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## Etiology of angina pectoris with special reference to coronary spasm

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ETIOLOGY OF ANGINA PECTORIS  
WITH SPECIAL REFERENCE TO CORONARY SPASM AS THE CAUSE.

BY  
John A. Kahl.

Dedicated  
to the memory of  
MY FATHER.

I present this thesis to the faculty of  
The University of Nebraska, School of Med-  
icine, as partial fulfillment of my work  
for the degree of Doctor of Medicine.

1935.

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## INTRODUCTION.

The etiology of angina pectoris has been at disagreement since the first recognition of the disease. Theories have been advanced by the hundreds, the views as to the one most sound have predominated the medical field at different areas.

The subject originally chosen was Coronary Spasm, but it became apparent that the other theories and ideas would have to be considered. The old literature was of little value, except as a historical purpose, and the understanding of the old theories. The most of this work had to be taken from recent work, mostly from journals and papers.

To narrow the field to coronary spasm, the cause, while believed by most of the leading authorities, has only recently found sufficient evidence to make it more than a theory. But one cannot forget that there are still cases for argument.

I have tried to cover the literature for last five years, attempting to present all the arguments and experimental evidence found, in a clear manner. But the question is far from finished and it will take considerable work to put the present ideas on a sound footing.

Angina pectoris the "Meditates monte" of Seneca of ancient literature was first described only 164 years ago by Heberden, is by no means a disease of recent origin.

Hippocrates undoubtedly observed some cases, although he did not mention any symptoms, there are never the less references in ancient literature which undoubtedly were angina, the most famous of these writings, is the description by Seneca, who told of the suddenness of the onset of an attack with the impetuosity of a tempest. (1)

Dionis, surgeon to Louis XIV, described two cases which were either Angina or its closely allied syndrome, coronary occlusion.

Hoffman in 1734 and Morgagni in 1689 described cases which were undoubtedly angina pectoris, the most famous being that report of Morgagni, of a well known Italian physician Ferrianni who died of this condition, on who a post-mortem was done. (1) In France Roushon, in February 1768, just five months previous to Heberden's description, described in a letter to Lorry, a case of a cavalry officer Monsieur Charles Captain of the Cavalry, which was the nearest complete description previous to Heberden. Most French authors claim this as the first description of angina pectoris. Huchard quoting Roushon's letter, does not use any expression which described pain as a symptom in the attacks, but Osler, on the other hand, who had evidently seen a copy of the original letter, quotes several sentences showing that

the feeling of suffocation felt by the patient was associated with pain of great intensity and believes that the suddenness of the attack, the pain in the region of the heart, the abrupt termination, and mode of death following exertion after a full meal, favors the decision of a true angina pectoris. (2)

Gaidiner quotes the philosopher Seneca as evidently suffering from the disease, although there is a dispute as to the meaning of Seneca's words. (2)

But there is no doubt that Heberden was the first to give a complete description of angina, but he did <sup>not</sup> separate pain from anguish and fear of death. But never-the-less it was a master piece. As Harlow Brooks states, "There are few instances in medical literature which equal in clarity, in detail of keen observation and in practical accuracy of application, the original publication of Heberden's. Heberden's article to-day stands as the most satisfactory and graphic description of the clinical picture which has yet been written. There is little to be found in any modern article, except as dealing with the etiology pathology, physiology and treatment of the subject which is so complete and accurate as this study. (3)

In 1768, in Transactions of the London College of Physicians, Heberden wrote an article entitled "Some Account of a Disorder of the Breast." The article was not long but very complete, and is as follows.

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"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 medical authors. The seat of it, and the sense of strangling and anxiety with which it is attended, may make it not improperly be called Angina pectoris.

Those, who are afflicted with it, are seized, while walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would take away their life, if it were to increase or to continue; the moment they stand still, all uneasiness vanishes. In all other respects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different.

After it has continued some months, it will not cease so instantaneously upon standing still; and will come on, not only when the persons are walking, but when they are lying down, and oblige them to rise up out of their beds every night for many months together; and in one or two very inveterate cases it has been brought on by the motion of a horse, or a carriage, and even by swallowing, coughing, going to stool or speaking, or by any disturbance of the mind. I have heard, one, and only one person say that he had known it attack him, while he was up and standing still or sitting.



