Angina pectoris: its pathology and treatment

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ANGINA PECTORIS
ITS PATHOLOGY AND TREATMENT

BY
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PREFACE

The original draft of this thesis was on the etiology of angina pectoris. But so uncertain are the etiological factors and so closely related is the etiology to the pathology that the final title chosen was the pathology of angina pectoris. The study of pathology naturally led to an investigation of treatment.

An attempt has been made to cover the important modern literature. However, in the firm belief that age does not lessen a truth, the older authorities such as Osler, Mackenzie and Allbutt have not been neglected. It is a remarkable fact that in spite of the avalanche of literature on the subject, the shifting views, and changing treatment, the opinions and methods of these men are still taken into counsel.

The custom of placing history in a separate section has been followed half-heartedly. In medicine only that which has been discarded can actually be called historical, hence the early history of the nitrites, the xanthines, and surgery is included in their respective sections under treatment.
HISTORY

On July 21, 1768, William Heberden presented before the Royal College of Physicians of London a discussion on disorders of the breast, a paper based on twenty cases none of which had gone to the autopsy table, but characterized by severe, cramping pain in the region of the breast and anxiety. He believed a "strong cramp or an ulcer or both" to be the probable pathology and because of this suggested the name, angina pectoris for the affliction. (104) His description is given here.

"But there is a disorder of the breast marked with strong and peculiar symptoms considerable for the kind of danger belonging to it, and not extremely rare which deserves to be mentioned more at length. The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris.

Those who are afflicted with it, are seized while they are walking, (more especially if it be up hill and soon after eating) with a painful most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to
increase or continue; but the moment they stand still, all this uneasiness vanishes.

In all other respects, the patients are at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of os sterni, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm. The pulse is, at least sometimes, not disturbed by this pain, as I have had opportunities of observing by feeling the pulse during the paroxysm. Males are more liable to this disease, especially such as have passed their fiftieth year." (61)

Heberden in his commentaries (61) offered no explanation of the pathology, for in his own words, "A very skillful anatomist could discover no fault in the heart, in the valves, in the arteries, nor neighboring veins, excepting small rudiments of ossification in the aorta. The brain was likewise everywhere sound."
There has been some discussion as to who actually first described the symptoms of the disease. Heberden in his commentaries was inclined to credit Coelius Aurelianus as the only ancient writer who had noticed the complaint, and he but slightly.

Some contend (104) that N.F. Rougnon, professor of medicine at the University of Besancon, first described the disease. In a letter written to Anne Charles Lorry, "Docteur-Regent de la Faculte de medicine de Paris", he describes the case and the autopsy of a captain in the French cavalry. However, it is debatable at present whether the case was a true angina pectoris, and it is certain that Rougnon failed to name this as a new entity although his report was written four months before Heberden's original paper.

It is generally agreed that Morgagni in 1761 described an authentic case, and the case of Henry Hyde, the manner of whose death in 1632 was depicted by his son Edward, first Earl of Clarendon, in his autobiography, has been in retrospect diagnosed as angina pectoris. (104) (95).
Osler (95) mentions the possibility of Seneca being the first to describe the affliction in the graphic account he gave of his own disorder. "The attack is very short and like a storm. It usually ends within an hour. I have undergone all bodily infirmities and dangers but none appears to me more grievous. Why not? Because to have any other malady is only to be sick; to have this is to be dying."

Edward Jenner was probably the first to suggest an involvement of the coronary arteries. (104) In the spring of 1777 John Hunter was troubled with an illness and went to convalesce at Bath. While there he was visited by his friend and pupil, Jenner. In writing to Heberden, Jenner diagnosed the illness as angina pectoris and for the first time suggested in writing that it was a disease of the coronary arteries. He based his conclusions on the results of two previous autopsies which he had performed on patients dying of angina pectoris. In both cases the coronary arteries were found to be sclerosed. Jenner refrained from publishing his thoughts out of deference for his friend. It is possible that Hunter already knew of the association of the coronary arteries and angina pectoris for he performed the autopsy which John Fothergill published
in 1772 in which the coronaries were described as one piece of bone. In an earlier necropsy made by John Hunter in 1772 on a case of angina pectoris, nothing more than small patches of ossification in the aorta was reported, but Jenner who was present wrote that he was certain that the coronary arteries were not examined.

As the years progressed Hunter's attacks became more frequent and more severe. They were brought on particularly by exercise, by worry and by anger; as he himself said that his life was in the hands of any rascal who chose to annoy or tease him. The end came in a fit of rage during a meeting of the governors of St. George Hospital. Autopsy revealed the coronaries to be open boney tubes and the aorta to be dilated. (104)

Soon after Hunter's death Jenner (95) reported in a paper before the Fleece Medical Society the association between coronary artery changes and angina pectoris. Parry (95) in 1779 confirmed Jenner's observations.
ASSOCIATED PATHOLOGY

"Angina pectoris is a disease of gradually increasing incidence. In his original description Heberden mentioned only twenty cases but by the time the commentaries were written his patients numbered close to a hundred. It appears to be much more common now than it was a generation or more ago, although one cannot rely wholly upon available statistical studies, especially on those of years ago when patients were examined less frequently, when people with mild symptoms were less apt than now to seek medical service and when criteria for diagnosis were less carefully outlined and less universally known. However, even allowing for missed diagnosis in the past, angina pectoris, has evidently increased in frequency, and is encountered more in communities where the strain of life is great and a hurried existence the habit, than in leisurely parts of the world. Austin Flint, actively practicing internal medicine, encountered no case of angina pectoris for one period of five years. Today every physician practicing general medicine sees several cases every year — — — — — — — — — — —. My own recent experience of encountering one hundred new private patients with undoubted angina pectoris
within eight months, and as many as three new cases in a single day, has made me believe that the situation is appalling and demands some action on our part." (126)

The rapidly increasing toll of this disease has stimulated research, but even today one cannot at the present state of our knowledge lay his finger on any definite pathology in angina pectoris. Boyd speaks of the disease as being still one of clinical diagnosis rather than one of definite morbid anatomy. In fairness to all the investigators of the disease it would seem more proper to speak of associated pathology, rather than the pathology of angina pectoris.

By far the greatest number of cases coming to autopsy show changes in the coronary arteries. (69) That is to say, so intimately associated is true angina pectoris with sclerotic conditions of the coronary arteries that it is extremely rare apart from them. (95) White (126) goes so far as to say that ninety-five percent of the cases have coronary involvement, either by diseases of the coronary arteries themselves due to sclerosis, infections, thrombosis or embolism; or blockage of coronaries at their mouth by swelling or inflammation in the aorta due to syphilis, or vegetations on the aortic intima, or bacterial endocarditis. Hirschfelder quotes Huchard
as having found one hundred and twenty-eight cases of coronary sclerosis out of one hundred and forty-five necropsies, and Vernon (69) found that slightly over fifty percent of the cases in a series of two hundred and eighty-three collected from the literature, showed coronary artery disease.

Although Aortic insufficiency ranks far behind coronary artery disease in incidence, this lesion is found in the bulk of cases of angina pectoris not associated with coronary disease. Often the two conditions occur together particularly when both are caused by syphilitic aortitis. (69). That angina pectoris is often associated with aortic insufficiency is commonly recognized and has been emphasized by Nuesser, Osler (96), Longcope, and Mackenzie. In Mackenzie's series over twenty percent of the cases had aortic insufficiency. He does not make clear how many of these were due to syphilis. In some in which the postmortem studies were available the coronary arteries were normal; in others some degree of obstruction of the coronary vessels was present, either by narrowing of the orifices or sclerosis of the vessels. Keefer and Resnik mention seven cases of syphilitic aortic insufficiency associated with angina pectoris. In two of these they were able to demonstrate partial occlusion of the coronary arteries.
Although it is true that when angina pectoris develops in a patient with aortic insufficiency the valvular lesion is usually of syphilitic origin, angina pectoris is also seen in instances of rheumatic aortic insufficiency. Angina pectoris with this type of pathology is found almost exclusively in young individuals. In a group of thirty-three cases of aortic insufficiency in young persons with a positive history of rheumatic infection, Clark (69) found that many of the patients suffered from attacks of angina pectoris. Allbutt (1) referred to similar cases, and other instances are recorded by Levine (75); Cutler and Fine (36), White and Mudd (29), and Keefer and Resnik. The latter pair attribute the greater incidence of angina pectoris in syphilitic regurgitation as compared to rheumatic aortitis to the fact that the aortic stenosis which frequently accompanies aortic regurgitation, when of rheumatic origin, counterbalances the insufficiency, and secondly, syphilitic regurgitation is more frequently accompanied by blockage of the coronary circulation.

Syphilis has been mentioned as a factor in angina pectoris, but its importance when uncomplicated is debatable. Some believe that the two diseases are so rarely associated that syphilis should be almost entirely eliminated as a probable factor. (57) Brooks (22) reported over two hundred cases of angina
pectoris and in few cases did he believe syphilis to be of any importance. Paullin, and Levine (75) agree with him. On the other hand Vaquez reports syphilis in thirty out of a hundred cases of angina pectoris and both Allbutt (2) and Mackenzie believe that angina pectoris early in life should always excite suspicion of syphilis.

Keefer and Resnik reported twenty-six cases of uncomplicated syphilitic aortitis and in not one instance was there a history of angina pectoris. In reviewing some of the cases in the literature, they point out that in every case where detailed information is given, it can be shown that if syphilitic aortitis and angina pectoris were associated then there was present either an aortic insufficiency or some type of coronary artery disease. As these investigators so aptly put the matter, "It is insufficient to state merely that syphilitic aortitis alone existed but whether this condition was complicated by presence of other lesions, namely an occlusion of coronary ostia, so commonly found in luetic aortitis. For example it has been stated by Lamb that angina pectoris occurred in 11.35% of six hundred and thirteen cases of syphilitic aortitis collected from the literature; yet it is difficult to determine from published data
the exact extent of the lesions found at necropsy. -- - - - - - - - - The above also is apparently true for case of angina associated with aneurism -- -
Thus Mackenzie states 'I am therefore of the opinion that, when pain in such cases (aneurism) is found in the region characteristic of angina pectoris, it is the heart trouble which induces the pain'. Similarly Graham Steele stated that the coronary orifices were always involved in cases of angina associated with aneurism."

