1954

A Discussion of the etiology and pathologic physiology of angina pectoris

Mayer Moskovitz
University of Nebraska Medical Center

A DISCUSSION OF THE ETIOLOGY AND PATHOLOGIC PHYSIOLOGY OF ANGINA PECTORIS

Mayer Moskovitz

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

March 24, 1954

Omaha, Nebraska

TABLE OF CONTENTS

I. INTRODUCTION

Angina pectoris is a very interesting and complex subject, and much has been written concerning it.

I have chosen to discuss one portion of this subject, the etiology and pathologic physiology. In reading about angina pectoris, I have found that this term and the names of its various manifestations have had different meanings to different people throughout the years. Therefore, I have included in this thesis a discussion of the definition of angina pectoris.

The thesis begins with a brief history dealing with the early knowledge of angina pectoris.

II. HISTORY

In the year 1768 William Heberden in a lecture before the Royal College of Physicians of London described the group of symptoms which he named angina Pectoris. His account of this syndrome was published in volume two of the "Medical Transactions of the Royal College of Physicians" in 1772, Heberden (1) and Segall (2).

Because of the location of the pain and because of the "sense of strangling and anxiety" associated with the pain, Heberden chose the name angina pectoris.

Heberden in his classic description drew a fairly complete picture of this fascinating syndrome. He stated that the pain may be brought on by walking, especially walking after meals. He also emphasized that rest will relieve the pain. The observation was made by Heberden that after having this condition a few months a patient cannot relieve the pain as rapidly by resting as he could before; also, the pain, he said, will come on when the patient is lying down. He found that it had been precipitated by the motion of a horse or carriage, by speaking, by swallowing, by coughing, or by going to stool.

Most of the patients of Heberden's series had short necks and were inclined to be fat.

Heberden said that the location of the pain is the os sterni, and it is more to the left side. He also stated that the pain sometimes is associated with a pain about in the middle of the left arm.

As far as prevention of attacks is concerned, he found that wine and cordials and especially opiates taken at bed time would prevent or at least decrease the severity of attacks at night.

In his original article William Heberden considered a theory of the cause of angina pectoris. Because of the sudden onset and conclusion of an attack, the intervals (which may be long) without any attacks, the relief produced by wine and cordials, emotional causes precipitating attacks, the relief which comes from varying the posture of the head and shoulders, Heberden said that angina pectoris may be "a convulsion of the part affected", Heberden (1).

In 1772 Heberden's description of angina pectoris was published. In March of 1772 a London physician, who has remained anonymous, diagnosed himself as having angina pectoris, after reading Heberden's article. Just a few weeks after this, the physician wrote Heberden a letter, in which he described his symptoms and in which

he said that in his will it was stated that upon his death Heberden should have the permission to perform an autopsy on his body.

The anonymous physician died three weeks after sending this letter. The body was placed in Heberden's care; and Heberden had John Hunter perform the autopsy, which was the first post mortem examination in a case of angina pectoris diagnosed during life, Segall (2) and Heberden (3).

Some of the statements in the letter from the anonymous physician were that he was fifty-two years old, had a short neck and was fat, and had attacks of angina pectoris when he was walking (always after dinner or in the evening). The doctor had a pain in his left arm which spread to the left side of his breast, and the pain made him stop walking. The pain became more frequent as the patient grew older; the patient had it about six years. The patient felt that he was more subject to the pain during the winter than during the summer. He felt completely well in between attacks.

At autopsy the cause of the doctor's death was not found - the autopsy did not reveal any pathology of the "heart and its vessels and valves", Segall (2) and Heberden (3).

It is interesting to note that when John Hunter died there were found at his own autopsy scars of an old myocardial infarction on the posterior wall of the left ventricle and atrium, and the coronary arteries and their branches were "arteriosclerotic to a great degree", Segall (2).

III. DEFINITION OF ANGINA PECTORIS

(a.) The Definition

Angina pectoris is a symptom complex (a symptom syndrome) and is not a disease, Friedberg (4). The diagnosis of angina pectoris is made from the history alone, and it does not depend upon physical examination or any laboratory procedure which we now have available, Marvin (5).

The following is a general definition which is followed by an examination of its component parts: Angina pectoris is a symptom complex in which there are usually paroxysmal attacks of substernal (retrosternal) pain or oppression, which is usually precipitated by certain factors; it lasts no longer than a specific period of time and may or may not be associated with a feeling of anxiety; the pain may or may not radiate; it is reproducible and is relieved by rest and/or certain nitrites. Angina pectoris may or may not be associated with pallor of the face and sweating. Sometimes the only manifestation of angina pectoris is the substernal pain, which may or may not radiate. The only manifestation of angina pectoris may be epigastric pain, pain in the interscapular region of the back, pain in the neck, throat, angles of the mandible, or pain in the arms, Marvin (5).

The following is an explanation of the above definition:

1. Angina pectoris is a symptom complex - this statement is discussed above the preceeding definition.

2. Paroxysmal attacks are usually present, Friedberg (4).

3. Location of the pain: The attacks have substernal (retrosternal) pain or oppression. The primary location of the pain during an attack is usually behind the middle or upper third of the sternum, Friedberg (4), White (6).

4. Character of the pain: There have been many adjectives used to describe the character of the pain; it is usually a sense of constriction, tightness, pressure or oppression. It may be boring; squeezing; vise-like; choking; strangling; "raw"; burning or "heartburn"; like a weight over the sternum; a vague indescribable distress, tension, or uneasiness; fullness; expanding; as if the contents of the chest were greater in size than the chest cavity; or as if an umbrella opened suddenly within the chest, Friedberg (4), Marvin (5), White (6). Rarely, the pain consists of shortness of breath, Segall (7).

The pain is usually dull, not sharp, and it is continuous. The pain may be mild to severe in its intensity, Friedberg (4), White (6).

5. Precipitating causes: These will be discussed in the portion of this thesis dealing with etiology. Angina pectoris may occur when the patient is at rest and no precipitating causes are present.

6. Duration of the pain: Attacks of angina pectoris usually last from fifteen seconds to three or five minutes; however many patients, overestimating the length of the attacks, usually believe that the paroxysms last longer. Attacks which occur when the patient is at rest often last from five to fifteen minutes or even up to a half hour, which also occurs with some attacks having definite precipitating causes. A mild local soreness may be present many hours after the attack, Friedberg (4), Marvin (5).

7. Radiation of the pain: The pain may not radiate. If it does radiate, it may do so in a variable manner. It may radiate to either or both shoulders, to either or both sides of the neck, to either or both angles of the mandible, to the throat, to the inner aspect of either or both of the upper arms, and into the ulnar aspect of either or both of the forearms and the little and ring fingers, into the interscapular region of the back, and into the epigastrium, Friedberg (4), Marvin (5), White (6), Harrick (8). The pain is more frequent on the left

than on the right side, Segall (7).

8. The feeling of anxiety: Accompanying the pain, there is a feeling of anxiety. Anxiety may not be present, however, during an attack of angina pectoris. The content of the anxiety is determined by the impact of the attack upon a person's significant emotional conflicts preceding the attack. The most common contents of the anxiety are fear of death, a sense of imminent dissolution, or an actual feeling that the person is dying. The anxiety which may be present, however, may be a fear of loss of love, a fear of being abandoned, a fear of aggressive impulses, or a fear of homosexual impulses. The presence or absence of anxiety during an attack is dependent upon the adequacy of the usual psychological defenses against anxiety. In situations of danger the person responds with anxiety as a warning signal. An anginal attack is a danger to the individual; hence anxiety is produced if the usual psychological defenses against anxiety fail. The anxiety of angina pectoris is the same type of anxiety produced by any other threat to the individual; there is nothing specific or organically distinctive about the anxiety of angina pectoris, Arlow (9).

9. Angina pectoris is reproducible: The pain of

angina pectoris may occur at rest, but if effort cannot reproduce a pain, the diagnosis of angina pectoris may not be correct, Friedberg (4), Marvin (5).

10. Relief of angina pectoris: Angina pectoris is relieved by rest and/or the administration of certain nitrites, glyceryl trinitrate (nitroglycerine) and amyl nitrite, Marvin (5), Evans (10).

Angina pectoris may or may not be associated with pallor of the face and sweating, Osler (11). Friedberg emphasizes that there are often no abnormal physical signs during an attack of angina pectoris. As a rule the blood pressure does not change, however there may be a rise in blood pressure sometimes during an attack. Also, there is usually no alteration of the pulse rate. If the underlying disease is syphilitic aortitis, rheumatic aortic insufficiency, or calcific aortic stenosis, the physical signs which are present are those of the disease which is an underlying cause of angina pectoris. When a person has underlying coronary disease, he frequently has hypertension, Friedberg (4).

(b.) Discussion of Terminology:

During my discussion of the above definition, I have purposely not used any of the Latin, Greek, or foreign words which are so prevalent throughout the

literature. My reason for not doing so is that these terms have been variously defined in the past, and hence these words not only have had different meanings but still have different meanings for many people. I shall, however, briefly discuss these terms.

1. Angina Pectoris: Angina comes from the Greek word meaning strangling, and pectus means breast bone or breast (pectoris is the possessive of this word), White (6). Synonyms have been angina cordis, cardiac angina, and stenocardia.

2. Dolor pectoris: Dolor comes from the Latin word meaning pain; hence this term means the pain of the breast, Osler (11).

3. Angor animi: This term has been defined as a sense of imminent dissolution, a fear of impending death which overwhelms the individual, a feeling of anguish, or an actual feeling of dying, Arlow (9), Osler (11). This term is usually synonymous with the anxiety mentioned above.

4. Angina abdominis: This means anginal pain in the abdomen, Osler (11).

5. Angina hypercyanotica: This is a heavy pain which is substernal and precordial, which may or may not radiate and which is felt by some persons with considerable cyanosis. This is found especially in people with marked mitral stenosis. Angina hypercyanotica is rare, White (6).

6. Angina pectoris sine dolore: The meaning of this term is angina pectoris without pain. The term could apply only in rare cases, if at all, White (6). However, Osler states that the mildest form of angina pectoris can be only a substernal tension, uneasiness, or distress, Osler (11).

7. Angina decubitus: When the attack occurs with the patient lying down, he is said to have angina decubitus, White (6). So-called angina pectoris has been described as occurring during attacks of paroxysmal nocturnal dyspnea (cardiac asthma) caused by left ventricular failure. Acute coronary occlusion may be the cause of some of these attacks. Sometimes acute dyspnea may cause precordial discomfort, which is not properly termed angina pectoris. Aside from the above exceptions, True angina pectoris does occur at night when patients are at rest, and attacks of angina pectoris may occur with or without concomitant paroxysmal dyspnea. Increased blood pressure, acute left ventricular dilatation, tachycardia and hence increased heart work have been some of the explanations for this type of angina pectoris, which is called angina decubitus; however, the actual cause is not known, Friedberg (4).

8. Angina pectoris vasomotoria: This is a condition which is precipitated by cold or "bouts of

drunkeness". There is first a blanching of the skin, especially of the extremities; then there may be pallor or cyanosis with a numbness and coldness of the limbs. Then there is a mild anginal pain, anxiety, and palpitation. There is a decreased pulse volume, and there may also be an increased pulse rate. Synonyms for this term are mock angina, angina notha, spurious angina, and false angina, Lewis (12), Blakiston (13).

9. Status anginosus: This is a condition in which there are repeated attacks of angina pectoris ending in myocardial infarction or death, Viar (14).

(c.) Cardiac Pain

There have been four types of cardiac pain described. Osler has described the mildest form. This is a condition in which there is angina pectoris consisting of substernal tension, uneasiness, or distress. At times definite pain may be present, Osler (11).

According to one author, Segall (7), there is the mild type of cardiac pain in which the pain may last up to five minutes in duration. With this pain a precipitating cause, for example, walking outdoors when it is cold, is always present. Nitroglycerine and rest relieve this type of pain.

The third or moderate type of cardiac pain may last from five to fifteen minutes, has no obvious precipitating cause, and requires a longer period of time for relief by nitroglycerine. Some authors say that this third type of cardiac pain may last up to a half hour and may have definite precipitating causes.

The fourth type of cardiac pain is the severe type. This pain lasts more than one-half hour, usually two to four hours. There is no precipitating cause. Nitroglycerine does not relieve this pain, and only a strong analgesic, such as morphine, will produce relief. Shock may occur in some cases, Friedberg (4), Marvin (5), Segall (7).

