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Treatment of cardiac pain, (angina pectoris)

Maxwell J. Harris
*University of Nebraska Medical Center*

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THE TREATMENT OF CARDIAC PAIN,

( ANGINA PECTORIS ).

Presented to the faculty of the
University of Nebraska, College of Medicine
as partial fulfilment of requirements for
the Degree of Doctor of medicine.

By, Maxwell J. Harris.

Omaha, Nebraska 1935.
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Our present civilization with its rapid, whirling progress has carried with it terrific stress and strain for the modern individual. It is little wonder, therefore, that medical observers have been startled by the increasing incidence of angina pectoris.

Women enjoying their new-found liberty, have found the sinister disease has risen in their ranks in proportion to the freedom gained.

Medical science has not lagged in its efforts to combat angina pectoris with efficient preventive medicine and treatment. This progress in the treatment of angina pectoris, from the time of Heberden to the present day is one of the most interesting and inspiring pageants in the records of medicine. In seeking the treatment, the scientists have had to probe into the possible cause of this symptom complex, in order to direct the proper therapeutic measures at the root of the disorder to better relieve the suffering of the afflicted individuals. Rapid advances have been made in recent years, and the feeling of hopeless despair among patients of the past, is losing much of its sting among the patients of the present.

The doctor, being in close personal contact with the individuals of his community, should feel it his duty to encourage the people to direct their lives at a more moderate pace in order to avoid the toll demanded by angina pectoris.

Paul D. White, in the following remarkable statement, clearly stresses this point and the present problem we are facing, "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. Almost certainly the most effective move that we can make is to call a halt on the world's mad rush of today.

The term "angina pectoris," originated by Heberden to describe the condition of distress in the chest, so aptly pictured by him, has been severely criticized in recent years by some writers. They base their objections on the grounds that the term emphasizes but one symptom in a symptom complex, and they question the belief that it is a disease entity at all. For this reason, I have used in the title of this thesis the term "cardiac pain, (angina pectoris)" only to call attention to this discussion. In the body of the paper, I will use the name "angina pectoris," as it is still supported by the best recent authorities as the proper term, and being in longer usage it is less confusing.

Willius suggests, that whenever possible the name of the etiologic disease should be used. Howes states, that while there is undoubtedly some foundation for this criticism, clinical and laboratory studies have supported the idea that angina pectoris, if not a distinct disease, is as much a clinical entity as asthma. Miller cites Parkinson in his contention, that if the term "sternal" or "cardiac pain" was more generally used, even discarding the term "angina pectoris," it would result in an earlier, more frequent, and more certain diagnosis of cardio-aortic disease. Brooks, P.D. and J.C. White agree with other notable writers that "angina pectoris" is quite
satisfactory.

In this paper, I have attempted to review the treatment of angina pectoris in the past, and to record the progress made up to the present time.

The therapy will be dealt with under subheadings, depending on the method of technique and the stage of the disease treated.
HISTORICAL SKETCH OF ANGINA PECTORIS
AND TREATMENT.

"Quiet, and warmth, and spirituous liquors, help to restore patients who are nearly exhausted and to dispel the effects of a fit when it does not soon go off."

Heberden - 1768

The syndrome, angina pectoris with its startling manifestations, must have called the attention of medical men long before the time of Heberden, but it remained for this keen eyed observer to name the condition he found, and to give us such a clear cut clinical description of the disease, that little has been added even to the present time.

Heberden's classical paper, "Some Account Of A Disorder Of The Breast", was read before the Royal College of Physicians in London, on July 21, 1768. In Part, he states, "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, of which I do not recollect any mention among the medical authors. The seat of it, and sense of strangling and anxiety with which it is attended may make it not improperly be called angina pectoris."

At this time, he reported that bleeding, vomits and other evacuations had not seemed to do any good. Spiritous liquors, rest and quiet accomplished very good results; but the most effective remedy he found to be the opiates.

Osler reports, that French writers have made attempts to claim the priority in the description of the disease for Rougnon, professor of medicine in the University of Besancon.
The claim is based on a letter addressed by Rougnon to M. Lor-ry, dated February 23, 1768, describing a case that was undoub-tedly angina pectoris, in the opinion of the reference author.

To Morgagni, rather than Rougnon, Osler gives credit for the first description of the syndrome. Some writers believe that Seneca, writing an account of the disease, he himself had, was the first to report it.

It is of interest to note that in 1776, John Hunter was convalescent from an attack of angina pectoris at Bath. He was visited by his friend and colleague, Edward Jenner. Jenner, by studying autopsy material, had suspected that angina pectoris was closely associated with disease of the coronary arteries of the heart. He wrote a letter to Heberden in which he diagnosted Hunter's condition and suggested for the first time that it was related to disease of the coronary vessels. Care was taken by these men to prevent Hunter from obtaining knowledge of this idea, for fear that he would feel that his illness was hopeless. At the time of Hunter's death, an autopsy disclosed coronary arteries that were calcified tubes and the aorta was dilated. Jenner announced his beliel in 1799.

These early observers were aware that mental strain would excite attacks of angina pectoris. Hunter often stated, "that his life was in the hands of any rascal who chose to annoy and tease him." He described colorfully the condition with which he was suffering, in terms that only one experiencing the distress could picture.

The Welsh physician, Parry, a contemporary of hunter, in 1799 recognized coronary sclerosis clinically. He first suggested clearly that it was the mechanical impediment to the free flow
of blood through the coronary vessels that resulted in ischemia of the heart muscle. Parry's work substantiated Jenner in his views on coronary disease being related to angina pectoris.

Hodgson, in 1815, called attention to the connection of sudden death to coronary disease.

One of the greatest advances in the understanding and treatment of angina pectoris was made in 1867 with the introduction of amyl nitrite by T. Lauder Brunton. The drug was brought to the attention of Brunton by the research work of Richardson and Gamgee, who had proved its vasodilator action. Brunton, because of the studies he had made of angina pectoris, was searching for just such an active drug, and proved its worth in the treatment of the disease. The discovery opened up a new field in the therapy of angina pectoris.

William Murrell, in 1879, introduced nitroglycerine, which proved very valuable. This drug and amyl nitrite are the two drugs most used to day to promote rapid coronary dilatation and relief of anginal spasm.

In 1883, Mathew Hay used sodium nitrite in the treatment of angina pectoris with favorable results.

Bradbury first used mannitol hexanitrate, in 1895, as a vasodilator.

The salts of caffeine and theobromine were first used therapeutically for cardiac symptoms by Askanazy in 1895, and were found to be of very definite value. It is an interesting reflection, in this connection, that in the early days of the treatment of angina pectoris, coffee and tea were used for relief. Caffeine, theobromine and their derivatives are very much in use today.
In 1896, Dock was the first investigator in America to describe coronary thrombosis, and, in 1912, Herrick definitely established the clinical description of the condition. This was an all important step, as it finally determined that coronary thrombosis and angina pectoris are closely related, and yet two separate and distinct syndromes.

Mackenzie, in 1914, emphasized the part played by the coronary arteries in angina pectoris, and called attention to exhaustion of the heart muscle as the possible cause of the attack.

Allbutt did not agree that coronary disease is the cause of angina, and in 1915 he expressed the opinion that the aorta was solely concerned. In recent years, his theory has been vigorously criticized.

Jonnesco, working in France in 1916, introduced the surgical approach in the treatment of angina pectoris, and in 1920 reported a cure of a case by resection of the left cervical sympathetic system. This opened an entirely new line of thought and action. Interestingly, this procedure was suggested, in 1899, by Franck of France, who had established relations between irritation of the cardio-aortic plexus and the production of the symptoms seen in angina pectoris.

In recent years, and at the present time, the study of the endocrine gland systems, and the action of the tissue extracts are unfolding vast possibilities in the treatment of angina pectoris.
PROPHYLACTIC TREATMENT OF ANGINA PECTORIS.

"The mechanism of angina pectoris is present in every individual. We therefore find the symptoms of angina pectoris occurring under a great variety of circumstances and presenting a great variety of modifications."

Mackenzie - 1923.

The prevention of angina pectoris, in the progressive countries of the world, is a problem that has been brought to the attention of clinicians in recent years. The rapid movement of the times has thrown great mental and physical strain on larger groups of individuals, who in former times were considered not so susceptible to this malady.

The incidence among women has noticeably increased. At the time Heberden studied the disease, he found three women patients in one-hundred cases. Now the proportion is one female to three males.

In former times, the disease was considered to be limited to a great extent to the intelligentsia; but recent studies have disclosed that the incidence is rising in the working classes. This is due undoubtedly to the greater strain of life. Then too, more accurate methods of diagnosis are employed today.

Now, as medical advisers, it is urgent that we should carefully investigate the young people coming under our care, select those, who may be grouped in the class of potential anginal sufferers when they reach middle life, and make definite efforts to direct their habits of living so that they might delay or avoid this calamity. It is the sensitive, intelligent, highly organized person, rather than the phlegmatic, insensitive, uneducated, that suffer from angina pectoris.
The Jewish people are very prone to it. People in more backward tropical countries are rarely effected.

White believes that the nervous sensitivity of the person is a factor as important as those causing coronary insufficiency. Alone, it is not enough probably, but the extra provoking factor may be very slight or not noticed at all. It has been recognized since the first description of the disease, that mental excitement undoubtedly is often the exciting cause of seizures.

The time of life at which the syndrome, angina pectoris, makes its appearance is in three-fourths of the cases past fifty years of age. Yet, not infrequently it develops in the forties, and more rarely in the thirties with or without luetic aortitis. Before the age of thirty years it is extremely rare, and then it occurs most often in individuals with rheumatic heart and marked aortic regurgitation.

A most interesting viewpoint is taken by Brooks, who lays great stress on the hereditary factor in angina pectoris. He has good cause for this belief, for even early clinicians noticed the familial tendency of the disease and the Arnold family was held up as an example. Osler states, that it may occur in several generations. It is an important thought to keep in mind while advising the care of young people in the home, as family physician.

Brooks emphasizes the prophylactic treatment to a greater extent than any other modern writer, and it is largely his plan that is followed under this heading.

The reason for this carefully planned regime must be cautiously explained to these young people, because making them extremely heart conscious and even neurotic is only complicat-
ing the problem.

The temperament of these individuals should be trained early, so that they will approach the difficulties of life more calmly, and avoid much of the nervous tension and irritability they might otherwise experience. Self control of their mental and physical being will reduce the incidence of exciting causes for attacks of angina pectoris, when they reach the dangerous age of middle and later life.

Healthful habits of living, regular and sufficient rest, and temperance in all things are important to form in the child's daily routine to be continued through life. Moderation in the use of alcohol and tobacco is especially urged. White remarks, that it is wise to omit tobacco, as it does in some people prepare the ground for attacks.

The life's career must be one that will protect the child of anginal parents against undue mental or physical fatigue. He must have time for healthful recreation and particularly the formation of a restful hobby that is a means of relaxation. It may be fishing, golf, trapshooting, or artistic occupation. Competitive athletics in college or later should not be entered, as it is undue work thrown on the heart muscle that must be avoided as much as possible. Good general outdoors exercise should be encouraged, but always short of excess. Older men, past the age of forty years, should be cautioned not to take up the sports of young men. Their activities should be suited to their age and physical condition.

Obesity should be prevented or corrected, especially in families with a tendency to excessive fat deposition and with a history of angina pectoris in the background. The diet should
be regulated so the person receives a well balanced food intake to meet all needs, with elimination of excess sweets, starches and fats.

If the individual indulges in too strenuous exercise, the appetite is increased and a habit of over-eating is established that will continue into middle life. Then excess fat will be deposited in the body as exercise is reduced. The heart then will have to pump against the increased resistance offered the blood flow in the capillary beds of the adipose tissue.

In connection with obesity, Brooks brings out, that any tendency toward endocrine unbalance, as in hypothyroidism or pituitary disfunction, producing abnormal fatty tissue, should be treated early. Thyroid extract may be used in small doses, from time to time; or iodine, its salts, or Lugol's solution given in occasional courses. He finds that these procedures help materially. It will be found later in this paper, under surgical treatment for angina pectoris, that actually a state of hypothyroidism is produced in the course of the disease to alleviate the symptoms. This is of course, under entirely different circumstances, and with a different therapeutic purpose in mind.