From the previous discussion one can fairly conclude that in most cases of angina pectoris the pathology will be; (126)

1. Disease of coronary arteries themselves due to sclerosis, infection, thrombosis, or embolism.
2. Blockage of coronary arteries at mouth by swelling or inflammation in aorta, in syphilitic aortitis, vegetations on aortic intima, or bacterial endocarditis.
3. Marked aortic regurgitation with very low diastolic blood pressure.

There are however rarer cases which show none of these lesions and one must look further for a possible pathological explanation. Anaemia has at times been
offered as a possible solution. Herrick and Nuzzum (64) reported four cases associated with pernicious anaemia; in no case was there an autopsy. Herrick (63) later stated that careful search of the literature bore out his contention of the infrequency of the complication. Since the original observation, numerous cases have been reported. (63) (69) (133) (116) (45)

In general most of the reports had common characteristics. The usual anaemia was pernicious anaemia. It was found that the severity of the pain was proportional to the degree of the anaemia; as the condition of the blood improved, the angina tended to disappear. In a few cases in which necropsy was performed the coronary vessels were found to be sclerotic; in some cases the vessels were found to be normal. The common interpretation was that these cases demonstrated the importance of the role played by diminished oxygen supply in angina pectoris. Levine (63) sums up current opinion, "Even with one-twelfth normal number of red blood cells, I do not believe that anaemia would initiate an attack without some background of coronary disease."

Diseases of the thyroid gland have occasionally been reported as probable factors. Osler (96)
Means, White and Krantz (87) Sturgis (117) and Beach have reported cases associated with hypothyroidism. Beach's case was relieved by the treatment of the hypothyroidism. In view of the fact that in recent years a surgical hypothyroidism has been used successfully in many severe cases, the possibility of hypothyroidism being an active factor seems remote. Sturgis probably furnishes the answer when he states that his case showed severe secondary anaemia and coronary artery changes.

It would seem logical that hyperthyroidism could possibly cause angina pectoris. Osler, Levine, and White make no mention of this possibility. Mackenzie reports one case in a man of thirty-six years with exophthalmic goitre and marked signs of angina pectoris. Hirschfelder speaks of vasomotor angina associated with hyperthyroidism and exophthalmic goitre and cites a case in a twenty-three year old girl. Lev and Hamberger report six cases. Means, White and Krantz; Keefer and Resnik have all seen cases in which the attacks of pain were all closely related to active periods of hyperthyroidism. The condition of the coronaries is not mentioned in these cases. Beach reports a case in which the symptoms of cardiac pain disappeared with the treatment of the hyperthyroidism.
Diabetes Mellitus has in a few instances been recorded as associated with angina pectoris. The literature is not specific as to whether it is the diabetes per se or the frequently associated arteriosclerosis which is the contributing factor. Osler never personally noted a case but did not doubt the association between the two diseases. It is possible that diabetes is associated much more frequently than is appreciated. Within recent years the literature has been studded with occasional reports. (21) (75) (68) (8)

If gout is to be considered, it is probable that it is a factor in that it precipitates arteriosclerosis. Osler, Levine (75) and Allbutt (2) have reported cases. Allbutt (2) speaks of the diseases being frequently associated.

One might almost classify as medical freaks the reports of anginal symptoms associated with paroxysmal tachycardia (83) (7), Addison's disease (106), Polycythema vera (69), Mitral stenosis (75) (83). In many of these cases reported, necropsy reports are lacking and when available are not clear as the possibility of some associated coronary disease.
PATHOGENESIS

"It has become evident that pathological changes shown in the coronary arteries by Jenner and Forthergill as existing in patients dying of angina pectoris is not universally present and later Blackall "Dropsies and appendix of angina pectoris," London 1814 showed that death from angina pectoris could occur with normal coronaries but with morbid conditions in the first part of the aorta. It has become increasingly evident that angina pectoris occurs in persons with or without arteriosclerosis of the coronary arteries and also in those with or without aortitis in the first portion of the aorta. Conversely many persons suffer from coronary arteriosclerosis and aortitis of the supravalvular portion of the aorta and never show symptoms of cardiac pain nor attacks of angina. These apparently incompatible conditions are still the basis of unsettled discussion on causation of angina pectoris.

Cardiac infarctions often produce intense pain and prolonged suffering from angina and yet not infrequently these infarcts occur causing a sudden or prolonged death without pain. Diseases of cardiac muscle are accompanied by pain so rarely that no theory yet advanced has explained satisfactorily a casual relationship between myocardial disease and
cardiac pain. In rare cases post mortem examination has shown normal aorta and normal coronaries after a death with anginal symptoms.

It seems therefore generally accepted that neither statistical reasoning nor pathological anatomy have led to any satisfactory solution of the causation of cardiac pain or the symptoms of angina pectoris." (70)

Among the earliest theories suggested as to the cause of pain in angina pectoris was the theory of coronary artery disease. Jenner (65) first proposed that the condition was due to an ischaemia which resulted from stenosis of the coronary arteries; he was supplemented in his views by Allen Burns (65) who held that an attack might be brought on by asphyxia of the heart muscle when there is a disproportion between the amount of blood it needs and the amount flowing to it. Potain (65) introduced the possibility that angina was due to the "intermittant claudication of the heart." His thought being that occlusion of the coronary arteries led to a condition similar that seen in the extremities when the circulation is impaired.

Objections to this theory are based on two facts; there are cases in which marked obstruction of the
coronary arteries occur and show no symptoms of angina pectoris and there are cases of angina pectoris without any coronary involvement. Herrick (62) offers an interesting answer to the first objection. He believes that a slow, progressive onset allows the muscle and nerve fibers to disintegrate so that by the time ischaemia occurs there can be no pain. To answer the second objection one can doubt the diagnosis or attribute the pain in such cases as being due to an aortic regurgitation which produces the anaemia. (69)

To account for anginal pains without coronary artery disease the idea of spasm of the coronaries was evolved. Lambert feels that this theory had its first real origin from Nothnagel's designation of "angina pectoris vasomotoria" of a condition of general vasoconstriction in four patients, who as Lewis (77) emphasizes did not have heart disease but in whom attacks of vasoconstriction followed exposure to cold or bouts of drunkenness. Kirch quoted by Lambert states that occasionally a nervous spastic condition of the coronaries due to vasoconstriction may produce infarcts, the arteries showing no pathological changes and points to Raynaud's disease as justifying this theoretical assumption. He also describes cases of epileptics dying with cardiac pain
who at necropsy show ischaemic necrosis in cardiac muscle without any anatomical changes in the coronary vessels. The findings of changes in the R-T segments of the electrocardiograph taken during spontaneous or invoked attacks has been considered as evidence of the occurrence of coronary spasm by Brow and Halman. Others who have lent strong support to the theory are Lewis (78), Leary (72), Latham, and Neusser (69).

This theory is difficult to understand in view of the fact that angina seems to be associated with only certain pathology such as aortitis, and why does not spasm occur in mitral stenosis? And then again how can a sclerotic artery go into spasm? (69) Bitzer attempted to produce a generalized vasoconstriction in cardiac patients by means of cold baths. Being unable to thus precipitate an attack, he concluded that coronary spasm was not the answer, but the true solution was rather an inability or failure of the vasodilatory mechanism to function. As Harrison puts the matter, "If the pain of angina pectoris was due coronary spasm, one would expect it be abolished by atropine. Actually Wayne and LaPlace have shown that following the administration of this drug, attacks are produced more readily."

Danielopulo (38) invoked a modification of the theory, saying that angina pectoris was due to
proportion between coronary artery flow and the work of the heart. Thus the angina could occur much more readily in a case with diseased coronaries; however a diseased artery would not in such cases be absolutely necessary. There is no evidence offered to support this theory.

Allbutt (1) Vaquez, Coffey and Brown (2) have identified themselves with a theory which depends for its support on a diseased aorta. Their chief strength lies in finding an aortitis in a great many cases of angina pectoris, for the commonest lesion is aortitis or luetic aortitis. Allbutt (12) maintains that with the exception of certain rare cardiac cases he has failed to discover a case of unmistakable angina pectoris in which, whatever the disease of the coronary arteries, the aorta on careful examination was demonstrated histologically to be inwardly and outwardly sound. Vaquez (12) and Jonesco (29) are in essential agreement with this. They believe that when the coronaries are involved it is but secondary to the aortitis. Effort distend the aorta. This stimulates the depressor nerve fibers of the vagus which would ordinarily be painless but due to loss of elasticity impulses are transmitted to the cardiac plexus and express themselves as anginal pains.

Coffey and Brown (30) reverse this conception and
believe an aortic spasm to be the cause. Sudden death occurs because this constriction deprives the heart of blood and is contributed to further by sclerosis of the coronaries and the aorta.

Mackenzie tried to solve this baffling problem by presenting a theory of myocardial exhaustion. He was convinced of the importance of coronary artery disease in angina pectoris for eighteen of the twenty-two of his patients coming to autopsy showed involvement of the coronaries. Being unable to explain the other four cases, he resorted to the conception of myocardial exhaustion, usually due to deficient blood supply, occasionally due to other causes. This coupled with a hypersensitive nervous system was sufficient to produce anginal pains. This theory has received little support. One must remember that practically when the myocardium shows its greatest exhaustion, in cardiac decompensation, it gives little pain, while patients with good cardiac reserve often have angina pectoris. (69)

Keefer and Resnik have done excellent work in support of their theory of an anoxemia of the myocardium. They believe that in all conditions of cardiac pain it can be shown that there is produced a condition favoring an anoxemia of the myocardium. That is, the attack occurs when the oxygen supply of the heart is inadequate to meet the oxygen demands of the heart. The anoxemia
is relative, being sufficient for demands of the heart at rest; insufficient for demands at work. They grant that anoxemia of the myocardium may exist without causing pain as occurs in congenital heart disease and pernicious anaemia. It appears that when the heart is uniformly affected, angina pectoris is absent. Only in cases where a part of the heart muscle is anoxemic such as occurs in coronary sclerosis do the symptoms of heart pain appear. They contend that it is not necessary to believe in coronary spasm to accept anoxemia as the basic cause. They point out the close similarity between angina pectoris and intermittent claudication; how stoppage of blood supply to the legs produces no pain until the muscles are used. Harrison believes that the most conclusive evidence that angina pectoris is due to a disproportion between the need for oxygen and its supply has been presented by Rothschild and Kissin, who showed that inhaling an oxygen poor mixture could produce an attack of angina pectoris in susceptible patients who never had an attack while at rest. Harrison confirmed this observation and attributed the sudden death in angina pectoris to ventricular fibrillation which results because of lack of oxygen in the cardiac muscle. The observations of angina pectoris in pernicious anaemia in which the pain cleared up with treatment lends further support to this theory.
Sutton and Leuth by animal experiments have advanced strong evidence against this theory. Their experiments showed that when a ligature was passed around the anterior descending branch of the left coronary artery or vein and traction was made interfering with the blood supply, pain was in the proportion to the amount of traction used. Pain ceased whenever traction ceased. However, if the ligature tore through the vessel the pain was severe, but ceased immediately when the vessel was entirely severed. If the artery and vein were dissected out and covered with alcohol, traction produced no pain. It would seem that traction caused pain by interfering with the sympathetic afferent nerves of the adventitia of the coronaries and not by interfering with the blood supply.