But most, whom I have seen, have been perfectly unaffected with riding in any manner, with speaking, swallowing, laughing, sneezing, or vomiting. One has told me, that this complaint was greatest in winter; another, that it was aggravated by warm weather; in the rest, the seasons were not suspected of making any difference.

I have observed something like this affection of the breast in one woman who was paralytic, and have heard one or two young men complain of it in a slight degree; but all the rest, whom I have seen, who are at least twenty, were men, and almost all above fifty years old, and most of them with a short neck, and inclining to be fat.

When a fit of this sort comes on by walking, it's duration is very short, as it goes off almost immediately upon stopping. If it comes on in the night, it will last an hour or two; and I have met with one, in whom it once continued several days, during all which time the patient seemed to be in imminent danger of death.

When I first took notice of this distemper, and could find no satisfaction from books, I consulted an able physician of long experience, who told me that he had known several ill of it, and that all of them had died suddenly. This observation I have reason to think is generally true of such patients, having known six of those, for whom I had been consulted, die in this manner; and more perhaps may have experienced the same death, which I had no opportunity of knowing.

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But though the natural tendency of this illness be to kill the patients suddenly, yet unless it have a power of preserving a person from all other ails, it will easily be believed, that some of those who are afflicted with it, may die in a different manner, since this disorder will last, as I have known it more than once, near twenty years, and most usually attacks only those who are above fifty years of age. I have accordingly observed one, who sunk under a lingering illness of a different nature.

The os sterni is usually pointed to as the seat of this malady, but it seems sometimes as if it were under the lower part of it, and at other times under the middle or upper part of it, but always inclining more to the left side, and sometimes there joined with pain about the middle of the left arm. What the particular mischief is, which is referred to these different parts of the sternum, it is not easy to guess, I have had no opportunity of knowing with certainty. It may be a strong cramp, or an ulcer, or possibly both.

The opinion of it being a convulsion of the part affected will readily present itself to anyone, who considers the sudden manner of it coming on and going off; the long intervals of perfect ease; the relief afforded by wine and spirituous cordials; the influence, which passionate affections of the mind have over it; the ease which comes from varying the posture of the head and shoulders, by straitening the vertebrae of the thorax or by bending them a little forward or back-

wards; the number years, which it will continue with out otherwise disordering the health; its generally bearing so well the motion of a horse, or carriage, which circumstances after distinguishes spasmodic pains from those which arise from ulcers; and lastly, its coming on in certain patients at night, just after the first sleep, at which time the incubus, convulsive, asthmas, numbness, epilepsies, hyponcondriac languors, and other illis justly attributed to the disturbed functions of the nerves, are peculiarly apt either to return or to be aggravated .

The pulse is, at least sometimes, not disturbed by this pain, and consequently the heart is not affected by it; which I have had an opportunity of knowing by feeling the pulse during the paroxysm; but I have never had it in my power to see anyone opened, who had died of it; the sudden death of the patients adding so much to the common difficulties of making such an enquiry, that most of those, with whose cases I have been acquainted, were buried before I had heard that they were dead.

But though it be most probable that a strong spasm be the true cause of this disease yet there is some reason for thinking, that it is sometimes accompanied with an ulcer, and may partly proceed from it; for I have seen two of these patients who often use to spit blood and purulent matter, one of whom constantly asserted that he felt it come from the seat of the disorder. Another had a painful sensation in

swallowing, and upon pressing the part, which seemed to be affected. From a fourth, who fell down dead without any notice there immediately arose such an offensive smell, as made all who happened to be present, judge, that some foul abcess had just then broken.

Bleeding, vomits and other enoculations, have not appeared to me to do any good. Wine and cordials taken at going to bed will prevent, or weaken, the night fits; but nothing does this so effectually as opiates. Ten, fifteen or twenty drops of Tinctura Theloina taken at lying down will enable those to keep their bed until morning, who had been forced to rise, and sit up two or three hours every night, for many months. Such a quantity ~~or~~ a greater might safely be continued, as long as it is required; and this relief afforded by opium maybe added to the arguments, which prove these fits to be of a convulsive nature. Time and attention will undoubtedly discover more helps against this trying and dangerous ailment; but it is not to be expected, that much can have been done towards establishing the method of cure for a distemper hitherto so unnoticed, that it has not yet, as far as I know, found a place or a name in the history of diseases." (4)

