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Mechanism of the anginal syndrome

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THE MECHANISM OF THE ANGINAL SYNDROME

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presented to

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CONTENTS

I. Introduction ...................................................... 1
II. Coronary Artery Disease ........................................ 6
III. Coronary Insufficiency ......................................... 11
IV. Myocardial Ischemia ........................................... 15
V. Myocardial Anoxemia ........................................... 18
VI. The "P" Factor .................................................. 23
VII. Coronary Spasm ............................................... 30
VIII. Biliary and Upper Gastro-Intestinal Tracts .............. 34
IX. Endocrine Disturbances ........................................ 38
X. Individual Sensitivity or Susceptibility to Pain .......... 41
XI. The Aorta ...................................................... 44
XII. Death .......................................................... 45
I. INTRODUCTION

The anginal syndrome is a condition characterized by (A) anginal pain and (B) the likelihood of resulting in sudden death.

Composition of this condition are coronary thrombosis and angina pectoris, the former being a disease characterized by pain of prolonged duration and definite pathological findings in the coronary arteries, the latter a state characterized by pain of short duration and variable or absent pathological findings in the coronary arteries, heart, or other parts of the body. Coronary thrombosis may be present without pain and in this respect cannot be said to truly exhibit the anginal syndrome, but this form will be considered in my discussion and explanations offered for its occurrence.

In this paper I shall limit myself to the mechanism by which the underlying cause or causes of the anginal syndrome produce a peripheral stimulation of the nervous system which is interpreted as pain.

Since Heberden first described the clinical picture of the angina pectoris component of the anginal syndrome in 1768 and thereby called attention to the condition, numerous theories have been advanced for its mechanism.
The description of coronary thrombosis by Herrick in 1912, by which the attention of physicians the world over was attracted to the presence of this condition in the hearts of individuals dying of what they had thought was angina pectoris, caused the advance of new theories and the revival of theories that were being pushed into the background. For, here was something more concrete to work with. Herrick's description of coronary thrombosis made it a clinical entity different from angina pectoris in regard to its underlying pathology, but gave a starting point for an explanation of the mechanism of anginal pain in both conditions. It has, however, resulted in an attempt by some authors to explain every case of angina pectoris on the basis of coronary artery disease. That coronary artery disease and the anginal syndrome are related seems evident, practically all the cases of coronary thrombosis being dependent upon underlying disease of the coronary arteries and approximately eighty to ninety per cent. of all cases of angina pectoris having their underlying factor in the coronary arteries, but there is a failure by some to realize that the anginal syndrome can exist without any coronary artery pathology. It is the remaining ten to twenty per cent. of cases of angina pectoris that causes confusion.
Since 1912 nearly all the theories have been centered about one hypothesis—that the anginal syndrome is caused by impaired nutrition of the heart muscle. In my discussion I shall consider the various interpretations and modifications of this hypothesis.

The chief difficulties which present themselves in an analysis of pain in the anginal syndrome are (A) inability to correlate the pain produced in experimental animals with anginal pain in man because animals are inarticulate or relatively undemonstrable in communicating the presence of anginal pain and because it is impossible to definitely be able to determine what procedure or procedures in the experiment were responsible for pain when pain was observed, (B) inaccurate clinical diagnoses of angina pectoris, there being a large number of other diseases which, even today, are diagnosed as angina pectoris, (C) incomplete records of histories and physical and laboratory findings of patients diagnosed as having angina pectoris, which records, were they complete, would enable investigators to arrive more nearly at the etiological factor or factors in cases with normal or nearly normal pathological findings at necropsy, (D) lack of evidence that skeletal and heart muscle behave similarly in all respects, (E) lack of an understanding of the relationship
of various toxic states to angina pectoris, and (F) the inadvisability of attempts to initiate or reproduce the anginal syndrome in man.

The last statement bears explanation. The danger of the anginal syndrome resulting in death is here the chief objection. Reproduction of pain of an anginal character and distribution in normal individuals and even in patients previously exhibiting the anginal syndrome can be carried out without appreciable danger to the life of the individual in contradistinction to reproduction of the anginal syndrome.

I shall discuss some of the above difficulties in more detail as the occasion arises.

In the literature there seems to be a failure to recognize that myocardial ischemia and anoxemia, though related, are two distinct conditions. The two are used interchangeably by most authors, which confuses the reader. Myocardial anoxemia, although it is probably nearly always due to ischemia, may be a part of a generalized anoxemia. Myocardial ischemia, on the other hand, although it is the commonest cause of anoxemia of the heart muscle, has the effect of decreasing the quantity of other substances carried to and from the heart muscle. The one may be present without the other.
It is my belief that a more comprehensive and thorough approach to the subject of mechanism of pain in the anginal syndrome can be arrived at by a consideration of the underlying factors thought to initiate the pain than by a review of the various theories. I shall, therefore, follow such a procedure as closely as possible.
II. CORONARY ARTERY DISEASE

Although it is generally recognized that coronary artery disease is the most commonly associated condition of the anginal syndrome (1,2,3,4,5), the view that coronary disease and the anginal syndrome are essentially the same condition is not justified (1,5,6,7).

