Pathophysiology of Cardiac Pain

By Richard Gorlin, M.D.

Angina pectoris can be no better described than in Heberden's original discussion some 160 years ago. Despite the enduring quality of his description, Heberden had no idea of the cause of angina pectoris, although he did appreciate its morbid quality. In the same era, Jenner, Parry, and Burns were among the first clinicians to associate angina pectoris with anatomic disease of the coronary arteries. This notion lost favor somewhat during the latter half of the nineteenth century when anginal pain was thought to originate in spasm of the coronary arteries or in disease of the aortic wall itself. The twentieth century witnessed the observations of Herrick, MacKenzie, Levine, Keefer and Resnik, and Blumgart, Schlesinger, and Davis, culminating in the theory that angina pectoris came about as the result of myocardial ischemia, usually in the presence of intraluminal coronary artery disease or disease causing cardiac hypertrophy, and elicited by disturbance of the balance between coronary oxygen supply and myocardial oxygen demand.

The purpose of this report is to indicate what new facts may be added to these masterful dissertations. The discussion is divided into three parts: mechanism of pain excitation within the heart; myocardio-neuronal reception and transmission of pain impulses; clinico-physiologic factors in the development of angina pectoris.

Mechanism of Pain Excitation within the Heart

Myocardial Ischemia

The "ischemia" theory of angina pectoris has been based in large measure on the results of retrospective observations, i.e., that the coronary arteries are narrowed or occluded; regions of myocardium served by these vessels are often necrotic or scarred, and that clinical factors favoring cardiac anoxemia precipitate or aggravate angina.

Figure 1

Myocardial lactate metabolism in coronary heart disease. Arterio-coronary venous lactate difference in a subject with rheumatic heart disease and normal coronary arteries (N) (solid lines); and a subject with totally occluded right coronary artery and major stenosis of both branches of the left coronary artery (CAD, coronary artery disease) (broken lines).
During the last few years, our laboratory has been able to document directly the occurrence of ischemia of the heart in association with angina pectoris. This was accomplished by placing a catheter in the coronary sinus, and by sampling oxygen and lactic acid concentration of coronary venous blood draining the left ventricular myocardium, and then comparing it with the concentration of arterial blood drawn simultaneously. The heart is a curious organ, and completely different from skeletal muscle in that, normally, it is totally aerobic, i.e., there is hardly ever breakdown of glucose or glycogen to lactic acid under normal or even stressful conditions. In fact, the normal heart extracts lactate from the blood and converts this to pyruvate. In figure 1 is shown lactate arteriovenous difference at rest and again when the heart is challenged by infusion of a powerful catecholamine, isoproterenol. In the heart with the normal coronary arteries, extraction of lactate occurred both at rest and while the heart was stimulated by isoproterenol. In the patient with angiographically proved severe coronary artery disease, however, while at rest there was lactate extraction, with "spontaneous" angina pectoris and again with isoproterenol infusion there was reversal of extraction, so that actual production of lactate, or evidence for glycolysis in excess of oxidation, occurred. When myocardial arteriovenous sampling of lactate has been performed at the time of an anginal attack, markedly reduced extraction (0 to 5 per cent) or actual production of lactate has been observed in 90 per cent of observations. On the other hand, lactate production was seen not infrequently in the complete absence of clinical pain in subjects with established angina pectoris. It is highly unlikely, therefore, that lactic acid itself is the primary cause of pain. However, lactate production is unique as a biochemical diagnostic test for myocardial ischemia, and in fact, it can serve as a functional indicator of the adequacy of any given degree or distribution of coronary arterial disease.