Jenner was the first to describe the association of the disease of the coronary arteries with angina. (2) This was done in a letter to Heberden in 1776 after Jenner had seen the famous John Hunter, who had his first attack of angina pectoris in 1773 and his second 1776. Jenner did not pub-

lish his letter, as he did not wish that Hunter should know and see his opinion. Hunter suffered for twenty years from angina pectoris, and, as it is known, died at a meeting of the Hospital Board of the St. John's Hospital in October 1793. Further descriptions of the disease were published by Frothergill, Parry, P.M. Lanthom, Stokes and other English physicians. Allan Burns, in 1809 was the first to bring forth the theory of intermittant claudications. (2)

Huchard collected 64 different opinions from many well-known physicians as to the cause of angina pectoris, a few of these will be mentioned. Rougnon and Heberden, as shown, believed in a spasm of the heart, Hunter and Jenner believed it to be due to ossification of the coronary arteries. Parry considered as possible a spasmodic condition of the myocardium, a momentary exaggeration of an existing feebleness of the heart. Frothergill, because most of the patients were obese, thought it was the result of fat in the mediastinum. P.M. Lanthom was the first to consider angina as a symptom complex and not a disease. (2)

Virchow, Cohnheim and Qerain believed it to be due to embolism, or thrombosis of the coronary arteries. Bouilland and Bucqury believed that there were two types of angina pectoris, one coronary and the other neuralgic or neuritis. (2) Trousseau was of the belief that angina pectoris was a form of epilepsy. Sir James Mackenzie in his latest writing believes it due to an exhaustion of the cardiac muscle and in

other places he speaks of it as if it were of nervous or vascular origin. Verdon believes it is a neurosis of the various segments of the cord, in which the neurons show evidence of inflammatory processes.

The last important discovered was that of Louder Brunton who was the first to suggest the use of nitrites in the (1) vascular spasm.

So in suming up this brief history, the outstanding contributions concerning angina pectoris was first Heberden who gave the first complete clinical description of the disease, second Jenner was the first to associate the clinical syndrome with diseases of the coronary arteries and third and last Louder Brunton who was the first to give a treatment which would relieve the attacks, the use of nitrites, now let us turn to a brief resume of the anatomy and physiology of the blood supply to the heart.

The blood supply to heart is mainly through two coronar-iesarteries. The left divides almost immediately after leaving the aorts, into the left circumflex and a larger ant ramus descendens. The former runs in the atrio-ventricular groove to the left terminating in a descending posterio~~ra~~ ramus. The anterior descending ramus encircles the pulmon-ory artery on its left and runs downward in the interven-tricular septum to the apex. Near its orgin septal branch-es are given off. The right coronary artery runs to the right in the fat of the atrio-ventricular sulcus and term-inates posteriorly in several descending branches in the right ventricle. Special twigs supply the Sino-aricular node and conducting system. Considerable variation occurs in the distribution and anastomoses of the several branches, both in different species and in different hearts of the same species. It is also probable that considerable modification in vasculorization of different areas occurs as age advances, this being certainly true as a sequence of disease. Gross believes that the left coronary develops more extensive an-astomosis and its branches supply increasingly greater areas, with greater numbers of tributaries as the individual be-comes older. This left coronary preponderance is probably a morphageral compensation for the gradually developing fibra-tic changes.

The branches of the main coronary rami pass superficially in the general direction of the apex, and from these intra-

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mural branches run directly inward - more perpendicularly into the left than into the right ventricular muscle. These subdivide repeatedly and form very extensive capillary plexuses around the muscle elements. The endothelial cells of these capillaries appear to form the boundaries of the lymph channels.

According to most authorities inter arterial anastomoses between branches of the same and different rami are numerous particularly in the interventricular septum, roots of the large vessels and in the auricles. (1)

In addition there are three subsidiary systems of arterial anastomoses exist; first an extensive anastomosis between the coronary branches and extra cardiac branches of the aorta, particularly at the site of the pericardial reflection around the ostia of large veins, second arterio-luminal vessels running directly from the coronary arteries into the cavities of the heart and last the arterio-sinusoidal vessels communicating with ventricular cavities by means of myocardial sinusoids. (1)