Hay and other medical investigators report, that hypoglycemia predisposes to anginal pain, because the heart muscle is not supplied with sufficient glucose for its metabolic needs and sofatigues more quickly. Any defect in the glycogen metabolism of the heart muscle may be a potent factor in the production of anginal pain. So, if a low blood sugar is found during examinations, it should be corrected to a proper level.
Infections should be carefully guarded against, and if contracted, should be diligently treated in children and adults of the suspected class. Respiratory and childhood diseases must be handled efficiently, and the convalescent rest period should be continued longer than in the normal individual. Osler emphatically states, that a number of cases of angina pectoris have followed influenza. With patients suffering from rheumatic fever the salicylates must be used to the point of saturation, as a protective and curative measure. Absolute bed rest, long after the symptoms have disappeared, must be enforced.

If foci of infection are suspected, they should promptly be sought out and eradicated. Miller, Smith and other men, interested in this possible factor in angina pectoris, point to hidden infectious areas of the body as causes of cardiac disease, including angina pectoris in particular.

Gout, diabetes and syphilis are important factors in the production of angina pectoris. Prophylactic measures should be instituted early, and the treatment of the active disease is urged as soon as the diagnosis can be made. These conditions will be discussed in their relation to angina pectoris under the heading of specific therapy.

By preventive measures and careful supervision in the early and adult life of the individuals in the anginal group, there is no question that materially the familial tendency toward cardio-vascular diseases may be lessened. Then too, they will have much more resistance against ordinary infections, which also may lead to pathological changes in the circulatory mechanism.
SPECIFIC TREATMENT OF ANGINA PECTORIS.

"A symptom so important that it has been practically regarded as a disease entity ever since it was given a name in 1768 by Heberden is angina pectoris". White, P. D. - 1931

The diagnosis of angina pectoris is not complete until exhaustive efforts have been made to find the causative factor or factors, so that proper and efficient treatment may be instituted. Brooks insists that the underlying pathology is basically concerned with the cause of death in angina pectoris, and that the symptoms, in themselves, are not lethal. The relief or cure of the pathological process may cure and alleviate the symptom complex; whereas, relief of the symptoms neither cures the disease, or eliminates its dangers.

The mechanism of angina pectoris is not definitely known, but from investigation it seems to be primarily dependent on absolute or relative insufficiency of the coronary circulation, producing anoxemia of the heart muscle. It is known that certain diseases contribute to a deficiency of the coronary circulation by damage produced in the vascular conducting system, or in the blood itself. Therefore, early recognition and control of the basic disease may prevent or cure angina pectoris in certain cases before extensive, permanent cardio-vascular damage is done.

In order to reach the seat of the disturbance, a careful and complete clinical study of the patient must be made, with special reference to the individuals habits, heredity, infections and nervous make-up.

Syphilis is recognized by all the modern writers as an important etiological factor in the production of chronic
cardio-vascular disease. Angina pectoris developing in men under the age of thirty-five is frequently found to be caused by syphilis. In order to avoid cardiac complications, the condition must be found early and treated vigorously. Regular Wassermann examinations of the blood and spinal fluid should be so spaced and prolonged, as to eliminate the danger of hidden disease continuing untreated. It has been found, that some degree of aortitis is usually present in all untreated syphilitic patients, even in children. When luetic aortitis is present in angina pectoris, it definitely adds to the gravity of the prognosis. A positive Wassermann reaction is found in all but 5 per cent of patients suffering from aortitis.

Marked aortic regurgitation with very low diastolic pressure causes poor coronary flow, because it is the diastolic pressure that normally maintains the circulation of the heart wall. When scar tissue, gumma or arterial closures have already developed in the aorta, coronary vessels, or in the myocardium, cure is not to be expected, although at times it does occur.

The exact way in which pain is produced is debatable, and the important ideas and theories that have been advanced will be discussed later.

The treatment of these cases must proceed cautiously. There is danger in initiating the treatment of cardiovascular syphilis with intravenous injections of arsphenamine, until the patient is well under the full effects of iodides, mercury, or bismuth. Severe reactions and sudden death, not clearly explained, have been the result in some instances by too vigorous treatment.
The luetic with angina pectoris is treated by Christian
17 along lines of care to avoid the reaction. He begins the treat-
ment with five drops of a saturated solution of potassium
iodide three times daily, increasing the dose by one drop a
day until the patient is receiving thirty drops three times a
day. Intramuscular injections of succinimide of mercury, 0.013-
0.026 grams, are given twice weekly. He finds the succinimide
of mercury is the most convenient form to use. After four in-
jections of mercury, the arsphenamine is begun. The starting
dose is 0.2 grams given intravenously, and if no bad effects
are recorded, at the end of five days a dose of 0.4 grams is
administered. This dosage is repeated at weekly intervals,
while the mercury and iodides are continued as above directed.
Then, when eight injections of arsphenamine are completed, a
period of four weeks is allowed for rest, and the course is re-
peated. He has obtained good results and with no bad effects
from the arsphenamine.

Hay has had good results from the use of large doses of pot-
26 assium iodide, 30-40 grains daily, accompanied, where possible,
by mercury imunctions. He finds the iodides are very valuable
at times in diminishing the nocturnal attacks in patients with
marked aortic regurgitation. The good effect on the circula-
tion in some cases by the action of the iodides is not yet sat-
sfactorily explained. Bismuth injections are used in place of
17 mercury by many practitioners, and with successful results.

Brooks has found that many early cases of angina pectoris,
10 caused by syphilis, can be cured by prompt and appropriate ther-
apy, or at least, benefited symptomatically.

Gout has long been associated as a factor in the etiology of
angina pectoris. Walshe mentions it in connection with angina, and warns that its removal should be attempted with care, in these cases. He reports that relief of gout is unquestionably sometimes followed by an increased severity of the cardiac affection. Brooks says that in a limited way, angina pectoris is caused by gout. The condition is distinguished by a history of excessive eating and improperly selected food. The ears show active trophi and characteristic lesions are found on the fingers and toes.

An important feature in gout, that relates it to the basic pathology in some cases of angina pectoris, is the chronic inflammation of the arteries, including the coronary system of the heart. Then too, cardiac hypertrophy may be associated with the arteriosclerosis produced. The manner in which the condition gout causes these changes is not certain. The relationship of the uric acid and salts to the lesions has not been demonstrated.

In 1862, Walshe wrote that the mustard pediluvum was useful, especially if the anginal patient was gouty.

The treatment advocated by Brooks is atophan and colchicine in large doses to tolerance. He finds best results with colchicine accompanied by a very strict anti-gout diet, and a copious fluid intake. Alkalies are very useful and hasten the response. He has had satisfactory results, but he finds it unusual to gain startling benefits, especially in long standing cases where permanent lesion and scars have developed to impede the coronary circulation.

Rheumatic fever has been an important and much overlooked disease contributing to angina pectoris.
It is one of the most frequent causes of fibroid heart and there is sufficient proof to the effect that fibrosis of the heart muscle is a frequent lesion in the symptomatic picture of angina pectoris. White contends, that mitral valvular disease rarely produces the pain of angina pectoris, and that it is even uncommon in aortic valvular lesions. Now, according to Brooks these are important factors, and these lesions may both be produced by rheumatic fever.

Brooks is most complete in dealing with the contributory diseases, and it is he who I am following most closely.

He recalls cases of angina pectoris developing during acute rheumatic fever, that were given considerable relief from the cardiac pain by the administration of large doses of the salicylates, 120-300 grains in twenty-four hours. Many patients will tolerate large doses by stomach, but there are many more who cannot, and rectal administration is used. He has found that the salicylates are of little value in treating chronic cases of rheumatic heart after angina has developed; but the drug should be tried.

The value of iodides in those cases originating from myocardial defects is an established clinical fact.

In young individuals with rheumatic fever, doses of sodium salicylate must be used to saturation, with alkalies given simultaneously to decrease the nausea. These children and young adults must have careful supervision and absolute bed rest for several weeks after the disappearance of the rheumatic symptoms, to reduce the possibility of cardiac damage.

Foci of infection must be eradicated if possible. Smith advises clearing up sites of chronic infection in the body, because he believes they may directly incite cardiac pat-
logy and angina pectoris. He has not been able to reach any
definite conclusion along this line. It is recognized, how­
ever, that fèci of infection are related to rheumatic fever
and thus, indirectly cause cardiac damage.

Diabetes mellitus has been cited as an important etiologi­
cal factor in some cases of angina pectoris by Osler, Beckman
and others. Smith has treated six severe cases of angina pect­
oris in non-diabetics with glucose and insulin, and has obtain­
ed almost complete relief of the cardiac pain. He feels that
anginal pain is linked up with deficient carbohydrate meta­
bolism in the heart muscle. This may account for many cases of
angina pectoris among the diabetic patients. More will be said
of this phase of treatment later in the paper.

Goodridge states, that the association of arteriosclerosis
with diabetes lends suspicion to the belief, that there is a
will defined relationship between the metabolic disturbance and
the disease of the arteries. When the coronary arteries become
sclerotic, the ground work is laid for angina pectoris, because
the blood supply of the heart muscle is limited. The heart,
therefore, cannot respond to the work thrown upon it. It is
important to establish correct, continuous dietary and insulin
regime for diabetics as soon as the diagnosis is made. It may
be that the possible damage to the circulatory system can be
reduced to a minimum.

Brooks reports one case of angina pectoris developing in
diphtheria, and the cardiac pain was quickly relieved by the
administration of diphtheria antitoxin. Diphtheria may involve
the media and intima of the coronary arteries in a necrotic and
hyperplastic process, which forms sclerotic changes in these
vessels. So early treatment of the disease with antitoxin should be accomplished in dosages that will prevent this damage. Complete rest for the heart is imperative.

Severe anemia, primary or secondary, may produce imperfect nutrition of the myocardium and a physiological state corresponding to coronary disease. Christian also reports that the defective blood supply to the heart muscle results, at times, in anginal pain during the cycles of pernicious anemia. He uses this as an illustration that an insufficient supply of blood to the heart wall is the basis for pain in angina pectoris. The anemic condition can be treated, so that the blood picture approaches normal or near normal, and the cardiac pain will disappear.

It is extremely important, therefore, that the cause of the cardiac pain is sought, and every effort made to correct it before irrepairable damage to the cardio-vascular system is established.
TREATMENT OF THE ATTACK IN ANGINA PECTORIS.

"To have any other malady is only to be sick; to have this is to be dying."

Seneca 43

Clinicians have probably never encountered so familiar a symptom complex, that has given rise to so much speculation as that of angina pectoris. The exact manner and mechanism of the attack has been a source of research and debate since the disease was called to the attention of the medical world by Heberden in 1768.

Mackenzie's descriptive definition of angina pectoris is concise, and yet complete and is quoted as follows: "Angina pectoris is a condition in which a series of symptoms are produced by the heart, of which pain is the most prominent. In its most characteristic form it occurs in "attacks", the patient being seized with pain, at first slight and ill-defined, but more or less speedily attaining a degree of great severity. The pain usually lasts a few seconds or a few minutes, generally passing off completely, but sometimes lingering for hours. Other symptoms may be present, such as a constriction across the chest, which sometimes precedes the pain, a sense of great depression, pallor in some, flushing in others, or an increasing flow of saliva. The pain is always felt in definite regions, generally limited to the front of the chest and arms, most frequently on the left side. It may also be felt along the jaws, in the neck, and behind the ears."

Radiation of the pain varies. Usually it begins in the region of the base of the heart; sometimes it remains here and is described as a grinding, crunching, vice-like, tearing sensation.
in the chest under the upper part of the sternum. Usually it radiates down the left arm in the distribution of the ulnar nerve. Much less often it is the right arm or right side of the neck which is involved. Following the attack, zones of hyperaesthesia may persist, which may be mapped out. At times, pressure on these areas may precipitate another attack. In severe attacks the patient has a feeling of impending death.

White reports, that the sensation described as pain, is often related as a pressing, choking or strangling feeling, acute, but not knife like. Infrequently it is burning in character. Dyspnea is not a very common finding in these cases.

Heberden, who first described the disease, keenly noted the exciting factors. He observed that those seized by an attack were usually walking after a meal and experienced a painful, disagreeable sensation in the breast, which seemed as if it would take their life away. The moment that the affected person stood still, all this distress vanished. Rest, therefore, is one of the cardinal steps in the treatment and must not be neglected. It will be shown, that complete physical and mental relaxation must be induced, and some of the most important medications for terminating the seizures have this useful action.