Because of the spotty nature of coronary artery lesions, myocardial ischemia may occur only in certain zones of muscle and only with provocation. Two principles are essential in laboratory diagnosis: the first is that myocardial ischemia must be provoked during the laboratory study by simulating those clinical conditions that lead to ischemia or pain, or both; the second is that sampling must be done at multiple sites in the coronary sinus to detect the different venous drainages from the anterolateral and inferoposterior walls of the heart. For example, lactate production sampled far out in the great cardiac vein can be diluted by venous drainage from other nonischemic areas, and therefore be undetected when sampling is obtained farther down the coronary sinus (table 1). The site of ischemia can be small, and yet result in angina pectoris. Also, as shown in table 1, the site of lactate production did not always match the demonstrated site of coronary disease. This discrepancy between locale of arterial disease and region of affected myocardium could have been predicted from the concept of "infarction at a distance" propounded by Blumgart, Schlesinger, and Davis. If deliberately and diligently sought for by multiple site samplings during stressful challenge to the heart, lactate production will almost always be elicited in the anginal subject.

It is also significant that but for a rare subject (5 per cent of the series), cardiac pain and lactate production always occurred in the presence of organic disease—either coronary artery disease or disease resulting in left ventricular hypertrophy. Due to the type of cases referred to our laboratory for study, aortic stenosis or insufficiency was the lesion most commonly leading to left ventricular hypertrophy. A small number of cases of hypertrophic subaortic stenosis or idiopathic hypertrophy constituted the remainder. Approximately 40 per cent of the aortic valve disease cases and all the other hypertrophic disorders had normal coronary arteries cineangiographically. The occurrence of angina and cardiac lactate production in these latter groups, supports the concept that
Table 1

Selective Coronary Sinus Site Sampling in Coronary Heart Disease

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Myocardial artery arteriovenous lactate difference, mM/L</th>
<th>Angina at time of measurement</th>
<th>LAD</th>
<th>Coronary arterial lesion</th>
<th>RCA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL</td>
<td>R&lt;br&gt;I +0.56&lt;br&gt; +0.45</td>
<td>+0.56&lt;br&gt;+0.45</td>
<td>0&lt;br&gt;0</td>
<td>—&lt;br&gt;—</td>
<td>—&lt;br&gt;—</td>
<td>—</td>
</tr>
<tr>
<td>FD</td>
<td>R&lt;br&gt;I +0.11&lt;br&gt; +0.12&lt;br&gt; +0.20</td>
<td>+0.09&lt;br&gt;+0.12&lt;br&gt; +0.20</td>
<td>0&lt;br&gt;0&lt;br&gt;0</td>
<td>Stenosis&lt;br&gt;distal&lt;br&gt;1/3 only</td>
<td>—&lt;br&gt;—&lt;br&gt;—</td>
<td>Had bizarre chest pain of inconstant occurrence; did not develop angina or lactate production during any state</td>
</tr>
<tr>
<td>SB</td>
<td>R&lt;br&gt;I +0.07&lt;br&gt; +0.04</td>
<td>+0.07&lt;br&gt;−0.04</td>
<td>+&lt;br&gt;−</td>
<td>Diffuse&lt;br&gt;narrowing</td>
<td>—</td>
<td>Patient had diffuse involvement of LAD and had lactate production detectable only deep in the coronary sinus</td>
</tr>
<tr>
<td>GP</td>
<td>R&lt;br&gt;I −0.07&lt;br&gt; +0.04</td>
<td>−0.07&lt;br&gt; +0.04</td>
<td>+&lt;br&gt;−</td>
<td>75% Occlusion</td>
<td>50-75% Narrowing throughout proximal &amp; distal 1/3</td>
<td>Despite severe disease of both LAD and RCA catheters induced ischemia only along inferior or posterior surface, suggesting collateral revascularization of anterolateral wall</td>
</tr>
<tr>
<td>DM*</td>
<td>AP&lt;br&gt;R&lt;br&gt;I −0.17&lt;br&gt; +0.06&lt;br&gt; −0.25</td>
<td>Major proximal stenosis&lt;br&gt;Proximal total occlusion with collaterals</td>
<td>+&lt;br&gt;0&lt;br&gt;0</td>
<td>As above but with internal mammary pedicle implant between LAD and circumflex arteries</td>
<td></td>
<td>Lactate production with spontaneous angina, and again at 2 sites during catechol infusion but without angina. Studies repeated 7 mo. after internal mammary pedicle implantation to anterolateral wall of left ventricle. Now, sampling from deep in coronary sinus during isoproterenol infusion indicated lactate extraction instead of production, suggesting successful revascularization. Sampling of inferior drainage revealed the same production seen preoperatively. This area of left ventricle should have been unaffected by pedicle implant</td>
</tr>
</tbody>
</table>

*Before operation.
†After operation.