The coronary arteries belong to the muscular type of artery with three coats, the intima, media and adventitia. Before Edholm (1912) reported his studies, little or nothing was written as to the normal histology of the coronary arteries, little was done until 1923, Wolkoff published his study of nine hearts of different ages. (2) McLeans work on 95 hearts supported the following 1) The small muscular art-



eries of the myocardium and the small epicardial arteries have a similar picture in normal healthy individuals, that is an intima bounded internally by a single layer of endothelial cells and externally by a waxy internal elastic lamina between which there is only a small amount of fine fibrous tissue. In the intima of the smallest arteries there is no fibrous tissue. The internal elastic lamina as McMeans has pointed out, consists of an acellular band of homogenous material, which under certain conditions will split and disclose its inner composition. This seems to be a laminated structure of fine fibrillar material. McMeans has shown that any inflammatory or toxic substance acting in sufficient concentrations results in a dissolution or alteration in the sheath of this elastic lamina and gives the appearance of splitting, once induced is permanent and maybe increased by further injury. The media is made up of involuntary smooth muscle fibers, varies in thickness with the diameter of the lumen. Between the muscle fibers which run in a circular direction, is the small amount of fine fibrous tissue showing a small number of fine elastic fibrils. The external coat or adventia consists of loose connective tissue bundles made up of collagen fibers inter-mixed with a considerable number of elastic fibrils and some muscle cells. As a rule this coat in the smaller arteries is two or three times the thickness of the media. The elastic tissue rarely forms a true external elastic lamina. In the medium sized arteries (a group usually

made of the descending and circumflex branches of the coronary arteries which run in the epicardial fat) the intima presents a few longitudinal muscle fibers lying internal to the internal elastic layer. (2)

The right and left Coronaries, the larger arteries, whose coats follow roughly the same proportional sizes to one another as those in the medium sized arteries. Small nutrient vessels and sympathetic nerve fibers are found throughout the adventia of these main stems. It has not been possible to determine definitely how far inward these nutrient vessels pass in a normal coronary, but in sclerosis they have been seen to pass the entire wall into the intima. (2)

Physiologists have long known the heart has a double nerve control, the cardio-inhibitory nerves (vagus) and cardio-accelerator the sympathetics. It is also known that these nerve fibers accompany the blood vessels, the coronaries as well, as shown by degeneration experiments. (3) PP 254

Experiments of Sutton and Lueth appeared to demonstrate conclusively that sudden mechanical constriction of the coronary vessels invariably gives rise to pain, referred to the left foreleg of dogs. The nerve fibers concerned accompany the blood vessels and proceed over the sympathetic system, for it was unaffected by vagus section and was abolished by painting the arterial walls with alcohol and by removal of the stellate ganglion. The exact action of the two nerve systems is still questionable, but it is thought that the va-

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gus is the pressor to the coronary arteries. It was found that section of the vagus caused an increased coronary flow, but stimulation of the distal end caused a decreased coronary flow and stimulation of the sympathetics causes an increase in blood flow through the coronaries. (3)

We shall now turn to the main theme of this subject. Angina pectoris is a condition improperly named in order to give us any concept of it. It is a disease only recently known to medicine as an entity in itself, and there is still some discussion as to whether it is such, and not a complex of symptoms.

This disease is not one of child-hood nor it is not unknown in the aged and decayed. But its greatest prevalence is at middle life, as autopsy study of 141 fatal cases of angina showed, the average age of onset for men was 56 years and women 58.1 years. (14) But angina in its typical manifestations is far from unknown in young persons. Heberden refers to case in a boy at 12 years, probably on a rheumatic basis. Fothergill publishes two typical cases at 25 and 30 years. Allan Burn's patient suffered it at ages 34 to 40 years, all of these probably being on syphilitic basis.

Verdon has seen two definite cases in children and three in adolescence, all of which ended in recovery, so they were undoubtedly on a rheumatic basis. Dr. Hugh Stewart has published a case in a boy age 7 years which come on at the conclusion of a severe rheumatic fever, first indefinitely, and then in frequent typical attacks, sudden pallor, pain and anxiety. Such was the child age 12½ years Verdon saw in his private practice. In these cases in young persons with heart sounds, generally end in recovery, so far as the angina is concerned. Many syphilitics develop angina between 40-50

and not rarely 25-35 years.

