keefer (42) (1928) and Hubble (34) (1930) as well as many others strongly believe that the aortic theory doesn't supply an adequate explanation for sudden death as does occur in angina pectoris. Allbutt said vagi stimulation was the cause of death in aortitis. In such cases, one would expect to find a definite decrease in heart rate, and it is well known angina pectoris produces no definite change in heart rate. A healthy heart withstands vagal stimulation as has been proven in experimental work.
IV. Functional Factors

A. Endocrine Disturbances

1. Hyperthyroidism

The association of hyperthyroidism and angina pectoris is not common. However, in all probability, the frequency of the association is slightly higher than is ordinarily supposed, as it is very easy to overlook angina pectoris in the presence of severe hyperthyroidism, or mild hyperthyroidism in a patient with angina pectoris. (30)

Lev and Hamburger reported six hyperthyroid cases, in four of which relief of angina followed partial thyroidectomy. Sturgis likewise reported a case of exophthalmic goiter and angina pectoris in which the latter condition was relieved following partial thyroidectomy. Hursthal analyzed 500 cases of cardiac failure in hyperthyroidism and found among them two patients with angina pectoris. Means, White, and Krantz reported an increase in the severity of the basal metabolic rate by the administration of thyroid preparations. (30)

The mechanism by which an increase in the basal heat production in the body, as induced by hyperthyroidism, ...
roidism, results in cardiac embarrassment has not been conclusively demonstrated. Haines and Keepler (1930) lean to the view that an elevation of the basal metabolic rate results in an increased volume output-per-minute from the heart, and that angina pectoris is largely the result of an inadequate supply of blood to satisfy the needs of the cardiac musculature for the moment. (30)

It is easy to conceive, then, of a heart, the coronary blood supply of which is sufficient under normal circumstances, but is inadequate to meet the demands placed on it by the added work of the heart produced by hyperthyroidism. Whitten (30) has shown in his injected preparations that there is great variability in the coronary circulation and that some apparently normal hearts may have a relatively small blood supply through the coronary arteries. Such hearts might withstand the stress of hyperthyroidism less well than hearts with a greater coronary circulation. Willius, Boothby, and Wilson (30) have called attention to the increase in the rate of blood flow in hyperthyroidism, and the resultant increase in the work of the heart.
Davies, Meakins, and Sands (30) found in patients with hyperthyroidism an increased volume output of the heart per minute; the increase is relatively proportional to the increase in basal metabolic rate. After thyroidectomy, the minute volume output of the heart dropped to normal and the output of the heart per beat diminished. Liljestrand and Senstrom (30) found an increased minute volume output from the heart in exophthalmic goiter. They felt that this fact accounted for the increased work of the heart in exophthalmic goiter and that the strain on the heart was dependent on the increased work. Robinson and Burwell (30) also found greatly increased cardiac output in a case of hyperthyroidism.

Sturgis (68) (1926) studied a series of patients complaining of thyroid disease at the Peter Bent Brigham Hospital over a period of nine years. He noted that angina pectoris occurred in some of the patients complaining of myxedema, as well as hyperthyroidism, and suggested some abnormal condition in each disease responsible for the occurrence of this syndrome. He stated that in exophthalmic goiter, patients have an elevated basal metabolism and, therefore, an increased load imposed upon the heart, even with the patient at 35.
complete rest. Sturgis states it is probably true also, that the mental status of a patient with exophthalmic goiter is of importance in relation to the cardiac seizures as they are constantly restless, irritable, and easily upset by minor incidents which would make but a slight impression on the average normal person. (68)

Hetzel (33) (1937) has shown by thyroidectomy if the basal metabolic rate is reduced to a minus twenty per cent or minus thirty per cent and then kept at minus fifteen to twenty per cent by giving thyroid extract, the patients suffering with angina pectoris are greatly relieved. The explanation would appear to be the lowering of the metabolic, so that the tissue requirements as regards oxygen are met by the lowered circulation; for as the pain of angina pectoris is due to an ischemia of cardiac muscle, a lowering of the metabolic rate may compensate for the inadequacy of the coronary circulation by decreasing the range of the tissue requirements to a level commensurate with the impaired blood supply. The lowered metabolism in general would also decrease the amount of work which the heart has to perform. (2) (14) (33)
2. Hypothyroidism

Hypothyroid states are frequently associated with angina pectoris as noted by several observers, including Zondek (1918), Assman (1919), Fahr (1925), and White (1931); but, many authors such as Brooks (1929) do not consider hypothyroidism as a direct cause of angina pectoris nor, per se, as a result of it. (4) (15)

Sturgis (68) (1926) in studying a series of patients with diseases of the thyroid at the Peter Bend Brigham Hospital over a period of nine years noticed a small group in whom the symptoms of angina pectoris were present. In the patients he noticed angina pectoris in cases of both hypothyroidism and hyperthyroidism. (68)