Proximal, site in coronary sinus approximately 2 cm. deep to junction with mid cardiac vein; distal, junction with great cardiac vein. LAD, left anterior descending coronary artery; LCI, left circumflex artery; RCA, right coronary artery; AP, angina pectoris; R, rest; I, isoproterenol; X, exercise; +, extraction; —, production.
angina and myocardial ischemia can occur without coronary disease, presumably because hypertrophy has outstripped its vascular supply.

**Coronary Spasm**

Seventy-five years ago, Latham and Gairdner advocated that spasm of the coronary arteries was the instigator of anginal pain. This idea received clinical support because the characteristically precipitous and violent anginal attack could be relieved quickly by the administration of smooth-muscle relaxants (nitroglycerin) and by carotid sinus pressure. The "spasm" theory has also been supported by various angiographic laboratories, which have documented the transient narrowing and occasional actual occlusion of coronary vessels. Figure 2 shows an example of such spasm. However, there has been an inconstant association of symptoms of any kind with the observed spasm. In a number of instances, the spasm has been attributed to direct stimulation by the tip of the angiographic catheter. In our experience, recorded sequences of spasm were totally unrecognized by the patient, and occasioned no alteration whatever in cardiac function. Certainly, systemic arterial spasm per se can elicit severe pain; however, coronary spasm can occur with or without causing pain. Pain associated with spasm may depend on whether the change in caliber of the vessel is occlusive enough to initiate ischemia of the myocardium downstream. Thus, in summary, spasm has been morphologically demonstrated to occur irrespective of the presence of coronary sclerosis; and it can occur without inciting pain. The precise relationship, if any, of such spasm to clinical angina pectoris is still unsettled.

**Acute Left Ventricular Failure**

In a study of patients with coronary heart disease, Muller and Rørvik described a rise in pulmonary capillary pressure during exercise that preceded the onset of anginal pain. Both the rise in pressure and the occurrence of pain were abolished by prior use of nitroglycerin. They suggested that the occurrence of pain might be related to sudden congestion of the heart or lungs. Such a chain of events has been uncommon in our experience. In at least 30 examples of stress-induced angina, an increase in left ventricular end-diastolic pressure was observed in only one instance. Here, left ventricular systolic pressure had risen remarkably because of the presence of severe aortic valvular disease. We...
have observed eight instances of “spontaneous” angina unrelated to any deliberate laboratory stress. Left ventricular end diastolic pressure rose on three occasions. In each, systolic blood pressure had risen considerably. Figure 3 shows the sequence in a patient with coronary disease with fixed heart rate due to complete heart block and controlled by an internal pacemaker. Left ventricular systolic pressure rose progressively, as well as end-diastolic pressure, and soon the patient complained of angina. Reciprocally, the cardiac output and mean ejection rate declined, indicating peripheral vasoconstriction as well as acute heart failure. A significant feature of the unprovoked anginal attack often appears to be acute vasoconstriction with acute hypertension and sometimes a rise in ventricular end-diastolic pressure. Cardiac performance can be profoundly affected by systemic vasoconstriction when the heart is diseased. In another patient, however, angina developed on two occasions at two completely different values of left ventricular systolic and end-diastolic pressure.\(^8\) Pain and failure of cardiac function are probably both dependent on myocardial ischemia, in part abetted by the obligatory pumping of the heart against hypertensive pressure; but pain and failure are not necessarily dependent on each other. It would seem unlikely that pain is due to heart failure per se.

**Myocardio-Neuronal Reception and Transmission of Pain Impulses**

It is unclear how the pain signal is initiated, but some factors are known. There are two networks of sensory fibers in the heart: the perivascular network encircling the coronary arteries and the paravascular fibers, running alongside the vessels and terminating between the muscle fibers in free-branching, unmyelinated and nonspecific nerve endings.\(^1^3\) These endings are not so numerous in muscle as in other structures.