In other respects, the patients are perfectly well and have no shortness of breath at the beginning of the disorder. But, when the condition had continued some months, the attacks were not relieved so soon by standing still and would even come on while the person was lying down. In a few severe cases the pain be incited by the motion of a conveyance, swallowing, coughing, straining at stool, speaking or by disturbance of the mind.
He found that men past the age of fifty years, who were stocky of build and were inclined to become obese, seemed to be most often afflicted with angina pectoris. White gives additional exciting causes as sudden changes of temperature, dreams, or unknown factors during absolute rest, but the attacks most often are produced by physical exertion. Peculiar nocturnal seizures are experienced by some patients, waking them out of deep sleep.

The fascinating, yet baffling problem of angina pectoris has been the possible mechanism that will bring about the painful symptoms. The response of the patient to therapeutic measures will be found, all along, to be used, more or less, as an indication of the cause of anginal attacks. Heberden made this statement, "What the particular mischief is, which is referred to these different parts of the sternum, it is not easy to guess, and I have had no opportunity of knowing with certainty. It may be a strong cramp, or an ulcer, or possibly both." He felt that it possibly was a convulsion or spasm involving the part effected, because of the sudden onset and leaving. Bleeding, vomits and other evacuations, he found did little good. Whereas, rest, warmth and spiritous liquors, such as wine and brandy, caused the spell to disappear quickly, and the patient was relieved. He learned that angina pectoris developing during the night could often be avoided by spiritous drinks, and best of all, by the opiates. The patient was given ten, fifteen, or twenty drops of tinctura thebaica, just before lying down. They became quiet and were mentally undisturbed, under treatment. Now, the therapeutic measures he used were known to have a sedative action and to dispel cramps and spasms. The relief
afforded by a change in the position of the head and body was noticed. The disease might continue a number of years without disordered the health. The pulse was not always disturbed and Heberden surmised that the heart was not effected by it. He did not see autopsies on the cases he reported in his initial paper, but it was largely from his work that the spasmodic theory arose. The angina pain was thought to be due to a spasm of the heart.

Alcohol is still a very useful drug in the treatment of the anginal syndrome. Beckman believes that we should not overlook the virtue of this drug, for it sometimes brings about prompt relief from the attack. Sometimes, it is effective when the nitrites have failed. Large doses are advocated by this writer, one to three ounces of good whiskey or brandy may be administered.

The opiates are, today, some of the most important drugs we have for combating angina pectoris. Brooks says that morphine is the most certain drug we have for relief. Its action is not as rapid as the nitrites, but if the nitrites fail to relieve, use it. This writer reports, that he has never had a true case of angina pectoris develop the drug habit. He finds that ½ gr. by mouth, or better, by hypodermic injection, will abort an attack. This is one disease, he feels, that in selected cases, morphine may be supplied for self administration, or by some one in the family, because the suffering is so great. He especially advocates this for patients living long distances away.

It is absolutely necessary to relieve and quiet the patient. When other measures failed in former times, ether or chloroform were used as anesthetics to bring relief. They are rarely used
Walshe said, in 1862, that the theory of cardiac spasm was still being disputed. This author recalls, that Parry and Stokes from their clinical observations, considered a temporary increase of weakness in an already weakened heart muscle, as the essential element of the anginal paroxysm. While he concluded, that the seizure was due, perhaps, to neurotic factors, because of the sudden advent and departure of the attacks; from the character of the attacks while present; the perfect ease experienced by the patient in the intervals; the impossibility of assigning any special anatomical characteristics to the affection; and the type of treatment that proves beneficial.

The treatment that Walshe instituted in caring for his cases was, in principle, not unlike that used by Heberden. He records that during the fit, sedatives and stimulant antispasmodics are the medicines essentially to be trusted. Opium given, according to the severity of the attack, in the form of laudanum, 40 to 60 drops, or the liquor opium sedatives may be used in severe cases. Brandy used at the same time as the opium was effective. Ether or aromatic spirits of ammonia in dosages of \( \frac{1}{2} \) to 1 drachm may be used repeatedly. He found musk, camphor, and belladonna of very inferior importance. Sometimes, added relief was obtained by mustard poultices, or clothes wet with strong liquor of ammonia being applied to the precordial surface and the dorsal spine. An electro-galvanic current is somewhat successfully used in the serious, quickly recurring paroxysms, which seemed indisposed to yield to the ordinary sedative management. He warns, that care be taken so that the
muscles would not become exhausted.

Brooks finds occasionally great relief is experienced by a hot water or clothes applied to the precordial region and held firmly. Sometimes, too, applications of oil of mustard or menthol ointment over the anterior surface of the chest is helpful. Electrical currents are rarely used today, and afford indifferent results when tried.

Under special circumstances, if the patient is found to be subject to undoubted athenic plethora, and if the heart is found well nourished, the withdrawal of blood from a vein, or cupping between the shoulder blades, is clearly indicated, Walshe believed.

If the patient has eaten a large meal shortly before the seizure, it should be removed by an emetic of sulfate of zinc. Hay finds, in the less severe attacks, flatulence may be a distressing symptom. It is relieved generally by a mouthful of brandy or a strong carminative. Partridge finds it helpful to empty the bowels with an enema and withhold all food temporarily.

White contends that actual tetanic spasm of the heart muscle is not the cause, because the heart continues to contract regularly and fully, generally with an increased rate and blood pressure.

The historical section records that, in 1799, Jenner reported his belief that the disease of the coronary arteries was associated with angina pectoris. This was a great incentive to the study of the pathological anatomy and physiology connected with the disease.

In 1867, Brunton made the important discovery of the thera-
peutic use of amyl nitrite in the treatment of angina pectoris. During his experimentation, he found that as the blood pressure rose, in the attack of angina, severe pain came on in the heart, and when the pressure fell the pain disappeared. Quoting from his works, he says, "It was, therefore, natural to look upon pressure as the cause, and my opinion was confirmed by the effects of bleeding. Each bleeding prevented an attack."

"So the pathology seemed clear, and the next question was how to treat it. The remedy wanted was one which would dilate the vessels, and this, the researches of Richardson and Gamgee supplied. Nitrite of amyl they had shown to possess the very power which I desired, and thus their experiments on the pharmacology of the drug and my observations on the pathology of the disease, united, led to successful therapeutics."

He administered the drug and the pain quickly disappeared. In other hands, he writes, it was usually successful, but once in a while it failed. Then in cases where there was no favorable response, the argument to prove that angina pectoris does not always depend on excessive blood pressure was used, he says. He believed the failures were due to the use of old stocks of the drug, that had lost its therapeutic value. Further, he says, that while angina seems to depend on the spasmodic contraction of the vessels generally, it may be that local spasm of the coronary vessels may cause pain or disturbance of function.

Later, he reported, that when the drug was inhaled it caused a very rapid dilatation of the blood vessels and a great fall in blood pressure. Due to this fall in the pressure the load on the heart was lessened, when it is unable to overcome the resistance which is opposed to it. He found the transient
action of the drug to be the greatest difficulty with it.

Brooks states, that the discovery of amyl nitrite for use in angina pectoris was one of the greatest advances made in the treatment of the disease.

Murrell, in 1879, introduced the drug nitroglycerine into the therapy of angina pectoris. This drug was found to be very effective, but had a tendency to produce a more persistent headache. The full action of the drug required six to seven minutes, while amyl nitrite acted in fifteen to twenty seconds, but the therapeutic effect of the newer drug was longer. Murrell advised that it was almost impossible to standardize the dosage, and that it was best to begin with 2/100 of a grain and gradually increase it. He found that prompt relief was given.

Amyl nitrite and nitroglycerine are the two most useful drugs we have to day for combating the pain of angina pectoris and terminating the attack, in the opinion of most modern clinicians. Amyl nitrite is dispensed in ampules containing 2 to 3 minims. When the seizure is felt coming on, the patient crushes the ampule in a handkerchief and inhales the vapor. Nitroglycerine is carried in tablet form containing 1/100 of a grain. The tablet is allowed to dissolve under the tongue or is swallowed. It has the advantage of being cheaper, more easily carried, and is effective enough, without being disagreeable. If no relief in five minutes, the dose may be repeated, even every five minutes for four to five doses without bad effects.

Christian finds that some patients are very susceptible to nitroglycerine and even small doses give them flushing of the neck and face, pounding in the head and headache. He advises small doses, 1/200 to 1/250 grain, and to remove from under
tongue at the first feeling of flushing. He feels, that amyl nitrite is no more effective than nitroglycerine and so prefers the later, as it is more convenient to carry. It is well to see that the drug is fresh. If the tablet will easily crush between the fingers, it will dissolve readily, so is satisfactory to use. Old tablets lose their potency.

Brooks prefers nitroglycerine given in the form of spirits of glonoin, one to three drops in a little water. He tells the patients to carry a dose already mixed with water in a vial, as it is more handy and just as effective. The intravenous administration of nitroglycerine is only slightly more rapid and impractical for the patient.

Prodger and Ayman declare, that in some cases nitroglycerine is a dangerous drug. In one-hundred and ten cases, four patients suffered alarming reactions from therapeutic doses. Severe constitutional symptoms developed with prespiration, weakness, restlessness, anxiety, and pallor. Each one appeared to be near collapse. The blood pressure in two became so low that it could not be recorded, and the pulse disappeared. Epinephrine revived them. A complete heart block developed in one case, and in another, the course of a coronary thrombosis was thought to be unfavorably influenced. They believe careful supervision of the patient is advisable when the first dose is administered, to watch for possible idiosyncrasy. A small initial dose of 1/200 to 1/300 is recommended.

Burgess enthusiastically reports, that nothing excels the nitrites for the relief of pain in angina pectoris. The fall of blood pressure, he contends, is not the cause for the relief; but it is the dilatation of the coronary vessels and the increased flow of blood through them, that relieves the ische-
ia of the heart muscle and stops the pain. The distress was relieved by both amyl nitrite and nitroglycerine, quite independent of the variations in blood pressure.

It is interesting to note, in connection with the pressure of the blood and the promotion of increased cardiac circulation, Brooks cites the work of Danzer, who introduced a hemostatic method that was tried on a limited number of angina cases with relief of some attacks. The method is often of great benefit in cases of cardiac collapse. Danzer places four blood pressure cuffs, one on each extremity, and the pressure is supplied from a central distributing point. It stops arterial flow in all the limbs at the same time, and seems to afford great benefit in cases with general collapse. It also appears to offer considerable relief in attacks of angina, which do not subside under the more usual methods of treatment.

Mackenzie advanced the theory that coronary disease is related to angina pectoris, in that a varying degree of constriction of the coronary arteries exist, plus activity on the part of the person to speed up the action of the heart muscle, so that insufficient blood reaches it to meet the demand thrown upon it. The exhaustion of the heart muscle is the condition necessary for the production of pain, he believes. The more the heart muscle is damaged, the earlier it fatigues.

He classifies angina pectoris into two groups, primary and secondary. The primary group includes those patients whose hearts are affected by organic disease and cannot be cured. The secondary group are curable, it being a reflex process, and with the removal of the cause, the attacks disappear. White says it is a great mistake to separate angina pectoris into true and false,
or into primary and secondary groups. He says it is always a real and not an imaginary symptom, it being often impossible to tell if there is underlying coronary pathology or not. He believes it is better to speak of light, moderate or severe angina pectoris; according to the degree and frequency of the attacks, and the determination of the presence or absence of organic cardiac disease.

Lewis presents a theory that is quite similar. He suggests, that anginal pain is a result of a relative ischemia of the heart muscle. This view does not ascribe the distress to a simple mechanical cause, but recognizes that it may be provoked in several distinct ways. The result is, that the blood supply is inadequate for the work done by the heart.

In 1915, Allbutt refuted the theory that coronary disease is the cause of angina pectoris, and was of the opinion that pathological changes in the aorta was solely concerned. He believed that irritation of the nerve endings in the aorta was the cause of the painful seizures. This idea for a time was given widespread recognition, but in following years attention has been again directed to the coronary circulation.

The recent statement of Keefer and Resnick is to the effect, that angina pectoris is always due to anoxemia of the myocardium; that is, the attack of pain occurs when the oxygen supply to the heart muscle is inadequate to meet the demand.

In connection with this last theory, Boothby, cited by Beckman and also read as a reference, has found advantage in the use of oxygen for short periods at the time of the attack. He uses it, especially, in cases where the seizures of angina come on while the patient is at rest. The patient is instruct-
ed in the manipulation of the apparatus, to be used as he needs relief.

The idea that nutritional disorders of the heart muscle is a probable cause for the pain in angina pectoris, has been advanced by Hay and Smith. Under the section on continuous treatment, this new means of therapy will be discussed further.