The occurrence of angina pectoris in patients with hypothyroidism is of interest from at least two stand points: (1) as a complicating factor, it introduces into the treatment of the disease with the thyroid gland; and (2) the possibility that hypothyroidism may be responsible, in rare instances, for some anatomical changes which causes angina pectoris. However, as this paper concerns only the pathogenesis and
not the treatment, we are only concerned with the latter. It is interesting to note that in about half the patients with myxedema that Sturgis studied, necropsy findings indicated an extensive atheroma of the aorta and also an endarteritis of the smaller arteries all over the body. Fishburg emphasized that various anatomic experimental and clinical findings indicate that a loss of thyroid secretion is, in some way, injurious to the vascular system. (68)

It has been noted in the majority of the patients with hypothyroidism who have been admitted to the Peter Bent Brigham Hospital that an unusual amount of thickening is present in the peripheral arteries. In some instances, these patients have been referred to the hospital with a diagnosis of generalized arteriosclerosis and the hypothyroidism overlooked. Therefore, it appears that hypothyroidism may be associated with arteriosclerotic changes in both large and small arteries. (68)

Beaumont (4) (1939) studied a case of hypothyroidism for three years. He was able to prove that sufficient thyroid would raise the patient's metabolism above the myxedema level to free him from anginal attacks. On the other hand, if sufficient thyroid was
given to raise the metabolism above a certain height (in the region of a minus one to a plus one) the anginal attacks reappeared. From this, he concluded that anginal symptoms in myxedema may result either from spasm or sclerosis of the coronary arteries or from myxedematous changes in the cardiac nerve cells and muscle. With the former, angina comes on after overdosage of thyroid, and with the latter, the anginal symptoms are relieved by adequate thyroid treatment. (4)
3. Diabetes Mellitus

Diabetes and angina pectoris have been recognized as clinical entities for many years, yet not until 1864 did Seegen (10) report on the occurrence of the two diseases in one patient. Nineteen years later, in 1883, Vergely (10) emphasized the frequent association of these two diseases. He became so impressed by the finding of the diseases together that he published a paper emphasizing the importance of examining with caution the urine of all patients with angina pectoris to make sure that diabetes was not also present. Many other workers made early observations on angina pectoris in relation to diabetes such as in France by Dreyfous and Huchard, in Germany, Meyer, and in England, by Ord.

Naunyn and Brunton, (10) before the days of insulin, wrote considerably on coronary disease in diabetes. More recently Warren and Root (10) at Joslin's clinic reported coronary sclerosis as an important pathological finding in 11 of 17 of their fatal cases over forty years of age. Wilder (10) in 17 of 49 fatal cases at the Mayo Clinic, and Strauss, (10) observed extensive cerebral or coronary sclerosis in 38 per cent of 54...
fatal cases in his clinic in Berlin. Blotner (10) noted coronary sclerosis as a pathological finding in nearly half of his cases.

Hetenyi (10) reported two cases of diabetes associated with angina pectoris in which the anginoid attacks appeared to be influenced by insulin. One of these patients developed precordial pain after insulin alone. However, the pain did not develop when glucose and insulin were given together. The other patient developed an attack of angina pectoris a few hours after an insulin injection and this was relieved immediately by an intravenous injection of glucose.

Edwards, Page, and Brown, (10) showed that insulin hypoglycemia produces a decreased dynamic action of the heart. Visscher and Muller, and Brems and Holten (10) found an increase in blood pressure after insulin injections. Budingen (10) proved that the diabetic heart, in order to function properly, requires a higher blood sugar concentration than normal. Each of these facts might account for the occurrence of a cardiac accident such as angina pectoris after an insulin injection.

Foote and Graybiel (25) found in 7,000 cases of diabetes mellitus, 210 cases of angina pectoris. This number exceeded so markedly the incidence of angina...
in a general hospital population, that they concluded there was a specific influence on the part of diabetes.

In the New England Deaconess Hospital and in a large series of cases reported by Warren (25) the incidence of coronary thrombosis with infarction of the heart was found in 12 per cent of diabetic patients. Blotner (25) reported in 77 cases of diabetes a marked disease of the coronary vessels in 45 per cent. Advanced coronary disease, as well as sclerosis of the myocardium, has been present in every case of angina pectoris examined postmortem at the New England Deaconess Hospital. The character of the sclerosis and calcification of the coronary arteries was uniform. The coronary arteries are of the muscular type and show changes strikingly similar to the changes found in muscular arteries of the legs in diabetic gangrene. The advanced character of the myocardial changes in diabetic patients, in spite of the mildness of the anginal attacks is a distinctive feature clearly shown by the autopsy data at the New England Deaconess Hospital. It is surprising how many diabetic patients with severe coronary sclerosis do escape having angina pectoris. (25)
There is very definite evidence to prove that patients with diabetes are prone to develop vascular disease. It is to be remembered that coronary vessels are likely to be implicated as well as other arteries of the body and, therefore, attacks of angina pectoris may follow. (6) (10) Diabetic patients with coronary disease may have a well-marked pathological process involving the heart muscle, and yet have no cardiac symptoms of any sort. On the other hand, they may have long-standing hypertension, and symptoms of congestive failure of angina pectoris. (10)
4. Hyperadrenalism

Raab, (58) (1938) reports several observations which might indicate that rapid excretion of adrenalin may have an essential part in the pathogenesis of an attack of angina pectoris. He states that muscle exertion, mental excitement, and cold, are conducive to attacks of angina pectoris. This mechanism takes place by means of the elimination of adrenalin on the cardiac muscle that is impaired by coronary sclerosis.