The present concept of pain (fig. 4) holds that with ischemia, various pain-producing substances or substances akin to or identical with the plasma kinins, are activated, possibly by kallikrein released from ischemic or inflamed tissue.\(^1^4\) Concentration of such substances is intensified by stagnation of blood flow, and their action to produce pain is augmented by heightened local concentration of H\(^+\) or K\(^+\)\(^1^5\)—a likely interstitial consequence of cellular hypoxia. Apparently, these agents affect the free-branching terminals, and pain is registered in proportion to the intensity of chemical stimulation and to the number of receptors sending signals (size of total area of ischemia produced as well as the number of live receptors, i.e., loss with prior infarction).

This theory does not answer three discrepancies: (1) pain is uncommon with acute myocarditis as opposed to myocardial ischemia, and inflammation is notorious in releasing pain-producing substances; (2) generalized ischemia of the heart as a whole may not necessarily cause pain, and yet a small area of ischemia may result in major discomfort; (3) similar degrees of chemical ischemia (seen in the same patient) may or may not initiate pain.

Once the receptors have initiated the signals, this information flows to the central nervous system through the eighth cervical and first four thoracic ganglia. In so doing, these impulses must utilize the same pathways as impulses bringing information from other organ systems. In addition, there is segmental “overflow” both along the ganglionic chain

\[\text{Free Branching Sensory Receptors} \quad \text{Dead}\]

\[\text{Increased} \quad \begin{array}{c} \text{Kinins or PPS} \\ \text{or} \\ \text{By-products of Ischemic Muscle} \end{array} \quad \text{Activation by Kallikrein} \]

**Figure 4**

*Pain generation within cardiac muscle.*
and within the lateral ascending pathways of the spinal cord. For these reasons, information coming from the heart cannot necessarily be distinguished as such, but may be expressed solely via a somatic referral—a projection onto that part of the body surface supplied by that particular spinal cord segment. Here again, the intensity of stimuli from the heart can be amplified or diminished depending on what other traffic is in this segment of the nervous system. For instance, impulses from another organ such as a diseased gallbladder (or hiatus hernia) may ordinarily be below the threshold of conscious recognition, but the summation effect of subliminal stimuli from the gallbladder and heart may elevate angina to conscious awareness and make perception of pain more likely with minimal degrees of cardiac ischemia. I have also observed that patients with particularly crippling angina pectoris almost always have some other pain-producing syndrome such as cervical spine disease, costochondritis, or a gastrointestinal disorder.

A 68-year-old patient was seen who had a 10-year history of relatively infrequent attacks of angina pectoris. For 1 week, substernal pain had increased in frequency and intensity, particularly after meals, and waking the patient from sleep. Electrocardiogram showed ST-segment depression over the left precordium. The patient was hospitalized for presumed preinfarctional angina. After 4 days there was a sudden increase in pain, with a shift in location for the first time to the epigastrium. He developed chills and fever to 103°F and subsequently became icteric with a rise in serum SGOT and LDH; within 48 hours all symptoms and signs of biliary tract obstruction receded; the anginal syndrome and ST changes on the electrocardiogram subsided within 3 days. Gallstones were subsequently demonstrated and his gallbladder was removed surgically. Angina has returned to its former mild tempo.

Thus, previously stabilized angina can be so increased in intensity and frequency by another disease, i.e., cholelithiasis, as to suggest the preinfarctional state. Complete remission resulted once the offending condition is corrected.

Finally, the information reaching the brain must be sorted and identified, allowing ample opportunity for reinterpretation. Indeed, the well-worn pathway of impulses streaming from the heart, as proposed by MacKenzie, can become part of a conditioned and easily provoked reflex. Is the load on the heart necessarily different in the morning while the patient is shaving or when rushing for a bus so that angina should be more frequent at such times than during similar activities later in the day? It is probable that conditioning of a reflex response plays some role here. It is not that ischemia does not occur on other occasions, but rather that under certain given circumstances, cardiac ischemia is more specifically directed to the patient’s conscious level. Thus pain awareness is not only a function of the occurrence of ischemia, but also of neuronal receptor stimulation, density, and intensity of sensory traffic, and finally its reception and interpretation by the brain itself.