White expresses the opinion held by most clinicians today, when he says that the mechanism of pain in angina pectoris is unknown, but it appears to be primarily, an absolute or relative insufficiency of the coronary circulation, giving rise to myocardial anoxemia.

Spasm of the coronary arteries may play a part in the etiology of angina pectoris. The sclerotic changes, often found in the smaller vessels at autopsy, tend to narrow the vessels mechanically, but they also may cause a tendency to increased arterial tone and spasm. The fact that the nitrites are not hypnotics, but only relieve the distress through vasodilator action on the coronary vessels and aorta, lends strength to the idea of local arterial spasm. White maintains, that spasm of the coronary arteries as a constant cause of the attacks seems unlikely, for he finds in some cases, that the arteries are hard and cannot contract. He further states, that in some, arterial spasm might be the cause. It is probably a combination of factors, and the nervous sensitivity of the individual has an important bearing on the subject.

The nocturnal attacks, occurring while the patient is asleep, may be due in some to dreams that lead to excitement and tachycardia. In others, it may be a fall in blood pressure, or some arrhythmia that precipitates the pain.
Sometimes, the patient with nocturnal spells finds that sitting up in bed or in a chair may help. The change in position, in some manner, often causes the distress to rapidly fade away. Brooks writes, that Dover's powders or opium, taken at bed time, are useful, and may be used for long periods of time without bad effect or habit. Codeine is rather less certain in its action. Hay advises, that opium and chloral be used in full doses for effective protection of the night rest. The nitrites, of course, should be kept handy for use at all times.

Certain cases of angina pectoris, perhaps, are incited by lack of proper cardiac tone, or failure in conductivity, referable to myocardial defects. In these cases, associated with acute heart failure, large doses of digitalis, given intravenously, may be a life saving measure.

Strychnine is useful where the myocardial lesions have resulted in a depressed muscle irritability. Mackenzie finds the use of strychnine, oil of camphor and caffeine sodio benzoate, in his experience with patients, to be of little benefit.

For feeble, weak heart sounds, Partridge finds caffeine sodio benzoate, given intravenously to whip up the heart, when it is in a condition of initial shock, is quite beneficial. He also recommends, that adrenalin, in dosage of 1 to 3 cc. of a 1/1000 solution, be injected directly into the heart muscle as a life saving measure in extreme collapse. It is only to be used in an extreme emergency in anginal cases.

After the acute attack has subsided, it is important that the patient be kept for a time in absolute rest. The reason for the enforced rest, is to protect against the possibility of a second attack following soon after the first, and the danger of
favoring coronary thrombosis. Most anginal patients are ambulatory, and some will not rest properly. In these cases it is wise to use a hypnotic such as chloral hydrate, allonal, adalin or other like drug to insure the patient relaxation.

In treating cases of angina pectoris, no matter how mild, it is always necessary to keep in mind the uncertainty of the patient's life in this condition. So, a guarded prognosis is justified.

Christian says, that the attack is really a warning sign and probably not harmful in its self. Other writers disagree with this idea, because so often the patient dies during a sudden attack, as observed by Heberden. White makes the following statement on the death of anginal patients, quoted here, "Patients frequently die suddenly during attacks; the mechanism of which is not understood; for it is not the more gradual death usual in coronary thrombosis, more is it apparently a state of vasomotor shock or disturbance of rhythm. A sudden cardiac standstill, a reflex phenomenon resulting from the shock of the angina pectoris, would best explain such cardiac deaths." He finds that an exact forecast of the fate of the patient cannot be given even in mild cases. They may live many years and be quite comfortable between attacks, or they may suffer a terminal coronary thrombosis within a few days or a few weeks.

So, in administering treatment to cases of angina pectoris during the attack, it is imperative that we recognize the condition and relieve it as promptly as possible. Each seizure must be considered by the physician as a potential threat to the life of the patient regardless of the mildness of the
paroxysm. Each attack lessens the resistance of the heart, and breaks down the muscle reserve. 10

It is a safe and reasonable procedure, in any suspected attack of angina pectoris, to treat the case first and diagnose later.
ASSOCIATED PATHOLOGY AND DIAGNOSTIC PROCEDURES
IN ANGINA PECTORIS.

"The life of him who has had an unmistakable attack of angina is not insurably safe for an hour. And yet existence may be protracted for years."

Walshe - 1862.

The pathological anatomy associated with angina pectoris is as varied as the theories arising from the clinical manifestations of the disease itself. It is extremely important, therefore, that an attempt be made to visualize the possible organic lesions in any given case, so that proper therapeutic measures might be applied.

Christian has found at autopsy, that the great majority of the cases, who have suffered anginal attacks in life, show coronary disease. Usually the lesions consist of atherosclerotic changes with calcification and narrowing of the lumen of the vessels. White finds that 95 per cent of the cases have coronary disease, usually involving the descending branch of the left coronary artery. But, on the other hand, he often finds extensive aortic and coronary arterial lesions, without any evidence of angina pectoris during life. Brooks reports, that in a few rare cases no visible pathology may be found to account for the history of anginal attacks. Christian further relates, that the atherosclerotic changes may be widespread, or only limited to one branch of the coronary arteries supplying blood to a portion of the ventricle. The myocardium will show little evidence of disease, as a rule. There may be, in some cases, patchy fibrosis with
cardiac hypertrophy. In the later respect, rheumatic fever infection is an important contributing factor. The myocardium, endocardium and blood vessel walls are involved by the inflammatory lesions called Aschoff bodies. Scarring is produced, and the contracting fibrous tissue distorts the valves and weakens the musculature of the heart.

Aortitis is not uncommonly found; sometimes of luetic origin, but may be due to some other infectious condition. The aorta, in its ascending and transverse parts, is most frequently effected in syphilitic infections producing anginal attacks. The diseased portion is usually dilated and may show aneurysmal pouchings. Perhaps, the aortic ring is dilated so that it tends to obstruct the openings of the coronary vessels. The intima is early effected and whitish areas of irregular shape are intermingled with patches of fatty degeneration. The elastic fibers are fragmented and granular, often much reduced in numbers. Finally, the lumen of the smaller vessels, as in the coronary system, is greatly reduced or entirely obliterated by new formed tissue. The mouths of the coronary vessels are frequently surrounded by a raised ring of hyperplastic tissue, and the openings may be reduced to pin-point size.

The aortic valves are involved in about half the cases of angina associated with syphilis, so that regurgitation is produced by the dilatation of the aortic ring or by fibrotic changes in the base of the valve cusps.

Syphilitic myocarditis accompanied by scar tissue formation in the walls of the heart, between the muscle fibers or in the walls of the blood vessels, limits the nutrition of the cardiac musculature.
Diagnostic procedures:— The diagnosis of angina pectoris is not difficult, as a rule, because of the striking group of symptoms associated with the seizure.

White says, there are no real signs of angina pectoris, as it is really a symptom that is dependent on a disturbance of function, with or without clinical evidence of organic disease. He finds, that about one-fourth of all cases show an apparently normal heart by all methods of examination.

Brooks states, that most cases of angina pectoris are almost wholly lacking in definite evidence of cardiac disease. In such instances, the syndrome is almost exclusively only a symptomatic picture. Yet, these cases are all subject to the same likelihood of sudden death, as those in which organic disease is found. The absence of physical findings does not exclude grave circulatory defects. So, it is best to treat, regardless of positive physical findings, in suspected cases.

Graves claims, that unlike most diseases, angina pectoris does not respond to any of the ordinary diagnostic methods or laboratory procedures. He finds them indefinite and useless. Recognition of the syndrome rests, in his opinion, on a group of symptoms mostly subjective in origin.

Amyl nitrite and nitroglycerine, as well as being our most useful drugs for relief of the painful symptoms of angina pectoris, are quite valuable for temporary diagnostic purposes. For example, if the symptoms are those of a severe anginal attack and the drugs give no relief, it is well to suspect coronary thrombosis. This test depends on the subjective symptoms and their possible alteration. If the seizure lasts for an hour or more, the diagnosis is certainly not angina pectoris,
but is most probably coronary occlusion. Then too, angina pectoris, must be differentiated from the long continued heart ache of neurocirculatory asthenia and heart strain, from the sharp pain of acute pericarditis, and from pain of pleural or abdominal origin, the nature of which is revealed by signs of pleuritis or of disease below the diaphragm.

Rarely atypical angina pectoris, especially when located solely or primarily in the arm, neck, or upper abdomen, particularly on the right side, may be difficult or impossible to identify, but careful study and continued observation will finally tell the story.

The electrocardiographic study of angina pectoris is making real progress, and is becoming an important means of bringing out of obscurity the mechanism and cause of this sinister disease.

White believes, that the most valuable evidence of underlying coronary disease is furnished by this means of examination. He found intraventricular block in 13 per cent of three-hundred and ninety-five cases examined. The auriculoventricular block is found in less than 4 per cent of the cases.

Changes in T waves, usually with inversion in Lead I, Lead II or both, are commonly seen. All these variations are seen more often after a complicating coronary thrombosis.

Christian refers to the work of Feil and Siegel, who studied four cases of angina pectoris, without infarction, and made records during the attacks. In all four, they found inversion of the ST portion of the curve.

More recently, Parkinson and Bedford have made electrocardiographic studies during brief attacks of angina pectoris. They
feel that the examination is valuable for detecting permanent lesions of the heart, and are able to determine if coronary thrombosis has occurred. They found that during the paroxysms of anginal pain, the ventricular deflections were modified. The modifications disappeared with the distress. These transitory changes included a depression of the R-T complex, and an diminution in the amplitude, or inversion of the T waves in one or more leads. The changes closely resembled, but were not as marked as those which followed cardiac infarction in the early stages. They believe, that it is significant, that both the transient anginal pain and cardiac infarction can effect the electrocardiographic records in a similar manner. It further seems, not unreasonable to infer, that the mechanism underlying the changes recorded, is essentially the same in both cases, that is, an ischemia of a part of the cardiac muscle. So, this new work tends to support the theory of coronary arterial involvement in the production of the anginal syndrome. These observers do not state that the electrocardiographic record is always modified.

It is by such observations, as the above, that medical men can direct the treatment of angina pectoris on a rational basis, and with increased confidence of gaining results.

Katz, Hamburger and Lev have used a rather dangerous form of diagnostic procedure, the use of epinephrine to induce attacks. They used 1 cc. of a 1/1000 dilution of epinephrine injected subcutaneously, and were able to produce attacks in cases of angina pectoris, but not in the control cases. Then electrocardiographic records were made of the seizures. Quoting from their article, they say, "Epinephrine as a test for angina pectoris was found to be unreliable in regard to both the
symptoms produced and the electrocardiographic changes. This unreliability makes the test of little value, particularly in view of the severe reactions sometimes encountered." We shall see later, under the heading of operative treatment, just how dangerous this procedure is and the possible action of the drug in these cases.
GENERAL AND CONTINUOUS TREATMENT
OF ANGINA PECTORIS.

"Rest as a means of treatment in this complex receives, perhaps, its most logical justification on a physical basis."

Brooks - 1929

In recent years, better prospects of a longer and more comfortable life have been offered patients afflicted with angina pectoris. Many medical men are becoming more optimistic in their views concerning the security of well treated patients. Hart especially urges a more happy attitude in the care of these 25 cases. Yet the ugly truth remains, that the course in angina pectoris is notoriously uncertain.

It is imperative that the life of the suffer be conducted and directed in such a manner that he will receive all the protection possible to insure his well-being.

Walshe has said, "angina belongs essentially to the class of recurrent affections. The fact of one seizure having taken place is a reason why others should follow." After the onset of the initial attack, the nervous mechanism seems to become more sensitized, so that an arc of abnormal distribution of stimuli becomes established. The associated areas of the spinal cord are more irritable, which under normal conditions are not particularly irritable. The sensitive, nervous condition of most patients appears significant in determining not only the occurrence, but, also, the continuation of the anginal syndrome.

Rest is absolutely essential in the treatment of this disease, and sleep is the acme of the rest therapy. The more absolute the mental and physical relaxation is maintained at the outset, the better are the results to be expected.
Most cases of angina pectoris are ambulatory between attacks, but if it is at all possible to sell the patient the value of resting his heart muscle, he will surely profit by it. The rest should be so controlled that the individual can avoid all bodily motions, or other activity that might excite attacks. This treatment should be continued until the patient can sit up without any distress; then activity is gradually reassumed.

Emotional and nervous rest are just as important as bodily relaxation. The patient must be relieved of all business and personal worries, if possible. The environment of the sick room should be such, as to encourage the patient to endure the restrictions placed upon him.