It has been shown that thyroidectomy is done, in some cases, because of the inhibiting effect on the production of adrenalin. However, Raab suggested a more simple and less dangerous means of inhibiting secretion of adrenalin by irradiation of the adrenals. In fifty-eight patients under observation for six months, forty were considerably improved or entirely free of complaints following irradiation. Seventeen cases were relieved of their symptoms with only one irradiation. (58)
B. Anemia

Herrick and Nuzum in 1918, were the first to describe cases of pernicious anemia with symptoms of angina pectoris. They found four cases in a group of two hundred patients suffering from primary anemias. Three of these patients died, one in an anginal seizure, but no autopsies were obtained. In 1926 Coombs, in a series of thirty-six patients with pernicious anemia found angina pectoris associated with this condition. One of these patients died and at autopsy diffuse atheroma of the aorta was found. The coronary arteries were not mentioned. Cabot's book on heart disease appeared about this time, in which he made the following statement: "I have seen three cases of intense and typical angina associated with pernicious anemia and without coronary change. One showed moderate sclerosis of the aorta, the others none. All were strictly dependent on exertion and were relieved by rest. Such cases, like those seen in convalescence from pneumonia and other infections makes one skeptical of any etiology based wholly on organic and permanent changes either in the coronaries or the aorta." (17) (23) (32) (66)

Hunter, Sturgin, Conners, Evans, Levine, Elliott, 45.
Smith, Colvin, Beech, and Donald (42) each told of but a single case, while others quoted from larger statistics; Reid (42) in 1923 reviewed the post-mortem records of cases of pernicious anemia at the Boston City Hospital from 1916 to 1921 and found eleven cases which presented cardiac aspects. Wilkinson (42) in a study of three hundred and seventy cases of pernicious anemia found three cases with symptoms of angina or coronary thrombosis. Keefer and Resnik, Porter, Pickering and Wayne, Hochrein and Mathes, Paschkis, Bloch, Zimmerman, Reichel, in large series of pernicious anemia cases found comparatively few with anginal symptoms. (42) (66)

Herrick (23) in 1927, described three more instances, in two of which arteriosclerotic changes of the coronary arteries were found. Herrick, in his review of the literature remarked that the combination of pernicious anemia and angina pectoris have been infrequently noted, and believed that coronary disease was partially responsible for the presence of the anginal syndrome. He assumed that blood of poor quality going through somewhat narrowed arteries might favor on slight provocation the development of an anginal attack. (66)
Willius and Giffin (23) reviewed fifteen hundred and sixty cases of pernicious anemia encountered at the Mayo Clinic. They found the anginal syndrome was present in forty-three (2.7 per cent) of these patients, in only one of whom a postmortem examination was made. Unfortunately, permission to remove the heart was not granted, and the smallness of its size was the only feature remarked upon.

Levine (66) in his study of pernicious anemia, complicated with angina pectoris, makes the following statement, "Even with 1/12 of the normal number of red blood cells, I do not believe that the anemia would initiate an attack of angina pectoris without some background of coronary disease." Many have reported improvement and often complete cessation of anginal attacks following transfusion, and, more recently, anti-anemia therapy. (22) (66)

Lewis, Wayne, Pickering, and LaPlace in a study of the influence of anemia on angina pectoris noted four of six severely anemic patients seized to have pain when the hemoglobin had risen above fifty per cent. Their observations lend additional support to the belief that angina pectoris and intermittent claudication are due to similar mechanisms in the heart and
skeletal muscles. They, as well as Keefer and Resnik, Willius and Giffin, Cabot, and many others, conclude that the anginal syndrome in pernicious anemia is due to anoxemia of the myocardium and not to the coronary or aortic sclerosis. (6) (23) (32) (42) (53) (66)
C. Gastrointestinal Disorders and Gall Bladder Disease

The similarity of the pain of angina pectoris and the pain due to certain lesions of the gastrointestinal tract and the gall bladder is not unusual, and is well known. The immediate cessation of an attack of angina pectoris following eructation of gas as well as the initiation of an anginal attack following a heavy meal or gaseous distention is not uncommon. (22)

Bellet (5) states that neither the evidence available in the literature nor his own clinical experience justifies the conclusion that gall bladder pathology can act as an etiologic agent in producing actual myocardial changes in an otherwise normal heart. However, he states that it can act as an aggravating factor in the presence of already existing myocardial disease and, in many cases, it may precipitate serious cardiac disturbances such as angina pectoris. Experimentally in dogs, Bellet and his associates have observed no change in the heart function upon distention of the gall bladder in the presence of a normal heart, but when the heart was diseased, serious cardiac disturbances were observed. (5)