Cardiac pain is usually divided into three main groups: Angina pectoris, coronary insufficiency, and myocardial infarction. Angina pectoris includes the first two types (the mildest and mild types) of cardiac pain listed above; coronary insufficiency includes the third or moderate type; and myocardial infarction includes the severe type of cardiac pain, Marvin (5). However, there are certain drawbacks to this customary classification. It is agreed that the severe type of cardiac pain described above is indicative of myocardial infarction; but with any of the other types of cardiac pain, one may have

a myocardial infarction. Dressler (15), states that a sudden onset or aggravation of angina of effort or brief attacks of angina of rest indicate progressive coronary insufficiency, and may indicate myocardial infarction. (It is interesting to note that myocardial infarction may occur without pain, Papp (16).) Also, since some authorities in cardiology, such as Friedberg (4) and White (6), state that even though angina pectoris usually lasts a few (three to five) minutes, it may last fifteen to thirty minutes, I have included in this thesis on angina pectoris a discussion of the mildest, the mild, and the moderate cardiac pain presented above.

In a discussion of angina pectoris, one must differentiate the pain associated with pulmonary hypertension. Pulmonary hypertensive pain may resemble the pain of angina pectoris in many respects, for example, in quality, intensity, location, radiation, and precipitation by physical exertion. However, pulmonary hypertensive pain also may have associated with it cyanosis, the presence of pain on breathing, a history of long-standing cough, the presence of pain with dyspnea, variability in the duration of pain, dramatic relief of pain with oxygen administration, symptoms and signs of right ventricular hypertrophy, and slight or no relief of the pain with nitroglycerine administration, Viar (14).

IV. ETIOLOGY

The following is a list of the causes of angina pectoris. Since a discussion of the causes is so closely linked with an explanation of how they produce abnormal function, I shall discuss the causes together with a discussion of the pathologic physiology, which follows below. (The references from which I obtained the following causes of angina pectoris will be stated when I discuss the causes individually under the specific mechanisms of the pathologic physiology below.)

The causes of angina pectoris are divided by Friedberg (4) into four general groups - precipitating, underlying, contributory, and predisposing. I shall use this general classification.

(a) Precipitating Causes:

1. Bodily exertion
2. Digestion
3. Cold
4. Emotion and dreams
5. Tachycardia
6. Hyperinsulinism and hypoglycemia
7. Diabetes mellitus
8. Administration of thyroid extract

9. Administration of Epinephrine
10. Administration of Ergot Alkoloids
11. Administration of Pituitrin
12. Administration of Prostigmine
13. Administration of Sodium Succinate.
14. Administration of Amyl Nitrite
15. Administration of Nitroglycerine
16. Administration of Aminophylline
17. Administration of Potassium Thiocyanate
18. Administration of Acetylsalicylic Acid
19. Administration of Trichloroethylene
20. Administration of Pentnucleotides
21. Exposure to Carbon Monoxide
22. Tobacco
23. Acute Spontaneous Pneumo-mediastinum
24. The recumbent position
25. Attacks may occur without apparent cause.

(b.) Underlying Causes:

The precipitating causes mentioned above induce attacks of angina pectoris only in people who are susceptible because of one or more of the following underlying causes:

1. Coronary Arteriosclerosis
2. Syphilitic aortitis with coronary ostial stenosis

3. Bacterial Endocarditis

4. Aortic Stenosis

5. Aortic Insufficiency

6. Mitral Stenosis

7. Anemia

8. Arterial Anoxemia

9. Arteriovenous Fistula

10. Hyperthyroidism

11. Hypothyroidism

12. Allergy

13. Climacterium

14. Trauma to the chest

(c.) Contributory Causes:

1. Diabetes Mellitus

2. Hypertension

3. Familial Xanthomatosis and Hypercholesterolemia

4. Acute Mediastinitis

5. Mediastinal Abscess

6. Mediastinal tumors, primary or metastatic

7. Pneumo-mediastinum

8. Partial or complete esophageal rupture within the mediastinum

9. A dissecting aneurysm of the aorta in the mediastinum

10. Aneurysmal dilatation of the pulmonary artery
11. Aneurysmal dilatation of the aorta
12. Diverticula of the esophagus
13. Acute spontaneous pneumo-mediastinum
14. Spontaneous or artificial pneumo-thorax
15. Active pulmonary tuberculosis
16. Pneumonia
17. Diaphragmatic flutter
18. Obesity
19. Infection
20. Fever
21. Acute toxic myocarditis
22. Hydatid infestation of the heart
23. Tumors of the myocardium
24. Abscess of the heart
25. Diseases of the Pancreas
26. Pericarditis
27. Chronic cholecystitis and cholelithiasis
28. Duodenal ulcer
29. Diverticula of the duodenum
30. Irritable colon
31. Diaphragmatic hernia
32. Pregnancy
33. Faulty movements of the diaphragm

34. Subacute and chronic appendicitis

35. Epidemic encephalitis

(d.) Predisposing Causes:

1. Age
2. Sex
3. Familial occurrence
4. Occupation
5. Social and Economic Status
6. Race
7. Constitution
8. Temperament
9. Obesity
10. Diabetes Mellitus
11. Hypothyroidism

V. PATHOLOGIC PHYSIOLOGY

(a) Basic Pathologic Physiology

Throughout the years there have been many theories proposed to explain the pathologic physiology of angina pectoris. William Heberden, in his original account of angina pectoris, given in 1768 and published in 1772, stated that the basic pathologic physiology was "a convulsion of the part affected", Heberden (1).

Heberden, however, had no objective findings as to the pathologic physiology of this symptom complex. Since his theory there have been various explanations given, and I shall now discuss these theories, including arguments both for and against them.

1. The Theory of Coronary Spasm:

This theory involves two important points for consideration. The first is that the actual spasm of the coronary arteries may produce angina pectoris. The other possibility is that spasm of the coronary arteries may produce myocardial ischemia, which produces myocardial anoxia, which produces angina pectoris. (The theory of myocardial anoxia itself will be discussed below.)

As far as the first point is concerned, no one has produced any proof to substantiate this theory.

Gilbert (17) describes an experiment on dogs which may be considered in a discussion of myocardial ischemia

caused by coronary arterial vasoconstriction or spasm. The dogs were lightly anesthetized, and a bag was put into the stomach of each dog. The bags were then inflated until they produced moderate distension of the stomachs of the dogs. Then, there was found to be a decrease of coronary flow. This decrease was marked if the bag was in the cardiac end of the stomach at the esophageal hiatus. When the vagus was severed, or if atropine was administered previously, no effect was obtained. When the abdominal cavity was distended with air, there was also found to be a decrease in coronary flow volume. This result also did not occur if the vagi were cut or if atropine was administered. No fall in blood pressure took place which could account for the change in coronary flow.

After these dogs made a complete recovery from their operations, observations were made on them in the conscious state. When the stomach was distended, the same decrease in coronary flow volume was observed, which did not occur if atropine was administered.

Experiments on patients demonstrated that if a vasodilator drug was given to a patient before a meal, the onset of angina pectoris was deferred. Another reason for believing that vasoconstriction of the coronary

arteries is the basic pathologic physiology of angina pectoris is that swallowing may produce an attack of angina pectoris. The immediate appearance of angina pectoris following swallowing and certain other precipitating causes suggests a mechanism which includes a nervous system reflex and then coronary vasoconstriction.

In experimental animals it has been found that when the blood pressure exceeds a certain high point, there is increased intracephalic pressure, which causes a reflex vasoconstriction of the coronary arteries, which is mediated through the carotid sinus; and in some cases of angina pectoris which occurred with high blood pressure, there was relief of the angina pectoris by vasodilator drugs, even if there was no fall in blood pressure.

Stimulation of the vagus produces vasoconstriction of the coronary arteries, Gilbert (17). Hess (18) states that irritation to the nucleus dorsalis vagi produces constriction of the coronary arteries. The vagus is the only pathway for efferent coronary constrictor nerves, Gilbert (17). Stimulation of the vasomotor center of the brain may cause spasm of the coronary arteries, Sansom (19), Maddin (20).

When cold is applied to certain areas of the body, angina pectoris may be precipitated in ten seconds in patients having angina pectoris. The speed of this reaction

suggests the presence of a reflex factor producing coronary artery spasm, Freedberg (21). This reaction is prevented if nirtoglycerine is administered before the application of cold.

Friedberg (4) writes that rarely there is complete disappearance of the radial pulse during an attack of angina pectoris. Except for this unexplained and rarely occurring phenomenon, there is no significant positive evidence for the coronary spasm theory, he states.

2. Theory of Myocardial Anoxia:

Friedberg (4) states that at the present time the theory of myocardial anoxia is the most widely accepted theory of the basic pathologic physiology of angina pectoris. Friedberg (4) defines coronary insufficiency as a disproportion between the blood supply, qualitatively or quantitatively, and the blood requirements of the myocardium. Coronary insufficiency may be due to a decreased coronary inflow, an increase in the size of the heart, an increase in the work of the heart, a deficiency in the oxygen content of the blood, or to two or more of these, Friedberg (4), Chew (22).

The coronary reserve is defined as the range which exists between the coronary flow under basal conditions and the increased coronary flow when myocardial requirements are at their maximum. When there is a decrease in

the coronary reserve to the extent that the coronary flow is sufficient only for usual needs, any sudden decrease of the blood supply or increase in myocardial requirements may result in coronary insufficiency. These episodes of acute coronary insufficiency which last for only short periods of time are believed, according to the theory of myocardial anoxia, to account for the development of angina pectoris.

There is certain evidence in favor of the theory of myocardial anoxia which is caused by coronary insufficiency: There is usually a mechanical interference with a large part of the blood supply to the myocardium. Segall (7) states that there is impairment in the balance of coronary circulation because of arteriosclerotic narrowing of the coronary arteries; he also states that this imbalance is quickly reversible by nervous reflexes and/or by the action of hormones. Cardiac pain lasting from five to thirty minutes may be caused by hemorrhage into an arteriosclerotic plaque. Obstruction of the coronary circulation may cause pain in unanesthetized dogs. Also, the pain in acute coronary occlusion is similar not only in character but also in location and distribution to the pain of angina pectoris.

It has been found that severe anemia in association

with underlying coronary pathology or by itself may cause angina pectoris. This phenomenon also supports the theory of myocardial anoxia.

In experiments on human beings in which low oxygen mixtures were breathed, attacks of angina pectoris were precipitated. In these experiments a mixture of 90% nitrogen and 10% oxygen was used. The pain was relieved instantly by breathing 100% oxygen. It was found that the appearance of pain was delayed by coronary arterial vasodilator drugs. It was also found that the pain occurred earlier with digitalis, Gilbert (17).

There has been an analogy drawn between the pathologic physiology of the pain of intermittent claudication which occurs in the lower extremities and the pathologic physiology of angina pectoris.

The evidence in favor of coronary arterial spasm producing angina pectoris resulting from myocardial anoxia has been presented in the section on coronary spasm discussed above.

Gilbert (23) suggests that sympathetic inhibition may prevent vasodilatation of the coronary arteries, making the coronary arteries unable to deliver an increased blood supply, when it is needed, to the myocardium, producing myocardial anoxia. If the mucous membrane of the nose of a decerebrate dog is stimulated with cold water, slowing

of the heart rate is produced. The slowing also results when the same stimulation is produced after section of the vagus, after atropine is administered, or after both. This reaction is interpreted as an inhibition of the sympathetic coronary arterial vasodilator tone.

Myocardial anoxia may produce ventricular fibrillation which causes sudden death, and sudden death may occur in patients with angina pectoris. This is another portion of the evidence in favor of the theory of myocardial anoxia, Friedberg (4), Keefer (24).

As a "sub-theory" of the theory of myocardial anoxia, Raab (25) discusses the catecholamine theory. He states that there is an "erroneous concept" prevalent in that temporarily increased cardiac work causes all of the increase of myocardial oxygen consumption. There are two principles which disprove this concept.

The first of these principles is that under the influence of sympathetic stimulation (that is, neurosecretory discharge of the catecholamines norepinephrine and epinephrine) the increase of myocardial oxygen consumption greatly exceeds the oxygen consumption used simultaneously for cardiac work. A large part of the oxygen consumption is for the production of heat and not mechanical energy. "The hypoxia-producing oxygen wastage of the heart muscle under sympathetic stimulation occurs

even without an increase of cardiac work as a specific chemical phenomenon, independent of cardiac dynamics", Raab (25).