It is generally believed that this disease is one which falls upon the upper classes, but Allbutt has not found it quite so rare in hospitals as generally supposed. Both gout and angina pectoris are supposed to be diseases of the easy and intellectual classes, and both are not infrequently associated with high blood pressure, with the people as a whole leading a sedentary life, consuming large quantities of rich foods. But Somberger quotes seventy three cases in the Poly-clinic of Prague in 1895 to 1898, of poor working people. (35)

In regard to sex, it is much more common in the males. Husband two hundred and seventy three cases show the proportion of one female in every sixty cases, Allbutt's show three in 100, and Osler 1 in every 40 cases. (35) For this great difference in sexual susceptibility no very definite explanation can be made, for the anatomy of the coronary arteries and the heart are the same. It has been said that the difference may lie in some measure to a lower incidence of syphilis and gout. Perhaps to some extent in a greater protection of the thoracic aorta from physical strain. This seems to point out that angina is not in the nature of a neurosis, otherwise it would be more prevalent in the female sex. (35)

Heridity is considered to play no part in angina pectoris, but nevertheless a proclivity seems to run in families not infrequently. Robert Hamilton was the first to call attention to this. Neuburger found 20 cases his 143 cases with

a blood kindred.

It is often stated that it is usual in angina pectoris, to find a hereditary tendency to irritability of the nervous system, but Allbutt thinks it is not so. (35)

Season change seems to have little influence on the incidence of the disease, as was stated by Heberden, and agreed to by subsequent teachers.

Allbutt seems to think that the causes of angina, have much in common with the causes of any arterial disease. Foremost is physical labor as upheld by Gibson, but this statement should be qualified, because of the higher incidence of syphilis and rheumatism in the cities. When the first attack does come on during exertion, it is usually of a mild type as walking against a wind, wielding of a fishing rod or a golf club. The moments of most seizures are often determined by effort, even by effort of mind or emotion. Yet Heberden has told us attacks come on during rest and even sleep. Didenot died of angina, a very severe attack awoke him from sleep, and so with many other cases.

Such nocturnal accesses maybe in obedience to secret tides of blood pressure, as we must remember, apoplexy not infrequently occurs during sleep.

Tobacco seizures, whether anginal or cardiac origin, occur at ghostly hours. It has been recently noted that smoke ing of cigarettes produces a marked temperature drop of surface of fingers and toes, even in the habitual user, the ave-

age drop from one cigarette was 5.3 <sup>o F.</sup> while the maxium was 15.5 <sup>o F.</sup> It was also found that this effect was the result of tobacco and not nicotine alone, as denicotinized cigarettes had the same effect. The underlying cause was the vaso constriction as in the capillaries of nail bed, by slowing and stoppage of blood.

So it is logical to think it might bring on the anginal attacks, by similar effects on the coronary arteries. (25)

The strain of continuous H.B.P. in order to damage the arterial walls, must have run for years at excessive heights. It is the general idea, that angina pectoris is commonly seen with a high blood pressure, but such is not the case as shown by Epplinger and Levine. They found in 141 fatal cases of angina that those having normal blood pressure showed the disease begins about four years earlier and lasts a little longer, but the age of death is an average of three years sooner. The blood pressure findings of the males of which there were 111 was an average of 149.2 systolic and 89.2 diastolic. While corresponding figures for women were 190 systolic and 102 diastolic. It is also important to note that there were 46 men with a systolic reading under 140 mm, there were no women with such a low reading. (14) It must also be remembered that angina for the greater part, is a disease of the elderly in whom pressures are notably a little higher. Kauffmann says that pain, with a normal heart, raises the minute volume, the B.P. and the heart's work. So it may be that the

arterial pressure maybe driven up during an attack. This seems to have been verified by Allbutt, Morrison, Mackenzie and Price. (35) But Huchard and Porter say that pain causes the B.P. to fall. But with all taken into consideration, we might consider B.P. as having little relationship to angina pectoris. Allbutt is of the opinion that too much mental and emotional strain is a basic cause for angina.

White lays emphasis on the stress and speed of modern life, and the news paper reports of frequent sudden deaths seem to corroborate this contention. It has more or less been accepted that brain workers at high tension are particularly liable, but Bass and Donnor report that the incidence in the working class is also high. Herrick is of the opinion that this condition, like cancer, the apparent increase is partly due to the fact that larger numbers are reaching the senescent years.

Now we must get to the causes of this condition, trying to find a reasonable and scientific basis. Since in coronary thrombosis we find a similar set of symptoms, and also electro-cardiogram changes. But in angina the pain is only transient as compared to the coronary thrombosis.