Those cases that Bellet and his associates (5)
observed where the gall bladder was considered to be the causative factor in the production of serious cardiac disturbances occurred in patients with myocardial disease. The occurrence of severe attacks of biliary colic in patients with various types of myocardial disease for example, arteriosclerosis or coronary artery disease, may be a serious matter. Attacks of biliary colic may produce a strain on the cardiovascular system sufficient to produce major cardiac attacks simulating that of angina pectoris. (5)

One must not overlook the fact that a considerable number of cases of myocardial diseases of various types may coexist with involvement of the gall bladder either due to a cholecystitis or a cholelithiasis. In those cases where it is difficult to distinguish attacks of gall bladder colic and myocardial ischemia as a result of coronary artery involvement, the possibility should be borne in mind that both conditions may coexist in the same patient.

Necropsy statistics indicate the presence of a high percentage of gall stones in cases of women over fifty years of age who have died from various causes other than cholelithiasis. Tennent and Zimmerman (15)
observed a series of 1,600 consecutive autopsies of which 694 were on individuals over forty years of age. They found 126 cases of arteriosclerotic heart disease of which 23 showed coexisting gall bladder disease. Rehfus (5) studied 200 consecutive cases of gall bladder disease and found that in 71 cases, 35.5 per cent, there was evidence of cardiac consciousness in some form. Angina pectoris was suspected in 6 cases, or 3 per cent. Willius and Fitzpatrick (5) report of 596 cases of chronic disease of the gall bladder of which 229 cases, or 39 per cent, had organic disease of the cardiovascular system. Of the entire series, 5 cases of angina pectoris were noted. Kahn and Barsky (5) reviewed 200 cases of angina pectoris and found gall bladder disease in 10 of the cases. From this, Bellet concluded that the association of gall bladder disease and cardiovascular pathology is by no means rare.

Edieken (22) reported a woman with spasm of the cardia which complicated effort angina of several years duration. He was able to show by electrocardiogram and X-ray examination, evidence of coronary disease, aortic disease, and spasm of the cardia. When the patient swallowed, the attacks of pain were elicited.
similar in final distribution, but somewhat different in initial location of true attacks of angina pectoris. The chief differences between the two types of attacks of pain were thus: The attacks of long standing angina pectoris were induced by effort or excitement, relieved by rest and glyceryl trinitrate, and uninfluenced by antispasmodics. The attacks that followed swallowing were not influenced by rest or glyceryl trinitrate but were relieved by antispasmodics. These observations suggest that spasm of the cardiac region was a significant factor in the mechanism responsible for the attacks of pain after swallowing. Von Bergmann has found by X-ray examination that distention of the esophagus at, or just above the cardiac region, is frequently found in patients with angina or "anginoid" symptoms.

Jackson and Jackson (36) in 1936 stated that angina pectoris is due to acute incoordinated spasmic contractions of the esophagus and stomach. Due to gas or other stomach contents entrapped under pressure, the walls of either viscus with their contained or adjacent nerves and tissues are strained or injured. They showed that the electro stimulation inside of the esophagus at an appropriate location within the chest produced muscular contractions and pain in exactly those
areas of the body in which pain is developed during acute attacks of angina pectoris and coronary thrombosis. They concluded the nerve innervation was strictly ipsilateral and does not come from the heart. (38)

Porter (35) described a case of diaphragmatic flutter with symptoms of angina pectoris. In this case, the fluttering movements of the diaphragm, 250 or more per minute, were superimposed on the respiratory diaphragm movements. The patient complained of an agonizing pain in the left pectoral area accompanied by a cramp-like pain in the left arm and ring and little finger of the left hand. The left phrenic nerve was injected with procain hydrochloride which caused the pain to disappear immediately. The diaphragmatic "flutter" ceased in the left side of the diaphragm it occurred on. Seven hours later (when the local effects of the drug had worn off) all of the earlier symptoms occurred. Procaine was again injected, but this time into the right phrenic nerve, which resulted in immediate disappearance of pain, relaxation of the right side of the diaphragm and disappearance of the "flutter". When the local anesthesia wore off the pain and "flutter" returned. The
heart and aorta were entirely normal. Porter was convinced that this case was instructive in showing that abnormal movements of the diaphragm, probably in the neighborhood of the central tendon and cardiac orifice, can lead to painful disturbances that undoubtedly involve the same sensory nerves that carry the pain from the left arm and ring and little finger in a typical attack of angina pectoris. Jackson and Jackson (35) believe a procaine paralysis of the phrenic nerves with immediate relief is practically analogous to the relief obtained by excision of the superior cervical ganglion or of one lobe of the thyroid gland, but with exception that these latter cases may involve two mechanisms instead of one motor mechanism involved of paralysis of one phrenic nerve.