The second of these principles is as follows: If either the quantity of the catecholamines norephineprine and epinephrine is excessive (as in pheochromocytoma, for example), or the coronary arteries are sclerotic and therefore not able to dilate and produce an increased coronary flow large enough to compensate for a large part of the chemically induced oxygen loss, the hypoxia produced by discharges of norepinephrine and epinephrine causes angina pectoris.

The sympathomimetic catecholamines enter the myocardial cells both from the sympathetic nerve endings supplying the heart muscle cell (neuro-secretion) and from the adrenal médulla by way of the blood. Except after sympathectomy, one to two micrograms per gram of norepinephrine and epinephrine are always found in normal heart muscle. It has been demonstrated in animals, under circumstances which are analagous to those which produce attacks of angina pectoris in humans (for example, physical exercise, exposure to cold, etc.), that the concentration of norepinephrine and epinephrine markedly increased when either catecholamines are injected into the body or additional catecholamines are secreted by the

body.

The mechanisms of the catecholamine theory are as follows: The precipitating causes of angina pectoris produce an acute influx into the heart muscle of norepinephrine and epinephrine secreted by the sympathetic nerve endings supplying the myocardium and by the adrenal glands; these chemicals instantaneously cause an excessive oxygen consumption, which causes a discrepancy between the oxygen supply and the oxygen demands of the myocardium, which causes hypoxia of the myocardium, which exceeds the pain threshold, which produces an attack of angina pectoris. If the coronary arteries are sclerotic and undilatable, the above chemically produced hypoxia causes an attack of angina pectoris no matter when degree of cardiac work is present, according to this theory.

The hypoxia-producing effects of norepinephrine and epinephrine are potentiated by the thyroid hormone.

The forms of causal treatment of angina pectoris can be interpreted as partially or completely eliminating the above discussed catecholamine mechanism of angina pectoris. These treatments are the following:

1. Thoracic sympathectomy; this treatment stops the catecholamines produced by the sympathetic nerve endings, notably norepinephrine, from coming from these efferent neurons into the myocardium.

2. Roentgen irradiation of the adrenal glands; this produces decreased secretion of catecholamines from the adrenal medulla.

3. Thyroidectomy, radioactive iodine, and thiourea derivatives; these decrease thyroid hormone production.

4. Nitroglycerine; not only does nitroglycerine dilate the coronary arteries, but also it directly antagonizes the local metabolic effects in the heart of the catecholamines produced by the adrenal glands and the sympathetic fibers.

3. The Energy Dis proportion Theory:

Beach (26) has proposed the idea that angina pectoris occurs when the available energy is less than the energy required by the myocardium for its function.

There may be many causes for this energy deficit. In angina pectoris a paroxysmal diminished coronary flow produces a disproportion between the blood supply to the myocardium and the requirements of the myocardium, Zoll (27). Myocardial ischemia may be due to arteriosclerotic narrowing of the coronary arteries, spasm of the coronary arteries (refer to the above theory), or shortening of diastole for a long period of time.

The energy deficit may also be caused by an oxygen deficiency, for example in anemias.

In hypoglycemia, there may be decreased energy to the myocardium. For proper function, the heart requires not only a good blood supply but also an adequate nutrition. Glucose is of utmost importance during contraction of the myocardium, and a decrease in the supply of glucose produces imperfect function. When there is a decrease of blood sugar, there are produced symptoms due to the resultant decrease of glucose to the myocardium. During hypoglycemia the pain may be an ache in the precordial area, frequently referred laterally along the pectoralis major; however, hypoglycemia may manifest itself as angina pectoris, including the typical radiation of pain, Sippe (28).

Patients with diabetes mellitus may have angina pectoris when they have a high blood sugar and glycosuria. Besides the presence of arteriosclerosis, there is another factor in the production of angina pectoris in diabetics who have a hyperglycemia and glycosuria. This factor is thought to be a decreased glycogen storage in the myocardium, Kahn (29).

Another point in favor of the energy disproportion theory is that a decreased rate of oxidation of products to produce energy occurs in myxedema. The decreased energy produced, according to this theory, is the basic cause of angina pectoris.

4. Chemical or physico-chemical Theory:

Lewis (30) states that the stimulus which causes angina pectoris is in the tissue spaces. When there is contraction of a muscle, there occurs within its fibers certain changes, such as the formation of metabolites. One of the possibilities which could result from the production of metabolites is that these metabolites diffuse out of the muscle cell and are the stimulating agents in the tissue spaces, Lewis (30), Gilson (31). However, Lewis states that it is also possible that changes within the muscle fiber may cause changes in the tissue spaces. He believes that it is necessary to keep changes inside and outside of the muscle fiber as possibly different ideas. Lewis and his co-workers have done so by naming changes outside of the muscle fiber the pain factor, or "factor P", because changes outside of the fiber compose the immediate pain stimulus. Factor P occurs in the muscle fiber during exercise. Even though the process inside of the muscle fiber is decided by the degree of exercise and is mostly independent of the state of the circulation, factor P accumulates in the tissue spaces in a quantity great enough to cause pain when the circulation is partially or completely interrupted.

In the anemic patient with free circulation, the occurrence of angina pectoris of effort is caused not by

an inadequate blood flow but by an inadequate oxygen supply to the myocardium. Factor P is considered to be not simple oxygen lack; factor P probably is the accumulation of chemical products usually removed by oxidation, Pickering (32).

Bedford (33) states that myocardial ischemia is the underlying pathologic physiology of angina pectoris. The stimulus which excites the pain is a chemical stimulus, which is caused by an accumulation of abnormal metabolites of muscular activity, which is caused by myocardial hypoxia, which is caused by myocardial ischemia.

Katz (34) states that the pain stimulus of angina pectoris is a metabolic product (or products) which can diffuse into the blood stream easily, and which can be changed rapidly in the presence of a sufficient oxygen supply. The accumulation of this metabolic product depends on the quality and the quantity of the person's physical exertion and the efficiency of the myocardium, on the one hand, and the quantity of the oxygen on the other hand. When this chemical product obtains a concentration which exceeds the threshold of the pain fibers, pain is produced. It is not clear whether the P factor is an acid metabolite or a non-acid metabolite. The metabolic product may be acid or a chemical product which

is additive with acid substances and may be "neutralized" by alkaline products. It may be some chemical like lactic acid, phosphoric acid, pyruvic acid, or succinic acid; factor P may be a metabolite which is not acid, such as histamine, phosphocreatine, adenosine, or potassium, Katz (34), Rinzler (35).

Since the pain-producing substance (or substances) may diffuse in and out of the blood stream, it is probable that angina pectoris may be precipitated not only by the collection of the substance producing pain which is formed by the heart, but also partly by the pain-producing substance (substances) from other parts of the body (for example, from exercising skeletal muscles in angina of effort) which pass via the blood stream to the heart. Normally the P factor, which is formed by heart or skeletal muscular contractions, is removed by an adequate blood flow, Rinzler (35), Katz (36).

Sometimes the reason that anginal pain or pain in intermittent claudication does not develop is that the earlier onset of small degrees of neuromuscular (and muscular) fatigue restricts the cardiac work or the work of the muscles and therefore limits the collection of the substance (substances) producing pain, Katz (36).

5. Theory of Anoxia in the Wall of a Thoracic Artery:

This theory has to do with anoxia, however the anoxia is not of the myocardium but is of the wall of a thoracic artery, coronary as well as any other thoracic artery. According to this theory, inflammation of the wall of a thoracic artery (amongst other causes) produces pressure on the vasa vasorum of the thoracic artery, coronary or any other, which causes impaired circulation in the wall of the thoracic artery. The addition of a precipitating cause of angina pectoris to this already impaired circulation causes a complete arrest of the circulation in the capillaries of the vasa vasorum of the area involved, which causes a local complete anoxia in the wall of the thoracic artery in which this process is taking place, which causes the pain of angina pectoris, Roder (37).

6. Myocardial Exhaustion Theory:

Mackenzie championed the theory of myocardial exhaustion. Because he was not able to account for the cases in which the coronary arteries had no pathology, he explained angina pectoris as being due to exhaustion of the myocardium, usually due to a deficient blood supply, however sometimes due to other causes.

This theory does not explain the frequency of angina pectoris in patients with aortic insufficiency or coronary disease, nor does it explain the infrequency of

angina pectoris in patients having mitral stenosis. Angina pectoris disappears when there is the most severe degree of exhaustion of the myocardium, namely, when congestive failure is greatest. On the other hand, when there is a good reserve in the myocardium (for example, when the patient is not dyspneic), angina pectoris is most marked. This theory does not account for the fact that all patients whose lives are terminated by heart failure (exhuastion of the myocardium) do not suffer from angina pectoris at some time during their lives, Keefer (24), Rucks (38).

7. Aortic Theory:

According to this theory, dilatation of the root of the aorta and stretching of the nerve fibers of the adventitial and periadventitial tissue of the aorta produce angina pectoris, Friedberg (4).

The following are the reasons against the aortic theory:

1. The aorta can be stretched only by an increase of the blood pressure; there is no rise in blood pressure before the presence of angina pectoris in many patients, however. Nitrites may relieve attacks of angina pectoris without any decrease of the blood pressure, Rucks (38).

2. Many times there is found no significant pathology of the aorta in patients with angina pectoris who

have rheumatic aortic insufficiency and calcific aortic stenosis.

3. The aortic theory of angina pectoris does not explain the occurrence of sudden death.

4. The aortic theory does not explain many of the clinical aspects of angina pectoris as completely as the theory of myocardial anoxia, Friedberg (4), Rinzler (35).

8. Distention of the Coronary Arteries Theory:

According to this theory, when there is distention of the coronary arteries, angina pectoris is produced, Rinzler (35). The mechanism for the production of angina pectoris may be the same as that of the aortic theory discussed above.

It has been suggested that angina pectoris may be caused by dilatation of the coronary artery proximal to the point of spasm or narrowing, if one accepts the theory of coronary spasm, Levine (39).

9. Theory of Excessive Attempts at Vasodilatation:

The activity of the heart, as well as any other organ of the body, is associated with a reflex hyperemia and also vasodilatation of its arteries. This arterial vasodilatation is effected by the vasodilator nerve fibers. Metabolites stimulate the afferant nerve endings.

Arteriosclerosis of the coronary arteries does not allow coronary vasodilatation during periods of increased cardiac work; hence, there is the collection of metabolites. These metabolites cause excessive reflex impulses in the vasodilator pain fibers in the coronary arteries in order to cause further dilatation of the coronary arteries. These excessive nervous reflex impulses cause excessive attempts at coronary arterial vasodilatation; and, according to this theory, these excessive attempts at coronary arterial vasodilatation cause angina pectoris.

The mediastinal tissues receive their vasodilator nerve supply from thoracic 1-5 posterior nerve roots; thoracic 1-5 posterior nerve roots supply the heart, also. Lesions of the mediastinal tissues cause an increased activity in the vasodilator nerve fibers, which are found in the same nerve roots that supply the coronary arteries. This increased activity causes excessive attempts at arterial vasodilatation, which causes angina pectoris.

Therefore, lesions either of the mediastinum or of the heart which produce excessive numbers of arterial vasodilator nerve impulses may cause angina pectoris, which, according to this theory, is due to excessive attempts at arterial vasodilatation, Wyburn-Mason (40),

Bitzer (41).

10. Theory of Localized Distention and Stretching:

A few of the authors who wrote around the turn of the 20th century on the subject of angina pectoris have suggested that the pain of angina pectoris is due to localized distention and stretching of the wall of the ventricle, Colbeck (42), Hood (43).

I have correlated the more accepted theories of the basic pathologic physiology of angina pectoris in the following discussion, which is diagramed in Chart I. The following is my own opinion of the basic pathologic physiology:

A precipitating cause may produce coronary arterial vasoconstriction, which causes myocardial ischemia, which produces a discrepancy between the oxygen supply and the oxygen demands of the myocardium, which produces myocardial anoxia, which causes the accumulation of chemical products ordinarily removed by oxidation (for the next step in this process refer below).