Lambert credits Danielopopoul in 1918 with presenting the thought that possibly the poisoning of the myocardium by the metabolites produced by fatigue of the muscle was sufficient to explain angina pectoris. Lewis Pickering and Rothschild have given this strong support. They showed that pain characterizing intermittent claudication can be reproduced precisely in an normal limb by exercising it after stopping the blood supply. If a normal limb to which the blood flow has been stopped is exercised, the vessels do not go into spasm, they dilate while the pain is acute.
The pain on muscular exercise in absence of blood supply is not the direct result of lack of oxygen but is determined by a stable chemical stimulus developed in a muscle during its exercise. It is related to the amount of exercise. When muscles contract changes such as a release of metabolites occur within its fibers. This stimulus to pain arises out of these changes in muscle fibers.

Lambert is a believer in the coronary thesis, but he tends to modernize the concept by involving the autonomic nervous system. He points out that there is a fine balance between the sympathetic and parasympathetic system, controlling respiration, digestion, secretion, etc. All this is influenced by emotion, fear, anger, joy. At the center of the balance is the heart, for if the circulation cannot remove waste and bring nutrition, all ceases. Under any stimulus such as emotional stress, exposure to cold, muscular exertion, there is a necessary cardiac readjustment. Thus under influence of fear, pain, or rage, there is a stimulation of splanchnic nerves, contraction visceral blood vessels causing a redistribution of blood from viscera to external areas of muscles, brain, heart. The sympathetic discharge also quickens the heart beat and by a contraction of the spleen increased amounts of red blood cells are discharged into the blood to carry increased supplies of oxygen to the tissues.
There is also larger ventilation of the lungs, dilatation of bronchioles, and stimulation of adrenals giving an increase of adrenalin which produces a discharge of sugar from liver to supply muscular energy. With emotion the heart is therefore called upon for immediate increase of action and for increased output per beat. When the myocardial muscles are incompetent to respond to these demands there occurs dyspnea on exertion, cardiac dilatation of the usual congestive failure type, but without pain. When however there is also degeneration in the walls of the coronary vessels supplying either myocardium or aorta, the sensory nerve endings of the autonomic system are involved and pain is produced.

A theory which has received but scant attention is the suggestion of Hirschfelder that the pain might be due to acute cardiac dilatation. Brooks quotes an number of French investigators who have described lesions in the cardiac plexus in cases of angina pectoris, but their work is generally not accepted.

Recently Jackson and Jackson have advocated a theory, unique in that it avoids a discussion of the circulation as a causative factor. They believe that angina pectoris is due to acute, spasmodic incoordinated, contractions of the oesophagus and stomach. They cite cases in the literature of rupture of the oesophagus in which the symptoms closely resembled angina. They argue
that even Heberden noted that occasionally angina sufferers vomited blood during an attack and every observer has noted that relief from an attack is associated with eructation of a large volume of gas. The authors contrived a stimulation electrode by means of which they stimulated various portions of the oesophagus of anaesthetized dogs and were able to produce reflex motor phenomena in the legs, auricular fibrillation, and changes in respiration. They point out that cases have been reported of completed coronary occlusion in which no anginal symptoms occurred. From these facts the writers reason that angina is primarily a digestive disturbance usually due to the trapping of gas in the oesophagus which by pressure produces the typical pain and symptoms of angina and may occasionally reflexly involve the coronaries by way of the vagus. They attribute sudden death in these attacks to auricular fibrillation: They interpret the action of drugs in angina, such as nitrites, as being due to relaxation of esophageal muscle, passage of gas and relief and finally they cite the cases of Verdon who was able to obtain relief in angina pectoris by passage of stomach tube and drawing off gas.
PRECIPITATING FACTORS

If one cannot adequately describe the pathology of a condition, it is obvious that a discussion of etiological factors will be difficult. There are, however, a few certain facts regarding angina pectoris. The disease is essentially one of the sixth decade of life. It is infrequent below forty and rare below thirty (21) (44) (96) (126). Kahn modifies this. He believes that the first attack occurs between forty-five and fifty-five years of age and that twenty-five percent of the cases have their first attack below forty. A case has been reported in a boy of six, associated with dry pericarditis (107). Heberden (129) in his original studies noted the disease in a boy of twelve; Vaquez noted sudden death in a boy of eighteen who at post-mortem showed aortitis and narrowing of the coronary arteries. Hirschfelder speaks of a child of eight years with mitral stenosis and angina pectoris. White and Mudd (129) found definite reports in the literature of forty-two cases under thirty years and to this group they added eight cases of their own. All cases below thirty had one common finding, aortic rheumatic regurgitation.

Cardiac pain is three to five times as common in the male as in the female (26). Heberden in his series
noted but three women out of one hundred cases (61). Osler (95) reports an average of one woman to forty cases. It is suggested that the greater incidence in men is due to their work and their greater muscular development (75). The rising tide of women may be due to the practice of including women with pseudo-angina in the series and also to the entrance of women into professional and business life. In the past the chief precipitating factors in women have seemed to be chronic hypertension and unusual family cares and worries. To these are now added the financial and other strains incident to professional work, and business factors which have unquestionably been responsible for the great majority of cases in men (127).

Osler (95) poetically describes the ailment as a disease of men of muscular build who have been devotees of Bacchus and Venus, more frequent among the rich than the poor. The disease is rare in the weak undernourished individuals, occurring usually in well set, sturdy, muscular type, with a tendency to be slightly overweight, with good physical development, and usually free from minor ailments (75). It is possible that the higher incidence in this type of individual is due to the fact that he is over-strenuous and not stopped by pain. It is probably the
nervous drive which is the factor and not the physique (127).

The toll is great in the highstrung, nervous, intelligent individual, such as the Jew, and is rare in the Negro (26). Emotional stress and strain, sex excitement, anger, even pleasureable excitement may precipitate an attack (21) (127). One must not assume that this is the only type of patient, for White (127) mentions that in his private practice seventy percent of his patients were Americans of English origin. He grants that his figures do not agree with dispensary records, and notes that he has never seen a case in Scandanavians.

Heredity plays an important part in the picture. There is a general agreement among authorities that those with a family history are predisposed to attacks (21) (44) (95) (122) (127). The Arnold family presents an interesting example (95). William Arnold, collector of customs of Cannes, died suddenly of spasm of the heart in 1881. His son, the celebrated Thomas Arnold of Rugby, died in his first attack. Mathew Arnold, his distinguished grandson, was a victim of the disease for many years and died suddenly. Brooks (21) goes so far as to recommend prophylactic treatment for those coming from predisposed families.
Occupations are a minor predisposing factor. It may occur in farmers and laborers, but is largely a disease of the professional man, doctors and lawyers, being especially hard hit (95) (127). It occurs most frequently in those fields which require excessive exertion, especially exertion in those who have previously been sedentary (68). Brooks (21) lists a typical distribution.

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domestic occupation</td>
<td>75</td>
</tr>
<tr>
<td>Work of physical stress</td>
<td></td>
</tr>
<tr>
<td>Farmers, soldiers, sailors</td>
<td>19</td>
</tr>
<tr>
<td>Skilled field</td>
<td></td>
</tr>
<tr>
<td>Professions</td>
<td></td>
</tr>
<tr>
<td>Medicine, law, clergy</td>
<td>31</td>
</tr>
<tr>
<td>Skilled laborers</td>
<td></td>
</tr>
<tr>
<td>Jewlers, painters, etc.</td>
<td>15</td>
</tr>
<tr>
<td>Financial endeavors</td>
<td>8</td>
</tr>
<tr>
<td>Engineers</td>
<td>3</td>
</tr>
<tr>
<td>Executives</td>
<td>50</td>
</tr>
<tr>
<td>Business men</td>
<td>93</td>
</tr>
</tbody>
</table>

The great preponderance of cases in the skilled fields should be noted.

Colder climates and season favor occurrence of angina pectoris. Some patients escape their usual aggravation of heart pain during the winter months by traveling South to Florida or Southern California. The intense heat or humidity of the summer may also provoke an attack. A comfortable house in a cold climate may actually, however be preferable to un-
suitable living quarters in the south (127)

Tobacco and alcohol have long been a debated question. It is generally felt that tobacco is not the cause although it may provoke an attack if the underlying pathology is present. (127) (53) (68) (30)

Vaquez credits Guillian and Gy as having poisoned thirty-three rabbits by intravenous and subcutaneous injections of nicotine, tobacco macerations, and tobacco smoke solution. In three cases atheromatous plaques were found in the aorta, but this is no higher than the incidence of atheromatous plaques in so-called normal rabbits. Rolleston (90) says that he has seen two severe cases of angina in physicians due to smoking. Moschowitz reports on four cases, all heavy smokers with severe anginal symptoms which ceased when the smoking was stopped. The pain was even more intense than in true angina. The mechanism of action is not known but in most cases probably the coronaries have undergone some change and are tobacco sensitive. No one can say as to whether smoking caused the change. As for alcohol, Osler tended to favor it as a probable factor. Recent writers have however shunned this thought. White and Schacker (130), and Kahn in large series of cases could not show that alcohol played an appreciable part. In one series
the incidence of angina pectoris was slightly higher in the abstainers.