Clinicophysiologic Factors in Development of Angina Pectoris

Anginal pain is not an automatic byproduct of cardiac ischemia. Nevertheless, angina does fall into certain well-known patterns and has a predisposing background.

Predisposing Background

Reduction in arterial oxygen content or capacity as with chronic anemia by reducing oxygen transport per milliliter of coronary flow, potentiates angina; and, although extremely rare, it is reported that severe enough anemia has caused angina in the absence of morphologic coronary disease. Cardiac activity and metabolism can be chronically heightened as in thyrotoxicosis, valvular heart disease, arteriovenous fistula, and pulmonary or systemic hypertension. These factors can so burden the oxygen transport system as to bring borderine areas of myocardium closer to frank ischemia. Polycythemia can augment a tendency to angina. Finally, changes in blood lipids can result in sludging or clumping of cells, or possibly inhibition of oxygen diffusion through the capillaries with intensification of already existing ischemic symptoms. Whether these latter factors
Angina with Tachycardia

Tachycardia reduces coronary artery filling time in diastole as well as augmenting cardiac oxygen requirement. This sets the stage for selective myocardial ischemia beyond a stenotic coronary artery.

Spontaneous Angina

Although angina at rest may occur without discernible hemodynamic change, Sir Thomas Lewis pointed out that blood pressure or pulse increases in most patients at the time of an attack. This has been true of the majority of patients observed in our laboratory during an attack of "spontaneous" or unprovoked pain. The patients are usually tense, nervous, or fearful. The rise in pulse or blood pressure,

*It is the author's belief that many patients with coronary heart disease have subliminal cardiac failure. Not only are there measurable deficiencies in the response of cardiac output to stress, but some patients exhibit moderate salt and water retention long before overt effort dyspnea or pedal edema occurs. This can be detected by the response to mercurial diuresis, which often will result in a surprising weight loss of 5 to 10 lb. as compared to a normal of about 3 lb.
of itself, would not seem to be enough of a mechanical load to precipitate angina through demand-energy imbalance alone (fig. 3). On the other hand, these changes may represent signs of generalized sympathet-ic nervous discharge involving vasoconstriction through vascular beds as well as direct inotropic and chronotropic stimulation to the heart.

Figure 6 represents a fortuitous set of observations made during a spontaneous anginal attack in a patient with severe, diffuse narrowing of the left anterior descending coronary artery. The figure shows a continuous krypton-85 left coronary blood flow determination initiated from a subostial position approximately 1 minute prior to the time that the patient began to complain of what was for her a typical attack of angina with severe substernal chest pain (by history the patient's pain had no apparent predictable provocation). It was noted that she developed hypertension of 180/110 from a nearly normal blood pressure, a relative tachycardia of 86 from a slow heart rate, and change in T waves of lead III. The portion of coronary flow curve recorded during the time of pain, yielded a value of 51 ml./100 Gm./min. This was significantly lower than a control value for coronary flow (71 ml./100 Gm./min.) in this patient measured at an earlier time in the study when hemodynamics were normal and cardiac oxygen demand was presumably much less. This patient then had a reduced coronary flow in the presence of increased cardiac work due to acute hypertension. Coronary vascular resistance was increased during the attack indicating that there must have been marked coronary artery or arteriolar constriction. Nitroglycerin, given sublingually, resulted in an almost immediate increase in coronary flow to 88 ml./100 Gm./min., and thereafter relief of pain and return of pulse, blood pressure, and T wave to baseline. This case represents documentation of a severe vasoconstrictor (or less likely arterio-spastic) episode occurring as part of a generalized sympathetic constrictor discharge. This may supply an important clue to the nature of many so-called spontaneous anginal attacks. It is probable that such phenomena occur frequently with sympathetic nervous discharge in all kinds of people (fig. 3). When this occurs in a patient with obstructive coronary artery disease and lowered pre-arteriolar arterial pressure, such arteriolar vasoconstriction may readily precipitate myocardial ischemia. It is well known that coronary vasoconstriction when produced by ergot and Pitressin can precipitate angina pectoris, and norepinephrine administered intravenously may cause coronary vasoconstriction. One of the important roles of both the long-acting and short-acting nitrates may be in the prevention or mitigation of such constrictor episodes.