A precipitating cause may produce increased cardiac work, which produces a discrepancy between the oxygen supply and the oxygen demands of the myocardium, which causes myocardial anoxia, which produces an accumulation of chemical products ordinarily removed by oxidation

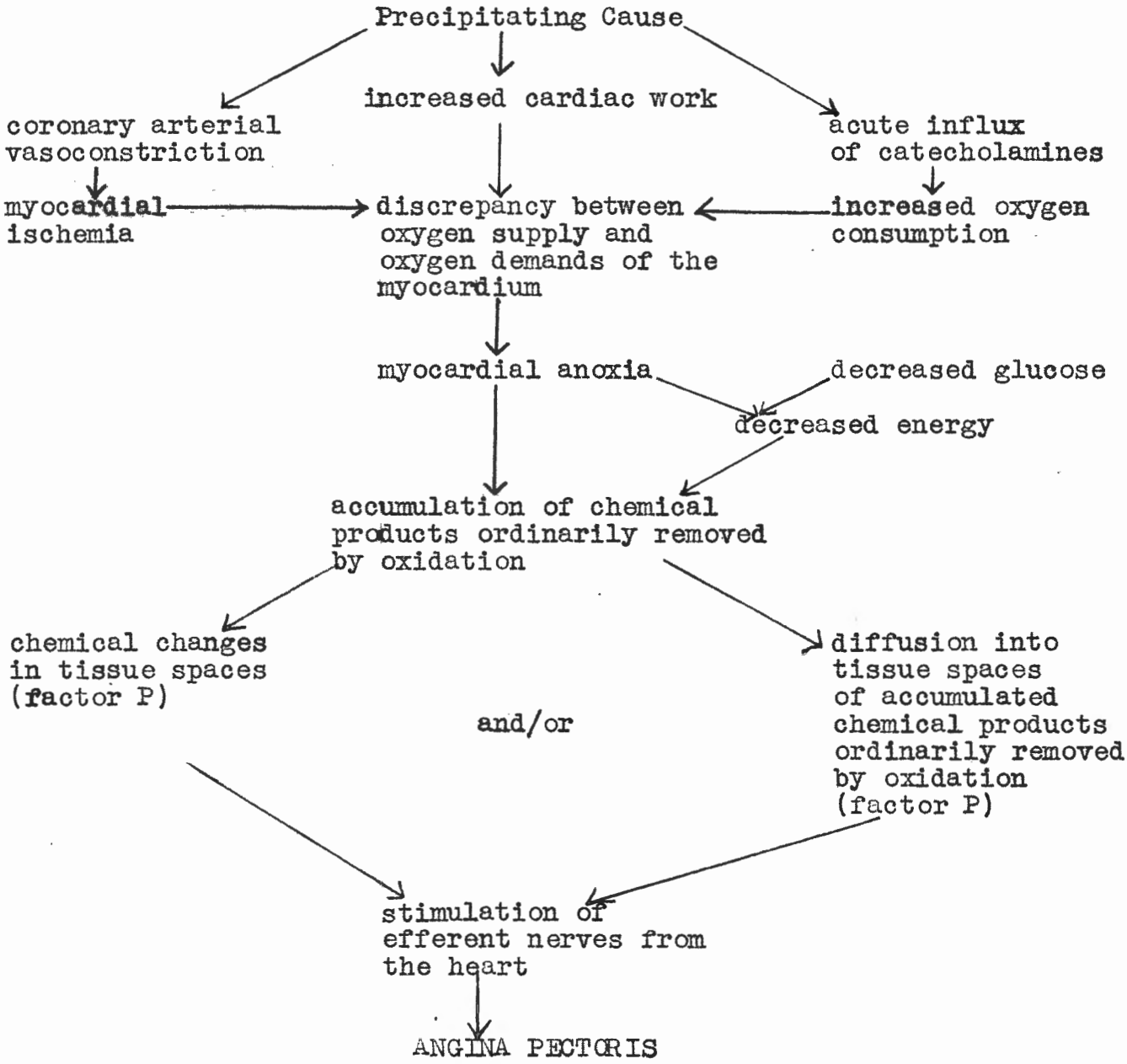

Chart I - A Correlation of the Theories of the Basic Pathologic Physiology of Angina Pectoris

(for the next step in this process refer below).

A precipitating cause may produce an acute influx of catecholamines, which causes an increased oxygen consumption, which produces a discrepancy between the oxygen supply and the oxygen demands of the myocardium, which produces myocardial anoxia, which causes an accumulation of chemical products ordinarily removed by oxidation (for the next step in this process refer below).

According to the energy disproportion theory, either anoxia of the myocardium or a decreased supply of glucose to the myocardium produces decreased energy. This decreased energy causes the accumulation of chemical products ordinarily removed by oxidation.

To continue with the process - the accumulation of chemical products ordinarily removed by oxidation may produce chemical changes in the tissue spaces (factor P), and/or there may be a diffusion into the tissue spaces of the accumulated chemical products ordinarily removed by oxidation (factor P). Factor P produces stimulation of the efferent nerves from the heart, which (by means of the neurologic pathways discussed in the following section) causes angina pectoris.

(b.) The Neurologic Basis for the Perception and Radiation of Anginal Pain

1. The Perception of Anginal Pain:

It is generally considered that the stimulus for the pain of angina pectoris is initiated in the myocardium (please refer to the above section). The efferent paths for pain from the heart have their nerve endings in the adventitia of the coronary arteries, in the subepicardial tissue around the arteries, and possibly in the endocardium and the myocardium. It is of interest to note that it has been demonstrated that after excision of the pericoronary nerves or after painting them with alcohol, pain was not produced in dogs (in whom it was present before) after experimental occlusion of the coronary arteries, Rinzler (35), Friedberg (4).

Even though afferent and motor fibers are present in the vagus, the pain impulses travel only through the sympathetic nerves. The pain impulses travel from the periarterial nerves to the superficial and deep cardiac plexuses, from which they then proceed through the thoracic cardiac nerves to the upper four or five thoracic sympathetic ganglia; there are other pain fibers from the cardiac plexuses which travel in the superior, middle, and inferior cervical cardiac nerves to

their respective cervical sympathetic ganglia and then descend to the superior four or five thoracic sympathetic ganglia. The pain fibers, having reached the upper thoracic sympathetic ganglia, either directly or indirectly, pass into the white rami communicantes of the upper four or five thoracic spinal nerves, which join these thoracic sympathetic ganglia to these thoracic spinal nerves. These nerve fibers at last reach their cell bodies in the dorsal root ganglia of the upper four or five thoracic spinal nerves. The synapse of each one of these neurons is located in the dorsal horn of the spinal cord at its respective level.

The internuncial neurons then decussate to the opposite side, where they travel cephalad in the spinothalamic tract to the nucleus centralis posterior of the thalamus. The fibers do not terminate in any of the nuclei next to the nucleus centralis posterior, nor do they travel into the anterior portion of the thalamus. The cortical projection from the nucleus centralis posterior is mostly to the post-central gyrus. This projection contains a definite order of arrangement, so that those fibers from the medial part of the nucleus (the cephalad portions of the body) terminate in the lower part of the gyrus; those fibers from the lateral part of the nucleus (caudad portions of the body) terminate in

the upper part of the gyrus; and those fibers from the intermediate part of the nucleus terminate in the middle part of the gyrus.

2. The Radiation of Anginal Pain

The locations of the radiation of anginal pain have already been discussed (refer to definition of anginal pain above).

The mechanisms for the radiation of anginal pain have been grouped under two theories. The first of these theories has been popularized by Lewis. This theory states that referred pain from the heart (just as from other viscera) is caused by poor localization in the cerebral cortex. According to this theory, we normally receive sensory impressions from relatively superficial regions of the body. In these regions we also normally have a positional sense. When visceral pain occurs, its site is not well localized by the cerebral cortex; and because we habitually localize pain impulses to more superficial areas and because these areas have a positional sense, visceral pain is localized by the cerebral cortex as occurring in relatively superficial areas, Rinzler (35).

The second theory concerning the referred pain of angina pectoris has as its chief proponent MacKenzie. This theory is called the "irritable focus theory".

This theory is explained as follows: The afferent neurons conducting pain sensations from the heart join the spinal nerves before they enter the cord. The same segments of the spinal cord (thoracic 1 to thoracic 5), it is believed, receive pain impulses from the heart and pain impulses from the corresponding regions of the body surface. Now, according to this theory, when visceral impulses reach the spinal cord, they set up an irritable focus or disturbance in the spinal cord, which spreads to and involves neighboring neurons which ordinarily receive impulses from the body surface, which causes a discharge of impulses to the brain over the pathway for pain, which usually is from the body surface. The sensation is then consciously projected to the body surface, Friedberg (4), Rinzler (35), Verden (44), Best (45). The corresponding body surface area (thoracic 1 to 4 mostly) encompasses the precordium, the medial portion of the anterior surface of the arm, the forearm, and the fifth finger.

It is not known why radiation of anginal pain may be different in different patients. These differences may be due partly to individual variations in sensitivity to pain. Libman, by observing the response of people to pressure over the styloid process, has divided man into

two general groups as regards sensitivity to pain in general. These groups are the hyposensitive and the sensitive. Patients in the sensitive group present the classic painful symptoms of any disease which has pain, and these patients also have the usual radiation of pain where pain is typically present. Hyposensitive individuals may not have pain, or they may have atypical radiation of pain, or substitution symptoms may be present. These substitution symptoms are referrable to the autonomic nervous system, and many of these symptoms are produced by nervous reflexes. Individuals with coronary disease who are in this hyposensitive group may have a sense of burning, coldness, or swelling of the arms or forearms, instead of having pain. When pain is present, it may be contralateral or have radiations to the opposite side.

The differences which are found between the sensitive and the hyposensitive individuals may be explained on the basis of there being in the sensitive individuals a more direct route of transmission of painful impulses to the central nervous system. The painful impulses are delayed in the autonomic nervous system of hyposensitive persons, Friedberg (4).

3. Associated Phenomena of Angina Pectoris:

Some of the characteristics of angina pectoris are due to vagal and sympathetic efferent and somatic motor reflexes which are caused by the afferent pain impulses. The shoulder pain, the weakness which is found in the upper extremities, the sense of compression, and the sense of fixation of the chest wall are partially due to reflex muscular spasm. In some cases reflex spasm of the pharyngeal muscles may cause the sense of strangling. Vagal and sympathetic reflexes may produce sweating and other vasomotor disturbances and gastrointestinal symptoms associated with angina pectoris, Friedberg (4), Cady (46).

Anginal anxiety is produced by stimuli over afferent neurons producing "an irritation to certain 'vegetative' structures within the diencephalon", which produces increased sympathotonia, which is associated with the anxiety of the anginal syndrome, Hess (47).

(c.) Specific Mechanisms of Angina Pectoris:

In this section I shall discuss the causes of angina pectoris, along with the mechanism of the production of the pathologic physiology by each.

A. Precipitating Causes:

1. Bodily Exertion:

Physical exercise, such as walking rapidly (especially outdoors), walking uphill, walking against a wind, running, going to stool, swallowing, coughing, having sexual intercourse, is one of the principal precipitating causes of angina pectoris. Bodily exertion requires an increased cardiac output, which requires increased cardiac work. The increased work of the heart produces an increased demand for oxygen by the myocardium. Normally, the increased oxygen demand by the myocardium produces, by way of physiologic mechanisms, an increase in the coronary blood flow. In persons with angina pectoris, an underlying disease (for example, coronary arteriosclerosis) prevents the physiologic adjustments necessary to produce a coronary blood flow proportionate to the increased demand of the heart; and, according to the theory of myocardial anoxia discussed above, angina pectoris is produced. When the physical exertion has ceased, the coronary blood flow is again adequate for the demands of the myocardium, and the attack of angina

pectoris leaves gradually. There may be a reactive hyperemia, following this temporary myocardial hypoxia produced by bodily exertion, which allows the patient to indulge in the bodily exertion, which had just precipitated an attack, without the production of angina pectoris, Heberden (1), Friedberg (4), Segall (7), Wolffe (48), Bedford (33), White (6).

2. Digestion:

When a patient eats a meal, the processes of digestion cause in increased cardiac work, which causes in increased demand for oxygen by the myocardium; and if the oxygen supply to the myocardium is inadequate to meet the oxygen demand, angina pectoris results, Friedberg (4), Berman (49). Gastric and abdominal distention cause a reflex coronary vasoconstriction, which causes myocardial ischemia, which causes angina pectoris, Berman (49), VonAhn (50). In experimental animals there was produced a marked decrease in the coronary flow when the stomach was distended with a balloon. It was observed that the decreased coronary flow did not occur after the vagus was severed or after atropine was administered; this observation proves that a reflex action was involved, Gilbert (51).