With these facts we can begin to study the autopsy findings in hope of finding an explanation of the disease. At the present time we must consider for pathology in angina pectoris, three parts of the vascular system. First the involvement of the coronary arteries, second the changes of the



first portion of the ascending aorta and, third the changes in the cardiac musculature.

The defenders of the first hypothesis attribute pain to ischemia caused by organic changes or spasms of the coronary vessels, many authors are inclined to believe that spasms are usually caused by anatomic changes. Recent investigations have shown that the heart as well as the coronary vessels possess sensory nerves and may perceive pain <sup>(4)</sup>, this being the basis for considering organic changes.

Koch and Kong made a special study of serial sections of hearts with special attention to the analysis of the coronary circulation in cases of stenosis and occlusion of the coronary artery. The Spalteholz's method of colored injections and preparation of transparent specimens were employed <sup>(12)</sup>. The specimens were obtained chiefly from persons with typical angina pectoris. The only pathologico-anatomic changes of the coronary arteries study were those of arterosclerotic and syphilitic processes, because they dominated the circulatory disturbance. The three processes responsible for occlusion or stenosis of the coronary arteries, were first, atheroma, second, fibrous occlusion and, third, thrombosis--very rarely endarteritis obliterans <sup>(4)</sup>. Frequently a combination of the three processes may be found. Predominance of one of the forms allows a conclusion as to the time of appearance. The non-calcifying soft atheromatosis is of great importance for coronary

occlusion while the calcifying arteries is of lesser importance for circulatory disturbances in the cardiac muscle. Recanalization of occlusions generally can not be identified with a communication of the interrupted section of blood vessels; it takes place only in spaces extending to a lateral branch; new lumina of vessels are formed also by the organization tissue in niches of altheromas. The syphilitic coronary occlusion is the result of a lesion of the wall of the aorta and not of the coronary arteries; usually the occlusion is only a few millimeters thick and develops in the course of a case of syphilis with a rapid course. When the coronary circulation is affected by an occlusion as discussed, the rich formation of anastomoses of the cardiac circulation must be considered. Main anastomoses are located between the areas of the right coronary and the circumflex arteries. The diameters and ramifications of such branches vary considerably. The anterior descending artery is an independent branch with few anastomoses except in the lower portion leading to the right coronary artery; therefore the above mentioned artery is inclined to formation of infarcts which, if confined to this area, are of minor functional importance. Occlusions in the three-main coronary branches develop as follows: in the proximal portion of the descending and in the peripheral portion of the other two branches. On account of the formation of the lateral branches, the location of the occlusions is of great significance. Cardiac infarcts may be ex-

pected in angina pectoris, which produces grave attacks or death. In such cases usually an occlusion of two of the main branches is found. A grave stenosis in a blood vessel and under development of one of the larger may create conditions similar to an occlusion, but if an occlusion follows in the second main branch, the picture resembles rather an acute cardiac failure, than an attack of angina pectoris.- A Syphilitic coronary occlusion is located close to the origin of the coronary arteries; therefore, the lateral branches can not participate in collateral circulation; the occlusion develops slowly, hence infarcts are relatively rare and formation of anastomoses is prevented; sudden death and also attacks of angina pectoris in cases with a syphilitic coronary occlusion are due to increasing limitation of the blood supply by a single artery; sudden overloading caused by various factors produces ischemia of the entire heart with resulting insufficiency.

The soft antheroma is much more dangerous than one with marked fibrous nodular development, because it rapidly fills out the lumen and maybe accompanied by acute swelling; the fibrous, nodular form is relatively benign and only rarely produces an occlusion. The secondary arteromatous calcification occupies a space between the two above mentioned forms. In cases with advanced calcification the walls become stiff but the lumen of the involved blood vessel is rather dilated, because calcification is preceded by loss of fluid and shrink-