Swalm and Morrison in 1938 (70) studied four patients with typical angina pectoris symptoms simultaneously with balloon distention and kymographic recordings of the muscle activity of the esophagus and stomach, electrocardiographic tracings were recorded. In three of the patients severe pain was produced. Characteristic pain was produced as seen in angina but still more severe. Swalm and Morrison concluded this was perfect demonstration of the fact that stimuli
arising from the esophagus and stomach can induce dangerous cardiac changes. Two patients developed marked changes in the R-T segments, including marked evidence of ventricular irritability evidenced by multifocal ventricular contractions. This likewise corroborates the work done by Fitz-Hugh and Wolferth (70) to the effect that gall stones can reflexly cause inverted R-T waves, and upon the performance of cholecystectomy for stones, a complete return to normal electrocardiogram in as early as six weeks post-operatively. Along with this, there is frequently disappearance of angina seizures and symptoms such as palpitation, heart consciousness, dyspnea on exertion, and effort limitations.

Wolffe and Digilo (70) have recently shown that there is a relationship of the gastrointestinal tract and the cardiovascular system. They brought out the fact that morphine sulphate per se, when administered in cases of acute coronary occlusion is distinctly detrimental except in cases of excruciating pain. They agree with Hymen and his associates (70) that the indiscriminate use of morphine sulphate in acute coronary thrombosis is one of the major facts in the production of the associated gastrointestinal dis-
turbances.

Swalm and Morrison (70) recently reported eleven patients complaining of gastrointestinal disease, six of whom had angina pectoris, three, proven coronary occlusion, and two, rheumatic hearts. It was possible to abolish completely, the anginoid syndrome in four of the six cases by concentrated gastrointestinal regime, involving diet, non-surgical biliary drainage, antispasmodics, sedatives to the autonomic and central nervous system, attention to the bowels and general hygienic measures. (70)

Bruno Kisch (28) and his pupils by explaining the mechanism of irradiation of autonomic reflexes, made it finally possible for us to understand how an affection of the gallbladder or of the kidneys, or some pathologic condition or accident in the abdomen or in the thorax can cause stenocardial pain. The angina pectoris thus reflexly produced is not different from true angina pectoris in as much as an ischemic condition of the myocardium is present in both. It is true, of course, that stenocardial pain need be the result of neither an organic heart lesion nor irradiation of the autonomic reflexes from a diseased or functionally disturbed extracardiac organ. The pain (always in

56.
the thoracic wall, not in the heart itself) may be radiated to the chest wall, for instance, from a diseased gallbladder. This is not the precordial pain known as angina pectoris. (28)

Katzman (41) states that all pains in the heart regions not due to anoxemia of the heart muscles are not anginal. There can be no pseudo-angina. The pain is due either to angina pectoris or it is not due to angina pectoris. Angina pectoris may be of all degrees of severity, from very mild to agonizing, and even to the production of a fatal termination. It may be diagnosed by the sudden onset of a pain of short duration causing the patient to stop short. There is no shock accompanying the characteristic vague indescribable sensation of unrest or distress. The pain is relieved by nitroglycerine or rest. There is no characteristic electrocardiogram. However, the electrocardiogram often shows changes during the attack of angina which subside after a nitroglycerine tablet is taken which would definitely prove the cardiac basis for the angina. Electrocardiographic evidence of a coronary artery disease is shown by about 80 per cent of the patients suffering from angina. The blood pressure in angina is not lowered, which differentiates the
anginal pain from that of coronary occlusion, in which condition, the blood pressure often drops precipitately. The demonstration of arteriosclerosis in retinal or leg arteries is of some aid. Exercise tests are important, as pains that disappear on exertion are not anginal.

(41)
D. Hypertension

Davis and Klainer (20) reported a series of cases in which essential hypertension played a major role in the production of angina pectoris. They studied 21 cases of angina pectoris in which there was no evidence of hypertension, and forty cases which showed hypertension. They were able to demonstrate that hypertensive heart disease predisposes to attacks of angina pectoris in patients with lesser degrees of coronary sclerosis.

Two factors which were present in these patients having hypertension and may have favored the occurrence of angina were: (1) cardiac hypertrophy, and (2) increased cardiac work. Wearr (20) suggested that cardiac hypertrophy interferes with the nutrition of the heart muscle, for the number of capillaries remains unchanged in spite of the increase of muscle mass. Harrison (20) demonstrated that oxygen diffusion into the muscle fibers is probably impaired when the muscle fibers increase in thickness. Cardiac hypertrophy was noted in 80 per cent of the cases of hypertension reported by Davis and Klainer. (20) Congestive failure itself is a factor in the production of hypertrophy, so
that in many of these cases it was impossible to ascer-
tain how much of the hypertrophy was caused by the hy-
pertension alone. Davis and Kleiner (20) reported 8
patients with angina pectoris unassociated with a se-
vere coronary disease in five of which the hearts were
markedly hypertrophied, weighing from 600 to 840 grams
at necropsy. In these cases, hypertrophy was probably
and important factor in the production of the anginal
syndrome.