Distention of the stomach or colon with gas may precipitate angina pectoris. The pathologic physiology

involved is probably the same as that discussed in the experiment above (reflex coronary arterial vasoconstriction, which causes myocardial anoxia), Wyburn-Mason (40), Verdon (52).

A heavy meal by itself occasionally may precipitate an attack of angina pectoris, Friedberg (4). Refer below for an example of angina precipitated by a combination of bodily exertion, meals, and cold.

3. Cold:

Cold is a very common precipitating cause of angina pectoris. Eating cold food, drinking cold drinks, getting into bed between cold sheets, walking against a cold wind, going from a warm room to a cold bed, or going from a warm room out into cold weather have all been precipitating causes of angina pectoris. Patients have reported that their exercise tolerance is reduced when they are outside in cold weather.

There are certain "cold spots" in the human body. The application of cold objects to these "cold spots" will precipitate attacks of angina pectoris more rapidly than the application of cold to other parts of the body. There is an accumulation of these "cold spots" on the anterior forearm, nose, nipple area of the chest, and upper abdomen. "Cold spots" are less numerous on the back of the hands. One of the important causes in

initiating attacks of angina in persons who are walking against the wind may be increased stimulation of the nerve endings of sensory nerves of the face, particularly about the nose, Berman (53).

The local application of cold may produce an attack of angina pectoris in ten seconds, and the effect is maximum in thirty to forty seconds after the application. The application of heat or the administration of nitroglycerine before the application of cold prevents an attack of angina. The short length of time in which cold may precipitate an attack indicates that a reflex factor may be present, Freedberg (21).

If one stimulates the nasal mucosa of the decerebrate dog, it has been shown experimentally, there is a decrease in the coronary flow. The same result is observed after section of the vagus, or the administration of atropine, or both. These findings suggest that cold produces a reflex inhibition of the sympathetic coronary vasodilator tone. This inhibition of the sympathetic tone may produce a discrepancy between the blood supply to the myocardium and the blood requirements of the myocardium, Gilbert (23).

The classic example of the precipitation of angina pectoris is the following: A fifty year old man, after having finished a heavy meal, walks rapidly up a hill against a wind in the winter time, and he has an attack of angina pectoris. (The bearing of age and sex will be

discussed under the "predisposing causes" below.)

4. Emotion and Dreams:

Emotions of all sorts may precipitate anginal attacks. The excitement of arguments, watching a football game, anger, sorrow, and anxiety have precipitated angina pectoris, Stevens (54), Friedberg (4), Hunt (55).

Melicow (56) describes the case of a man who became impotent soon after his marriage. His periods of anxiety about the condition precipitated attacks of angina pectoris.

Dreams have been known to precipitate angina pectoris, White (6).

Emotions cause hypersecretion of epinephrine, which produces increased cardiac work, which (when one or more underlying causes of angina are present) causes a discrepancy between the myocardial oxygen supply and the myocardial oxygen demand, and hence produces angina pectoris, Friedberg (4). Wolffe (48) states that emotional conditions produce an autonomic imbalance, which causes angina pectoris.

5. Tachycardia:

Paroxysmal tachycardia (paroxysmal auricular fibrillation, paroxysmal nodal tachycardia) may precipitate an anginal attack in individuals with a diminished coronary reserve. The ventricular rate is the important

precipitating factor, and the type of rhythm is usually not significant in the production of angina pectoris. When the ventricular rate is less than 150 (some authors say 160) per minute, tachycardia is usually not the exciting cause of attacks. Tachycardia above 160 (some say 150) per minute increases the consumption of oxygen by the heart; the oxygen requirements of the heart are greater at rapid rates than they are at slow rates for any given minute output. When the oxygen demands of the heart are greater than the oxygen supply, angina pectoris results (refer to the discussion of the myocardial anoxia theory above), Wyburn-Mason (40), Wolff (57), Friedberg (4).

6. Hyperinsulinism and Hypoglycemia:

Hyperinsulinism and the resultant hypoglycemia (following an overdose of insulin, existing with an islet cell tumor of the pancreas, present with a post-prandial hypoglycemia) may produce attacks of angina pectoris, Gilbert (51). The pathologic physiology of the attacks may be explained in various manners. According to Beach (26), angina occurs when the energy available to the myocardium is less than the energy required by the myocardium for its function. The energy deficit in hypoglycemia may be due to the decrease of glucose which is supplied to the myocardium. (please refer to the

discussion of the Energy Disproportion Theory above).

The low blood sugar may effect an increase in epinephrine production. The epinephrine production, according to one view, causes increased cardiac work, which produces a discrepancy between the oxygen supply to the myocardium and the myocardial oxygen requirements, which provokes an attack of angina pectoris (as explained by the theory of myocardial anoxia). According to the catecholamine theory, when the low blood sugar effects an increase in epinephrine production, angina pectoris is produced (please refer above to the discussion of the catecholamine theory).

7. Diabetes Mellitus:

Diabetes mellitus is usually thought of as a contributory factor in the production of angina pectoris, because of the relation of diabetes to coronary arteriosclerosis, Friedberg (4). However, diabetics may have angina pectoris when their blood sugar is high, and they have glycosuria. When diabetics are in this condition, a decreased glycogen storage in the myocardium is thought to produce angina pectoris, Kahn (29) (refer to the Energy Disproportion Theory above).

8. Administration of Thyroid Extract:

Anginal attacks have been precipitated by the administration of thyroid extract, Friedberg (4). Thyroid

extract produces increased work of the heart, Wolffe (48), and, if this increased cardiac work is present in a patient having a decreased coronary reserve, angina pectoris will result, according to the theory of myocardial anoxia.

9. Administration of Epinephrine:

The administration of epinephrine has been known to cause attacks of angina, Friedberg (4), Wyburn-Mason (40). The action of epinephrine may produce increased cardiac work, which produces angina pectoris, according to the theory of myocardial anoxia; or epinephrine may cause angina pectoris, which is explained on the basis of the catecholamine theory.

10. Administration of Ergot Alkaloids:

The administration of ergot alkaloids (ergotamine tartrate, ergotoxine, ergonovine) produces angina pectoris by means of inhibiting vasodilitation by the coronary arteries caused by sympathetic stimulation, Gilbert (23), Goodman (58), Blumgart (59). There is then produced myocardial ischemia and hence myocardial anoxia when there is increased work of the heart.

11. Administration of Pituitrin:

The administration of pituitrin precipitates attacks of angina pectoris by producing a decreased heart rate and decreased oxygen consumption by the heart. There is

then produced a decreased tissue supply of oxygen, which provokes attacks of angina, according to the myocardial anoxia theory, Goodman (58), Blumgart (59).

12. Administration of Prostigmine:

When prostigmine is administered to a patient, it may precipitate angina pectoris by inhibiting cholinesterase, which allows the preservation of acetylcholine, which stimulates the constriction of the coronary arteries, which produces myocardial ischemia, which provokes angina pectoris, as explained by the theory of myocardial anoxia, Goodman (58), Blumgart (59).

13. Administration of Sodium Succinate:

Intravenous sodium succinate has precipitated anginal attacks, Dwyer (60). The mechanism of this action is not understood, however it may be that the administration of this drug produces a vasodilatation of the coronary arteries and also of the peripheral arteries; the vasodilatation of the peripheral arteries prevents a normal blood flow to the heart, which produces a decreased oxygen supply to the myocardium, which provokes attacks of angina pectoris, Dwyer (60). It may be that the mechanism of the production of angina pectoris is on an allergic basis (refer below to the discussion of allergy as an underlying cause).

14. Administration of Amyl Nitrite:

The mechanism by which the inhalation of amyl nitrite produces angina pectoris is considered to be that there is produced an increase of cardiac work and a decrease of blood supply to the myocardium (caused by a fall in blood pressure, caused by peripheral vasodilatation), both of which cause a disproportion between the oxygen supply to the myocardium and the oxygen requirements of the myocardium, which (as explained by the theory of myocardial anoxia) produces anginal attacks, Contro (61).

Amyl nitrite may produce attacks on an allergic basis (refer below to the discussion of allergy).

The theory of the production of angina pectoris by excessive attempts at vasodilatation by the coronary arteries may explain the mechanism by which amyl nitrite produces attacks (refer above to the discussion concerning the theory of excessive attempts at vasodilatation).

15. Administration of Nitroglycerine:

The administration of nitroglycerine may provoke attacks of angina in the following manner: In patients whose arteries are sclerotic, these arteries can dilate only to a certain degree when acted upon by any vasodilating drug. Nitroglycerine also causes peripheral vasodilatation. When the vasodilatation of the peripheral vessels produces a decreased blood flow to the heart

(taking into consideration the lesser effects of the coronary arterial vasodilatation), there is produced a smaller oxygen supply to the myocardium than it demands; and, as explained by the theory of myocardial anoxia, angina pectoris is produced, Kerr (62).

Nitroglycerine may provoke attacks due to an allergy to this drug (refer below to the discussion of allergy).

Angina may be produced by this drug according to the theory of excessive attempts at vasodilatation by the coronary arteries.

16. Administration of Aminophylline (Theophylline plus Ethylene Diamine):

When one administers aminophylline, he may produce angina by the same mechanisms suggested above for the production of attacks by nitroglycerine.

17. Administration of Potassium Thiocyanate:

The administration of potassium thiocyanate may precipitate attacks of angina pectoris by the same mechanisms discussed above for nitroglycerine, Kerr (62). Odel (63), in a discussion of angina produced by sensitivity to potassium thiocyanate, states that the intravenous administration of histamine eradicates this sensitivity.

18. Administration of Acetylsalicylic Acid:

Acetylsalicylic acid has precipitated anginal attacks. The mechanism is thought to be on a hypersensitivity basis;

most of the cases in this series were associated with urticaria, Shookhoff (64).

19. Administration of Trichloroethylene:

Trichloroethylene administration may precipitate angina pectoris, Wyburn-Mason (40). The mechanism is thought to be that this drug produces vasodilatation not only of the coronary arteries but also of the peripheral vessels. The vasodilatation of the coronary arteries accompanying vasodilatation of the peripheral vessels produces a decreased blood supply to the myocardium, because the coronary arterial vasodilatation is only possible to a certain degree due to coronary arterial sclerosis; and this is a lesser degree than is needed to produce an adequate myocardial blood supply, because of the decreased blood flow produced by the peripheral vasodilatation. This decreased myocardial blood supply, according to the theory of myocardial anoxia, produces angina pectoris.

20. Administration of Pentnucleotides:

Pentnucleotides may also precipitate angina pectoris, Wyburn-Mason (40). The mechanism by which it produces angina is thought to be the same mechanism discussed above by which trichloroethylene produces attacks.

21. Exposure to Carbon Monoxide:

Exposure to carbon monoxide may precipitate angina

pectoris, Wyburn-Mason (40).

Carbon Monoxide combines with hemoglobin and forms carboxyhemoglobin. The same amount of carbon monoxide combines with hemoglobin, as does the same amount of oxygen. Both carbon monoxide and oxygen react with the same portion of the hemoglobin molecule. Therefore, carboxyhemoglobin is not able to carry oxygen, and hence the available hemoglobin for the carriage of oxygen is decreased when a person is exposed to carbon monoxide, Goodman (58). This produces decreased oxygen in the blood; and when the oxygen of the blood is decreased to the extent that the myocardial oxygen supply is less than the myocardial oxygen requirements, angina pectoris results.

22. Tobacco:

Tobacco may be one of the precipitating causes of angina pectoris, White (6), Von Ahn (50), Bryant (65).

Pickering (66) and Bryant (67) state that tobacco may produce angina by causing an increased cardiac work (resulting from an increase of the heart rate and of the blood pressure) and/or by causing coronary arterial vasoconstriction. The increased cardiac work causes a discrepancy between the myocardial requirements of oxygen and its actual supply of oxygen, which provokes attacks of angina. Coronary arterial vasoconstriction produces myocardial ischemia, which causes myocardial

anoxia, which produces angina.