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

There is no specific diet for the anginal patient, unless the condition is associated with diabetes, gout, nephritis or other complicating ailment. Most writers agree that the diet is important in controlling possible etiological factors. Walshe noticed that these patients were more comfortable on an easily digestible, bland diet of moderate proportions. Preston also advises care in the management of the diet.

Care should be taken that gastric irritation, distention and intestinal flatulence by food or drink be avoided, because some cases suffer paroxysms definitely excited by this type of reflex stimulation. Irritative lesion of the gastrointestinal tract, as duodenal ulcers, chronic appendicitis, colitis and
gall-bladder disease may be closely confused with attacks of angina pectoris. It has been shown that these conditions, not properly cared for by diet or other therapeutic measures, may incite anginal distress. 11, 38

The selection of food should be made with regard to the patient's appetite, in order that he will take sufficient nourishment. The feedings should be small, and if a large meal is desired, it should be served at noon. Coffee and tea, in moderate amounts can be encouraged, unless they have a bad effect, because of the relative vasodilator effect on the coronary arteries by the caffeine contained may be helpful. Brooks warns that it is unwise to allow the patient to lie down after he has taken enough food to distend the gastrointestinal tract to the usual degree. Many severe seizures are caused in this way. 10

It was early recognized that anginal individuals must live anginal lives. Moderation should be practiced in all things, if the patient hopes for any security. They must adjust themselves to meet the problems of life with a more even tempered attitude and avoid excitement. 10

The use of tobacco and over indulgence in alcoholic drinks should be abolished, because the attacks of distress are often increased in frequency and severity by these drugs. 11, 58, 47, 39.

Attacks of the most severe nature may be precipitated by coitus or even mild sexual excitement. The patient should be carefully advised to use great discretion in this respect. 10

The bowels must be kept open and the stools should be made soft by use of mineral oil and proper dietetic control. The bowel movement should occur without straining and warn against using any force in producing the evacuation. It is well to
advise the patient to take a nitroglycerine tablet before going to stool.

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

Miller has made some interesting studies concerning the gall-bladder and cardiac pain. He reports, that it is a common occurrence for the cardiac condition to improve after the removal of septic foci, and at least, the general health of the patient is bettered. Many times, Miller says, practitioners have been perplexed as to whether they were dealing with a cardiac or a gall-bladder disorder. The innervation of the two organs is from closely located regions in the central nervous system, so reflex disorders in the heart maybe incited by the diseased gall-bladder, as well as by toxic irritation and damage to the cardio-vascular system.

The study of the morbid anatomy reveals that subjects with gall-bladder disease had a higher incidence of severe arterial degeneration that those with normal, healthy gall-bladders. Miller advises, that if there is any reason to suspect the gall-bladder in any patient, who has cardiac pain, a complete examination of the organ is in order. If sufficient evidence is found to indicate pathology, removal of the gall-bladder should be advocated.

Climatic methods of treatment are very beneficial in many
instances. The mild climate is very much suited to the anginal patient, as violent changes in temperature often cause them much distress. They do not fare well at altitudes over 2000 feet above sea level. The conditions in Southern California and Florida are very favorable. It is important that the patient be where he is happy and contented.

Drug therapy:— Alcohol, in its proper form, has long been favored in the treatment of angina pectoris in selected cases. It is useful for its sedative action, and may have some vasodilator effect on the coronary vessels, when given as a matter of routine. Some find it very useful for its carminative effect and for quickly absorbed nutritional supply with entire lack of stress on the metabolic mechanism of the body. It is especially beneficial in elderly people. The patient feels easier and more contented following an alcoholic drink. The dosage, advocated by Beckman, to be satisfactory is at least 1 to 3 ounces of whiskey or brandy mixed to suit the patient. It may be repeated according to the reaction of the patient.

Walshe, in 1862, wrote that a belladonna plaster worm over the heart, or a perpetual blister to the arm, had seemed useful in some cases. He advised counter-irritants, especially if the patient desired them.

The bromides are of great service in controlling the nervousness and irritability of the nervous system, so lessening the frequency and the severity of the attacks. The bromide of ammonium is used by Mackenzie, as he finds it not as depressing as the sodium or potassium salt. He gradually increases the amount of the drug till a certain degree of apathy results and the attacks diminish. The dosage may be moved up to 20 grains, three to four times a day.
If the bromides fail, the best drug is chloral hydrate given in small doses, 3 to 5 grains, repeated three to five times daily. The drug is continued till the patient is slightly drowsy, then discontinue for a few days and resume again, if necessary. Chloral hydrate is preferred to the opium preparations because it does not upset digestion, and mental disturbances are less frequent. Larger doses of chloral hydrate maybe necessary when attacks are easily incited, or it may be imperative to use the opiates.

The persistent use of chloral or an opiate in large doses over a period of three to four days, often results in much mental disturbance and even delirium. To avoid this unpleasant effect it is necessary to keep changing the drug, giving the opiate for two to three days, and then use the chloral hydrate for the same length of time.

The nitrites are valuable, not only for the purpose of dispelling the acute attack, but also, for attempting to forestall the recurrent seizures.

Sodium nitrite is effective in about five minutes after it is given, much slower than the action of amyl nitrite or nitroglycerine, but the drug's activity continues for one to two hours. It is administered in a dosage of 2 to 3 grains (0.13 - 0.2 grams) in capsules by mouth. The drug is being replaced in the continuous treatment by compounds of the nitrite group with even more enduring action.

Erythrol tetranitrite and mannitol hexanitrate have much longer effect, being active in half an hour and continuing for three to five hours. These new compounds are supplied in tablets and the dosage is: \( \frac{1}{2} \) to 1 grain (0.03 - 0.06 grams.) by mouth every four to six hours. These nitrite compounds are of marked
usefulness, when the patient is suffering frequent, severe attacks during the day or disturbing night seizures. The therapeutic action of these drugs is brought about through vaso-dilator action on the coronary vessels. 4, 14

The salts of caffeine and theobromine have been known for many years, but the therapeutic application to these drugs to cardiac cases did not develop until Askanazy introduced them, as such, in 1895. 22

It is found that theobromine, caffeine and their salts, as well as the more recent, theophylline and its derivatives, have never become as well established as results warrant. This may be due, chiefly, to the unpleasant symptoms often elicited by their use.

Brooks is enthusiastic about the action of the purine-base compounds. His statement is quoted as follows: "The last few years have furnished a group of drugs with such direct action in angina pectoris, especially on the basic lesions of the complex, that we may almost consider them in the nature of specifics." He finds that they are of definite value in many cases. The pharmacologists, he reports, finds that they are specific dilators of the coronary vessels and probably otherwise improve the circulation in the heart muscle.

Gilbert and Kerr find that the weight of the evidence points to increased coronary blood flow. They report the salts of theobromine quite as useful as theobromine or the salts of theophylline, when used in commensurate doses.

Caffeine has definite value, but they get better results with the other preparations.

In their series of cases none of the patients were completely
free from attacks, but they were definitely helped to a great-
er degree than with other drugs used in the control cases.

The dosages they used on their ambulatory cases are not fixed
and must be varied to suit the individual. The drugs are ad-
ministered orally. Gilbert and Kerr used the following dosages:

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Theobromine, -------------- 5 grains (0.3 grams), in capsules.
Theobromine sodium acetate, --10 grains (0.7 grams), in capsules.
Theobromine sodiosalicylate, 10 grains (0.7 grams), in capsules.
Theobromine calcium salicylate, (Theocalcine) 7½ to 10 grains
(0.5–0.7 grams), in tablet form.
Theophylline, -------------- 2 grains (0.1 grams), in capsules.
Theophylline-ethylendiamine (Euphyllin), 1½ to 3 grains (0.1–
0.2 grams), in tablet form.

Usually four doses are given daily, but the dosage is guided
by the patients reaction. They find less ill-effect when the
drugs are taken after a meal. Except in the case of theobromine,
calcium salicylate and euphyllin, few patients can tolerate
these preparations daily for more than a few days. Untoward
effects, such as, nausea, burning pain in the epigastrium or
under the sternum, palpitation, dizziness, headache, or nervous-
ness may result. Then too, a tolerance for the drug is likely
to develop in many. So it is necessary to administer the drugs
for three to four days and then discontinue for three to four
days.

White finds that their use may or may not bring favorable
results, but that it is wise to try the purine derivitives for
a week or two in cases not yeilding to a limitation of activity.

The combination of theobromine, 5 grains (0.3 grams) and
phenobarbitol, ¼ grain (0.03 grams), in tablet form, called
theominol, is usually more effective than theobromine and
allied preparations alone, probably because of the mildly sedative action of the phenobarbital. A tablet may be given at bed time or two to four times during the twenty-four hours, as needed.

Preston finds ephedrine and theophylline useful in cases of angina pectoris with an arteriosclerotic background. Ephedrine he finds has proved the more useful of the purine-base group, and increases the flow of blood in the coronary arteries 40 to 90 per cent, in experimental animals. He says there are no contraindications for the drug and it may be used for long periods of time with good results.

Evans and Hoyle in their work on the comparative value of drugs in the continuous treatment of angina pectoris find that there is no agreement on the best drug to use, and that a great deal of confusion exists. They are quite unsatisfied with the results gained by use of the present day drugs, after treating a long series of anginal cases.

Digitalis and related drugs used in cases of angina pectoris, caused by lesions of the coronary vessels, commonly increase the frequency and severity of the seizures, except, when angina is associated with definite evidence of myocardial deficiency. In these instances, the symptoms of angina are lessened as the tone of the cardiac musculature is improved. The presence of heart block or arrhythmia does not contraindicate its use.

In angina pectoris developing after acute infectious diseases, due to myocardial weakness, digitalis is definitely indicated.

Christian writes, that it is well to try the effect of long continued digitalis in any patient with angina pectoris. He often has good results. The dosages he uses are just short of nausea, being $\frac{3}{4}$ grain (0.05 gram) of powered leaves night
and morning, on the average.

Iodine, generally the salt of sodium or potassium is extremely useful in the interattack phases of angina pectoris. This favorable action is believed to be due to the effect of the drug on the arteriosclerotic changes found in most of the cases. Christian agrees that the iodides are useful. He gives 5 drops of a saturated solution of potassium iodide three times a day for three weeks, then a week of rest, and the course is repeated. This treatment he continues indefinitely.

Sajodin is used in place of the potassium iodide in some cases, because it is less nauseating and is solid so that it can be carried by ambulatory patients. The dosage is 5 grains (0.3 grams), three times a day.

Babcock, cited by Brooks, has prescribed benzyl benzoate for twenty or more cases. Six of the patients were so benefited, that the drug was used daily for months. No harmful effects were elicited, altho the other cases were only slightly benefited or not relieved at all. The drug was given in doses of 30 drops four times a day, in milk. Brooks says, that he finds little value in the use of this drug, and it is only rarely used at the present time. White has found the compound to be inert, unreliable and too toxic in action.

Magnesium chloride has been used by Bandmann, cited by Beckman, in cases of angina pectoris that did not respond to other medical measures. Intravenous injections of 5 cc. of a sterile 10 per cent solution of magnesium chloride was used three times a week. The dosage was gradually increased to 10 cc. each injection, and on the average twelve injections were given. The patient, in each instance, felt a flushing sensation at the time of the treatment.
In Bandmann's series of fifty patients, twenty-nine showed a considerable decrease in the frequency and severity of the attacks. The improvement was most marked among those with associated hypertension.

Glucose and insulin therapy is an interesting phase of modern treatment in angina pectoris. This regime, used by Smith, is based on the theory that nutritional disturbances of the heart muscle may be the basis for anginal pain or cardiac failure. Smith states, that dangerous conditions of circulatory insufficiency often occur in later life when arterial, and especially coronary degeneration begins. It is reasonable to believe, in this cases, that an increased content of nutrient material in the blood should be valuable. He gives 5 units of insulin before breakfast and before the evening meal. Each dose is followed by 30 grams of glucose, taken with the meal. This therapeutic regime was continued over periods of from two to seventeen weeks, with beneficial results successfully obtained in six cases.

Smith believes the pain is related to faulty carbohydrate metabolism in the heart muscle. The improvement then, he feels, is due to the immediate stimulating effect of the insulin on the glycogen metabolism in the heart muscle, and progressively, by promotion of the combustion of fat. The process of fat utilization leads to resolution of early atheromatous changes in the coronary arteries, he believes.