A factor present in all cases of essential hyper-
tension is increased cardiac work; this has been shown
to be of importance in the angina pectoris associated
with thyrotoxicosis, and perhaps in chronic anemia.
It is probably important in the production of angina
pectoris, in cases of hypertension without severe coro-
nary disease. (20)

Groedel (28) states that many cases of angina
pectoris and some cases of acute coronary occlusion
are primarily blood pressure patients. He points out
that one must not forget the important fact that an
unstable blood pressure can lead to temporary dilat-
tion of the aorta and, in turn, to a temporary par-
tial stenosis of the mouth of the coronaries. A sud-
den depression or elevation of the blood pressure
60.
disturbs the coronary circulation more markedly and more unfavorably than that of any other organ. It is true that the resultant coronary attacks are usually mild, but they can be followed by substantial changes in the heart. This is especially true when the coronaries are diseased. (28)
V. Mechanism of Pain

Keefer and Resnik report the striking similarity between angina pectoris and intermittent claudication as having long been noted. In both instances, the pain is brought on by effort, it is cramp-like in character, and rapidly relieved by rest. In intermittent claudication, there is not any question about the cause of the pain. It is due to diminished blood supply to the muscles. (42)

The experimental work of MacWilliam and Webster (42) is important in explaining the pain in skeletal muscles. They found that when the blood supply to the arm is shut off by constriction, pain is not caused, even at the end of twenty minutes, provided the muscles remain quiet. When, however, the ischemic arm is made to contract, fatigue is brought on much more quickly than it is in the normal arm, and at the fatigue point, there is severe pain. Moreover, pain can be elicited even before the fatigue point is reached, at a time when the contractile power of the muscle is still good. This latter fact is of importance, since it is at least a partial answer to the objection that may be raised, namely, that heart muscle cannot be
fatigued. It demonstrates that whether or not there is any relationship between pain and fatigue under the circumstances of a muscle contracting when its oxygen supply is inadequate, pain is the earlier manifestation. In view of the close correspondence of these results with the clinical facts of angina pectoris, these authors suggest that processes of essentially the same nature are responsible for the pain in angina pectoris.

Even more convincing evidence is produced by the natural experiment of acute coronary obstruction, a condition characterized by an outstanding circumstance, the production of a sudden acute anoxemia of the myocardium. It is scarcely necessary to call attention to the similarity of this pain to that of angina pectoris. (42)

It has been stated before that the term "angina pectoris" should be applied only to the condition that corresponds to the one described by Heberden, characterized by a more or less typical pain and by the likelihood of termination by sudden death. Keefer and Resnik have insisted on the importance of this second feature, because they believe the evidence is sufficiently strong to attribute its occurrence to the same underlying cause that brings in the pain, anoxemia of
the heart muscle.

There is not any doubt that there are other types of cardiac pain which closely simulate "true" angina pectoris. One may add that in some instances, the pain may be indistinguishable clinically from the pain of the condition described by Heberden. Yet these pains do not deserve the name "angina pectoris" since they do not have the same cause. They do not depend on a disturbance of function that may lead to sudden death. The fact that the pain may closely resemble that of angina pectoris need not lead us astray in our formulation of a conception of the pathogenesis of angina. It must not be assumed that pain occurring in a certain region of the chest and radiating in a characteristic way is necessarily synonymous with the condition called angina pectoris. (42)

The pain produced is, to some extent, dependent upon the sensitivity of the patient. The peripheral origin of this pain theoretically may be found in any part of the heart and aorta, since nerve terminals which seem to be sensory are found scattered diffusely throughout the walls of the heart and aorta. Experimental mechanical stimulation of the coronary sheath and adventitia of the aorta has shown these to be sensitive, (44)
while the endo, myo, and epicardium are said to be relatively insensitive. The stimulus for the pain is thought to be due to the accumulation of some metabolite, perhaps lactic acid in the myocardium. However, these questions are not entirely settled. (42)

The course of the pain producing stimulus is better known at present. Most of the painful stimuli are conducted along the sympathetic afferents which include the superior, middle and inferior sympathetic cardiac nerves, and the most recently discovered thoracic cardiac ganglia respectively. However, some unconscious stimuli are conveyed to the medulla through the vagi. The sympathetic cervical ganglia have few direct connections with the spinal cord, so that impulses must be relayed over connections between these and the upper five thoracic sympathetic ganglia from which white white ramii communicantes run to the spinal cord. A difference of opinion exists as to whether these sensory impulses are conveyed up the spinal cord by direct or indirect pathways, or both, to the thalamus. (42)

Katz (42) believes that the greatest support of the ischemic theory has come out of the work on human skeletal muscle. "The pain which develops in contracting muscle during ischemia might be caused (1) by the
direct or indirect action of the lack of oxygen which accompanies ischemia. (2) by the diminution of other materials normally supplied by the arterial blood, (3) by the incomplete mechanical removal of products of muscular metabolism which follows the retardation of the blood flow, or (4) by the combined action of several of these factors."