Coronary artery disease is a pathological entity, but its clinical manifestations are varied, and although it is frequently attended by characteristic symptoms, in some instances such symptoms may be entirely absent or may be so obscure that the condition remains unrecognized throughout life (2,4,8,9,10,11,12,13,14). It is estimated that nearly fifty per cent. of all cases of coronary thrombosis have no history of anginal pain (2, 4,8,15,16).

In nearly all cases of clinical coronary thrombosis there is a pathological background in the coronary arteries, but in angina pectoris the pathological findings vary from complete absence of anatomical changes in the coronary vessels (5,12,17,18) to the presence of extensive alterations involving the coronary arteries (1,5,6,12,17, 18,19,20).

Coronary disease includes any condition of the coronary arteries which interferes with their circulation of blood to the heart. These conditions are (A) narrowing
or obstruction of the lumen (2,8,21,22,23), and (B) thickening or hardening of their walls (22,24).

(A) Narrowing of the lumen may occur in one or more branches of a coronary artery, in the main branch of one coronary artery, or in the main branches of both coronary arteries. A chronic generalized or localized narrowing may result from sclerosis of the coronary arteries (1,2,4,5,11,20,23), and rarely from syphilitic (23,25) or rheumatic (23,26) infection of their walls. A narrowing of the mouths of the coronaries may result from syphilitic involvement of the aorta or aortic valve (1,19,20,24,25,27), by vegetations extending up from the aortic valve cusps in bacterial endocarditis (1,23), or by vegetations on the aortic intima (23). A complete narrowing or occlusion may be due to a thrombus (2,4,15,27,28), and rarely embolism (23,24,27,29) or endarteritis obliterans (27,29).

(B) Thickening or hardening of the walls is nearly always due to arteriosclerosis (4,11); the mechanism of pain production in these cases is thought to be inability of the vessels to dilate when an increased coronary circulation is demanded by the heart (30,31).

It is not the desire here to go into more detail concerning the etiology of the above-named causes except to
dwell further on the narrowing which is due to a thrombus. It is the general opinion among authorities that thrombi have, as their underlying factor, any condition already mentioned which may cause narrowing of the lumen of a coronary vessel, sclerosis being the most important cause (1, 4, 11, 19, 22, 24, 25, 29, 32, 33). Slowing of the blood stream may be a contributing factor (23), but Graybiel and White (34) state that coronary thrombosis may occur in persons who present little, if any, evidence of coronary insufficiency.

The heart, under normal conditions, may perform without any difficulty in the presence of chronic coronary disease (2, 4, 8, 9, 11, 21). It is when the heart is suddenly subjected to unusual stress or strain that the coronary circulation may be insufficient and the anginal syndrome result (15, 21, 23, 31, 33, 34, 35). Acute coronary occlusion by a thrombus, regardless of the activity of the heart, may result in the anginal syndrome; occlusion does not, however, always produce the syndrome, for pain is frequently not experienced in cases proved at necropsy (2, 4, 6, 8, 9, 15).

Whether or not anastomoses between branches of normal coronary arteries exist is still a matter of dispute (15, 36, 37), but in individuals with coronary sclerosis it is
believed that anastomoses may form in sufficient size and number to furnish adequate collateral circulation to an area in the event the vessel normally supplying that area becomes gradually or suddenly completely occluded (5,15, 36,37). These anastomoses are localized in the regions where they are needed (36,37). The more gradually the obstruction occurs, the more apt is an adequate collateral circulation to establish itself (5,15). This fact probably accounts for the numerous cases of marked obstruction of coronary vessels demonstrated at necropsy without the anginal syndrome presenting itself at any time during life (2,5). However, when the narrowing or occlusion progresses so far that the coronary circulation, together with its collateral circulation, is insufficient to meet the needs of the heart during periods of increased work, the anginal syndrome may result (15). The Thebesian vessels have recently been recognized as important sources of supplementary circulation in coronary artery obstruction, but further investigation is necessary to prove their importance (6,22,24).

Infarction of the myocardium may result from coronary disease, especially from acute obstruction (3,5,10, 12,23,34). Whether infarction takes place usually depends on whether coronary insufficiency is absolute or relative.
However, infarction may result from chronic narrowing of a coronary lumen or mouth (23), whereas occlusion of a coronary artery may produce no alterations in the myocardium whatsoever (5,15,24,36). Death may so quickly follow occlusion that there is not sufficient time for any detectable change to be produced in the heart muscle (24). The adequacy of the collateral circulation is an important factor in determining whether or not infarction results (5,6,24). The situation of the infarct is naturally determined by the branch of the artery involved (24,38,39). An infarct may result in a mural thrombus if it extends to the endocardial surface (24), fibrinous pericarditis if the necrotic mass lies just beneath the pericardium (23,24), rupture of the heart, of a papillary muscle, or of the interventricular septum (3,12,24,31), or, with healing of the infarct, large areas of scarring may bulge, giving rise to aneurysmal dilatation (3,12,24,31). Infarction may or may not be accompanied by anginal pain (5,9,10).
III. CORONARY INSUFFICIENCY

Coronary insufficiency may result from (A) coronary artery disease or from (B) impairment of the mechanism, or pressure gradients, by means of which the blood is propelled into and through the coronary arteries.

The manner in which coronary artery disease interferes with coronary circulation by obstruction of the coronary vessels or their orifices has already been discussed. It is the chief cause of coronary insufficiency (4,21,27).