Harkavy (68) found in one series of tests that 36% of the patients tested gave positive intradermal reactions (urticarial) to one or another tobacco. This would suggest that angina pectoris precipitated by tobacco may be due to a hypersensitivity reaction.

23. Acute Spontaneous Pneumo-mediastinum:

Another precipitating cause of angina is acute spontaneous pneumo-mediastinum, Scott (69). The mechanism is thought to be on the basis of a reflex arterial vasoconstriction, which produces myocardial ischemia and results in an attack of angina pectoris.

24. The Recumbent Position:

Angina may be precipitated by the recumbent position, especially at night, Friedberg (4). This type of angina is usually designated as angina decubitus, which has already been discussed in the section on definition above. The pathologic physiology involved in this condition is that recumbency produces an increased cardiac output and cardiac work, which causes a discrepancy between the myocardial oxygen supply and demand, which produces an attack of angina pectoris.

25. Attacks may occur without apparent cause:

Friedberg (4) states that attacks may occur without any apparent cause or during ordinary conversation. The

pathologic physiology probably involves myocardial anoxia.

B. Underlying Causes:

The causes discussed in the preceding section precipitate attacks of angina pectoris only in people who are susceptible because of one or more of the following underlying causes:

1. Coronary Arteriosclerosis:

Coronary arteriosclerosis is one of the chief underlying causes of angina pectoris, Friedberg (4), Evans (10), Henry (70). When increased cardiac work is demanded, coronary arteriosclerosis prevents the necessary vasodilatation, which produces myocardial ischemia, which produces a discrepancy between the myocardial oxygen requirements and the myocardial oxygen supply, which produces angina pectoris, Zoll (27), Wolffe (48).

2. Syphilitic Aortitis with Coronary Ostial Stenosis:

Kissane (71), in a study of 3,329 clinical cases of syphilis, found that the incidence of angina pectoris was almost ten times greater in the non-syphilitic group than in the syphilitic group. All the other authors whose articles I have read state that syphilitic aortitis with coronary ostial stenosis is an underlying cause of angina pectoris.

The pathologic physiology involved is that there is inflammation of the tissue at the root of the aorta and also inflammation of the coronary ostia and the coronary arteries. The inflammation of the aortic wall produces a narrowing, partially or completely of the coronary ostia, Friedberg (4), Bedford (33), White (6), Wolffe (48), Allbutt (72). When there is increased cardiac work, the inflammatory reaction and the coronary ostial stenosis produce a coronary flow, which is inadequate for the demands of the myocardium, which causes myocardial anoxia, which causes angina pectoris.

3. Bacterial Endocarditis:

Vegetations of bacterial endocarditis either on the aortic intima or extending upwards from the cusps of the aortic valve may produce partial or complete blocking of the coronary ostia, White (6). When there is an increased cardiac work, this blocking of the coronary ostia will not allow an adequate blood flow through the coronary arteries, which produces myocardial ischemia, which (as explained by the theory of myocardial anoxia) causes an attack of angina.

4. Aortic Stenosis:

The mechanisms by which aortic stenosis produces angina are as follows: Aortic stenosis causes a low pulse pressure and a limited cardiac output per beat;

aortic stenosis also causes a forceful stream of blood to be directed up the aorta with each systole, which produces suction past the coronary ostia. Both of these mechanisms effect a decrease in coronary circulation, White (6), Boas (73), Contratto (74). The decrease in coronary circulation produces myocardial ischemia when there is an increased demand on the myocardium; this myocardial ischemia causes myocardial anoxia, which provokes angina pectoris.

5. Aortic Insufficiency:

Aortic insufficiency produces a low diastolic blood pressure, which produces a diminished coronary blood flow, White (6), Bedford (33). The diminished coronary blood flow, during conditions of increased cardiac work, produces myocardial ischemia, which produces myocardial anoxia, which causes angina pectoris.

6. Mitral Stenosis:

There are many mechanisms which may produce angina when the underlying cause is mitral stenosis. The pulmonary disorder with pulmonary congestion produces a decreased oxygen saturation of the blood, which helps to produce myocardial anoxia. The narrowed mitral valve produces a decreased cardiac output, which diminishes the coronary arterial blood flow, which produces myocardial ischemia. The narrowedmitral valve produces

resistance to blood flow, which causes an increased cardiac work, which produces an increased demand for oxygen. The distorted anterior cusp of the mitral valve produces traction on the left coronary ostium, which produces a narrowing of the left coronary ostium, which allows a decreased blood flow through this ostium, which produces myocardial ischemia, Zoll (27), Wyburn-Mason (40). All of these mechanisms produce myocardial anoxia, which causes angina pectoris.

7. Anemia:

Both secondary anemias or pernicious anemia may be underlying causes of angina. The pathologic physiology may be one or both of the following mechanisms: Anemic blood carries decreased oxygen; this blood delivers decreased oxygen to the myocardium, producing myocardial anoxia. The other mechanism is that anemia causes an increased cardiac output, which may cause myocardial hypertrophy, which requires an increased blood supply; when the myocardial hypertrophy is to the degree that the adaptive limit of the coronary arteries is reached at rest, there is a discrepancy between the myocardial oxygen requirements and the myocardial oxygen supply when increased cardiac work takes place, Wolffe (48), Vatcher, (75), Elliott (76). Both of these mechanisms, therefore, produce myocardial anoxia, which provokes an attack of angina.

8. Arterial Anoxemia:

Arterial anoxemia, for example, that which is present when a person is at a high altitude, is an underlying cause of angina pectoris. Arterial anoxemia produces myocardial anoxia, which produces angina pectoris; also, arterial anoxemia may produce increased cardiac work, which augments myocardial anoxia, which produces attacks of angina, Friedberg (4), Stewart (77), Marbarger (78).

9. Arteriovenous Fistula:

Arteriovenous fistula causes a decreased oxygen content of the blood, which causes myocardial anoxia, which produces angina pectoris, Resnik (79).

10. Hyperthyroidism:

In hyperthyroidism there is produced an increased work of the heart; and if a patient with hyperthyroidism has a decreased coronary reserve, angina pectoris will result, Wolffe (48).

11. Hypothyroidism:

There are many theories concerning the pathologic physiology of the production of angina pectoris in persons with hypothyroidism. Beach (26) and Wolffe (48) state that there is a decreased rate of oxidation of fuel to produce energy, which causes angina when there is increased cardiac work. Other theories are that vagotonia,

hypoglycemia, anemia, and myocardial anoxemia secondary to the decreased minute volume output of the heart produce angina pectoris in patients with hypothyroidism, Fournier (80).

12. Allergy:

Werley (81) found that 93% of a group of 135 cases of angina pectoris and myocardial infarction gave a history of allergy. In a series of cases he found that elimination of foods to which patients were hypersensitive resulted in relief from angina pectoris, and resumption of eating these foods caused a return of angina, which was again relieved when the foods were eliminated, Werley (81). Hypersensitive reactions to potassium thiocyanate, acetyl salicylic acid, and other chemicals have been mentioned above. Werley (82) suggests that the coronary arteries and nerves are sensitized to one or more allergens; and that when a precipitating cause is present, there is produced spasm of the coronary arteries, which causes angina pectoris.

13. Climacterium:

McGavack (83) states that a pain which is like that of angina pectoris in all respects except that it is not relieved by vasodilator drugs and sedatives may be present during the male climacterium; and this pain is promptly relieved by the administration of testos-

terone. Since this pain fits the definition of the pain of angina pectoris so closely and since androgens have been used in the successful treatment of angina pectoris (Rinzler (35)), the climacterium and/or an androgen deficiency may be considered as a cause of angina pectoris. It has been postulated that testosterone may produce its effect by coronary arterial vasodilatation, by development of a collateral circulation or by an increased metabolism of phosphorus and creatine by cardiac muscle, Rinzler (35).

14. Trauma to the Chest:

Trauma to the chest may be an underlying cause of anginal attacks in a person in whom the precipitating causes of angina produced no attacks before the individual's injury, Wolffe (48). The pathology present may be rupture of muscle fibers and extravasation of blood, Campbell (84).

C. Contributory Causes

There are many factors which contribute to the production of angina pectoris. In the above two sections dealing with the precipitating and underlying causes of angina, it was necessary for completeness to discuss each of the causes individually; for the pathologic physiology of one cause did not completely explain

the pathologic physiology of another cause, except where stated. In this section on the contributory causes, many of these causes have the same pathologic physiology; and hence they will be discussed together.

1. Diabetes Mellitus:

Because of its relation to coronary arteriosclerosis, diabetes mellitus is a contributory factor to angina pectoris, Friedberg (4).

2. Hypertension:

Hypertension from many causes (essential, renal, adrenal medullary tumors, or adrenal cortical tumors) may contribute to the production of angina pectoris, Wyburn-Mason (40). The mechanisms of the action of hypertension are as follows: Hypertension causes increased cardiac work, which produces cardiac hypertrophy. Both the increased cardiac work and the cardiac hypertrophy produce an increased oxygen requirement of the heart. When a precipitating cause and an underlying cause of angina pectoris are present, there is easily produced a discrepancy between the oxygen requirements of and the oxygen supply to the myocardium, which produces angina pectoris, Friedberg (4), Zoll (27), Davis (85).

When the blood pressure in a person with hypertension rapidly rises to a level above the accustomed level, there

is produced an increased intracephalic pressure, which causes a reflex coronary vasoconstriction by means of the vagus, which causes angina pectoris, Gilbert (51).

3. Familial Xanthomatosis and Hypercholesterolemia:

In persons with familial xanthomatosis and hypercholesterolemia, there is commonly found generalized arteriosclerosis and especially coronary arteriosclerosis. Thus, familial xanthomatosis and hypercholesterolemia contribute to the formation of an underlying cause of angina pectoris, Friedberg (4), Zoll (27).

4. Acute Mediastinitis

5. Mediastinal Abscess

6. Mediastinal Tumors, Primary or Metastatic

7. Pneumo-mediastinum

8. Partial or complete esophageal rupture within the mediastinum.

9. A Dissecting aneurysm of the aorta in the mediastinum.

10. Aneurysmal Dilatation of the Pulmonary Artery

11. Aneurysmal Dilatation of the Aorta

12. Diverticula of the Esophagus

13. Acute Spontaneous Pneumo-mediastinum:

The above named causes from number four through number thirteen, inclusive, are believed to cause angina by means of reflexes which, by way of the vagus, cause arterial vasoconstriction, which produces

myocardial ischemia and hence anoxia, which produces angina pectoris; Gilbert (17), Gilbert (51), Wyburn-Mason (40) state that the pathologic physiology of the above conditions can be explained by means of the theory of excessive attempts at vasodilatation.

14. Spontaneous or Artificial Pneumo-thorax:

The pathologic physiology by means of which this condition may contribute to the formation of angina is that there is a reflex coronary vasoconstriction produced by diaphragmatic irritation; the coronary vasoconstriction produces myocardial ischemia and hence anoxia, which provokes angina pectoris. Another explanation of the pathologic physiology in this condition is found in the theory of excessive attempts at vasodilatation, Wyburn-Mason (40). Another possible explanation of the pathologic physiology is that the pneumo-thorax decreases the available area for oxygenation of blood, which contributes to the production of attacks in patients having underlying causes of angina pectoris.

15. Active Pulmonary Tuberculosis:

16. Pneumonia:

Both active pulmonary tuberculosis and pneumonia may contribute to the formation of angina pectoris by means of decreasing pulmonary oxygenation and by increasing cardiac work, Zoll (27), Wyburn-Mason (40).

17. Diaphragmatic Flutter:

Diaphragmatic flutter may produce a reflex coronary arterial vasoconstriction through the vagus by means of diaphragmatic irritation; the coronary vasoconstriction produces myocardial ischemia, which causes myocardial anoxia, which provokes angina pectoris.

18. Obesity:

Obesity contributes to the production of angina by increasing cardiac work and hence nutritional requirements of the myocardium, Friedberg (4).

19. Infection:

20. Fever:

Fever and infectious diseases, especially influenza, may contribute to the production of angina pectoris. It is believed that both fever and infectious processes increase the work of the heart; and hence, if there is an underlying cause of angina present, there may be a discrepancy between the myocardial oxygen supply and the myocardial oxygen demands, which provokes angina pectoris, Gilbert (17), Zoll (27), Wolffe (48).