Ray-therapy:- Ultraviolet irradiations over the whole body have been used by Freud, cited by Partridge, who claims to have obtained some good results. Freud's theory, to explain the useful action of this treatment, is that when the skin is ex-
posed to the rays sufficiently to give an erythematous reaction, there is a histamine substance released into the blood stream, which acts similar to the nitrites, in that vascular spasm is relieved.

Roentgen ray therapy has been applied the last few years in the treatment of angina pectoris. White cites the work of Lian, Barrieu and Nemours-Augustie. Sedative anterior thoracic irradiation and ddp X-ray therapy bilaterally over the back, directed at the upper six thoracic sympathetic rami communicantes has been tried. In some cases the treatment has been followed by a considerable decrease in the intensity and frequency of the attacks. White feels it is too early to estimate its place in the treatment.

Dlathermy has been recommended in recent years, according to White, but he says, the results have been disappointing, as would seem logical on theoretical basis.

The therapy of tissue extracts: The therapy of tissue extracts, developing at the present time, promises to be of great interest in the control of angina pectoris.

European investigators have made the discovery and are doing by far the greatest amount of work on substances extracted from the urine and body tissues. They have called the attention of the medical world to the vast possibilities in this field of research. American clinicians have, only recently, begun investigating these peculiar constituents of the body.

Most of the literature on tissue extract therapy has been translated by English writers, and it is to their articles that I will refer.
In 1920, Pribram and Herrnheiser found that the non-dialysable fraction of the human urine caused a fall in blood pressure on being injected into a rabbit.

Then, in 1926, Frey and Kraut drew attention to the possible therapeutic use of tissue extracts, by isolating a substance from the urine, which lowered the blood pressure, when injected intravenously into animals. This substance was named Kallikrein (later padutin), and was found by Frey to inhibit the distress of angina pectoris, and intermittent claudication. He also demonstrated that the blood pressure was lowered in cases of hypertension, when the substance was administered intramuscularly in human subjects.

Frey found later, that fluid extracted from a pancreatic cyst would bring about a similar series of reactions. He concluded, therefore, that the effects of Kallikrein were attributable to a hormone probably present in many tissues of the body, but produced in the pancreas.

It is of interest to note here, that Heberden described a case of angina pectoris, which showed a very extensive sclerosis of the coronary arteries at autopsy. This patient, during life, found that he could gain marked relief by exercising vigorously to dispel the pain, when the attack occurred. From this early observation, Schwartzman reasoned, that some substance might be given off by the skeletal muscles during active contraction, which tends to relieve the seizure.

He extracted a substance from the skeletal muscles of animals, free from histamine, cholera, insulin, and protein, and injected the solution intramuscularly, each day, into patients with angina pectoris. He reported the improvement to be striking,
and attributed the effect to vasodilation. Schwartzman named
the extract, myoston.  
3,45,33,
Vaquez, Gley and Kisthinios prepared a substance from the
pancreas, quite independently of each other, which had the
same properties as the urine extract. The substance had a
depressor effect on the blood pressure and antagonized the ac-
tion of epinephrine.

All these compounds gave relief in angiospastic conditions
quite successfully. 61
Drury and Szent-Gyorgi studied the effect of extracts from
various body tissues and concluded that each of these extracts
have quite similar properties. They believed the extracts di-
lated the coronary vessels.

The chemical nature of the substance is not definitely known.
Anitschkow and Schwarzmann believe the active principle is a
nuclioside. They find that the coronary vessels of experimental
animals will dilate two to three times their original diameter.

Wolffe named the extract they obtained, "desympatone," and
he believes the substance is an adenosine compound. He finds
the action of adenosine phosphoric acid is similar, but not
identical with the extracted substance. This writer cites the
work of Webb, who showed that adenosine brought about a
marked increase in the coronary flow of perfused rabbits heart,
exceeding that by sodium nitrite or the purine group of drugs.

Wolffe has reached the conclusion, that the extract relieves
angiospastic syndromes by its epinephrine neutralizing proper-
ties. Haberlandt has proposed that the unknown extracts are
true circulatory hormones produced in the pancreas.
Wolffe found in twenty cases of angina pectoris treated by desympatone, that 55 per cent obtained clinical relief, 30 per cent were partially relieved and 15 per cent received no benefit. He administers the substance intramuscularly or subcutaneously in doses of 2 cc.-5 cc. daily, depending on the severity of the condition. When symptoms are relieved, injections are given every second to third day and the dosage is gradually reduced. After three to four weeks, the patient receives the extract orally for at least four to six weeks, depending on the condition of the individual treated.

From clinical and laboratory observations on the action of the extracted substance, Wolffe has found that he can not abide by former theories of angina pectoris. He believes that all angio-spastic manifestations can be explained on the basis of disturbed balance between the sympathetic and parasympathetic systems. It is, he proposes, the result of sympathetic over-stimulation by diverse causes. It is this sympathetic over-stimulation, and not the etiology of angina pectoris, that is feared. The patient will live regardless of pathology, until the time when another attack so stimulates the sympathetic system as to produce an overwhelming sympathetic-parasympathetic imbalance, death occurring instantaneously.

From Wolffe's statement, I quote, "In vasodilator tissue extract, no matter where obtained, we have a substance which depresses the sensitivity of the sympathetic nervous system, counteracts the pain reflexes, removes the fear of impending death, overcomes transitory glycosuria and hyperglycemia of non-diabetic origin, and the digestive disturbances associated with the anginal syndrome."
Bagdassajanz and Turteltaub treated fifty-four ambulatory cases of angina pectoris, with tissue extracts. The electrocardiographic records showed a slowing of tachycardia in cases so effected, but with very little influence on those with normal rate or bradycardia. The slowing of the cardiac rate was found to be due to lengthening of the diastole without change in the ventricular complex. Not only was the anginal distress stopped, but hypertension was reduced. The normal arterial tensions were either slightly reduced or uneffected, and hypotension, when present, was slightly raised. Disturbances of rhythm were corrected.

Fahrenkamp and Schneider have reported the use of muscle extract of beef heart, injected intramuscularly in thirty-two cases of angina pectoris. They claim to have obtained a greater measure of relief for their patients, than by any other form of treatment. They were able to immediately relieve an attack of angina with an intravenous dose of 1 cc. of skeletal muscle extract, except when the patient was fully digitalized. They found it much superior to morphine in favorable cases.

When used for emergency purposes, the initial dose of kallikrein, angioxyl or padulin is 1 cc. intravenously. This dosage can be repeated every ten minutes until the patient is relieved, if needed.

The heart muscle extract (hormoncardiol) or skeletal muscle extract (myoston, invol or lacarnol) can be given intramuscularly in doses as high as 4 cc. per day. Klein reports no injurious effect is noticed by large doses except in three conditions: First, Leshke found that the normal blood sugar is not raised,
but diabetic hyperglycemia is markedly increased by the use of pancreatic extract (kallikrein), because of the concomitant pancreatic vasodilation; secondly, Fakrenkamp noted sensitization of the myocardium after the use of muscle extract, so that small doses of digitalis were as effective as large doses were before; and thirdly, the systolic and diastolic blood pressure often dropped thirty to fifty milligrams and remained low for months, except in hypertension with interstitial nephritis. The potential danger is of pushing the blood pressure so low in cases of nephritis that anuria might result, so, daily blood pressure readings must be taken. If anuria is produced, it is quickly relieved by adrenalin.

Klein is enthusiastic about the new therapy, but states frankly, that he believes it is merely palliative, but feels that even this is an enormous advantage.

Nuzum and Elliot report that the available studies in angina pectoris are conflicting, but they say Frey and Leschke, who have had most experience with this therapy have secured a favorable response in some cases.

These clinicians reported, in 1932, the results of this new treatment on twenty cases of angina pectoris, using a control group of forty cases. The pancreatic extract was given intramuscularly in doses of 30 to 60 hypotensive units on alternate days, or twice weekly for a total of ten to twenty injections. The course was repeated two or three times if no results were gained in the first series. The average time during which the treated cases were observed was 6.7 months and the results
reported were as follows: fifty-five per cent were greatly
relieved; twenty-five percent were somewhat helped; and ten per
cent were refractory. These results were better than in the
control group.

The opinion they express in their more recent article is here
quoted, "We do not wish to draw a definite conclusion that this
substance will prove valueless in the treatment of angina pectoris,
but we believe that its primary field of usefulness lies
elsewhere." They do however, recommend that the pancreatic
extract be tried in cases of angina pectoris.

Beckman feels that pautin, produced by Frey and Kraut, will
eventually be shown to exert a true hormonal action on the
caliber of the vessel wall. He believes most writers agree,
that excellent results have been obtained in treating cases
of angina pectoris.

In the treatment of angina pectoris, it is important to al-
ways remember, that the heart once afflicted with angina
pectoris should never again be expected to rise to normal
levels for function, and an acceptance of this fact by the
patient is a long step in progress.
SURGICAL TREATMENT OF ANGINA PECTORIS.

"Even if some patients die sooner because they do not have the warning that pain gives to overexertion, the mental relief to them to be free from pain and the anticipation of it, is well worth a few months of their lives."

Howes - 1932.

It is not strange, with the modern knowledge of the physiological and pathological function of the heart, that surgery has been called for in treatment of angina pectoris.

At the present time, several surgical measures are offered the medical world, and it must be realized that absolute cures are rarely accomplished, but relief of the terrible symptoms is granted a much larger group of patients.

Cervical sympathectomy:— Jonnesco, in France, accomplished the first operative procedure of this kind, in 1916, but very little attention was given his work, even after he reported the cure of a case of angina pectoris, in 1920, by resection of the left cervical sympathetic system under local anesthesia.

It remained for Coffey and Brown, in 1923, to revive the work and bring it to the attention of clinicians.

Franck, also of France, found a relationship between the irritation of the cardio-aortic plexus and the more or less distant factors producing the symptoms observed in angina pectoris. He suggested an operation in the nature of a cervical sympathectomy, in 1899.

Jonnesco believed that the anginal pain was due to the resulting irritation of the cardio-aortic plexus producing a neuralgia of this nervous structure. He argued, that a variously
pronounced chronic aortitis is always present in angina pectoris. The aortitis irritates the nervous filaments of the plexus. He understood the work that Franck had published, showing the predominant role of the sensory fibers ascending from the cardio-aortic plexus, passing to the cervicothoracic sympathetic chain and reaching the medulla and higher brain centers by three distinct routes; the paravertebral chain, the vertebral nerve, and communicating dorsal branches of the first thoracic ganglion.

The belief of these surgeons was, therefore, that there were in the cervico-thoracic sympathetic system, both centrifugal and centripetal nerves which transmit to the central nervous centers impressions arising in the thoracic viscera. So, Jonnesco, Franck, and the authors surmised that this explained how irritation of the cardio-aortic plexus caused reflex sensory and motor circulatory disturbances.

Now, in order to prevent these reflex disturbances, an attempt must be made to interrupt the pathways between the aorta and the central nervous system. The ideal plan would be to cut the centripetal fibers, but this being impossible, a resection of whole strands of ganglia, surrounding both centripetal and centrifugal fibers, had to be made.

Observers had decided, that there was a definite vasoconstrictor action of the cervical sympathetics on the bulbar vessels by way of the vertebral nerve. So, the sudden death in angina seemed to be due to a spasm of the arteries in the medulla, due to a reflex from the aortic irritation.

The first Jonnesco operation consists of the complete removal of the upper three cervical ganglia, and the first dorsal
sympathetic ganglion, cutting the vertebral nerve, on the left side, or the effected side. The operation seemed relatively safe and simple, so after the first operation, to complete the procedure, he performed bilateral cervical sympathectomies. Babcock says, that this procedure was followed by complete relief or decided improvement in 8 per cent of the cases, and with a mortality of 11 per cent.

Coffey and Brown followed closely the theoretical beliefs expressed above, but they did not believe the radical Jonnesco operation was necessary. They selected an anginal patient, severely afflicted, and under general anesthesia, cut the vertebral connections of the superior cardiac branch of the superior cervical ganglion. The patient became progressively worse in frequency and severity of the attacks. They believed this difficulty, in the first case, was due to stimuli from the brain, so determined, thereafter, to sever the upper end of the sympathetic trunk as the first operative step, cutting the superior cardiac nerve, and main trunk of the cervical sympathetics below the superior cervical ganglion.