The two most important extra-coronary factors which determine coronary circulation are aortic pressure and the intramural resistance resulting from phasic activity of the cardiac muscle (6). Hence, anything which interferes with adequate systolic and more especially with adequate diastolic pressure or with the length of diastole, since the coronary arteries are compressed during systole, will interfere with efficient coronary flow (6, 19).

Aortic insufficiency: The most common condition in this category is aortic insufficiency due to aortic regurgitation on either a rheumatic or syphilitic basis (1,5, 19,22,23,25,35,40), and less commonly to aortic or mitral stenosis resulting from rheumatic infection (1,8). Levine
(19) believes that the relationship of aortic valvular
disease and angina pectoris explains the occurrence of the
latter in a small number of young individuals and has
observed that there are persons of both sexes in the sec-
ond and third decades of life with rheumatic aortic valv-
ular disease who have typical attacks of angina pectoris.
The explanation of the mechanism of coronary insufficiency
in individuals with aortic insufficiency is based on the
presence of a diastolic pressure which is too low to ade-
quately fill the coronary arteries (19,23,25,38). This
mechanism does not explain the exact precipitating causes
of the attack, for the defect of the aortic valve is per-
manent and constant, present when the patient is free from
attacks, and so some other factor is required that sets
off the spark to produce a spell of anginal pain; this
mechanism merely explains how aortic insufficiency may
be a predisposing factor (19).

Tachycardia: Tachycardia is not itself thought to
be a primary cause of angina pectoris, but when excessive,
as in paroxysmal attacks, it may induce angina pectoris
on the basis of coronary insufficiency in individuals
whose coronary arteries, though they may be sclerotic,
function adequately when the heart beat remains at a nor-
mal rate (1,2,6,19,22,23,35). In such cases angina pectoris
may persist as long as the paroxysms of auricular fibrillation or regular tachycardia last and may be mistaken for coronary thrombosis (1).

Hyperthyroidism: Hyperthyroidism is uncommonly associated with coronary insufficiency (1,2,19,22,41,42,43). Lewis (22) has observed anginal attacks with auricular fibrillation on a thyrotoxic basis, but states that attacks may occur in hyperthyroidism without auricular fibrillation. Levine (2) and Blumgart (44) explain the mechanism of angina pectoris in these cases on the basis of a generalized anoxemia induced by the increased metabolic rate in this condition. Others explain the production of pain on the basis of increased work of the heart resulting in coronary insufficiency and ischemia, the increased work of the heart being due either to the accelerated metabolic rate or increased heart rate commonly found with hyperthyroidism (41,42). That hyperthyroidism aggravates or precipitates attacks of angina pectoris is further shown by cases of hyperthyroidism which improve following thyroidectomy, the improvement being thought to result from the establishment of a normal metabolic rate and a diminished demand on the heart so that the coronary flow becomes sufficient, even during strain (41,42,43,44,45).
Hypothyroidism: Hypothyroidism may be accompanied by the anginal syndrome (1,5,43), probably due to bradycardia (23,43) or hypotension (23,27).

Hypotension due to other causes may be accompanied by the anginal syndrome (23,27). Sudden elevation of blood pressure or pulse rate at rest or while asleep may produce a coronary insufficiency due to failure of the coronary arteries, even though they are normal, to dilate; this mechanism may explain sudden attacks of angina pectoris during sleep or rest (5,23). This phenomenon may be on a functional vasomotor basis (6).
IV. MYOCARDIAL ISCHEMIA

It is almost universally accepted that anything which can produce coronary insufficiency results in ischemia of the myocardium and that it is the ischemia which is the underlying factor in the production of the anginal syndrome (3, 4, 5, 8, 12, 14, 15, 20, 21, 22, 28, 30, 34, 35, 40, 46, 47, 48, 49). There is much less agreement on how the ischemia produces anginal pain in the syndrome.

Experimental observations on animals have shown that a coronary vessel which normally nourishes a complementary section of heart muscle cannot function when suddenly and tightly ligated (14) and results in changes of electrical potential in the area affected (50). These changes produce electrocardiographic curves closely resembling those obtained following coronary thrombosis and during attacks of angina pectoris in humans (18, 50). That electrocardiographic records show the location of the area of damaged myocardium following coronary occlusion and that this area corresponds to the area nourished by the occluded vessel has been observed (51, 52, 53, 54). Transient electrocardiographic changes similar to those of myocardial infarction have been noted with attacks of angina pectoris (18, 19, 55, 56). These findings suggest a similarity between the effects of experimentally-induced
ischemia and the underlying factor of the anginal syndrome on the myocardium.

Sutton and Lueth (57), by studies upon the unanesthetized dog, found that temporary partial to complete occlusion of a coronary artery promptly produced pain, which as promptly ceased when the occlusion was removed. They further showed that this pain is due to the decrease of blood flow to the heart muscle, other possible factors having been eliminated by further experiments (58).

Just how myocardial ischemia acts to stimulate the sensory nerve endings is a subject of much dispute, but aching can be produced in any muscle by shutting off or limiting its circulation, especially when the muscle is actively contracting (23). According to White (23) the more the coronary circulation is limited, the less exertion is needed to cause an attack of angina pectoris; with a good coronary circulation an extreme degree of exertion is needed before angina pectoris results, but usually it is not possible to attain such a high degree of exertion because of other limiting factors like breathlessness and muscular fatigue.