age of the detritus material in the arthroma. On this basis the theory was advanced by Loffler, of foam thrombosis. With a rapid fall in blood pressure, and the insufficient regulatory capacity of the coronary arteries lost there results a liberation of gas from the arterial blood. The gas and blood obstructs the smaller arteries and capillaries (26). But one must take into consideration that this relative dilation is compensated for, by organization of the artheroma and cicatricial sclerosis producing a stenosis. The relative harmlessness of calcification of the intima, but not of the media is exemplified by the senile-ectotic arterial system. The degree of involvement of the media determines the malignancy of the artheroma. Regressive changes in the intima with artheroma may lead to a special stenosis produced by hemorrhage and formation of small thrombi; ultimately they may cause an occlusion. This condition however is rare. The fibrous occlusion plays relatively important role in chronic coronary occlusion, the process is preceded by an atherosclerotic lesion of the blood vessel. Not the soft artheromas but calcifying artheromas or such which under-go organization are responsible for a fibrous occlusion, but this condition was found less frequently than young connective tissue. A slow obliteration of the capillaries seems to be rather the cause than the result of fibrous transformation. Such fibrous occlusions do not seem to have any relation to an organized thrombosis. In serial sections it can be seen that the thrombosis takes

origin from an atheromatous ulcer, the contents of the arteroma being in direct contact with the thrombosis.

The possibility of an exclusive syphilitic lesion of the coronary arteries must be admitted but is of no practical importance. Usually the syphilitic process is located in the wall of the ascending aorta; proliferation of the intima and cicatrization produce a stenosis and resulting occlusion of the ostia of the coronary arteries. It was found in mostly young and middle aged persons. It was found that in young people proliferation of the intima dominates the picture, while in older people the aneurism is more frequent.

For the study of circulation as a result of coronary occlusion, Koch and Kong, used hearts which were made transparent with wintergreen oil and benzyl benzoate, the arteries were injected with chromium yellow gelatin. It was found that the lumen of both arteries and the area supplied by them varied considerably. Knowledge of the main anastomoses and variations of the course of the arteries, is essential for evaluation of the importance of stenosis and occlusion, in regard to the function of the myocardium. It was found that the arterial descending artery is the one chiefly affected by occlusion of arterosclerotic origin, next most common is the right coronary and circumflexed artery, either in the first portion or more distally in the vicinity of the left border of the heart. The right artery is most frequently in the vicinity of the formation of the posterior descending

artery.

In cases with occlusion of the descending artery, the deep, subendocardial layers of the anterior wall of the left ventricle and the anterior ventricular septum are affected, (23) while the circumflexed artery has relations to the deep, lower and lateral layers of the left ventricle. The more external and upper layers of the left ventricle on the posterior wall, including the upper ventricular septum, are supplied chiefly by the right coronary artery; hence the right ventricle except its part in the ventricular septum is relatively rarely affected. Occlusions in the right coronary are found chiefly in its peripheral portion in which the branches supply not the right but the left ventricle. This gives the pathological changes in coronary disease, even here Koch and Kong admit that pathology is not found in all cases of angina pectoris and is probably the result of a spasm. (12) Now

let us consider the second part of the vascular system, that is the incipient portion of the aorta. We can consider pathological changes here as of three sources of origin, first athermatous changes, second syphilitic aortitis, and third the non-specific inflammatory diseases associated with necrosis of the media. (35) The clinical picture of these diseases is sufficiently known, but their consequences in the patho-physiologic sense remain to be specified, especially as regards syphilitic aortitis in its incipient stage, arteriosclerotic changes are present almost regularly in old people,

causing but little trouble and non specific aortitis is rather rare. (18)

In discussing the patho-physiological changes of the aorta the first noticeable change is an accentuated second aortic sound. The cause for this is an increased tension of the vascular wall, which in turn, depends, in the presence of a normal blood pressure, upon an increase of the vascular caliber, decrease in thickness of the wall, and an increase in the electricity modulus. An increase in the electricity modulus is observed in syphilitic aortitis before any morphological change can be found, while in severely atherosclerotic or non-specifically changed aortae may still possess their normal extensibility. With an increase in the electricity modulus in the presence of a normal blood pressure impairs the air chamber function of the aorta. This increases the insufficiency volume and so decreases the coronary circulation. To prove this Hochrein constructed a model having the same circulatory possibilities as the sinus Valsalvae and the incipient portion of the aorta and to which an air chamber was attached. In a site corresponding to the coronary orifices, an outer tube permitted measuring of the inflow pressure or of the fluid allowed to flow in. The periodical perfusion was regulated by a "rhythmization" constructed by Braemser. The pulse rate, speed of the stream from the heart to the aorta and the size of the air chamber function, the aortic and coronary pressure and circulation could be var-

ied. By increasing the volume 50-100% passing through the aorta, while at short intervals had little effect, but accumulating with time may lead to cardiac insufficiency, as shown in table below.