Now, when this operation was performed on a selected case, the attacks of pain ceased immediately and no recurrences were had over a period of eight months. Coffey and Brown obtained this successful result, altho many physiologists, at that time, agreed that cervical sympathetic ganglia had no connection with the brain and cord, except through the sympathetic trunk and the white rami communicantes of the thoracic nerves, which connect with the cervical sympathetics through the lower cervical and first thoracic ganglion and thoracic cord. Now, in this operation, what was considered the main path from the heart to the brain remained intact.
With other cases, they repeated this procedure and came to the belief that by this method sufficient changes take place in the heart and brain to prevent attacks, in which the symptoms occurred on the left side. The results of their therapy in fifteen severe cases, two presumably suffering from syphilitic aortitis, were encouraging. One died soon after the operation, but the other four were markedly improved.

A description of the operation of Coffey and Brown is as follows:—An incision is made on the left side of the neck, at the posterior border of the sternocleidomastoid muscle. At the inferior end of the incision, the approach is opened by blunt dissection. In this space are found the internal jugular vein, carotid artery, vagus and phrenic nerves. With retractors these structures and neighboring muscles are pulled medially. The vertebral plane is exposed, and the sympathetic trunk is found here.

The superior cervical ganglion is a swelling of the trunk and lies in front of the transverse processes of the second to fourth cervical vertebrae on the prevertebral fascia and the longus capitus muscle, adjoining the internal carotid artery and laterally the vagus nerve. The ganglion is located and removal of this structure with the disengagement of the trunk is begun. The branches by which it is attached to the two borders are cut with a blunt scissors, so the ganglion is left attached to the cardiac trunk below and the cranial branches above. To remove the ganglion entirely, grasp it with a hemostat after separating the trunk and cardiac branches, them with
traction it can be pulled from the cranial attachment.

Only in one case it was dissected away from its branches. In all the others, only the main trunk below the ganglion and the cardiac branches were severed. The wound was closed by primary union.

During the postoperative observation, no eye changes were found in their patients.

Brooks records, that since these first operations, Coffey and Brown have removed the superior cardiac ganglion. He cites them as adhering to the theory, that angina pectoris is due primarily to spasm of the aorta, but it might be also of the coronary arteries, and that the superior cardiac nerve has constrictor fibers that fail to cause spasm after they are cut.

Now, altho Coffey and Brown reported no eye changes even when the superior cervical ganglion is removed, Holmes and Ranson state, that the objective signs resulting from removal of the superior cervical ganglion are enophthalmus, myosis, ptosis of the upper eye lid, contraction of the pupil, and absence of sweating or flushing on the effected side-- constituting the Horner syndrome.

If the entire cervical sympathetic chain on one side is injured or removed, as in the Jonnesco operation, the exact area in which sweating does not occur is bounded by a line which runs down along the middle of the head and neck, and turns horizontally across the chest at the level of the third rib in front, and the spine of the scapula behind, including the whole of the upper limb.

White finds in addition, that hyperesthesias, burning sensations in face, mouth, ear, neck and upper chest, with varying degrees
of anesthesia are usually experienced. The extent of the after effects vary extremely in intensity and duration. Some patients suffering but little and only a few days postoperative, while others complain of extreme discomfort for weeks and months. In the course of time these after effects fade away.

Holmes and Ranson tried the Goffey-Brown operation on one case and it was successful.

Now as far as they could discover, none of the cardiac sensory fibers pass through the superior cardiac ganglion; for by histological methods it is possible to trace the sensory fibers by their large size. So, they concluded that the benefit of the high cervical sympathectomy was due to the section of the vasoconstrictor fibers.

Levine and Newton stress the importance of selecting anginal patients for sympathectomy, if the treatment is to be given a fair trial. The patients should be possessed of such resistance, that the operative mortality could be maintained at a low level. The procedure should be offered patients, who will live long enough to benefit from any satisfactory results obtained.

Lewis believes that the cervical sympathectomy is an operation sufficiently dangerous to render its legitimacy doubtful. It should only be used in hopeless cases that have failed to respond to more conservative measures.

It seems that there may be different nervous tracts and connections in different individuals, for the variations in the results of the same time of operation to break the reflex chain causing the pain of angina pectoris, proves this to be quite probable.
The effectiveness of cervical sympathectomy in relieving the patient in angina pectoris is recorded by White as being 59 per cent, which is considered to be successful.

Brooks says, that the literature on the subject is still very discordant as to results and their permanency. He believes it is best to use medical treatment in the early cases.

Division of the Posterior roots:— This procedure has been advised by Spiegel, cited by Brooks, because he finds that pain originating in the heart or aorta passes from the heart by sympathetic fibers to the stellate ganglion, through which they pass to the cord along the rami communicantes and the posterior roots of the spinal nerves. The posterior roots involved are those between the eighth and fourth dorsal vertebrae. In these segments lie the trophic centers of pain perception. He has shown that the stellate ganglion contains sensitive fibers even after the division of the brachial plexus and the four first intercostal nerves on the same side. This, he feels, indicates that the central process of the spinal ganglion cells governs the sensibility of the heart and aorta, and that it reaches the spinal cord directly and not through other tracts. He believes the operation is safe and effective.

Singer, in 1927, cited by White, performed a dorsal laminectomy on one case of angina pectoris. The posterior nerve roots were severed, and complete relief of pain resulted at the level of the laminectomy, but below the effected area the pain continued.

Dorsal Sympathectomy:— This therapeutic measure was carried out by White, J.C., in 1929, and he refers to this work in his articles. He records, that in exceptional cases, who are un-
usually favorable operative risks, it seems the logical form of operative approach to resect the upper dorsal sympathetic ganglia, in light of our present knowledge of cardiac pain. He says, that he knows of no instances when this operative measure has been used in other clinics.

The method of technic is as follows: First, a small segment of the second rib, subperiostially, is removed. The parietal pleura is then pushed away from the vertebral bodies until the sympathetic trunk can be seen. It is then quite simple to excise the first dorsal portion, or the stellate ganglion, the second, and in two cases operated, the third ganglion. The extra-pleural approach seemed to cause no shock and all three patients in this group made good postoperative recovery. In all these cases, left sided angina pectoris disappeared completely.

White recommends the dorsal sympathectomy as being a much more effective therapeutic measure than the cervical sympathectomy. He feels it is a greater undertaking than the injection methods, but has the great advantage of definitely limiting the destructive process to structures which are to be interfered with. The method has been successful, but as yet, it is too early to determine its place in the therapy of angina pectoris.

Paravertebral Alcohol block:— Mandl, in Germany, first suggested this method of treatment in angina pectoris by his care of sixteen cases by paravertebral injections, using a ½ per cent novocaine solution, in 1925. The effect lasted a considerable while, and he reported the results as excellent. He had no complications that were severe.
Swetlow, in 1926, introduced the use of alcohol injections in producing the paravertebral block.

He reviewed the various surgical procedures in use, and it seemed evident that men using these methods were still experimenting as to the pathway of pain. The different patterns of nervous structures in the neck of different individuals was confusing and productive of uncertain results. Now, Swetlow and White were both acquainted with the knowledge, that the most important routes of the cardiac afferent fibers are by way of the superior, middle, and inferior cardiac nerves to the cervical sympathetic trunk, and also by way of a large number of fibers coming to the stellate ganglion and further caudally, into the dorsal sympathetic chain. Therefore, even if the entire cervical sympathetic cord and the stellate ganglion were removed, the lowest fibers will still be functional. The chief communications between the cervicodorsal sympathetic system and the spinal cord are by way of the rami communicantes of the upper dorsal nerves. This suggested a new site for therapeutic approach.

The object of this method of treatment was to destroy the poorly myelinated afferent sensory fibers from the heart, which pass through the sympathetic cords to enter the dorsal root ganglion.

Swetlow treated a group of eight patients, suffering from very severe precordial pain, by paravertebral alcohol injections and reported prompt relief in each instance.

He found that the freedom from pain after a single injection was continued several months. No complications were experienced
and no serious after effects were seen.

The technic used by Swetlow is as follows: The patient was placed on the side opposite the one to be injected. The knees were flexed on the thighs and the thighs on the abdomen. The head was approximated to the lower extremities. Taking the twelfth rib as a landmark, the intercostal spaces are palpated in preparation for injection. A line is drawn on the skin through the midline of the vertebral spinous processes. Then at points four centimeters to the left, or the affected side, from the line over the ribs, above the spaces to be injected, wheals of novocaine are raised.

The needle for injection is eight centimeters long. It is introduced perpendicular to the posterior surface of the rib just above the space to be injected. As soon as the needle touches the rib, slightly withdraw and change the direction. The shaft of the needle is directed downward, inward and forward at an angle of 45 degrees. The point of the needle is advanced two centimeters further from the lower border of the rib. The point is then between the internal and external intercostal muscles. The needle is then attached to a water manometer to see if it is in the pleural cavity. If the pressure fluctuates with breathing, it is in the pleural space and must be withdrawn and replaced.

Now, 5 to 8 cc. of an 85 per cent alcohol solution is placed in the syringe and about half of it is injected with the needle in place. The remainder is slowly injected, with a to and fro motion, as the needle is withdrawn. Each injected ganglion receives this amount of the alcohol solution.
The alcohol produces a Wallerian axonal degeneration of the thoracic nerve near to the cell body in the dorsal ganglion. Some of the drug may act on the ganglion itself.

In his series of cases, it seemed that the sites of injection were determined by the pain pattern, for in his cases the alcohol was placed near the 3rd, 4th, 5th, 6th or 7th dorsal roots.

White and White became interested in this work at their clinic. The treatment of five severe cases of angina pectoris was reported by them, after injecting the upper five left dorsal nerves. These patients were observed for periods varying from four to thirteen months. Two patients gained complete relief from left sided pain, but still had mild right sided seizures. The severe attacks of two others were converted into milder and less frequent paroxysms. The fifth patient was helped only a few days. They had no permanent bad results from the treatment, but felt that injections used so close to the spinal cord and the pleura is dangerous. So, they have only used it in very severe cases, or as a last resort to relieve the patients.

The reasoning they used for this approach is identical with that of Swetlow, and their technical plan varies only with these added points: They inserted all five needles and aspirated each to see if it had entered a blood vessel or spinal fluid.

Then 5 cc. of a 1 per cent solution of procaine was injected and if the needle happened to be in the pleural cavity the patient would cough. Within ten minutes of the procain injection, there should be an anesthesia from the midline in back to the sternum in front, anf from the 5th interspace up to the region where the descending branches of the cervical plexus overlap the three upper ribs.
If the first and second dorsal nerves are properly blocked, there should be good anesthesia of the axilla along with the contracted pupil and narrowed palpebral fissure on that side—Horner's syndrome.

As soon as the anesthesia is complete, 5 cc. of 85 per cent alcohol is injected and the needles are withdrawn.

The operators have found, by animal experimentation, that the zone of necrosis is only 2 centimeters in diameter. So it is necessary to place the alcohol as near as possible to the nerve at the point at which it leaves the intercostal foramen.

Altho, they have not had any harmful complications, all their patients complained of more or less hyperesthesia of the injected nerves lasting two to four weeks.

In 1930, Swetlow again reported on the use of the therapeutic paravertebral alcohol block for the relief of pain. He confines the injection of the irritated ganglia to those between the eighth cervical and seventh thoracic segments.

He writes, that of twenty-two cases, so treated, eleven gained 90- to 100 per cent relief; seven were given 50 to 85 per cent relief; and four showed no improvement.

The alleviation of pain from a single injection usually lasted several months, then the treatment was repeated.

Swetlow believes the discomfort following the treatment is due to a neuritis produced by the chemical irritation of the alcohol.

He finds that the nerve cells in the dorsal ganglion, that is being bombarded with painful impulses from the heart, are hypersensitive to external stimuli. Then, if a dermatome sup-
plied by an irritable dorsal root ganglion is stimulated, a greater sensory reaction is produced than normally. So, careful protopathic and epicritic sensory tests are made, by him, to determine the dorsal root ganglion that is being bombarded by pain impulses. He especially directs the treatment to these sites in the reflex chain.

White, writing in 1930, states, that nerves have recently been discovered, which run directly across the mediastinum from the posterior cardiac plexus to the upper dorsal sympathetic ganglia. The painful stimuli are then carried to the spinal cord over preganglionic, myelinated fibers in the upper dorsal white rami communicantes. As there are no white rami in the cervical region, all pain sensation is referred over the cervical sympathetic trunk must descend to the upper dorsal region before it can reach the spinal cord.

He claims, after using this method of treatment for some time, that the alcohol injection is difficult technically, because of the depth of the rami and the small area sclerosed by the drug, but it is still the safest surgical procedure we have.

The majority of White's cases, successfully treated, have shown other signs of sympathetic block, such as Horner's syndrome, vasodilation, and cessation of sweating of the arm on the effected side.