Keefer and Resnik (5) believe that anginal pain is similar to that of intermittent claudication in which there is no doubt about the cause of the pain, that cause
being diminished blood supply to the muscles.

The coronary insufficiency is a mechanical event; the significant changes that follow this are chemical (45). Opinions vary considerably among authorities as to whether the chemical irritant which initiates pain is (A) the lack of oxygen itself, (B) a product of the lack of oxygen, or (C) an accumulation or concentration of the metabolites of myocardial activity due to the failure of the diminished blood supply to wash them away (36).

As a result, two main theories have been advanced to explain how the stimulus arises. One is the theory of myocardial anoxemia, which is concerned only with the deficiency of oxygen resulting from the inadequate blood supply to the heart; the other is the theory that a "P" factor is responsible, its adherents stressing the importance of the decreased supply of other substances, as well as oxygen, leading to failure of the "P" factor to be minimized or neutralized, and also considering the washing away of the "P" factor by an adequate blood supply to prevent its accumulation an important part of the mechanism.

I shall discuss both theories in more detail.
V. MYOCARDIAL ANOXEMIA

That myocardial ischemia results in anoxemia of the ischemic area and that it is the anoxemia which acts as the stimulus for pain is the belief expressed by a great many authorities (2,6,8,15,19,28,29,30,40,59).

It is the opinion of advocates of the anoxemia theory that it is not only local anoxemia of the heart muscle which can precipitate an attack of anginal pain, but that anything which can cause a generalized anoxemia may act on the sensitive myocardium when its demands for oxygen are suddenly increased (2,6,8,15,19,28,40). Brill (6) summarizes the theory by stating that the essential pathological physiology underlying the anginal syndrome is believed to be an anoxemia of the myocardium brought about by a deficiency in the quantity or quality of its blood supply. The belief that generalized anoxemia may produce the anginal syndrome in the absence of coronary artery disease or insufficiency is advanced by those adhering to the anoxemia theory (36).

The causes of a generalized anoxemia which may be sufficient to produce the syndrome are severe anemias, either secondary (2,6,19,20,21,23,27,59,60) or pernicious (6,19,23,27,40,61,62), or working at high altitudes or under other conditions resulting in a deficient intake of
oxygen (8,14,19,36,40,48,63,64). In addition to these causes Levine (2) believes that the oxygen demand of the heart may be sufficiently increased to cause anginal pain in hyperthyroidism due to an increased demand for oxygen in all parts of the body as well as in the accelerated heart usually present with this condition.

In anemias the generalized anoxemia is due to a diminished oxygen-carrying power of the blood as the result of a lowered hemoglobin or decreased number of erythrocytes (2,27). Stalker (61) and Vatcher (62) have reported marked improvement of the angina pectoris in patients presenting both angina pectoris and pernicious anemia following specific therapy for the latter. Anemia, without any other abnormal findings, including the coronary vessels at necropsy, may cause anginal attacks (23,59,60).

White (1) states that it is well known that anemia, either primary or secondary, may precipitate or aggravate attacks of angina pectoris in a patient with disease of the coronary arteries and that proper treatment of the anemia may result in the decrease or the disappearance of the symptoms, but that it has never been shown that anemia alone is responsible or is a common factor in producing the anginal syndrome.

Elliot (59) believes that anemia, by increasing
cardiac output, may cause myocardial hypertrophy; that under these conditions the adaptive limit of the coronary flow may be reached in the resting state and easily exceeded under additional physiologic circulatory burden; and that resultant myocardial anoxemia might express itself as an anginal seizure.

Experimental work and observation has shown that anoxemia due to an inadequate inspiration of oxygen is related to the anginal syndrome. Riseman and Brown (63) have observed that many patients with angina pectoris could do more work before developing pain if they breathed oxygen before and during exercise. Levinson (40), Rothschild (48), and Levine (19) have found that insufficient oxygen induced in man by inhalation of air with a decreased amount of oxygen or by rebreathing sometimes reproduces attacks of anginal pain. Katz and Hamburger (65), Burnett (3), and May (64) report that experimentally-induced anoxemia in normal individuals frequently results in transient electrocardiographic curves identical with the temporary changes in attacks of angina pectoris or the more permanent changes following coronary occlusion. Katz (14) has observed that severe exercise, in both normal individuals and patients with angina pectoris, may result in anginal pain with characteristic electrocardiographic
signs or the latter without anginal pain. Monge (66) and Wiggers (36) report attacks of angina pectoris in individuals suddenly subjected to low oxygen tension such as attaining great mountain heights.

Sutton and Lueth (58) state that anoxemia may result from pulmonary lesions such as emphysema, resulting in a constant undernutrition of the heart muscle, making it more susceptible to the effects of decrease in blood supply and that it is well known that irritability of nerve endings is increased by lack of oxygen.

On the other hand, Wiggers (27) reports that oxygen administration in anginal pain following coronary thrombosis does not relieve the pain; this is probably due to the inability of the anoxemic area to be reached by the blood supply, he ventures.