Hypertension is of no significance. In Brook's series only ninety-six out of three hundred cases had an elevated blood pressure. Eppinger and Levine noted that angina pectoris with hypertension is commonest in the female. In their series no woman had a diastolic pressure below one hundred and forty.
<table>
<thead>
<tr>
<th>YEAR</th>
<th>AUTHOR</th>
<th>COUNTRY</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1768</td>
<td>Heberden</td>
<td>England</td>
<td>quiet, warmth, spirituous liquors, opium, counter-irritation</td>
</tr>
<tr>
<td>1776</td>
<td>Fothergill</td>
<td>England</td>
<td>Essence of pepermint to promote eructation</td>
</tr>
<tr>
<td>1790</td>
<td>Alexander</td>
<td>England</td>
<td>arsenic solution</td>
</tr>
<tr>
<td>1792</td>
<td>Perkins</td>
<td>England</td>
<td>zinc sulphate</td>
</tr>
<tr>
<td>1809</td>
<td>Schlesinger</td>
<td>Germany</td>
<td>extract lactuae virosae (lettuce leaves)</td>
</tr>
<tr>
<td>1817</td>
<td>Reid</td>
<td>Ireland</td>
<td>inhalation of oxygen</td>
</tr>
<tr>
<td>1826</td>
<td>Laennec</td>
<td>France</td>
<td>venesection</td>
</tr>
<tr>
<td>1832</td>
<td>Mantell</td>
<td>England</td>
<td>venesection and a seton</td>
</tr>
<tr>
<td>1834</td>
<td>Newton</td>
<td>Ireland</td>
<td>hydrosulphureted ammonia</td>
</tr>
<tr>
<td>1834</td>
<td>Batten</td>
<td>England</td>
<td>venesection and belladonnae</td>
</tr>
<tr>
<td>1840</td>
<td>Munk</td>
<td>England</td>
<td>sulphur</td>
</tr>
<tr>
<td>1841</td>
<td>Schleiser</td>
<td>Germany</td>
<td>dilute hydrocyanic acid</td>
</tr>
<tr>
<td>1841</td>
<td>Szerlecki</td>
<td>Germany</td>
<td>subcutaneous injections of morphine acetate</td>
</tr>
<tr>
<td>1846</td>
<td>Latham</td>
<td>England</td>
<td>laudanum</td>
</tr>
<tr>
<td>1854</td>
<td>Stokes</td>
<td>Ireland</td>
<td>draughts of chloroform spirituous liquors, ammonia, Hoffman's anodyne</td>
</tr>
<tr>
<td>1857</td>
<td>Gripouilleau</td>
<td>France</td>
<td>counterirritation</td>
</tr>
<tr>
<td>1864</td>
<td>Piorry</td>
<td>France</td>
<td>quinine sulphate</td>
</tr>
<tr>
<td>1867</td>
<td>Brunton</td>
<td>England</td>
<td>inhalation of amyl nitrite</td>
</tr>
<tr>
<td>1867</td>
<td>Trousseau</td>
<td>France</td>
<td>atropine, alcoholic infusion of mint</td>
</tr>
<tr>
<td>1869</td>
<td>Rockwell &amp;</td>
<td>U.S.</td>
<td>galvanic current</td>
</tr>
<tr>
<td></td>
<td>Beard</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YEAR</td>
<td>AUTHOR</td>
<td>COUNTRY</td>
<td>TREATMENT</td>
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</tr>
<tr>
<td>1873</td>
<td>Papillaud</td>
<td>France</td>
<td>potassium bromide</td>
</tr>
<tr>
<td>1876</td>
<td>Balfour</td>
<td>England</td>
<td>iodides</td>
</tr>
<tr>
<td>1879</td>
<td>Murrell</td>
<td>England</td>
<td>nitroglycerine</td>
</tr>
<tr>
<td>1880</td>
<td>Dieulafoy</td>
<td>France</td>
<td>icebag</td>
</tr>
<tr>
<td>1883</td>
<td>Hay, Matthew</td>
<td>England</td>
<td>sodium nitrite</td>
</tr>
<tr>
<td>1883</td>
<td>Jakubouski</td>
<td>Russia</td>
<td>viburnum opulus</td>
</tr>
<tr>
<td>1885</td>
<td>Mangub</td>
<td>Russia</td>
<td>viburnum opulus</td>
</tr>
<tr>
<td>1886</td>
<td>VonMorden</td>
<td>Germany</td>
<td>cocaine</td>
</tr>
<tr>
<td>1886</td>
<td>Loschkeuitch</td>
<td>France</td>
<td>cocaine</td>
</tr>
<tr>
<td>1887</td>
<td>Huchard</td>
<td>France</td>
<td>iodine</td>
</tr>
<tr>
<td>1889</td>
<td>Broadbent</td>
<td>England</td>
<td>belladonnae, canabis indica, arsenic, phosphorus, colchicum, counterirritation</td>
</tr>
<tr>
<td>1889</td>
<td>Martin</td>
<td>U.S.</td>
<td>antipyrine</td>
</tr>
<tr>
<td>1889</td>
<td>Evans</td>
<td>U.S.</td>
<td>spartein sulphate</td>
</tr>
<tr>
<td>1889</td>
<td>See</td>
<td>France</td>
<td>antipyrine (phenazone)</td>
</tr>
<tr>
<td>1894</td>
<td>Lenoine</td>
<td>France</td>
<td>methylene blue</td>
</tr>
<tr>
<td>1895</td>
<td>Askanazy</td>
<td>Germany</td>
<td>theobromine sodium salicylate</td>
</tr>
<tr>
<td>1897</td>
<td>Page</td>
<td>U.S.</td>
<td>water</td>
</tr>
<tr>
<td>1897</td>
<td>Bradbury</td>
<td>England</td>
<td>erythrol tetranitrate</td>
</tr>
<tr>
<td>1897</td>
<td>Bostwick</td>
<td>U.S.</td>
<td>hyoscine</td>
</tr>
<tr>
<td>1898</td>
<td>Clements</td>
<td>U.S.</td>
<td>Catrogeus oxycantha (english hawthorne)</td>
</tr>
<tr>
<td>1899</td>
<td>Ewart</td>
<td>England</td>
<td>inhalation of carbon dioxide</td>
</tr>
<tr>
<td>1900</td>
<td>Steele</td>
<td>England</td>
<td>inhalation of carbon dioxide</td>
</tr>
<tr>
<td>YEAR</td>
<td>AUTHOR</td>
<td>COUNTRY</td>
<td>TREATMENT</td>
</tr>
<tr>
<td>------</td>
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<td>-------------</td>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>1902</td>
<td>Marshall &amp; Wigner</td>
<td>England</td>
<td>mannitol pentanitrate</td>
</tr>
<tr>
<td>1902</td>
<td>Strumpel</td>
<td>Germany</td>
<td>camphor, strophanthus, chloral, chloralamide</td>
</tr>
<tr>
<td>1902</td>
<td>Kaufman &amp; Pauli</td>
<td>Austria</td>
<td>theobromine</td>
</tr>
<tr>
<td>1902</td>
<td>Breuer</td>
<td>Germany</td>
<td>theobromine</td>
</tr>
<tr>
<td>1903</td>
<td>Pineles</td>
<td>Austria</td>
<td>theocin</td>
</tr>
<tr>
<td>1907</td>
<td>Rumpf</td>
<td>Germany</td>
<td>electric baths with sinusoidal current</td>
</tr>
<tr>
<td>1907</td>
<td>Hasselbach &amp; Jacobous</td>
<td>Germany</td>
<td>exposure to Finsen light</td>
</tr>
<tr>
<td>1908</td>
<td>Mackenzie</td>
<td>England</td>
<td>chloral, ammonium bromide</td>
</tr>
<tr>
<td>1916</td>
<td>Jonnesco</td>
<td>France</td>
<td>cervical sympathectomy</td>
</tr>
<tr>
<td>1922</td>
<td>Klewitz &amp; Kirckheim</td>
<td>Germany</td>
<td>intravenous injections of hypertonic glucose</td>
</tr>
<tr>
<td>1922</td>
<td>Niemyer</td>
<td>Germany</td>
<td>hypertonia glucose injections</td>
</tr>
<tr>
<td>1923</td>
<td>Danielopolu</td>
<td>France</td>
<td>resection of paravertebral nerves</td>
</tr>
<tr>
<td>1924</td>
<td>Babcock</td>
<td>U.S.</td>
<td>benzyl benzoate</td>
</tr>
<tr>
<td>1925</td>
<td>Mandl</td>
<td>Austria</td>
<td>nerve injection with procaine</td>
</tr>
<tr>
<td>1926</td>
<td>Hay &amp; Ince</td>
<td>England</td>
<td>diathermy</td>
</tr>
<tr>
<td>1927</td>
<td>Ecker</td>
<td>U.S.</td>
<td>Roentgen rays</td>
</tr>
<tr>
<td>1929</td>
<td>Vaquez</td>
<td>France</td>
<td>Insulin free pancreatic extract</td>
</tr>
<tr>
<td>1933</td>
<td>Blumgart</td>
<td>U.S.</td>
<td>total ablation of thyroid</td>
</tr>
<tr>
<td>1935</td>
<td>Beck</td>
<td>U.S.</td>
<td>grafts to heart</td>
</tr>
<tr>
<td>1935</td>
<td>Krantz</td>
<td>U.S.</td>
<td>inhalation of trichlorethylene</td>
</tr>
</tbody>
</table>
GENERAL TREATMENT

It becomes obvious that the treatment for angina pectoris is an uncertain, tedious process. With the etiology uncertain the treatment cannot hope to rest upon any firm foundation. The chart on the previous page shows the commonest measures advocated since Heberden. As one glances at it one cannot help but wonder if we have gone far from Heberden's original "Opium and spirituous liquors."

There are certain general measures which are commonly used. Those which follow are from White (127) except were noted. These measures are generally accepted by such authorities as Lambert, Christian, Brooks, and Gilbert (53).

"The most important therapeutic measure is relaxation both physical and mental. If partial rest such as may be obtained by staying away from work, taking a vacation, by reduction of work is not sufficient to end attacks of pain on slight or moderate exertion or while at rest; complete relaxation in bed for weeks if necessary may give relief, lasting over months or even years, if on resuming work a slow pace is maintained. Hurry, worry, overexertion, overeating and cold stormy weather are to be avoided at all times. Remain
indoors in raw blustering weather. Sanatorium treatment is of value in the rest, regulation, and diet it gives."

The question of diet is difficult. In general overeating should be avoided; five small meals a day being desirable. Gilbert (53), and Mackenzie suggest lying down after meals. Brooks warns against this practice. The diet should be especially digestible. Gas forming foods should be avoided as well as heavy meals. There should be no restrictions on protein. If the patient is diabetic, it is better that a trace of urinary sugar be present. Other dietary problems such as ulcer, diabetes, constipation should be controlled (53).