21. Acute Toxic Myocarditis

22. Hydatid Infestation of the Heart

23. Tumors of the Myocardium

24. Abscess of the Heart:

Acute toxic myocarditis, hydatid infestation of the

heart, tumors of the myocardium and abscess of the heart may cause an increase in the cardiac work. These four conditions may also cause in increased accumulation of metabolites in the heart. Both of these conditions may contribute to the production of angina pectoris in patients with one or more of the underlying causes, Wyburn-Mason (40).

25. Diseases of the Pancreas:

Diseases of the pancreas, other than diabetes mellitus and islet cell tumor, may contribute toward the production of anginal attacks. The mechanism has not been proved as yet, however it may be on the basis of reflex coronary vasoconstriction or excessive attempts at vasodilatation by the coronary arteries, Wolffe (48).

26. Pericarditis:

Pericarditis may be one of the contributory causes of angina by producing irritation of the sympathetic plexuses, which are very close to the epicardium; this is true mainly during the stage of organization, Wolffe (48).

27. Chronic Cholecystitis and Cholelithiasis

28. Duodenal Ulcer

29. Diverticula of the Duodenum

30. Irritable Colon:

The pathologic physiology in the production of angina

pectoris of the conditions listed as 27 through 30, inclusive, involves a reflex through the vagus, Wyburn-Mason (40), Gilbert (51), Vest (86), Chideckel (87), Haloner (88).

31. Diaphragmatic Hernia:

Diaphragmatic hernia may produce typical attacks of angina pectoris, Friedberg (4), Gilbert (51), Jones (89). The pathologic physiology involves reflex phenomena through the vagus, Gilbert (51).

32. Pregnancy:

Angina pectoris is rarely found during pregnancy. Pregnancy does produce increased cardiac work; and, if there is an underlying cause of angina pectoris present in the patient (for example, aortic insufficiency), pregnancy may be a contributory cause, Schott (90). Gilbert (17) found that in experiments on dogs there is a decrease in the coronary flow when generalized abdominal distension is produced. It may be possible that generalized abdominal distension produced by pregnancy may contribute to the formation of angina pectoris in humans.

33. Faulty movements of the Diaphragm:

The "postural syndrome" is a syndrome which includes obesity or visceroptosis, increase in the spinal curves, emphysema, cough, radiculitis, angina pectoris, and cerebral symptoms. Because of the obesity or visceroptosis and

because of the curvature of the spine, there is a collapsing anteriorly of the upper ribs, and there is a flaring and raising of the lower ribs. The diaphragm is flattened by the pull of the fat which is suspended on the omentum, mesentary, and abdominal organs; and the diaphragm is flattened to some degree by the flared lower ribs. When the patient is in the standing position, this weight interferes with the diaphragmatic movements superiorly during expiration.

The movements of the diaphragm and the intermittent contraction and relaxation of the diaphragmatic musculature at the point where the inferior vena cava passes through the diaphragm aid in the return of blood to the heart.

In persons having the "postural syndrome" the pathologic physiology may be explained as follows: In the erect posture, because of the decreased diaphragmatic excursion and the flattened diaphragm, there is a decreased return of blood to the heart, which causes a decreased cardiac output, which causes a decreased flow of blood to the coronary vessels, which (if there is an underlying cause of angina present, for example, coronary arteriosclerosis) produces a discrepancy between the oxygen supply to and the oxygen demands of the myocardium, when a precipitating cause of angina pectoris is present; and this discrepancy provokes angina pectoris, Kerr (91).

34. Subacute and chronic appendicitis:

Bassler (92) reported a patient 50 years of age who was completely free of all symptoms of angina pectoris within three months after an appendectomy, which produced an appendix showing subacute and chronic appendicitis. Immediately after the appendectomy and from that time on, the patient's only complaint was an occasional burning in the chest. This article was written one year after the appendectomy. The pathologic physiology is probably a reflex mechanism.

35. Epidemic Encephalitis:

Laubry (93) reported a patient about sixty years old who had epidemic encephalitis and angina pectoris. Laubry explained the production of angina pectoris by the involvement in the disease process of the autonomic system in the brain.

D. Predisposing Causes:

1. Age:

Friedberg (4) states that 90 to 95% of patients with angina pectoris have passed the age of forty; he also states that more than 70% are beyond fifty years of age. Harrison (94) states that angina is sometimes present during the second or third decade of life.

2. Sex:

The ratio of males to females varies from 2.5 to 1 to 6 to 1 on different series of cases, Friedberg (4), Zoll (27). Angina pectoris occurs only rarely in women below the age of 60, except when hypertension or diabetes are present, Harrison (94).

3. Familial Occurrence:

Familial occurrence is a predisposing factor in angina pectoris, Friedberg (4).

4. Occupation:

Angina pectoris may be present in persons of any occupation; however, it is particularly found in persons who are under continuous mental tension, for example, professional people (especially physicians and lawyers) and executives, White (6), Friedberg (4).

5. Social and Economic Status:

Angina pectoris is present in all social and economic levels of our society, however it is more common in people of the upper levels, Friedberg (4), White (6).

6. Race:

Angina pectoris occurs most frequently in the Caucasian race. Angina was thought to be infrequent in the Negroid race in the past, however it has been found to be more frequent in the negroid race in recent years, Friedberg (4).

7. Constitution:

People who are short, stocky, short-necked, overweight, and who have barrel-shaped chests may be predisposed to angina pectoris, Heberden (1), Friedberg (4).

8. Temperament:

People with angina pectoris are often ambitious, serious, and aggressive. These people may have extreme emotional reactions, and these emotions either are repressed or are manifested in explosive outbursts. Friedberg (4).

9. Obesity:

10. Diabetes Mellitus

11. Hypothyroidism:

The pathologic physiology of obesity, diabetes mellitus, and hypothyroidism in the production of angina pectoris has been discussed above.

VI. SUMMARY

In 1768 William Heberden delivered a lecture to the Royal College of Physicians of London. In this lecture he gave an excellent description of the group of symptoms which he named angina pectoris.

The following is a definition which is explained at length in the thesis: Angina pectoris is a symptom complex in which there are usually paroxysmal attacks of substernal (retrosternal) pain or oppression which is usually precipitated by certain factors, which lasts no longer than a specific period of time, which may or may not radiate, which may or may not be associated with a feeling of anxiety, which is reproducible, and which is relieved by rest and/or certain nitrites. Angina pectoris may or may not be associated with pallor of the face and sweating. Sometimes the only manifestation of an anginal attack is the substernal pain, which may or may not radiate.

There have been four forms of cardiac pain described: The mildest type, the mild type, the moderate type, and the severe type.

I have discussed the differential points of these various types.

There are four general groups of causes of angina

pectoris - the precipitating causes, the underlying causes, the contributory causes, and the predisposing causes.

The basic pathologic physiology of angina pectoris has been explained by many theories. William Heberden stated that the basic pathologic physiology was "a convulsion of the part affected". The following is an enumeration of the various theories of angina pectoris which have been proposed:

1. The Theory of Coronary Spasm
2. The Theory of Myocardial Anoxia
3. The Energy Disproportion Theory
4. Chemical or Physico-Chemical Theory
5. Theory of Anoxia in the Wall of a Thoracic Artery
6. Myocardial Exhaustion Theory
7. Aortic Theory
8. Distention of the Coronary Arteries Theory
9. Theory of Excessive Attempts at Vasodilatation
10. Theory of Localized Distension and Stretching

There is included a correlation of the theories of the basic pathologic physiology of angina pectoris. It should be stressed that myocardial anoxia is paramount in the pathologic physiology.

A discussion of the nurologic basis for the perception and radiation of anginal pain is followed by an explanation of the pathologic physiology of the associated

phenomena of angina pectoris.

The body of the thesis is concluded by a discussion of the pathologic physiology of the specific causes of angina pectoris.

VII. CONCLUSIONS

1. William Heberden named angina pectoris in 1768. The early history of angina pectoris is discussed.

2. Angina pectoris is a clinical syndrome. A definition of angina pectoris is presented and discussed.

3. The various types of cardiac pain are presented.

4. There are four groups of causes of angina pectoris:

a. precipitating

b. underlying

c. contributory

d. predisposing

5. The pathologic physiology of angina pectoris is discussed, and there is included a correlation of the various theories of the basic pathologic physiology. Myocardial anoxia is paramount in the pathologic physiology of angina pectoris.

VIII. ACKNOWLEDGMENTS

I wish to thank Dr. Eugene E. Simmons for the advice and guidance which he has given me in the preparation of my thesis.

I would also like to thank Dr. Robert L. Grissom for the assistance he has given me.

BIBLIOGRAPHY

1. Heberden, W.: Some Account of a disorder of the Breast. Med. Tr. Royal College of Physicians, London. 2: 59. 1772.

2. Segall, H. N.: First Clinicopathologic Case History of Angina Pectoris; Self Diagnosis by Anonymous Physician; Autopsy by John Hunter; Reported by William Heberden in 1772. 18: 102-108 (June) 1945.

3. Heberden, W.: A Letter to Dr. Heberden, Concerning the Angina Pectoris; and Dr. Heberden's Account of the Dissection of One Who Had Been Troubled With This Disorder. Med. Trans. Royal Coll. Phys., London. 3: 1. 1785.

4. Friedberg, C. K.: Diseases of the Heart. W. B. Saunders Co., Phil. & London, 353-377. 1950.

5. Marvin, H. M.: The Differential Diagnosis of Pain in the Anterior Chest. Modern Concepts of Cardiovascular Disease. 21: 148-151 (Oct.) 1952.

6. White, P. D.: Heart Disease. The MacMillan Co., N. Y. pp. 26 & 816-851. 1944.

7. Segall, H. M.: Principal Patterns of Cardiac Pain Related to Arteriosclerotic Coronary Artery Disease. Canad. M. A. J. 62: 341-344 (April) 1950.

8. Herrick, J. B.: Certain Popular but Erroneous Notions Concerning Angina Pectoris. J. A. M. A., Chicago. 55: 1423-1427. 1910.

9. Arlow, J. A.: Anxiety Patterns in Angina Pectoris. Psychosomat. M. 14: 461-468 (Nov.-Dec.) 1952.

10. Evans, T. W.: Angina Pectoris: Its Cause, and the Use of Nitrite of Amyl. Ohio M. Recorder, Columbus. 4: 247-248. 1879-1880.

11. Osler, W.: The Principles and Practice of Medicine. D. Appleton and Co., New York and London. 836-847. 1918.

12. Lewis, T.: Diseases of the Heart; Described for Practitioners and Students. The MacMillan Co., New York. pp. 50-61. 1933.

13. Blakiston's New Gould Medical Dictionary. The Blakiston Co. Phil., Toronto. 1949.

14. Viar, W. M., and Harrison, T. R.: Chest Pain in Association with Pulmonary Hypertension; Its Similarity to the Pain of Coronary Disease. Circulation. 5: 1-11 (Jan.) 1952.

15. Dressler, W.: Myocardial Infarction Indicated by Angina Pectoris of Effort or by Brief Attacks of Angina of Rest, With Remarks on Premonitory Pain. Am. Heart J. 28: 81-97 (July) 1944.

16. Papp, C.: Acute Cardiac Infarction Without Pain. From the Cardiac Department of the Charing Cross Hospital. 250-260 (Sept.) 1950.

17. Gilbert, N. C.: Reflex Variations of the Coronary Flow. Nebraska M. J. 27: 117-123 (April) 1942.

18. Hess, L.: The Relationship of the Vegetative Nervous System to Angina Pectoris (Abdominalis). J. Nerv. and Ment. Dis. 103: 60-80 (Jan.) 1946.

19. Sansom, A. E.: The Pathology of Angina Pectoris. Internat. Clin., Phila. 2: 42-49. 1891.

20. Maddin, T. L.: True (Idiopathic) Angina Pectoris, Its Etiol., Pathol, and Therapeutics. J. A. M. A., Chicago. 28: 1211-1275. 1897.

21. Freedberg, A. S., et al: Effect of External Heat and Cold on Patients with Angina Pectoris; Evidence for Existence of Reflex Factor. Am. Heart. J. 27: 611-622 (May) 1944.

22. Chew, S. C.: Chronic Interstitial Nephritis and Angina Pectoris. Med. News, Phila. 53: 548-552, 1888.

23. Gilbert, N. C., et al: Role of "Sympathetic Inhibition" in the Production of Attacks of Angina Pectoris. Tr. A. Am. Physicians. 56: 279-290, 1941.