Keefer and Resnik (5) state that "it can be shown that anoxemia of the myocardium explains every characteristic of angina, including the likelihood of sudden death, which must be considered an integral feature of the condition. The percentage of instances in which conditions capable of producing anoxemia of the myocardium have been found in cases of undoubted angina is so high that the accuracy of the diagnosis in the few remaining instances seems open to question."
Miller (45) believes that the availability of adequate quantities of oxygen is important in the removal of the "D" factor, and that this substance may pile up in the absence of sufficient oxygen, resulting in anal pain.

The "D" factor will be discussed next and its relationship to oxygen more fully explained.
VI. THE "P" FACTOR

Much experimental work forms the view that anginal pain is due to chemical irritants arising from myocardial ischemia. The studies of Lewis, Pickering, and Rothschild (67) upon the development of pain in contracting skeletal muscles led to the conclusion that lack of oxygen is not the factor evoking pain but that the production of pain is related in some way to the contraction process. They applied pressure to the arm by a blood pressure cuff and then regularly contracted the forearm muscles. Under such conditions pain began to develop in from twenty-five to forty-five seconds and reached an intolerable intensity in about seventy seconds. In one set of experiments exercise was stopped a few seconds before pain was anticipated, while arterial compression was continued for another five minutes. No pain was experienced, despite the fact that any oxygen remaining must have been readily utilized, owing to the oxygen debt developed by preceding contractions. They made the logical deduction that a substance causing pain arises only during contraction of muscle, and inasmuch as pain which developed during contraction under ischemic conditions disappeared rapidly after restoration of blood supply, the further inference was drawn that the accumulation of metabolites in tissue spaces
rather than within muscle fibers constitutes the chemical stimulus for pain. Briefly restated, the conception of Lewis (35, 67) holds (A) that special metabolic products, called the "P" factor, formed by contracting but not by resting muscle constitute the chemical stimulus for pain endings, (B) that the location of this action is in connective tissue and not within muscle cells, and (C) that the chief value of a good circulation results in its ability to flush these substances away and not in its ability to supply oxygen.

While the main experimental facts have been supported by Perlow, Markle, and Katz (68), some noteworthy differences have been found which may require a reinterpretation of the mechanism. If oxygen lack is unimportant, no difference should be found in the time that a limb can be exercised before pain develops (36). Kissin (69) noted that anoxemia produced by breathing low oxygen mixtures reduces this time in the case of an exercising forearm, but that the degree of anoxemia must be rather severe in order to become a factor in the production of pain in an exercising muscle.

Perlow, Markle, and Katz (68) added evidence that the "P" factor causing pain in ischemic contracting muscle is not solely produced during contraction but can be formed
by muscle at rest, of course at a much slower rate. They
noted, contrary to the findings of Lewis (35) and Lewis,
Pickering, and Rothschild (67) that the time required for
development of pain during exercise was decreased when the
arm had been previously rendered ischemic by a pressure
cuff for five or ten minutes and that continuation of
ischemia for a somewhat longer time than was used by Lewis
and his collaborators did lead to development of pain.
They interpreted these findings to signify that resting
muscle elaborates the same substances as contracting mus-
cle, the difference being merely one of degree. Further-
more, they logically pointed out that the rate at which
such substances form in contracting muscle depends not
only upon the rate and strength of contraction but upon the
efficiency with which contraction takes place, and that
accordingly an accumulation of metabolites would occur more
rapidly when the heart contracts against a high aortic pres-
sure and when exceedingly dilated.

There has been much speculation as to the nature of
this mysterious "P" factor (45). Wiggers (27,36) states
that the best known of the various metabolites of muscular
contraction, at least skeletal, is lactic acid, and that
it accumulates faster when muscular activity is increased.
It has been shown to accumulate rapidly at the expense of
glycogen after experimental ligation of a coronary ramus (68, 70). It has been shown to have a relation to abolition of muscular contraction (71). Injection of lactic acid or other weak acids into femoral and brachial arteries or intravenously gives rise to manifestations suggestive of pain (72). The products formed by exercising one group of skeletal muscles apparently diffuse into the blood stream and when carried to another group hasten the onset of pain when these muscles in turn are examined under ischemic conditions (73). Finally, the ingestion of bicarbonate by human subjects delays considerably the onset of pain in an exercising ischemic arm (14). Such cumulative evidence certainly points toward the identity, or at least the close similarity, of lactic acid and the "P" substance (45).

If this be the case, however, the conclusion must be drawn that while the formation of lactic acid is certainly a muscular event, its accumulation or removal is decidedly affected by the availability of oxygen (36). It cannot be denied that anoxemia plays an important, though hidden role, in the production of pain (45).

The production of lactic acid or a "P" substance, however, is but part of the story; the other part depends upon the circulation to the tissue affected. The piling up or removal of metabolites is governed by conditions
which either facilitate or prevent anoxemia (19,45). A blood supply insufficient to prevent, by neutralization or physical displacement, the concentration of these chemicals above a certain threshold shares in the mechanism that touches off the pain nerve endings to produce pain (45).

A natural corollary is the alleviation or termination of pain in a muscle when its circulation is improved and the oxygen lack or debt in the tissue is thereby wiped out. Muscular pain, therefore, in the heart and its allied structures is determined and regulated by the accumulation and concentration of metabolic products and by the availability of adequate quantities of oxygen transported through the circulation (45).