As for alcohol and tobacco some restrict it entirely. The best solution is suggested by Gilbert (53) who recommends tobacco and alcohol according to the patient. That is, he believes it is better to smoke an after dinner cigar if it gives relaxation than to interdict it and cause irritableness. Brooks feels the same way about the matter and points out that alcohol may have a vaso-dilating effect.

Foci of infection should be eradicated if possible. More and more evidence is being brought up to link the basic causes or exciting factors in angina pectoris to
various hidden septic centers (126). Smith (110) has studied a small number of cases in relation to infectious sites. Although he is unable to reach a definite conclusion, he suggests the importance of early removal of foci of infection.

To perfect the rest regime it may be necessary to overcome nervousness and restlessness by discrete uses of sedatives. The bromides are indispensible in some cases. Chloral hydrate, phenobarbital, codeine or opium given at night will in most instances insure complete rest. (21)

The iodides are frequently given on empirical basis. Digitalis is usually avoided unless there are indications aside from the angina pectoris. Christian speaks highly of the routine use of digitalis. Gilbert and Fenn by animal experiments showed that digitalis preparations have vasoconstricting effect upon the coronaries. From their experiments these investigators concluded that in angina pectoris and an overlabile nervous system digitalis is very likely to cause vasoconstriction.

For those who have a hereditary tendency towards angina pectoris the following points are advised: (21)

1. Diet to avoid obesity
2. Exercise of mild nature
3. Vacations which do not place the individual under undue stress and strain.
4. Removal of all foci of infection
5. Temperance in the use of alcohol, tobacco, and condiments.
6. Vacations
7. Temperance in sexual matters.

It is important to treat any coexisting disease. Colchicine and atophan should be prescribed in cases of gout; large doses of salicylates are necessary in acute rhematism (21). Christian recommends special treatment in cases complicated by syphilis. Arsenamine must be used with caution. The courses with mercury and iodide should be the first procedure, the usual method being five drops of saturated solution of potassium iodide three times a day, gradually increasing the dosage until a total of thirty drops three times a day is reached. Intramuscular injections of succinimide of mercury 0.013 to 0.026 gram twice weekly for four courses then start a course of intravenous arsphenamine. The first dose is usually 0.2 gram and five days later 0.4 gram which is continued weekly with the mercury and potassium iodide until a total of eight doses of arsphenamine is given. This is followed by four weeks of rest.
and then a second course follows.

For the treatment of the immediate attack: (21)

1. Application of heat to precordium

2. Nitroglycerine tablets, 0.0006 to 0.0012 gram (1/100 to 1/50 grain) every fifteen minutes until there is dilation of capillaries, flushing of face. Spirits of glonoin or ampules of amyl nitrite may be used instead.

3. Morphine—beginning with 0.015 gram (1/4 grain) doses if there is no response to the nitrites.

4. Alcohol according to the patients tolerance

5. Warm tub baths

6. Blood pressure cuffs around all four extremities inflated together -- thus lessening blood flow for awhile.
SPECIFIC DRUG THERAPY

The nitrites have long been in good standing for the treatment of angina pectoris both as preventive measures and during the immediate attack. The commonly used forms are amyl nitrite 0.12-0.3 gram (3-5 minims), sodium nitrite 0.03-0.012 gram (0.5-2 grains), glyceryl trinitrate in the form of Liquor glyceryl trinitrate 0.03-0.12 grams (0.5-2 minims), or tablets of glyceryl trinitrate 0.0012 grams (1/50 grain), Erythrol tetranitrate 0.03-0.06 (1/2 grain), Manitol hexanitrate 0.06 gram (1 grain). These drugs act chiefly by dilation of blood vessels and drop in circulation. They frequently produce toxic side effects such as digestive disturbances, eruptions, nausea, vomiting, syncope, headache, and flushing of the face. (42)

The drugs were first introduced by Murrell who in 1879 used a one percent alcoholic solution of glyceryl trinitrate. Amyl nitrite had been described previously by Richardson (47) but he did not recommend it for medical use. It was Lauder Brunton who in 1891 gave a full account of its action as a vasodilator, and tried it for anginal attacks. In less than a minute attacks which formerly lasted three to four hours were relieved by inhalations of three to five minims of the drug. Subsequent writers have
added little to our knowledge of the drug, but have
drawn attention to the fact that it is sometimes in-
effective and at times dangerous. Thus Jones mentioned
that the dosage had to be increased sometimes to twenty
drops or more because tolerance developed rapidly, and
Yeo mentioned that amyl nitrite did not give relief,
while Allbutt thought that it was not effective in
some persons and in others worked unpleasant after
effects. Osler (95) states that it is singularly
uncertain, sometimes quite inert, and it might pro-
duce physiological effects without relieving pain.
The common method of administration is in sealed
ampules 0.3 gram (5 grains). Patients are instructed
to break the ampule in a handkerchief and hold it
close to the nose, inspiring through the nose, ex-
piring through the mouth. (46)

Sodium nitrite was introduced by Hay in 1883.
He was impressed by the similarity of its action
to amyl nitrite and used it for the first time
successfully in angina pectoris. His original
paper reported one case in which relief was less
rapid but more complete than with amyl nitrite.
Trying it for the immediate prevention of attacks,
the patient would take 0.06 gram (1 grain) before
undertaking any exertion known to produce pain.
Sodium nitrite has not received good reports from most men with the exception of Brooks who recommends its administration constantly for the best results. Evans and Hoyle (46) (47) White (127), Vaquez considered the drug inferior to other preparations and Osler does not even mention it.

Manitol hexanitrate and Erythrol tetranitrate were introduced by Bradbury in 1895 (20).

There has been some discussion as to the preferred form. In general it may be said that glyceryl trinitrate is preferred by the majority. For the best results the tablets should be allowed to dissolve in the mouth (46) (47). It is generally believed that amyl nitrite and glyceryl trinitrate produce more rapid but less sustained action; while erythrol tetranitrate and manitol hexanitrate while requiring longer to become effective, produce effects of longer duration (42) (85).

Evans and Hoyle (46) (47) after a thorough investigation of the various nitrates on clinical basis were led to conclude that no particular one of them was better than a simple placebo.
Of recent years there has sprung into common use the xanthine derivatives, caffeine, theobromine, theophylline. Askanazy (113) was the first to recommend the drug in diseases of the coronary arteries having observed favorable results from the use of the theobromine sodiosalicylate in the case of angina pectoris. These results were later confirmed by Bruer Dessaur (113) in 1908 who introduced theophylline with ethylenediamine. Since that time there have been constant experiments with these derivatives in an attempt to discover their merits and relative values. The result has been the introduction of so many variations and so many proprietary names for these derivatives, all claiming the highest merit, that the average practitioner wonders if they are worthwhile at all, and if so, which to choose.

The council on drugs of the American Medical Association (31) sums up current opinion, "Theobromine and theophylline surpass caffeine in their diuretic and perhaps in cardiac and muscular actions. They are therefore generally preferred in cardiac edemas, etc.; since they are equally, or more effective, more prompt, and largely avoid the unpleasant side effects (insomnia, nervousness, gastric disturbances),
which often interfere with the use of caffeine in adequate doses. This freedom from side effects holds particularly true for theobromine. Theophylline surpasses theobromine in diuretic efficacy, but its action is probably not so lasting; it may produce gastrointestinal disturbances; renal irritation has been reported. Theobromine is therefore generally preferred sometimes precede for a few days by theophylline.

Because of their slight solubility, these compounds are used almost exclusively as salts, but there is little reason to believe that the particular salt has any effect on therapeutic action.

In anginal pain theophylline probably produces relief more readily than theobromine."

The various forms accepted by the American Medical Association (31) are;

Theobromine
Theobromine sodium acetate
Agurin—a brand of theobromine sodium acetate
Theocalcin
Theophylline
Theocin—a brand of theophylline
Theophylline with sodium acetate
Theocin soluble—a brand of theophylline with sodium acetate.
Aminophylline (Theophylline with ethylenediamine)

Experimentally Eppinger and Hess (50) observed stretching of strips of coronary arteries when placed in a solution of caffeine. This soon led to a study of the problem by the perfusion method, and Heabon (50) was able to report and increase in coronary flow using caffeine in dilutions of one to twenty thousand. Smith, Muller, and Graber (92) using aminophylline were able to show that the rate of perfusion in the intact heart increased forty to ninety percent, a gain comparing favorably with the use of glyceryl trinitrate and with even more sustained reactions.

Sakai and Soneyaski (54) through work on intact animals pointed out that to obtain vasodilation, doses larger than those used clinically were necessary, and Wiggers with Grun showed in dogs that no xanthine derivative could build up collateral circulation in case of coronary occlusion.

Which of the drugs are the most efficient vasodilators? Neither experimental nor clinical evidence has given any certain proof. One can sum up experimental work by saying that it is agreed that caffeine has the poorest vasodilatory effects, while results comparing theobromine, theophylline aminophylline are not consistent, even in the hands of the same investigators (50) (60) (112) (54).
Clinically the results are similarly uncertain. Gilbert and Kerr used theobromine sodium acetate, theophylline, theophylline with ethylenediamine. The drugs were given in capsules of various standard doses, four times a day after meals, from three to four days. Then followed a rest period of three to four days. Except for theobromine calcium salicylate and theophylline ethylenediamine the drugs frequently caused side effects such as nausea and vomiting. They noted no changes in blood pressure and in point of efficiency there was little choice between them unless possibly a slight margin of favor for theobromine sodium acetate. Theophylline was used in a few cases with poor results. Aminophylline did not in general appear to equal theobromine but did work in a few cases resistant to theobromine.

Smith et al. (113) report the successful use of aminophylline in eight cases. They used 0.1–0.3 gram (1 1/2 – 3 grains) aminophylline three times a day. Smith (113) used the drug in a series of one hundred patients observed for over a year. He noted improvement in over seventy-two percent of his cases and recommended the use of aminophylline as an adjunctive to general measures.
Gold et al. (56), however, present a different view. They report the careful observation of one hundred cases for a period of five years. Theobromine and aminophylline were both used alternating with courses of placebos, unknown to the patient. Careful records of the patients' symptoms, blood pressure, and complaints were kept. As a result of this study the following conclusions were reached;  

1. The xanthines caused no appreciable change in blood pressure.  
2. Every type of change in pain observed during the use of a xanthine was reproduced in the same individual by a period in which a placebo was used.  