This method of treatment has become the one of choice, because it is simpler, more effective, and less of a strain on the patient. It is suitable for any case, even when they are quite ill from a recent coronary thrombosis.
Thyroidectomy:— The relationship of the thyroid gland as a possible factor in cases of angina pectoris and cardiac failure is an interesting source of study and speculation at the present time.

Rosenblum and Levine noticed many times that patients with hyperthyroidism and associated angina pectoris or heart failure were refractory to all ordinary therapeutic measures to control the cardiac condition. Then, after a subtotal thyroidectomy, were restored to normal or nearly normal and could undertake almost normal activity without distress.

These men have been studying statistics on "thyro-cardiac" cases in order to gain a better knowledge of this problem. They found the preoperative basal metabolism to be on the average, plus 51.1 per cent, and after subtotal thyroidectomy it averaged plus 4.3 per cent. In the series of cases observed, there were nine cases of angina pectoris associated with hyperthyroidism. Although females far outnumbered the males among the hyperthyroid cases in general, yet in the group of nine anginal cases, six were men.

The average duration of the symptoms of angina pectoris in this group was thirty-one months, and after operation the recovery from the attacks was amazing. In every instance, the seizures either completely disappeared, or they occurred more rarely and were milder. These cases were observed over periods ranging from a few months to four years.

It is the opinion of these authors, that all these patients were suffering from angina pectoris as a result of the same causes that produce the disease in cases with normal thyroid
glands. Probably all had varying degrees of coronary artery disease.

When the thyroid gland is overactive, the accompanying elevation of the metabolic rate throws an added burden on the heart even with the patient resting in bed. So that these patient's hearts were working at a rate equivalent to one in the normal individual during exertion.

The operation, they feel, relieved the patient of this added load on the heart muscle, but the underlying coronary pathology, altho possibly mild, was still present. The attacks of anginal pain could still be produced, but greater physical or mental effort was required. It is unlikely, in their opinion, that hyperthyroidism alone would cause angina pectoris in a normal heart.

Blumgart, Levine and Berlin have reasoned that whether or not a patient with heart disease suffers from the signs and symptoms of circulatory insufficiency depends on whether the supply of blood is adequate to meet the metabolic demands of the tissues. In patients with congestive heart failure and a normal basal metabolism, the basal velocity of the blood flow is greatly slowed. The circulation may be similarly slowed in patients with the low metabolic rate of myxedema, but they show no clinical symptoms or signs of congestive heart failure. The diminished blood flow still meets the diminished demands of the body, including the heart muscle.

So they arrived at the idea, that persons with angina pectoris or congestive heart failure and a normal basal metabolic rate might be benefited if the basal metabolism was lowered sufficiently.
In their series of cases, they had two patients with congestive heart failure and one case of angina pectoris, with no evidence of thyroid disease. These patients had not responded to any previous medical treatment.

A subtotal thyroidectomy was performed on all three cases and the fall in the metabolic rate reached a maximum of -15 per cent, three weeks after the operation. The metabolic rate then rose slowly to normal in nine to eleven weeks.

The clinical improvement in the cases followed closely the lowered metabolic rate. The patient with angina pectoris experienced no recurrences of attacks since the operation, although he resumed his work and active life. The two cases of congestive heart failure, improved, the edema disappeared and they could be around the ward with no discomfort, but as the basal metabolic rate returned to normal, their clinical condition grew less favorable.

These men feel, that the operation should be reserved for the extreme cases.

Blumgart, Riseman, Davis and Berlin have continued this work and have attempted the use of total ablation of the normal thyroid gland in angina pectoris and congestive heart failure.

Now, in angina pectoris, they believe, the demands of the cardiac muscle on increased action of the heart necessitates an increased coronary blood supply. The intrinsic metabolic needs of the myocardium rises along with the other tissues of the body. So, the blood supply must be greater at normal metabolic rates, than at the lower rate of myxedema. When arteriosclerotic narrowing of the coronary vessels has occurred, the blood supply may be inadequate to meet the needs of the muscle
at a normal metabolic rate, although sufficient for the demand at a lower metabolic rate.

One patient with angina pectoris had attacks that were precipitated by a certain amount of exercise under standard conditions. Three and a half months following a total ablation of the thyroid gland, he experienced no recurrences of cardiac pain even after exercising to the exhaustion, far in excess of the standard before operation.

Other patients were improved too, but it seemed to these clinicians that there were several types of angina pectoris, necessitating further observations on this phase of treatment.

Some of the possible factors that brought about relief of the patients were, the decreased work of the heart, the decreased metabolism of the heart muscle, and the decreased sensitivity to epinephrine.

The development of the signs and symptoms of clinical myxedema has been carefully observed. With the reduction in the basal metabolic rate, the patients have felt easier and less nervous. The heart rate and respiration tended to be lower, but the temperature was not perceptibly changed. Within four to six weeks the skin became somewhat paler, acquired a yellowish tint and was drier. After the metabolic rate fell to -30 per cent, some patients complained of coldness and required more blankets. Several patients noticed a decrease in the rate of growth of their beard.

These authors were impressed by the fact that in every patient, instead of mental lethargy of myxedema, unusual brightness and alertness have been present in the months under observation.
Thyroid substance has only been used for short periods in two cases; in others, its administration has not been indicated. The patients have all been restored to moderate activity and a condition of occupational usefulness.

The authors believe, because, at this time, the durability of the beneficial results is not known, the operation should be used only on patients, who are fair operative risks, and where other medical measures have failed.

Eppinger and Levine state that Levine (one of the authors), Ernstene and Jacobson, noted that intramuscular injections of adrenalin, when given to patients suffering with angina pectoris, would provoke seizures of anginal pain.

After total thyroidectomy on patients with daily attacks of angina, the attacks disappeared immediately following the operation; long before any changes in the basal metabolism or in the rate of blood flow. It was suspected, therefore, that removal of the thyroid gland might be producing a fundamental alteration in the response of the cardiovascular system to adrenalin. They found that cases, that would have increased pulse, marked rise in blood pressure, with anginal pain, before operation with .3 to .5 cc. of 1/1000 solution of adrenalin; after operation had no pain, pulse usually not effected, and blood pressure usually only slightly changed with twice as large a dose.

These writers believe the relief of anginal pain by total thyroidectomy is due to the alteration of the cardiovascular response to adrenalin, in a large part.
Blumgart, Davis, Weinstein and Riseman found that if the basal metabolic level continued at or below -30 per cent, many patients showed weakness of the legs, puffiness of the face and hands, drowsiness, and irritability. These untoward manifestations could be controlled by small doses of thyroid, one-eighth to one-half grain daily.

Changes in the seven foot roentgenogram in eight of the ten cases examined showed an increase of 0.5 centimeters in the width of the heart postoperatively.

Shambaugh and Cutler believe thyroidectomy brings relief by change in the reaction to adrenalin. The beneficial effect of the operation may be due, in part at least, to a diminished effectiveness of the physiological adrenalin output.

Paroxysms of pain may be explained, they believe, in patients with coronary disease to an increased output of adrenalin in the person's body, from time to time. It might cause a constriction of the coronary arteries, which would directly produce myocardial ischemia, or it might, by raising the blood pressure and heart rate, so increase the vascular demands of the heart muscle, that in the presence of already narrowed coronary arteries preventing dilatation, cause a relative ischemia of the muscle.

Blumgart, Berlin, Davis, Riseman and Weinstein have reported on a large number of cardiac patients under their observation, who have had a total ablation of the thyroid gland. Twenty-five cases of angina pectoris, with ages of from forty-one to seventy years, are included in this series. Twenty-three had
arteriosclerosis or hypertension; two had rheumatic hearts. Eight of this number, showed no recurrence of attacks of anginal pain in spite of activity after periods of three to eighteen months. Five have only occasional attacks since operation. They were bed-ridden before, and are now capable of much more activity, even working. Two were completely relieved, but an accident caused recurrence of symptoms in one, and the other suffered a coronary thrombosis. Four found no increase in their exercise tolerance, but the attacks were milder.

All these patients were poor operative risks before total thyroidectomy was done, and postoperative complications are not uncommon.

After the operation, to control developing myxedema, these writers find that the best basal metabolic level for clinical results is between -25 and -30 per cent. To maintain this level, \( \frac{1}{4} \) grain of thyroid substance is given daily.

Horgan and Lyon concluded, after long observation of patients following subtotal thyroidectomy, on account of persistent recurrent hyperthyroidism, that the cutting and ligation of both the superior and inferior thyroid arteries was responsible for no further evidence of hyperthyroidism and cardiac symptoms.

They reasoned that it was not the removal of the thyroid tissue that mattered, but the destruction of the pathway of nervous stimuli, along the superior and inferior thyroid vessels, from the sympathetic nervous system. So, preventing regeneration of the thyroid tissue or over activity of that remaining, along with reduction of the blood supply to the gland. The heart symptoms being altered by the physiological changes in the gland.
It was decided to use this method in cases of angina pectoris and congestive heart failure.

The operation was tried on one case of angina pectoris and the results over a period of four and a half months were very favorable.

The effect of this procedure is to cut down the amount of blood entering the thyroid, to cut off all stimuli from the sympathetic nervous system, to lower the basal metabolism, to lessen the circulatory demands, and thus lighten the work of the heart. So, exciting causes of the attacks of angina may be prevented.

The anginal patient had no shock from the operation. The basal metabolism dropped from plus 5 to -7 per cent and no seizures occurred after the sixth day postoperative for a period of four months. He has resumed active life.

White states, that all the operative procedures require skillful technique and experience. All are more or less effective in that they do not always afford complete relief, and since disagreeable after effects often follow for a few weeks or longer. They should, therefore, be reserved for patients in whom other measures have wholly or partly failed, so that they are crippled and miserable.
THE SUMMARY.

1. The history of the treatment in angina pectoris has been continuous succession of theories, as to the mechanism of the paroxysms, arising from the reaction of the patient to therapeutic measures.

2. The prevention of angina pectoris by a prophylactic regime is especially advocated by Brooks. This plan of treatment is applicable to young individuals, especially, who have a family history or physical and mental characteristics of one who may be a potential anginal sufferer, when they reach middle or later life.

3. Specific treatment of cardiac pain has been urged, since more and more study has been made of the etiological factors concerned. All the modern medical men agree, that the early diagnosis of basic disease holds the possibility of prevention, cure, or improvement of angina pectoris.

4. The treatment of the attack of angina pectoris has been successfully carried on by the use of general care and very effective drugs.

Heberden, in 1768, recognized the importance of rest, and the effective results obtained by the use of alcoholic drinks and the opiates.

Brunton wrote history in the treatment of angina pectoris, when he introduced the use of the nitrites.

5. The pathological changes associated with angina pectoris are not characteristic of the disease, and fail to account for the symptoms in many cases.
The new advance in studying cases of angina pectoris, with the purpose of developing more accurate diagnostic methods, is the use of the electrocardiograph. This work promises to disclose much of the possible underlying pathology connected with the clinical symptoms.  

6. The general care of the patient seems to be all important after the syndrome has developed.  

10 The introduction of the purine-base diuretics in the treatment of heart disease, especially angina pectoris, by Ask-anazy, in 1895, has been of definite but disputed value in the continuous care of these patients.  

The insulin and glucose therapy used by Smith may open new leads in the continuous treatment of this disease.  

17 The therapy of tissue extracts is one of the present contributions to the treatment and study of angina pectoris. Most of the work has been done in Europe, but American clinicians are becoming interested in this amazing discovery.  

22 7. The surgical treatment of angina pectoris has been restricted, so far, to the extreme cases, that have not responded to any medical treatment. The real worth of these methods must be determined in the future.  

51 The first surgery used in angina pectoris, was the development of the cervical sympathectomy by Jonnesco, in 1916. Later the plan was brought to the attention of the medical world by Coffey and Brown.  

61 The division of the posterior roots of the thoracic nerves was advanced by Spiegel, cited by Brooks, and later, the dorsal laminectomy was performed by Singer, cited by White.
A very effective procedure has been the dorsal sympathectomy used by J.C. White. He has obtained good results.  
\[55,56\]
Paravertebral alcohol block, suggested by Mandl and developed by Swetlow and White, has given very promising results \[52,53\] in their hands.

The thyroidectomy, subtotal or total, has suggested a new approach to the problem of angina pectoris. Much work is being done on this surgical phase of the treatment by Blumgart, Levine, Berlin, Davis, Riseman, and Weinstein. Further study \[5,6,7,8\] must be made before the value of this method is determined.
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