Observations of Tennant and Wiggers (75) have clearly demonstrated that ventricular contractions fail rapidly in the ischemic area after coronary occlusion and in approximately a minute cease entirely. Therefore, to account for the pain following coronary occlusion on the theory of Lewis (35,67) demands the production, in less than one minute, of larger quantities of metabolites than seems possible, by continually decreasing muscular contraction in the region; whereas the accumulation can be accounted for if the effect of anoxemia is superadded. As a matter of
fact, the clever experiments upon contracting skeletal muscle under ischemic conditions do not quite reduplicate conditions in the heart after coronary occlusion, for in this organ contractions do not persist long; therefore, results obtained under such different conditions must be transferred to the ischemic heart with care and caution (36).

Katz (14) states: "It would appear that the stimulus for pain is a metabolic product (or products) which can readily diffuse into the blood stream and which can be quickly altered in the presence of an adequate supply of oxygen. The accumulation of this product is dependent upon the amount and character of the physical work and the efficiency of the heart, on the one hand, and the quantity of oxygen and blood supply on the other. When this substance reaches a concentration above the threshold of the pain end organs, pain results. This chemical product appears to be acid in character, or at least one that is additive with acid substances and is 'neutralized' by alkaline substances. In all probability it is some substance like lactic or phosphoric acid formed during the catabolism of muscular activity."

Bogue, Evans, and Hsu (74), to further complicate the identity of the "P" factor, found that in contrast to
VII. CORONARY SPASM

That temporary or intermittent myocardial ischemia may be the result of coronary vasoconstriction on a functional basis where no evidence of damage to coronaries is demonstrable which might render them unable to meet the increased demands which accompany increased work of the heart is ventured by many authors (18,19,20,23, 27,28,30,33,41,47,76,77,78). Blumgart and Riseman (41) believe that such a condition may be present in individuals with disturbed metabolism, as is present in thyrotoxicosis. Gilbert (76) believes that since myocardial ischemia is due to failure of the coronaries, for any reason, to increase in caliber in response to increased needs, this same disproportion would result also in cases in which the needs of the muscle remained constant, increased, or even decreased, but in which the blood flow was diminished in consequence of a vasomotor action. He demonstrated coronary vasoconstriction following inflation of a balloon in the stomach of a dog which could be abolished by atropine or vagus section.

Greene (30) explains the vasomotor control of the coronaries as follows: "Coronary blood vessels are richly supplied with efferent neurons of both dilator and
constrictor type. Dilator neurons are normally greater in mass effect and must obviously increase coronary flow during augmented myocardial work. These two coronary nervous mechanisms are delicately controlled by very specific nervous mechanisms in adaptation to every delicate changing activity of the whole body. These reflexes are primarily coronary dilator in type; nevertheless, there may occur associated reflex coronary constriction."

He believes that the over-functional activity of the coronary constrictor mechanism may induce anginal attacks.

Anrep and Segall (79) reported from their results in animal experimentation that sympathetic impulses under normal physiologic conditions induced coronary dilatation. This was verified by Koutz, Pearson, and Koenig (80) and others (77). Koutz and his collaborators (80) further observed that when the normal physiological conditions in the coronary system were altered, for example, in arteriosclerosis or change in hydrogen ion concentration of the perfusion fluid, the action was variable, often reversed.

During an actual attack of angina pectoris all outward signs are those of sympathetic overactivity, such as increased pulse rate and blood pressure, and sweating (23, 77). The fact that adrenalin aggravates or precipitates
and sympathectomy relieves anginal pain in many instances would suggest a vasoconstrictor, or sympathetic action to be responsible (77). Katz and Lindner (21), however, have demonstrated that adrenalin produces a dilatation of the coronaries. They believe the anginal pain produced by adrenalin due either to increased work of the heart or failure of sclerotic coronary vessels to dilate, or both. They have found, on the other hand, that transient constriction may precede dilatation.

White (23) believes that the theory of coronary spasm as a constant cause is definitely ruled out by the fact that in many cases presenting the anginal syndrome examined post mortem the coronary arteries are hard and cannot contract. Keefer and Resnik (5) believe the coronary spasm theory is open to such serious criticism that it is unacceptable even as a possibility in the mechanism of ischemia and anginal pain. Another objection is that coronary channels occluded by spasm may not show, as one would expect, a reduction in blood volume; instead they probably show dilatation of their lumen and an increase in blood volume, as in the case of ischemia of skeletal muscle '67). The Jacksons (81) believe the coronary artery spasm theory of angina pectoris is erroneous.