Angina of Emotion

It seems most likely that this form of angina has a dual origin similar to that of "spontaneous" angina. Undoubtedly, with sympathetic stimulation an increased blood pressure, heart rate, and vigor of contraction augment the cardiac need for oxygen. To this may be added the possible further aggravation of ischemia by participation of the coronary system in systemic vasoconstriction. The very same response pattern to emotion may take place in any individual. Only if there is underlying segmental vascular disease and antecedent drop in line pressure will superimposed constriction seriously impair segmental coronary flow.

Angina of Deglutition

This is poorly understood. Occasionally, if this symptom is outstanding, it may serve as a clue to the presence of an associated disease in the gastrointestinal tract, such as cholelithiasis or hiatus hernia, working through the summation phenomenon discussed earlier. More often, however, angina with eating is usually a sign of advanced coronary disease or of the pre-infarctional state. The few studies of hemodynamics during eating have failed to indicate major changes either in blood pressure or in cardiac output, and heart rate does not rise much above 110. Perhaps unrecog-
nized visceral coronary reflexes or alterations in the chemical constituents of the blood may be important in angina of eating.

**Angina with Cold Wind**

This symptom is virtually characteristic for angina related to coronary heart disease, and is less commonly seen when other disease underlies the anginal state. Its mechanism is unclear. Freedburg and co-workers demonstrated that anginal pain and electrocardiographic abnormalities following exercise were more readily elicited if the subject were in a cold as opposed to a warm room, or held ice cubes in his hands. Murray has shown that a blast of cold air can cause electrocardiographic changes in some subjects with coronary disease. He has recently demonstrated in the dog that cold air triggers a marked vasoconstrictor reflex in the systemic and possibly the pulmonary vasculature which can be blocked by local anesthesia to the pulmonary airway. Perhaps similar to observations reported during “spontaneous” angina, hypertension and concurrent coronary vasoconstriction result from exposure to cold air.

**Nocturnal Angina**

This form of angina was once considered solely a late and quite serious manifestation of myocardial ischemia. We now know that this can be the *presenting* manifestation of angina even preceding angina of effort. Its mechanism is unclear, but three possibilities seem reasonable: (1) nocturnal angina may point to early heart failure and be a symptom equivalent to paroxysmal nocturnal dyspnea; (2) nocturnal angina may be due to fall in blood pressure at night with inadequate perfusion of the myocardium beyond a stenosed coronary artery; and (3) nocturnal angina may be due to sympathetic discharge as in “spontaneous” angina, and may be brought about as a reaction to a dream.

Angina can also occur with idiosyncrasy to tobacco, coffee, drugs, etc. The reasons are as yet unclarified.

**Amelioration of Angina Pectoris**

Angina pectoris can be mitigated in various ways.

1. Morphologic: Total infarction may destroy the nerve receptors of an ischemic region or new anastomotic collateral ingrowths may eventually revascularize a region formerly ischemic. The development of heart failure may alleviate angina as well. This is usually attributed to lessened physical activity, but it may involve, to a greater degree, the mode or vigor of contraction of the heart plus a more sluggish mechanical response of the failing heart to environmental stress. (In this connection an occasional patient will suffer *aggravation* of angina pectoris upon development of heart failure with relief by specific therapy of failure.)

2. Physiologic: Cessation of physical effort or control of emotional tension can alleviate angina. Carotid sinus pressure usually stops an anginal attack for reasons unknown. The relief is too rapid to be due solely to slowing of the pulse, and may involve inhibition of sympathetic constrictor activity.