Katz (40) concluded that the stimulus for pain appears to consist of some metabolic product (or products) which is produced quantitatively in proportion to the work done by the heart. The amount of the chemical product produced for a given quantity of work is increased when the diastolic blood pressure is elevated, because the heart has to exert more effort in raising the pressure of its content above the diastolic aortic pressure before it can expel the blood. This, in part, is also the cause for the inefficiency of the rapidly beating heart. A similar inefficiency occurs when the heart is failing, because the heart dilates in order to do its work.

Katz believes the accumulation of the metabolic product which acts to stimulate pain is checked, in part, by a mechanical, and, in part by a chemical process. The first is a washing away of the substance by the cir-
culating blood, the second is a local conversion to some other substance in the presence of oxygen. This pain producing substance will, therefore, increase in concentration whenever the circulation is slowed or whenever the oxygen content of the blood entering the coronary arteries is decreased.

Gilbert (29) believes there is a reason to assume that, in some cases angina may be due to vasomotor factors which are responsible for the lack of equilibrium between the blood supply and the demand of the heart muscle. One would have to consider a failure of the vasodilator mechanism to respond to increased demand, a failure of relaxation of the vagus tone which Rein has shown to be present or, in some cases, an actual vasoconstriction. Theoretically, one or the other mechanism might be the determining factor in different cases.

If one assumes that the lack of equilibrium between the needs of the heart muscle and the blood supply can result from vasomotor changes or from lack of such changes, as well as from anatomic changes, one might explain a great many of the observations regarding not only angina pectoris but degenerative changes in the heart muscle which it is difficult to explain.
on a purely structural basis. (29)

It is recognized, for example, that angina pectoris frequently occurs in patients of whom there is no clinical reason to suspect pathologic changes in the heart or its vessels and in whom there is no clinical or laboratory evidence of such changes. At autopsy such persons frequently show only such alterations as would be expected at the age at which they die. It must always be borne in mind that most persons will have very definite coronary changes by the age of 45, as shown by Brooks. (29)

Gilbert (29) states that the assumption of a vasomotor factor would also explain why angina seems to be more frequent in a group of persons who appear to be more highly organized or less stable nervously or who have what Houston referred to as the "spasmogenic aptitude." In such a group, autonomic imbalance is frequently expressed in many ways.

Gilbert (29) continues to state the assumption of such vasomotor phenomena would also explain the frequent occurrence of angina in patients working tensely, under conditions of stress and strain, with inadequate rest and relaxation. There is reason to think that fatigue and emotional stress also tend to produce an
autonomic imbalance, just as during the World War the aviators showed evidence of an overlabile autonomic system as the result of staledness. This condition would be relieved by a period in the rest camp. (29)

This vasomotor phenomena would also explain why the patient who suffers daily attacks of anginapectoris of effort under the strain of his daily work is able to undergo much more physical effort without attacks while he is away on vacation. It has been noted that patients on their return from vacations experience the return of attacks of angina.

It would explain also the occurrence of anginal pain in the so-called effort syndrome, or neuro-circulatory asthenia. Whatever the group with this condition may or may not be, it is a group of younger persons characterized by an overlabile autonomic system, responding to smaller stimuli than normal. This condition frequently follows as the result of fatigue or of physical or psychic trauma. It may follow such trauma in normal persons, if the trauma is severe enough or exerted over a long enough period. It will result more readily in the group which Campbell classified as "constitutionally inferior." (29)
Riseman and Brown (61) studied the effect of oxygen on the exercise tolerance of 17 patients with angina pectoris. Tests were carried out in a room of constant temperature (45°-55°F.) and consisted of having the patients repeatedly mount and descend a two-step staircase until an attack of angina developed. The exercises were carried out at least one hour after a light breakfast; only one test was performed on any given day; and no medication was taken by the patient for one week prior to the test.

The effect of the oxygen was studied by having these individuals inhale pure, undiluted oxygen for ten minutes while standing at rest, and then having them exercise under the usual standard conditions, while they continued to breathe oxygen. A series of Douglas bags connected to a stationary manifold served as a reservoir for the oxygen. Rubber tubing with an inside diameter of 3/4 inch was led from this reservoir to a Krogh valve, in order to prevent rebreathing; the tubing and the valves were attached to the patient in such a way as to allow exercise with complete freedom. Control experiments were carried out in a manner which was identical except that the Douglas bags were filled.
with room air instead of oxygen. The patients were not aware of the composition of the gas breathed or its possible effect in their exercise tolerance. (61)

Breathing oxygen from the Douglas bags enabled 11 of the 17 patients to do considerably more work; 4 exercised until forced to stop because of fatigue without developing pain. 9 of these 11 patients were 39 to 53 years of age, and the remaining two were 57 and 58 years old. In 7 patients, more than 35 trips were necessary to induce pain while breathing room air; the other 4 patients developed pain in less than 35 trips. (61)

The remaining 6 of 17 patients were not able to do any more work while breathing oxygen. Only one of these patients was less than 53 years of age, and only 2 could perform more than 35 trips before developing angina. (61)