Here a few words might be in order concerning
another phase of the coronary spasm version of anginal pain. There are a few adherents to the theory that coronary spasm acts directly as a stimulus on the sensory nerve endings to produce pain in angina pectoris, but proof is lacking (27,35). To Wiggers (36) it seems impossible that the few muscle fibers found in the walls of the coronary vessels can develop sufficient tension to produce pain.
VIII. BILIARY AND UPPER GASTRO-INTESTINAL TRACTS

That the biliary and gastro-intestinal tracts may have a role in the production of anginal pain has been a subject of some interest for several years (78). von Bon (82) in 1920 advanced the hypothesis that angina pectoris may be due to spasmodic incoordinated contractions of the esophagus or stomach set up by local "gas trans" and gaseous pressure. The Jacksons (81) expressed the same belief and by electrical stimulation inside the esophagus 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 reported relief of anginal pain by the elimination of gas or fluid contents of the stomach or esophagus in patients with "indigestion". According to Morrison and Swalm (78) Von Bergman and Lunde and Giannoni described the occurrence of anginal pain in diseases of the esophagus, including cardiospasm and herniations of the esophagus. Lendrum (83) reported sudden deaths similar to those occurring in the anginal syndrome proved at post mortem examination to have been due to cardiospasm. Edeiken (84) reported pain of anginal distribution on swallowing in patients with cardiospasm. He observed that initiation of the pain by a heavy meal and relief by gaseous eructations and
antispasmodics was not uncommon. Weiss and Davis (85), on the other hand, investigated the effect on the heart of distention of the esophagus in a group of normal subjects and found no cardiac abnormalities or irregularities in any case, which led to the belief that anginal pain could be reproduced only in patients who had previously displayed the anginal syndrome or were susceptible to the production of anginal pain. Morrison and Swalm (78) performed experiments on such patients and by distention of the stomach and esophagus at different levels with balloons produced typical attacks of angina pectoris or substernal distress of an anginal distribution, accompanied by characteristic electrocardiographic findings of transient myocardial damage. They also reported observations of occasional occurrence of substernal pain with radiation simulating angina pectoris during pneumatic dilation of the esophagus of patients with cardiospasm or preventriculosis. They conclude that a reflex nerve arc between the upper part of the digestive tract and the heart is involved in the production of anginal pain in disorders and disturbances of the upper part of the gastro-intestinal tract and that gas formation in this part of the digestive tract can, by accumulation and distention of the viscus, directly initiate a paroxysm
of angina pectoris.

Boas and Levy (86) reported that pain arising in a peptic ulcer or from gallbladder disease may follow the anginal radiation. They state that there are patients with gallbladder disease with reference of the pain to the precordium and T-wave changes in the electrocardiogram in whom operative removal of the gallbladder is followed by disappearance of precordial pain and a return of the electrocardiogram to normal. They observed that when a patient with a peptic ulcer develops coronary artery disease the ulcer pain may follow the distribution of the anginal pain and that this pain can be relieved by treatment of the ulcer, but the anginal pain which comes on with exertion and at times when the ulcer pain is absent, persists. They explain this phenomenon on the belief that the ulcer pain travels along the cardiac pathways sensitized by the angina pectoris. They further reported that it has been shown experimentally in human subjects that inflation of the common bile duct by means of a rubber balloon may cause pain which is referred to the precordium, and that in the absence of a previous anginal attack it is unusual for the pain of gallbladder disease to follow the anginal radiation but not uncommon where the patient has suffered a previous attack of angina pectoris or
coronary thrombosis.

Studies of Fitz-Hugh and Wolferth (87) seem to indicate that at times gallbladder disease may cause injury to the myocardium, giving rise to anginoid pain and T-wave changes in the electrocardiogram, and that after operative cure of the gallbladder condition the precordial pain may completely disappear and the electrocardiogram return to normal. They state that there is a growing conviction among internists and surgeons alike that chronic disease of the gallbladder may either initiate or aggravate coronary artery disease.
IX. ENDOCRINE DISTURBANCES

It is the opinion of some authorities that endocrine disturbances may play an important role in producing the anginal syndrome, aggravating it, or predisposing the individual to anginal attacks (8, 19, 40, 88, 89, 90, 91, 92, 93, 94).

Levinson (40), Smith (94), and Strouse, Soskin, and Katz (88) stress the importance of an adequate glucose supply to the myocardium. Levinson states that in hyperglycemia adequate insulin is not available to enable the myocardium to utilize the glucose and that the anginal syndrome may be relieved by glucose administration in hypoglycemic conditions. Turner (89) and Parsonnet and Hyman (90) report cases of insulin shock as the cause of anginal pain. Weinstein and Mattikow (91) report a case of spontaneous hypoglycemia with angina pectoris as the predominating symptom, while Scherf and Weissberg (92) believe hypoglycemia can precipitate anginal pain. Modern (95) reports that attacks of angina pectoris can be caused by prolonged hypoglycemia. Smith (94) believes there is no doubt that hypoglycemia is an important factor in the production of a deleterious effect upon the heart and suggests that the blood sugar level and the carbohydrates available for the use of the myocardium.
may be the essential factor involved in anginal pain.

Insulin has been shown to produce changes in the T-wave of the electrocardiogram (93,96). Elliot and Evans (96) have observed similar changes with hyperglycemia. White (1) states that diabetes mellitus is sometimes associated with angina pectoris. Levine (19) states that a large number of diabetics, especially the mild elderly ones, eventually develop coronary artery disease; he believes this may merely indicate that diabetes occurs in the same type of individual who has vascular vulnerability. Smith (94) believes that in the presence of coronary insufficiency the available supply of carbohydrates, as of other substances, to the myocardium may be reduced to an inadequate level and that this result is even more apparent when deficiency of the coronary circulation is associated with an endocrine or metabolic disturbance affecting the utilization of carbohydrates, as in diabetes mellitus.

Disturbances of the thyroid gland have been discussed earlier.