The results showed that patients with cardiac pain were unable to distinguish the effect of a placebo from those of an xanthine when measures were taken to preclude the identification of the agent by any means other than by relief of pain. It was concluded that xanthines exert no specific action which is useful in the treatment of cardiac pain.

Evans and Hoyle in 1934 on the basis of their work equally carefully carried out, were forced to the same conclusions as Gold et al. In their series they even included nitrites, iodides, sedatives.
In their own words, "No one drug appeared to be outstanding, nor did any drug appear to be much better than a simple placebo."

An interesting but still academic procedure is the treatment of angina pectoris by means of insulin. Heterendyl et al. (111) and Nuzum (93) observed that diabetics who also suffered from angina pectoris when treated with insulin, would sometimes receive relief from their attacks. Ambard (111) and Bickel (111) observed similar satisfactory results in non-diabetic angina pectoris patients treated with glucose and insulin. K. S. Smith believed that many cases of angina pectoris were due to a defect of carbohydrate metabolism in heart muscle. By giving glucose and insulin he hoped to establish normal muscle metabolism. The patients selected had definite anginal attacks frequently. A record of their course before treatment was kept. They were then put on a minimum regime of five units insulin before morning and evening meals followed by thirty grams of glucose at meal time. Previous activity and medication were continued. Six cases were observed and all obtained some relief.
In 1926 E. K. Frey and H. Kraut (134) found a substance in the urine which they demonstrated to have vasodilating properties. Further work led them to believe that this hormone was elaborated by the pancreas, carried inertly by the blood and excreted in active form by the urine. This hormone proved effective in treatment of such conditions as angina pectoris and intermittent claudication.

Gley and Kisthinios in 1929 (93) prepared a pancreatic extract which apparently had the same properties as Frey's and Kraut's hormone. Schwartzman prepared a similar extract from heart muscle (93). Both extracts gave gratifying results in treatment of angina pectoris. Gley and Kisthinios demonstrated that the effective substance was not insulin but another substance present in the pancreas. They reported twenty-nine successful cases, and concluded that this therapy was far more successful than any surgical measures suggested up to that time.

Wolffe et al. (135) introduced the therapy into this country in 1931. At that time they were of the opinion that the compounds thus far used were either adenylic acid or adenosine. They prepared an extract of ground pancreas and selected twenty cases for trial which had resisted previous treatment.
Treatment consisted of daily intramuscular injections of sixty to one hundred and fifty hypotensive units and besides a regime of theobromine, sedatives, and rest. Symptomatic relief was obtained in eleven cases leading Wolffe to recommend use of the substance. Although no toxic effects were demonstrated, caution against its use in coronary thrombosis was given.

At about the same time as Wollfe, Elliot and Nuzum (43) prepared a similar pancreatic extract which they too found to have vasodilating effect in experimental animals and perfused hearts. The extract had properties similar to the circulating hormone of Frey and Kisthinios and the authors suspected them to be one and the same. They also disagreed with Wolffe claiming that the extract did not contain histamine, choline, adenylic acid, nor adenosine in sufficient quantities to explain its action. These men noted that experimentally this extract had a vasodilating power exceeding by one half the action obtained through the use of aminophylline. For purpose of therapy they defined a hypotensive unit as that amount of extract which injected intravenously is sufficient to cause a barely susceptible fall in blood pressure in a rabbit weighing three kilograms.
They gave thirty to sixty hypotensive units intravenously every other day to twenty patients for ten to twelve days and noted benefits in all but ten percent of the cases.

In 1935 Wollfe et al. retracted his previous statements claiming that previous experiments had convinced him that the extract was not active because of histamine or choline. He suggested the name desympatome for the compound. At this time he reported the results of treating two hundred and four cases of angina pectoris over a five year period by use of his extract. He described his results as, "Very good." It should be noted that the extract was but a supplementary treatment since diet, rest, sedatives, and nitrites were given simultaneously.

There have been numerous procedures recommended which except for one or two supporters, have received scant attention. Spath in 1921 suggested the use of benzyl benzoate having noted good results in six cases of angina pectoris thus treated. Babcock prescribed thirty drops of the drug in milk four times a day. He observed no ill effects and mentions good results as far as relief of pain went in six patients. He admits however that he had some failures.
Feinberg was impressed by the attempts to establish collateral circulation in Buerger's disease by intravenous hypertonic saline solutions, and wondered of the possible effect in coronary artery disease. He was afraid to try the procedure until he had a patient with Buerger's disease who was receiving intravenous saline before a cardiac examination had been made. Later studies showed that the patient had had a coronary thrombosis ten years ago and could not walk more than five or six blocks. After receiving three hundred c.c. of a five percent solution of sodium chloride weekly for three years, the patient could walk for blocks without an attack of pain. Encouraged by this fifteen more cases with arteriosclerosis of leg vessels and coronary vessels were added to the series. None of these cases had responded to ordinary medical care. The initial dose was one hundred c.c. of sterile five percent sodium chloride solution. Subsequent doses were increased weekly, fifty c.c. to a maximum of two hundred and fifty c.c.; injections were given three times a week. No other drugs were used. Definite and continued improvement resulted. Feinberg felt that the treatment encouraged a more rapid development of collateral circulation.
Love in 1937 noting the effectiveness of trichlorethylene in trigeminal neuralgia and seeing that it could cause a drop of blood pressure in hypertensive subjects, determined to try the drug in angina pectoris. Treatment consisted of three ampules of one c.c. each a day. Although he obtained relief in some cases he did not believe that his results justified his advocating the use of the drug in cases of cardiac pain.

Beckmen describes a procedure advocated by Bandman. Intravenous injections of five c.c. of sterile ten percent solutions of magnesium sulphate were given three times a week to patients who did not respond to ordinary medical management. The dosage was gradually increased to ten c.c., until a total of twelve injections had been given. Marked improvement was noted in over half the cases.

Ultraviolet irradiations over the whole body has been used by Freud (97). This is based on the theory that when the skin is exposed to enough light to produce an erythematos reaction, a histamine like substance is released into the circulation which releases vascular spasm.
Beckman describes the use of physical therapy and X-ray radiations attempted generally by foreign investigators. In general these reports have received little attention in the American literature.
SURGICAL TREATMENT — SYMPATHECTOMY

Surgical treatment of angina pectoris is not new but has remained largely in the experimental stage being seldom used by the general physician.

In 1920 Jonnesco (29) reported the cure of a case of angina pectoris by resection of the left cervical sympathetic system under local anaesthesia. The patient was a male, thirty-eight years old, with a positive Wassermann and a typical anginal syndrome. The operation was performed April 2, 1916, and consisted of resection of the left great sympathetic chain from the base of the neck into the thorax, including the last two cervical ganglia and the first thoracic ganglion. It was not clear whether the cardiac branch from the superior cervical ganglion was severed or not. Following the operation there was a diminution of the left palpebral fissure, extreme diminution and fixity of the left pupil, retrocession of the left eye into the orbit. The patient refused extirpation of the right sympathetic because he felt well without it. The man returned April 3, 1920; he had suffered no further attacks and had received no therapy for his syphilis. Radioscopic examination showed a slight dilatation.
Fig. 1
OPERATIONS ON SYMPATHETIC NERVOUS SYSTEM (con.)

Fig. 2
OPERATIONS ON SYMPATHETIC NERVOUS SYSTEM (con.)

Fig. 3
of the aorta with the wall thickened and irregular atheromatous plaques. The left palpebral fissure was diminished, the pupil was sunken, there was facial asymmetry. It is of importance to note these symptoms for they must be considered as an aftermath of operations upon the sympathetic nervous system.

The operation was originally suggested by Franck in 1899 who established relationship between irritation of the cardio-aortic plexus and symptoms of angina pectoris. He did not however attempt the procedure (29). There have been claims that Mayo (86) first performed a similar operation in 1915, but he failed to report it.

Since Jonnesco's report there has arisen a series of operations for angina pectoris dealing with the sympathetic nervous system. These operations have become so modified, that at present interpretation of results, methods, and terminology is difficult. The various operations have been diagramed by Leriche and Fontaine and are shown on the previous page.

Coffey and Brown in 1923 introduced the operation into this country. They made no attempt to follow the original operation of Jonnesco. In their first patient the main trunk of the sympa-
thetic was severed below the superior cervical ganglion and the superior cardiac nerve. The attacks ceased in the patient and there was no recurrence eight months post-operative. Later these men intended to remove the inferior cervical and the first thoracic ganglia but this proved unnecessary. The operation was labeled sympathectomy and following the first success, it was attempted in four more cases. Three of these obtained relief; one died. The investigators admitted that they had no sound physiological basis for their method but insisted that the results justified the procedure. A year later Coffey and Brown (30) suggested complete removal of the superior cervical ganglion as the operation of choice. They believed this procedure to be far superior to Jonnesco's original method.

The various operative procedures suggested may be summarized as follows; (73)

1. Resection of middle and lower cervical and upper thoracic ganglia on the left side
   Jonnesco, Tuffier.

2. Resection of all three ganglia of the left cervical sympathetic chain and upper thoracic ganglion, - Brunning, Kummel, Kapis.
3. Resection of the main trunk and the superior cardiac branch of the superior cervical ganglion.

4. Severing of the depressor vagi.

5. Severing of the depressor vagi and extirpation of the lower half of the left superior ganglion to the lower half of the middle ganglion.

6. Removal of the superior cervical ganglion by Coffey, King, and Brown.

7. Inferior cervico-thoracic ramisection. This operation was strongly advocated by Leriche et al. (73). They believed this to be the operation of choice pointing out that only the sensory fibers are interrupted and no motor fibers are cut by cutting the rami communicantes. As a further measure of assurance, they advocated a supra-stellate sympatheticectomy, but no ganglion should be removed.

8. Danielopolu (39) suggested resection of cervical sympathetic with section of fibers of cervical vagus and its intrathoracic branches, section of vertebral nerve, and section of communication of branches uniting inferior cervical ganglion and first thoracic nerve the sixth, seventh, eight cervical and first dorsal. If a
nerve is present which connects the superior laryngeal and the vagus, it must also be cut.

It is natural that these operations on the sympathetic system should be objected to on the grounds that severe damage might be done to the organism. Mackenzie and Danielopolu (38) both claiming that the procedure might produce irremediable injury to cardiac function or the myocardium.