Risman and Brown (61) state that it is evident that many patients with angina can do work before developing pain if they breathe oxygen before and during exertion. Their findings are consistent with the anoxemia theory of angina pectoris. Breathing oxygen both before and during exertion, therefore, tends to prevent myocardial anoxemia and its sequelae. These mechanisms, however, do not entirely compensate for a deficient coronary
flow, for Riseman and Brown (61) found that the more elderly patients with a relatively small tolerance to exercise, who presumably have a greater degree of coronary arteriosclerosis are likely to be benefited by oxygen. Furthermore, many of those patients who are helped by oxygen inhalation will develop pain if they exercise for sufficiently long periods of time. (61)

Rothschild and Kissin (61) (63) have shown that attacks can be induced in the same patients with angina by having them breath room air depleted of its oxygen. This adds additional evidence in favor of the anoxemic theory, for it shows that all cases of angina pectoris can be prevented by preventing anoxemia. (61)

Rothschild and Kissin (63) in their experiment, induced in 46 individuals a general anoxemia, several of whom were subjected to the experiment twice. 26 of the individuals had a previous history of angina pectoris. 18 of the 26 experienced attacks of anginal pain when the anoxemia was induced, while the 20 subjects not having had attacks previously did not witness any such pain. (63)

Those patients in which the attacks were induced witnessed the same type of pain as when spontaneous attacks occurred. A patient who gave a history of pain
beginning in the left elbow and radiating to the chest, developed the pain in the same side and with the same radiation during anoxemia. Several patients remarked "This is the same pain that bothers me." The pain subsided, as a rule, as soon as air (20.9 per cent oxygen) was admitted to the lungs. (63)
4. The coronary blood supply of which is sufficient under normal circumstances, is inadequate to meet the demand placed on it by the added work of the heart, produced by hyperthyroidism. Therefore, the anoxemia produced is responsible for the angina produced in such cases.

5. It has been noticed in the majority of patients complaining of hypothyroidism admitted to the Peter Bent Brigham Hospital, that an unusual amount of thickening is present in the peripheral arteries. Therefore, it appears that patients with hypothyroidism suffering from angina have considerable amount of sclerosis of the coronary arteries.

6. There is definite evidence to prove that patients with diabetes are prone to develop vascular disease. It is to be remembered that the coronary vessels are likely to be implicated as well as arteries of the body and, therefore, attacks of angina pectoris may follow.

7. The rapid excretion of adrenalin with impaired coronary arteries by sclerosis brings about anginal attacks. The inadequate blood flow does not meet with the demand of the cardiac muscles.

8. It is assumed by many authors that anginal
attacks associated with pernicious anemia are due to the lack of oxygen to the cardiac muscle. Anti-anemic therapy often relieves the patient of his anginal symptoms.

9. Bellet states that gastrointestinal disorders and gall bladder disease can act as an aggravating factor in the presence of already existing myocardial disease and, in many cases, it may precipitate serious cardiac disturbances. However, the pain reflexly produced by such disturbances is not the true anginal pain and is only "anginoid" in character. Katzman states that all pains in the heart region not due to anoxemia of the heart muscle are not anginal.

10. A factor present in all cases of essential hypertension is increased cardiac work. This has been shown to be of importance in the angina pectoris associated with thyrotoxicosis, and perhaps in chronic anemia. Also hypertrophy is noticed in many cases. Wearn suggested that cardiac hypertrophy interferes with the nutrition of the heart muscle, for the number of capillaries remains unchanged in spite of the increase of muscle mass.

11. Keefer and Resnik report the striking similarity between angina pectoris and intermittent claudication. The experimental work of MacWilliam and Webster.
pointed out certain characteristics in the pain produced in skeletal muscles. There are other types of cardiac pain which closely simulate "true" angina pectoris, yet these pains do not deserve the name "angina pectoris" since they do not have the same cause. The anginal pain produced is to some extent dependent upon the sensitivity of the patient. Katz believes that the stimulus for pain is due to some metabolic product which is produced quantitatively in proportion to the work done by the heart. It is believed by the majority of authors that the stimulus for the pain is due to the accumulation of some metabolite, perhaps lactic acid in the myocardium. However, this is not entirely settled.

Gilbert believes there is a reason to assume that in some cases angina may be due to vasomotor factors which are responsible for the lack of equilibrium between supply and demand.

Riseman and Brown studied the effects of oxygen on the exercise tolerance of 17 patients with angina pectoris and found that many patients with angina can do work before developing pain if they breath oxygen before and during exertion.

Rothschild and Kissin have shown that attacks can
be induced in the same patients with angina by having them breathe room air depleted of its oxygen. This adds additional evidence in favor of the anoxemic theory for it shows that all cases of angina pectoris can be prevented by preventing the anoxemia.
VII. Conclusion

In review of the literature, most authors strongly support the theory that anoxemia of the myocardium is the most accepted cause of angina pectoris. Regardless of how the anoxemia of the cardiac muscle is brought about, whether by an organic factor, or by some functional means, the lack of oxygen to the tissue is responsible for this syndrome.
VIII. References


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