That adrenalin almost invariably brings on typical attacks in patients suffering from angina pectoris has been observed by Levine (19), Burnett (8), and Raney (77). Katz and Lindner (21) have made similar observations. This has led to the suggestion (8,19) that hyperfunction
of the adrenal glands may be related to the anginal syndrome in some cases. Just how the pain in these cases is produced is not known; Katz and Lindner (21) have advanced the belief that pain is probably due to the increased work in response to the adrenalin or to a failure of sclerotic vessels to dilate, adrenalin producing dilatation of these vessels, or both. That disturbance of adrenal function may be an important factor is further brought out by the fact that anginal pain is sometimes relieved by sympathectomy (1,45,77) and that the symptoms in angina pectoris, such as increased pulse rate, elevated blood pressure, and perspiration are predominantly sympathetic (23,77).

Fitz-Hugh and Wolferth (87) and Levine (2) have mentioned the possibility of abnormal parathyroid function, most probably hyperparathyroidism, as being a causative factor in the mechanism of anginal pain in some cases.
X. INDIVIDUAL SENSITIVITY OR SUSCEPTIBILITY TO PAIN

It is thought by many authors that individual sensitivity or susceptibility of the nervous system to pain plays an important role in the clinical picture the anginal syndrome may present in a given case (1, 5, 6, 8, 23, 33, 97, 98).

Brill (6) states that variations in clinical types of coronary artery disease are dependent on the sensitivity of the patient or the variance of a pain threshold, that this individual sensitiveness is assumed as an explanation for the variation in the degree of pain and other symptoms which attend sudden coronary occlusion in different individuals.

What anatomical or physiological variations of the nervous system are responsible for such sensitiveness is not known with any certainty (23). It has been amply proved that extensive limitation of the coronary circulation may exist without pain or other evidence of the anginal syndrome (5, 6, 8, 23). Burnett (8) and Keefer and Resnik (5) assume that such individuals have a high threshold of sensitivity to those influences which act as a "trigger mechanism" and set off the painful attack in susceptible individuals. White (23) and Leary (33) state that angina pectoris may arise in individuals with
a widespread hypersensitiveness of the nervous system
and not in less sensitive individuals with the same under-
lying factors responsible for predisposing the person to
an attack of anginal pain. White (23) states that a
sensitive person may have little obvious pathology,
anatomical or physiological, and yet suffer from serious
angina pectoris, and that an insensitive person may have
extensive coronary disease or other factors limiting the
coronary circulation and yet have no angina pectoris at
all.

White (23) believes there may be individual varia-
tions of nerve distributions, of the type of cardiac
sensations, or of the nerve thresholds. Perhaps the
pounding of the heart so common in patients with neuro-
circulatory asthenia causes sensory impulses which are
translated into pain in another patient, he ventures.
White stresses the importance of individual sensitivity
to pain as being as important as all of those thought to
cause coronary insufficiency. He states that alone, this
nervous sensitivity is probably not enough to cause angina
pectoris, but that the extra provoking factor may be very
slight and may escape notice during life or even at post
mortem examination; that sometimes fatigue of nervous
type is the precipitating factor that lowers the nervous
threshold sufficiently to permit angina pectoris to appear.

Katz (14) states that work remains yet to be done on this aspect of the problem of pain production to account for the variations in pain responses under what seem to be similar conditions and believes an important factor responsible for this variability is the inconstancy of the state of the pain receptors and pain pathways and the fluctuations in the sensorium for perception of pain sensation.

Libman (97) believes that instead of pain the hyposensitive patient may have substitution symptoms. He states that if, in coronary thrombosis or angina pectoris, the patient is hyposensitive, dyspnea may be the predominating symptom instead of pain, or burning, coldness, a sense of pressure or constriction in the chest, a feeling of swelling in the arms or forearms, or other sensations may be substituted for pain. Levy (25) states that substitution symptoms of anginal pain may be headache, dizziness, a sudden feeling of great weakness, sweating, or nausea and vomiting.
XI. THE AORTA

That anginal pain and the entire anginal syndrome is produced in the aorta was advanced by Allbutt (17), and this theory has had the support of Wenckebach (13) and Vaquez (12). They believed that the mechanism of pain was initiated in the first or ascending portion of the aorta, due to stretching, especially in the presence of aortitis. The theory has rapidly lost ground (19), since in many cases of anginal pain the aortic wall is normal and there may be present little or no increase in blood pressure to stretch the wall (23). The aorta has reached a state of unimportance so far as its relationship, other than aortitis sometimes blocking the mouths of the coronaries, to the anginal syndrome is concerned (5,6).
Angina pectoris, at some time during the life of its victim, is very apt to result in coronary thrombosis, infarction, and sudden death (6,19). Blumgart, Schlesinger, and Davis (15) believe that death occurs whenever a sufficiently large area of myocardium undergoes ischemia, with or without necrosis, or when, because of ischemia, asystole, ventricular fibrillation, or congestive failure occurs. Lewis (22) supports the belief that death in coronary thrombosis is due to ventricular fibrillation. Sutton and Lueth (58) believe that the occurrence of ventricular fibrillation during an attack of angina pectoris is a probable explanation of the cause of sudden death in those cases in which no coronary thrombosis is found.
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