Aside from the development of Horner's syndrome as described by Jonnesco (29) the results have not confirmed these fears. Jonnesco was unable to observe any damage clinically, nor was Cannon experimentally according to personal communication to Cutler and Fine (36). Montgomery removed the superior cervical ganglion in animals. In the cats, rats, and rabbits studied he could find no endocrine function in the sympathetic system which was essential to life. Cox et al. carefully trained and tested twenty dogs for resting and exercise heart rate, respiratory rate, blood pressure. Ten were subjected to coronary ligation and bilateral stellate ganglionectomy. At which time at least several of the upper dorsal ganglia were also removed. The dogs with stellate ganglia removed were not affected by this procedure as judged by above criteria of
### SUMMARY OF RESULTS WITH SYMPATHECTOMY (33)
120 cases from the literature

<table>
<thead>
<tr>
<th>GROUPS OF CASES</th>
<th>NUMBER OF CASES</th>
<th>OPERATIVE MORTALITY</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-A</td>
<td>9</td>
<td>0-0.0%</td>
<td>9-G</td>
</tr>
<tr>
<td>I-B</td>
<td>18</td>
<td>3-16.6%</td>
<td>8-G 5-1 2-N.R. L7 5 2 62.9%, 18.5%, 7.4%</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>29</td>
<td>2-6.9%</td>
<td>10-G 11-I 4-N.R. 8-? 1-2mo. 34.4%, 37.9%, 13.8% 1-8 days</td>
</tr>
<tr>
<td>A'</td>
<td>2</td>
<td>1-50%</td>
<td>1-G</td>
</tr>
<tr>
<td>A-B</td>
<td>0</td>
<td></td>
<td>3-I</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td></td>
<td>1-N.R.</td>
</tr>
<tr>
<td>A+B</td>
<td>4</td>
<td>0</td>
<td>2-I</td>
</tr>
<tr>
<td>B/C</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>A,B/C</td>
<td>13</td>
<td>1-7.6%</td>
<td>9-G 3-I 1-N.R. 22 19 6 41.5%, 35.8%, 11.2% 1-2wks.</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>4-7.5%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>12</td>
<td>0</td>
<td>9-G</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>0</td>
<td>2-I</td>
</tr>
<tr>
<td>V</td>
<td>26</td>
<td>0</td>
<td>26-I?</td>
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<tr>
<td>TOTAL</td>
<td>120</td>
<td>7-5.8%</td>
<td>48-G 52-I 10-N.R. 3-? 40.0%, 43.3%, 8.3%, 2.5%</td>
</tr>
</tbody>
</table>

**Key**
- **G-good**
- **I-incomplete relief**
- **N.R.-no relief**

**Group I**—Complete Jonesco
- A.-bilateral
- B.-unilateral, left or right

**Group II**—Operations upon cervical sympathetic chain
- A.—superior cervical ganglion procedures, either excision of ganglion or division of the superior cardiac nerve, or
- A'—of the ramus communicans, that is the main connecting trunk
- B—middle cervical ganglion procedures, either excision of ganglion or division of middle cardiac nerve, or of the ramus communicans below ganglion
- C—inferior cervical ganglion procedures, either excision of ganglion or division of inferior cardiac nerve, or of the ramus communicans below ganglion

**Group III**—Operations upon depressor nerve
**Group IV**—Combined operations, atypical, upon both vagus and sympathetic elements
**Group V**—Procedures aimed at posterior nerve roots themselves
cardiac function. When coronary ligation was done there was no change in cardiac output, heart rate, respiratory rate or blood pressure. Only one dog out of the group died of cardiac failure. In the control group in which coronary ligation was done but no ganglionectomy the effects were much more severe. Their pulse, respiration and blood pressure were unaffected, but resting cardiac output was elevated and five out of the ten dogs died of cardiac failure.

The results of the operations are difficult to interpret largely because of the variations in methods. Thus Leriche and Fontaine in a study of one hundred cases reported disappearance of the crisis in fifty-nine cases (62.7%), complete failure occurred in but six cases (6.4%), the rest received at least slight temporary relief. The operative mortality due to the operation was thirteen cases (13.8%). They attribute failures to either improper diagnosis, operations were the pain was due to intra-abdominal disease such as gall bladder, or a true tobacco angina, or a secondary to a poor choice of operative procedure.

Cutler (33) in 1927 reviewed one hundred and twenty cases from the literature and the results as he summarized them are shown on the previous page.
Richardson and White attempted removal of the superior cervical ganglion in five cases; in two cases removal of the cervical sympathetic chain; two cases removal of inferior cervical and first thoracic; one case sympathectomy. They had an operative mortality of twenty-five percent. The poorest results were obtained by superior ganglionectomy. In all they did not believe that the results justified the procedure.

White et al. in 1933 (128) summarized the reported cases subjected to one or other type of sympathectomy and reported as follows, "Of one hundred and eighteen cases subjected to upper cervical sympathectomy (Coffey and Brown) forty-eight percent had satisfactory results. The operative mortality was from seven and a half to twelve and a half percent for the simpler procedures and twenty percent for the complete Jonnesco.

Reid et al. (101) collected sixty-two cases from the literature. Fifty of these had operations on the depressor nerve and two had a combined operation. They felt that the results were published so soon after operation that it was unfair to draw any conclusions. The operation of choice according
to their interpretation was a cervico-thoracic sympathectomy.

Cutler and Levine state (84) "It seems to us that the results in all procedures enumerated and so frequently practiced failed to give a sufficiently satisfactory percentage of good results to let us feel that we are on the right track in dealing with this disorder. --- It is true also that the risk of major operation is something to be considered. We have convinced ourselves that figures for the various procedures on the sympathetic apparatus in treatment of angina pectoris are not sufficiently hopeful to justify continued minor perfection in technique already at hand. Certainly the changes brought about are only of the quantitative nature and complete relief has rarely been given." It would appear that the basis for consideration must be somewhere faulty."

Marvin reports that he has written to many authors who originally tried the operation and most of them report that they no longer employ the procedures.
ALCOHOL INJECTIONS

The failure of sympathectomy led investigators to seek a simpler surgical treatment. Mandl (118) in 1925 reported sixteen cases of severe angina which he treated by paravertebral injections of one-half of one percent novocaine. The results were excellent. There were no fatalities and no severe unyielding complications. The relief persisted for a long time. This led Swetlow (118) to introduce alcohol injections. His method consisted of locating a zone of hyperalgesia and in these dorsal segments he injected paravertebrally eighty-five percent alcohol. In his first series he reported eight cases with excellent results and no serious after effects.

White (125) modified the technique slightly. He first infiltrated with two c.c. of a two percent procaine solution around the trunks of the upper thoracic nerves as the emerge from the intervertebral foramin and give off their sympathetic rami. The needles are not moved, and as soon as the intercostal anaesthesia develops, proving that they are accurately placed, five c.c. of ninety-five percent alcohol is slowly injected.

The after effects of the procedure are few. In most cases after skin anaesthesia wears off hyperaesthesia develops in the intercostal spaces lasting
two to six weeks. The majority of cases thus treated show Horner's syndrome, and vasodilation with cessation of perspiration on the treated side. During the procedure, care must be taken to prevent pneumothorax. Smithwick warns that great care must be taken not to damage lungs or pleura and one must be sure that a large blood vessel or subarachnoid space is not entered. Intercostal neuralgia may be avoided by inserting the needle two to three centimeters deep to the intercostal nerves and having the patient lie on the abdomen.

As a whole results with this method have been good. In 1930 Swetlow was able to report twenty two cases in which eighteen had obtained some relief. In some cases the relief appeared to be permanent. White (125) was able to report a series of eighteen cases with failure in but 15.8% and no fatalities; 26.5% obtained marked relief. Schnabel reported one successful case.

The method is generally conceded to be superior to operative procedures. Thus Richardson and White (102) selected eight cases all with symptoms equal in severity to cases on which they had previously done operative procedures. All of them noted relief after alcohol injections. There were no lasting ill effects and no mortality. These men believe
paravertebral alcohol block to be superior to sympathectomy and suggest its use in obstinate angina pectoris which persists in spite of ample medical measures, and which makes life impossible, work miserable. Smithwick is in essential agreement with the above statement. He believes that experience and accuracy should offer relief in seventy-five to eighty percent of the cases.

In 1932 Outler (35) speaking of alcoholic injections and sympathectomies stated that in all about five hundred cases had been presented. About two hundred of these were worth considering and no one method had been done sufficiently to be able to properly evaluate it. He believed best results were obtained by removal of both cervical sympathetic chains.
Levine and Rosenblum (17) noted that in a patient with angina pectoris suspected of marked hyperthyroidism, extirpation of the thyroid showed a normal gland, yet clinically there was great improvement. This led them to wonder what would happen to a normal cardiac if the thyroid was removed. Blumgart et al. (17) had shown in previous experiments in patients with congestive heart failure and normal B.M.R. that the basal velocity of the blood flow was greatly diminished, on the other hand patients with low B.M.R. have also a lowered basal blood velocity flow, yet show no sign of congestive heart failure, evidently because diminished circulation is sufficient to meet diminished body demands. It was also noted that patients with hyperthyroidism and congestive failure showed remarkable improvement following thyroidectomy. From these facts it was reasoned if diminished blood flow be made sufficient for body needs then signs of cardiac failure should vanish.

Subtotal thyroidectomy was thus performed on three patients with congestive heart failure and one patient with angina pectoris. The patient with angina pectoris had a B.M.R. of plus twenty-five and
plus thirty percent. He was put on iodine until the B.M.R. dropped to plus ten percent. Pathologically and surgically the thyroid was diagnosed as normal. Post operatively the basal metabolic rate was minus five percent. The patient, formerly bedridden was so much improved that he could return to work.

As figures and facts began to accumulate thyroidectomy became the current fashion for angina pectoris. Return of symptoms in some of the early cases led Friedman and Blumgart (52) to warn all those who would attempt the operation to perform total thyroidectomy if permanent results were to be expected, and that X-ray and radium attempts to lower the B.M.R. were of no value.

Selection of patients proved to be a problem. This led Blumgart et al. (15) to issue the following suggestions.

1. Only those patients who are cardiac invalids and on whom all medical treatment has failed should be considered.

2. Decompensation should be reduced.

3. Pulmonary congestion predisposes to pneumonia and should be guarded against.
4. Patients whose conditions is slowly progressive are the best subjects.

5. Poor candidates are those with syphilitic heart disease, malignant hypertension, rheumatic or arteriosclerotic heart with short progressive history of failure.