24. Keefer, C. S., and Resnick, W. H.: Angina Pectoris, A Syndrome Caused by Anoxemia of the Myocardium. Arch. Int. Med. 41: 769-807, 1908.

25. Raab, W.: The Biochemical Nature of Angina Pectoris. Tr. Am. Coll. Card. 1: 56-69, 1951.

26. Beach, C. H.: Anginal Symptoms Associated With Certain Constitutional Diseases. J. A. M. A. 105: 871-873 (Sept. 14) 1935.

27. Zoll, P. M., Wessler, S., and Blumgart, H. L.: Angina Pectoris, A Clinical and Pathologic Correlation. Am. J. Med. 11: 331-57 (Sept.) 1951.

28. Sippe, C.: Hypoglycemic Angina, With a Report of Five Cases. M. J. Australia. 2: 302-306 (Sept. ") 1933.

29. Kahn, M.: Angina Pectoris of Diabetes. J. A. M. A. 76: 570-571 (Febr. 26) 1921.

30. Lewis, T.: Pain in Muscular Ischemia. Its Relation to Anginal Pain. Arch. Int. Med. 49: 713-727, 1932.

31. Gilson, J. S., and Day, C. M.: Observations on the Relationship of Pain to the Process of Myocardial Infarction, as Shown by Electrocardiographs in "Latent" Cases. 470-476 (June) 1952.

32. Pickering, G. W., and Wayne, E. A.: Observations on Angina Pectoris and Intermittant Claudication in Anæmia. Clin. Sc. 1: 305-325 (Nov.) 1934.

33. Bedford, D. E.: Cardiac Pain and Its Problems. Practitioner. 158: 245-251 (March) 1947.

34. Katz, L. M.: Mechanism of Pain Production in Angina Pectoris. Am. Heart Jour. 10: 322-327, 1934-35.

35. Rinzler, H.: Cardiac Pain - Present Status of Its Mechanism and Therapy. Amer. Journal of Medicine. 5: 736-748 (Nov.) 1948.

36. Katz, L. M., et al: On the Nature of Substances Producing Pain in Contracting Skeletal Muscle; its Bearing on the Problem of Angina Pectoris and Intermittent Claudication. J. Clin. Investigation. 14: 807-821 (Nov.) 1935.

37. Roder, F.: The Problem of Angina Pectoris. M. Rec. 160: 542-544 (Sept.) 1947.

38. Rucks, W. W., Jr.: Cardiac Pain. J. Oklahoma M. A. 28: 10-13 (Jan.) 1935.

39. Levine, S. A.: Some Notes Concerning Angina Pectoris. Bull. New England M. Center. 9: 97-201 (June) 1947.

40. Wyburn-Mason, R.: A New Conception of Angina Pectoris. Brit. M. J. 1: 972-975 (May 22) 1948.

41. Bitzer, E. W.: Effect of Sudden Changes in Arterial Tension in Angina Pectoris. Amm. Int. Med. 9: 1120-1128 (Febr.) 1936.

42. Colbeck, E. H.: Angina Pectoris; a Criticism and a Hypothesis. Laucet, London. 1: 793-795, 1903.

43. Hood, D.: Case of Angina Pectoris Immediately Followed by Pericarditis. Tr. Clin. Soc. Lond. 17: 82-85, 1884.

44. Verdon, H. W.: Common Origin of the Various Types of Angina Pectoris. Brit. M. J., London. 2: 998, 1912.

45. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, 5th Edition. The Williams & Williams Co., Baltimore, Md., 1950. pp. 598-603.

46. Cady, J. B.: Shoulder Disabilities Associated with Coronary Disease. Pennsylvania M. J. 55: 549-552 (June) 1952.

47. Hess, L.: The Relationship of the Vegetative Nervous System to Anginal Anxiety. J. Nerv. and Ment. Dis. 104: 480-485. (Nov.) 1946.

48. Wolffe, J. B.: Angina Pectoris, Its Possible Causes and Treatment. Pennsylvania M. J. 36: 901-103. (Sept.) 1933.

49. Berman, B., et al.: Effect of Meals on Electrocardiogram and Ballistocardiogram in Patients with Angina Pectoris. Circulation. 1: 1017-1025. (April) pt. 2, 1950.

50. Von Ahn, B., and Gohle, O.: A case of Angina Pectoris Precipitated Chiefly by Tobacco Smoking and Meals. Am. Heart J. 38: 775-780 (Nov.) 1949.

51. Gilbert, N. C.: Importance of Certain Extracardial Conditions in Coronary Disease. Wisconsin M. J. 44: 512-516 (May) 1945.

52. Verdon, W.: Angina Pectoris. W. T. Moulton & Co., Ltd., Printers & Publishers, Brighton. Bailliere, Tindall and Cox, London. 1920.

53. Berman, B., and McGuire, J.: Electrocardiographic Changes Induced by Cold Application to Various Body Sites in Patients With Angina Pectoris. Preliminary Report. Am. J. M. Sc. 219: 82-85 (Jan.) 1950.

54. Stevens, A. A.: Angina Pectoris and Allied Conditions. Med. Clinics N. America. 1: 293-308 (Sept.) 1917.

55. Hunt, H. D., et al.: Critical Analysis of Emotional Factors in 100 Cases of Coronary Disease with Angina Pectoris. Internat. Clin. 3: 15-20 (Sept.) 1940.

56. Melicow, M. M.: Coitus, Impotentia, and Angina. New York State J. Med. 45: 1325-1378 (June 15) 1945.

57. Wolff, L.: Cardinal Manifestations of Paroxysmal Tachycardia; Anginal Pain. New England J. Med. 232: 491-495 (May 3) 1945.

58. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics. The MacMillan Co., N. Y., pp. 482-483, 664-667, 376-387, 694-699, 1951.

59. Blumbart, H. L.: V. Pathogenesis of Angina Pectoris and Some Clinical Implications. Rhode Island M. J. 34: 21-22 (Jan.) 1951.

60. Dwyer, C. S.; Kronenberg, S.; and Saklad, M.: Anginal Syndrome During Sodium Succinate Therapy. Ann. Int. Med. 31: 148-153 (July) 1949.

61. Contro, S., et al.: Paradoxic Action of Amyl Nitrite in Coronary Patients. Circulation. 6: 250-256 (Aug.) 1952.

62. Kerr, W. J.: Angina Pectoris Provoked by the Injudicious Use of Vasodilating Drugs and Its Treatment. Tr. A. Am. Physicians. 57: 135-138, 1942.

63. Odel, H. M., and Horton, B. T.: Angina Pectoris; Manifestation of Thiocyanate Sensitivity Treated with Histamine; Report of Three Cases. Proc. Staff Meet., Mayo Clin. 18: 279-285 (Aug. 11) 1943.

64. Shookhoff, C. and Lieberman, D. L.: Hypersensitiveness to Acetylsalicylic Acid Expressed with and without Urticaria, By an Angina Pectoris Syndrome. J. Allergy. 4: 506-512 (Sept.) 1933.

65. Bryant, J. M., and Wood, J. E., Jr.: Tobacco Angina. Proc. Am. Federation Clin. Research (1946). 3: 11-12, 1947.

66. Pickering, G. W. and Sanderson, P. H.: Angina Pectoris and Tobacco. Clinical Science. pp. 5-6, 275-288. 1944-48.

67. Bryant, J. M. and Wood, J. E., Jr.: Tobacco Angina; Electrocardiographic Study. Am. Heart J. 34: 20-34 (July) 1947.

68. Harkavy, J.: Tobacco Sensitiveness in Angina Pectoris and Coronary Artery Disease. Proc. Soc. Exper. Biol. & Med. 30: 683-684 (Feb.) 1933.

69. Scott, A. M.: Significance of Anginal Syndrome in Acute spontaneous Pneumo-mediastinum. Laucet. 1: 1327-1330. (June 5) 1937.

70. Henry, F. P.: Specimens of Contraction and Dilatation of the Orifices of the Coronary Arteries. Phila. M. Times. 10: 18-20, 1879-1880.

71. Kissane, R. W., et al.: The Role of Syphilis In Coronary Artery Sclerosis, Occlusion and Angina Pectoris. Urol. & Cutan. Rev. 43: 42-44 (Jan.) 1939.

72. Albutt, T. C., et al.: Discussion of Angina Pectoris. Brit. M. J., Lond., 2: 1122-1129, 1909.

73. Boas, E. P.: Angina Pectoris and Heart Block, as Symptoms of Calcereous Aortic Stenosis. Am. J. M. Sc. 190: 376-383 (Sept.) 1935.

74. Contratto, A. W., and Levine, S. A.: Aortic Stenosis With Special Reference to Angina Pectoris and Syncope. Am. Int. Med. 10: 1636-1653 (May) 1937.

75. Vatcher, S.: Angina in Pernicious Anemia, with Electrocardiographic Changes and Abdominal Aneurysm. Laucet. 2: 192-193 (July 22) 1939.

76. Elliot, A. H.: Anemia As the Cause of Angina Pectoris in the Presence of Healthy Coronary and Aortic Arteries; Report of Cases. Am. J. M. Sc. 187: 185-190 (Febr.) 1934.

77. Stewart, H. J., et al.: Experience with "Anoxemia Test" in Patients with Typical Angina of Effort and in Patients with Atypical Pain which May be Due to Coronary Insufficiency. Tr. A. Am. Physicians. 60: 244-254. 1947.

78. Margarger, J. P.; Wechsberg, P. A.; Vauter, G. F. and Franzblau, S. A.: Attitude Stress in Subjects with Impaired Cardio-Respiratory Function. B. Studies on Patients with Angina Pectoris. Air Force School of Aviation Medicine. Project No. 21-23-0191 Report No. 2: 1-25 (March) 1953.

79. Resnik, W. H.: The Causation of Angina Pectoris. Bull. New York Acad. Med. 4: 662-663 (May) 1928.

80. Fournier, Juan C. Mussio: Circulatory Apparatus in Myxedema. Proc. Staff Meet. Mayo Clinic. 17: 212-215 (Apr. 8) 1942.

81. Werley, G.: Food Allergy and Other Food Factors in Angina Pectoris. South. M. J. 28: 1156-1161 (Dec.) 1935.

82. Werley, G.: Is Allergy a Factor in Angina Pectoris and Cardiac Infarct? M. J. & Rec. 136: 417-421 (Nov. 16) 1932.

83. McGavack, T. H.: Angina-Like Pain; Manifestation of Male Climacterium. (Treated By Testosterone, Androgen). J. Clin. Endocrinol. 3: 71-80 (Febr.) 1943.

84. Campbell, M.: Angina Following Crushing Accident. Brit. Heart J. 1: 177-180 (April) 1939.

85. Davis, D., and Klainer, M. J.: Studies in Hypertensive Heart Disease; Factors in Production of Angina Pectoris. Am. Heart J. 19: 198-205 (Febr.) 1940.

86. Vest, W. E.: Anginoid Symptoms of Gall Bladder Disease. South. M. J. 27: 410-413 (May) 1934.

87. Chideckel, W.: Digestive Tract Diseases as Possible Causative Factors of Angina Pectoris. M. Rec. 146; 526-528 (Dec. 15) 1937.

88. Haloner, P. I. and Autio, L.: (Extracardiac Causes of Angina Pectoris) Ueber Dies Extrakardialen Ursachen der Angina Pectoris. Ann. Med. Intern. Fenn. 41: 235-242, 1952.

89. Jones, C. M. and Chapman, W. P.: Studies on Mechanism of Pain With Particular Relation to Hiatus Hernia. Tr. A. Am. Physicians. 57: 139-151, 1942.

90. Schott, A.: Angina of Effort in Pregnancy (report of a case). J. Obst. Gynaec. Brit. Emp. 55: 428-431 (August) 1948.

91. Kerr, W. J.: Faulty Movements of Diaphragm as Cause of Nonobstructive Emphysema and Angina Pectoris. Radiology. 39: 153-156 (August) 1942.

92. Bassler, A.: Chronic (with Subacute) Appendicitis Simulating Angina Pectoris. J. A. M. A. 80: 1454 (May 19) 1923.

93. Laubry, C.: Angina Pectoris and Epidemic Encephalitis. J. A. M. A. 84: 235 (Jan. 17) 1925.

94. Harrison, T. R.: Principles of Internal Medicine. The Blakiston Co., Phil. 1282-1285, 1951.