3. Pharmacologic: Smooth muscle relaxants can relieve angina. The caliber of large arteries can be visibly increased by nitrates, but this implies nothing about total blood flow along the vessel. It may well be that distribution of blood flow may be improved through dilatation of collateral vessels. If severe arteriolar constriction or spasm occurs, as in “spontaneous” angina (fig. 6), the nitrates can effect dilatation and therefore relief of ischemia. The fact that relief of pain cannot always be attributed to relief of ischemia is illustrated in the relief of pain with monamine oxidase inhibitors. Patients on such agents often obtain pain relief, but continue to show gross alterations in electrocardiographic response to exercise, and they occasionally develop frank myocardial infarction without pain. This indicates how pain transmission or perception can be dramatically diminished without change in the underlying pathologic process.
General Formulation Concerning Angina Pectoris (Fig. 7)

Almost invariably angina pectoris occurs in the presence of obstructive coronary artery disease or of myocardial hypertrophy. Ischemia can be precipitated by any set of circumstances which disturbs the balance between oxygen supply and oxygen demand. Oxygen demand can be chronically augmented by any disease process chronically increasing cardiac activity. This demand can be acutely increased by any stress which acutely increases cardiac pressure, contraction, or rate. Emotion, through autonomic stimuli to the heart, can even be more detrimental than effort in provoking ischemia. Conversely, the reserve mechanism of oxygen supply can be chronically compromised by disease processes chronically affecting oxygen transport (anemia). Oxygen supply can be acutely compromised by reduction in perfusion pressure or time and, more important, by acute coronary vasoconstriction (or coronary spasm if it occurs clinically). Acting as a resistance in series with arterial obstruction, constriction can readily induce ischemia in the diseased heart. Thus, the potential exists for ischemia to occur with varying degrees of morphologic coronary disease, depending solely on what other influences play upon the heart. For example, severe coronary disease may be decompensated by even a mild anemia or mild physical effort. By contrast, a single moderate coronary stenosis can be made highly significant by the simultaneous effect of increased cardiac effort and coronary vasoconstriction. Special emphasis must be given to reflexes from the central nervous system in changing cardiac activity. The response to an emotional stress or to external stimuli, such as environmental cold, may involve acute hypertension, tachycardia, and augmented vigor of contraction. Such stimulation may be poorly tolerated in the damaged and potentially ischemic heart. In addition, active coronary vasoconstriction, an "inappropriate" sympathetic nervous system response, may be a major factor in many attacks of angina. Vasoconstriction further compromises coronary supply in areas distal to arterial obstruction or narrowing, particularly under circumstances demanding augmented cardiac performance.

The interplay of all these factors may well explain some hitherto confusing aspects of clinical angina. The occurrence of ischemia is not necessarily a good yardstick for the significance of morphologic coronary disease. Not only is there the anatomic variable of collateral flow, but there is the functional

Figure 7

This figure encompasses those factors believed to enter into the production of angina pectoris. A partially obstructing atherosclerotic plaque is depicted in one vessel and not in another. PPS, pain-producing substances; $P_P$, arterial pressure; $P_B$, postobstruction arterial pressure; $P_A$, arteriolar pressure. Because $P_A$ is less than $P_P$, the superimposition of sympathetically mediated arteriolar constriction (or arteriolar spasm) will act to reduce $P_A$ further, and therefore reduce segmental flow. Thus, regional ischemia can readily be induced. Also effective are autonomic impulses increasing inotropic or chronotropic activity of the heart (and particularly in the ischemic zone). The induction of ischemia releases pain-producing substances (PPS), stimulating unmyelinated, free-branching nerve endings. This sensory information passes via a paracaval network to the autonomic ganglia through a series of synapses to the brain. These impulses are also integrated with sensory impulses arising from other nearby organs.
variable of load on the heart and antagonistic reflexes to modify the ischemic resultant of any given degree of coronary disease.

Once ischemia occurs, it may be recognized biochemically as cardiac lactate production, and is often associated with abnormalities in the electrocardiogram and in cardiac performance. Ischemia releases chemical by-products, of the polypeptide variety, which act on nonspecific nerve endings in the heart. This stimulus is returned to the spinal cord, sorted, and sent to the cerebral cortex for further analysis. Whether ischemia actually results in pain or causes more pain than seems appropriate, will depend on the amount of pain substances produced, on the number of intact receptors stimulated, on reception, and finally on the competition and augmentation within the nervous system from information originating in other organs or from conditioned pathways developed from prior psychic experiences.

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References

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