6. Patients with pulmonary disease such as bronchiectasis are predisposed to pneumonia.

7. Recurrent attacks of coronary thrombosis and presence of renal insufficiency are contraindications.

8. If the B.M.R. is less than minus fifteen, results are usually unfavorable, and if less than minus twenty operation is contraindicated.

The best hypothetical patient would be an individual between twenty and fifty years of age with arteriosclerotic or rheumatic heart disease. The basal metabolism should be an average normal. There should be no evidence of bronchiectasis, severe renal insufficiency, acute rheumatic infection nor recent coronary thrombosis. He has suffered for several years. His condition has not become rapidly worse but he is incapacitated. He has attacks on
slight exertion but not while at rest.

Preoperatively (15) the cardiac condition should be treated with digitalis if necessary. All sedatives to be used post operatively should be tried preoperatively. Some suggest a pre and post-operative residency in the oxygen chamber (16). The nurses selected should be especially trained for complications. During the operation a medical advisor should be present. When surgery is half completed, the larynx should be inspected, if the recurrent laryngeal nerve is damaged, the operation should be stopped. Post operatively the patient must be watched carefully for complications. Bed rest should be maintained until the B.M.R. drops twenty points below the preoperative level. Thyroid is given as necessary to maintain the basal metabolic rate at minus twenty percent to minus twenty-five percent. Medical treatment should be continued as before operation and over exertion must be carefully avoided. (15) (16).

The surgical hazards to be guarded against are cardiac failure, bronchopneumonia, recurrent nerve injury, parathyroid insufficiency and incomplete removal of the gland (16) (41).
It is apparent that an operation of this magnitude would produce secondary effects. The obvious result is a myxedema, but this is guarded against by judicious administration of thyroid. There may be some cardiac enlargement, however the heart function is still adequate for the lowered B.M.R. If the basal metabolic rate is kept at a level not lower than a minus twenty-five, there is no mental change except for a slowed speech. There is no evidence of arteriosclerosis due to high blood cholersterol. There are no changes in renal function; there may be a slight drop in red blood cells and hemoglobin but not enough to require treatment. There is a lowering of the gastric hydrochloric acid but no anacidity (16). "Myxedema heart" in the sense of aggravating or precipitating attacks does not develop when hypothyroidism is produced by total ablation of the thyroid, if the patient's metabolism is maintained at about minus thirty (40).

Schnitker et al. (109) noted that the average decline of the B.M.R. was minus 22.8% in 9.9 weeks post-operatively. Administration of 0.015 grams of thyroid daily caused a return to normal capacity in three to four weeks. Cholesterol of the blood rose on an average to four hundred and four milligram
percent. In five percent of the patients the vital capacity decreased greatly but returned to normal within a week. The following changes in blood chemistry were noted:

1. Calcium and phosphorous fluctuated considerably but remained within normal limits.
2. The total protein dropped to a low normal; the albumin-globulin ratio remained unchanged.
3. Potassium remained relatively constant.
4. There was no significant change in sugar tolerance.
5. There was diminished vasomotor tone.
6. Patients seemed to have increased mental function, but were more sensitive, shy, and prone to worry.
7. Histological studies of the ductless glands of patients showed no change.

The output volume per minute and work of the heart were found to be greatly diminished. The velocity of the blood flow is also slowed. The findings obtained were in complete harmony with the conception that relief is due principally to reduction of the work of the heart. (109)
Early experiences puzzled workers in that it was noted that relief of pain occurred in patients subjected to thyroidectomy before there was a drop in the metabolic rate. Thus Levine and Eppinger (76) reported that in certain of their cases presenting congestive heart failure, the rate of blood flow was unaltered by thyroidectomy despite myxedema and improvement. Weinstein et al. showed that relief of pain cannot be attributed to changes in the amount of circulating thyroxin, for it appears before changes in metabolic rate can be detected and persists for days when the B.M.R. is maintained at normal with thyroxin, also when only one lobe of the thyroid gland is removed, relief occurs only on that side. This suggested that relief is due to injury to sympathetic nerves which later regenerate. By their study of three cases of hyperaesthesia and hyperalgesia following thyroidectomy, and by anatomical dissection of ten fetuses and six adults, Weinstein et al. concluded that the immediate relief of pain is due to injury to superior and middle cardiac nerves plexuses on the posterior surface of the thyroid and its vessels.

Blumgart (16) felt that the early relief of symptoms was due to interruption of nerves and their
pathways. These eventually return, permanent relief being due to the reduced B.M.R. which causes the oxygen supply necessary for heart muscle to be lessened and hence relief follows.

Bisgard suggested that cardiac benefit results from a change in the state of the vascular bed due to a changed relationship of the endocrines with removal of the thyroid. Cutler and Schnitker (37) however, disagree. They believe that in cases of angina pectoris relief following thyroidectomy comes thru a diminished efficiency of the adrenal secretion. This must produce clinical relief from pain by decreasing the sensitivity of the heart to the adrenalin effect, since it has been shown that thyroidectomy does not decrease the adrenalin output. Clinically these men found that in patients in whom adrenalin injections produced pain before operation, were not affected by the drug post-operatively.

Riseman et al. (103) maintained that clinical improvement was independent of any change in sensitivity to epinephrine and contrary to the demonstration of Cutler et al. (37), they could demonstrate no change in sensitivity to adrenalin as judged by heart rate, blood pressure, rate and depth of respiration, oxygen
consumption, and blood sugar. They do not however
mention alterations in pain response.

The results with thyroidectomy have been
variable depending largely on the operators and the
clinic. Thus Blumgart et al. (16) in 1935 reported
no deaths except for one woman past seventy in a
series of twenty-five cases. Eight patients had
no attacks in spite of activity from three to
eighteen months post-operative, and they required
no glyceryl trinitrate. Of the remaining seventeen,
five bedridden preoperatively have experienced
only occasional attacks since operation and are
capable of undertaking considerably more activity
in some cases even returning to remunerative occu­
pations. The average duration of moderate relief
is five to ten months. Exercise tolerance has
increased over one hundred percent. Two patients
were completely relieved for four to nine months.
Three patients after having striking relief have
had reoccurrences due to thyroid medication which
has been discontinued.

Cutler (34) the same year in a series of
thirty-one cases reported an immediate mortality
of six and a half percent, and a late mortality,
unrelated to operation of sixteen percent. As
for complications over nine percent developed parathyroid tetany and over seven percent had a recurrent laryngeal nerve paralysis. Excellent results followed in twelve cases, good results in four, and fair results in six cases.

After two and a half years Berlin (12) claimed no mortality in a series of sixty-two cases and relief in about seventy percent of his operations. Ochsner reported success in a case which had previously failed to respond to sympathectomy.

Dinnerstein (41) collected one hundred cases by questionnaire. His results are tabulated thus:

- Deaths - immediate: 3%
- Late - not related to operation: 15%
- Markedly improved: 51.2%
- No pain, no drugs, normal activity:
- Moderate improvement: 40.2%
- Mild attacks at irregular intervals
- No improvement: 8.5%

These results are essentially in agreement with the findings of Parsons (98), Mixter (88), Cutler and Schnitker (37).

Lately there has been some discontentment with the procedure. Clark et al. reported twenty-one total ablations, two of which were for angina, as a whole they were not satisfied with the results.
Clairborne and Huxthal were led to state, "Our results after operation have been fairly satisfactory in some cases. This appears to be owing in a large part to the fact that many of the patients selected for operation were not extremely ill. In some cases they might have been symptom free while on a regime of partial rest and inactivity. It is important to remember that the average patient is a good deal more careful in following instructions after operation than before. -- -- -- In following patients with angina pectoris after total thyroidectomy it has been obvious that amelioration of pain is a temporary affair. We have had to change the grading of results on several occasions because of favorable results at first and less satisfactory results later. -- -- -- The decrease in number of total thyroidectomies performed at present is indicative of a swing back from enthusiastic trial of a new procedure. Physicians caring for patients at home after total thyroidectomies are noting at times that the patients are in a condition similar to that present before operation. There are some patients on whom total thyroidectomy seems justifiable; however they are few in number."

Lyon and Harris in 1934 suggested a simpler procedure than thyroidectomy, ligation of the superior and inferior thyroid arteries on both sides. They
obtained good results with this procedure in five cases. Friedman (51) suggested the same method two years later. Week (123) attempted the method in two cases, one died and the other obtained no relief.
SURGICALLY PRODUCED CARDIAC BLOOD SUPPLY

The newest and probably the one requiring the most skill is the procedure advocated by Beck. Dr. Allan Moritz first pointed out to Beck the observations of C. H. Thorack who in 1903 noted in patients who had complete coronary occlusion the development of pericardial adhesions which furnished a blood supply to the heart (9). Beck then carried out experiments on one hundred and three dogs attempting to produce collateral heart circulation using adjacent muscles, omentum, and pericardial adhesions. He felt his animal work to be successful enough to attempt the procedure on humans. The first case was operated on February 13, 1935. In this case the pectoralis major muscle was sutured to the pericardium. The patient was reported well and working seven months later (10).

The basis of Beck's operation lies in the fact that the fat at the base of the heart contains blood vessels that form anastomosis between coronary arteries and other branches of the aorta, including internal mammary, pericardial, phrenic, intercostal and oesophageal. Normally the anastomosis are of no significance but in case of coronary occlusion they enlarge and attempt to form collateral circulation. It has
also been shown that adhesions to the heart carry a blood supply (9) (10).

The operation consists of grafting vascularized fat and muscle on the heart. Skeletal muscle from the chest wall is readily available, available fat lies in the mediastinum, subcutaneous fat may be used, and experimentally the omentum has been brought up thru the diaphragm. In early operations the costal cartilages on each side were removed and a large graft of each pectoralis muscle was applied to the heart. The epicardium was removed so that the graft came in contact with the coronary arteries. The pericardium was roughened so that pericordial fat receiving its blood supply from extra ordinary sources became attached to the myocardium (9) (10).

In later operations the approach was made only from the left side of the sternum and a graft from the left pectoralis major was used. Powdered beef bone was placed on the surface of the heart to produce a low grade inflammatory reaction between grafts and heart. Quinidin is used as a routine pre and post-operative along with the oxygen tent. In the first twelve attempts six died. In the last nine cases there has been no mortality. Thirteen patients were observed for five months or longer after operation. Almost all cases showed some relief. In a few cases the results were excellent (48).
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