Pulse rate	Beat volume c c	Maximal aortic cm. of water	Physiologic insufficiency vol.	
			Pressure with air chamber	Without air chamber
68	40	50	0.70	1.00
68	40	70	0.70	1.08
68	40	90	1.00	1.15
68	80	50	0.49	0.58
68	80	90	0.60	0.65

A further injurious moment the fact, shown in the table below, that the blood supply of the coronary arteries in the absence of the air chamber is effected under higher pressure and in unarranged jets, while it is continuous and smooth in the presence of an air chamber. It is obvious that under such conditions, the heart cannot adapt itself to a greater strain, since the indispensable premise for it, namely, an increased coronary circulation is not given. Greater strain and impossibility for the heart to adapt itself are therefore the causes cardiac insufficiency resulting from aortic involvement. (18)

Pulse rate per minute.

With air chamber			Without air chamber		
Aortic pressure in cm. of water	Coronary pressure in cm of water	Coron- ary cir- cc per minute	Aortic press- ure in cm of water	Coronary pressure in cm of water	Coronary cir- culation in cc per minute
53.5/47.0	52.5/46.0	890	53.5/33.5	54.3/34.0	720
72.0/66.5	69.5/63.0	1000	72.0/51.5	73.0/51.0	880
95.0/90.0	92.0/86.0	1150	92.0/70.5	94.5/71.5	1030
110.0/105.0	107.0/103.0	1120	110.0/88.0	112.0/88.0	1060



28

Hochrein concludes that the theory of aortalgia cannot be generalized, as has been shown by a large autoptically controlled material; the coronary theory is limited by the fact that angina pectoris does not at all appear each time the anatomic conditions are given. But he does show how the condition is brought about that is loss of the elasticity of the aorta. (18)

Biger and Parode found that contraction of the heart had no decreasing effect on coronary flow, but on the contrary an increase, beginning at systole and a maximum flow was found at the height of systole. And so against Hochrein's idea that excessive activity of the heart lead to insufficiency, they found that cardiac contraction promoted the coronary flow. (30)

Now the last factor to be considered from local pathological changes is the cardiac musculature. Buchner made studies of ten patients who had attacks of angina shortly before death. Necrotic foci were found in all cases, although the macroscopic inspection did not reveal any pathology. Attacks which occurred a considerable time before death left traces in the form of cicatrices. The necrotic areas were found chiefly in the internal layers of the left ventricle, particularly in its papillary muscles and trabeculae. Myocardial necroses of recent origin were located mostly in the vicinity of older foci. Large defects of the myocardium may originate from a confluence of a few foci of various ages. The cause of predilection of the above mentioned areas for necrosis may be due to involvement of the corresponding areas of the coronary system,

however, this theory can be applied only to cases of coronary sclerosis, but not to patients with syphilitic stenosis of the coronary ostia; peculiarities of the distribution of blood vessels or variations of functional demands by certain portions of the myocardium may be responsible for the frequent lesions of the internal layers of the left ventricle. (8) An anemic infarct of the myocardium may also be produced not only by an embolic or thrombotic occlusion, but also by a prolonged spasm of one coronary artery which may lead to anemia and make possible necrosis of a circumscribed region, which may later become complicated by inflammatory changes. In the cases where the foci of softening are situated close to the surface there develops simultaneously a fibrinous inflammation of the pericardium an epistenocardiac epicarditis. If the patient does not die during an anginous attack there occurs a substitution of the focus of softening by connective tissue, the myocardial wall becomes thinner and in some cases a cardiac aneurysm develops. (13)

But Buchner does not agree to the spasm as a cause of the necrosis, he says that under these conditions, a strain is thrown on the heart and indirectly on the coronary circulation influenced by the vagus nerve, and so anatomic changes take place with a resulting ischemia not of a hypothetical spasm. (8) He states that the pain is result of the cardiac muscle squeezing out the products of autolysis from infarcted areas with a resulting irritation of the sensory terminal appar-

atuses in the heart.

Now that we have discussed the local pathology and physiopathology, we can now turn to the final analysis, namely the autopsy records.

Verdon collected autopsy records of cases of angina pectoris, from Tocchi, Sir John Forbes, Potain, Gothwair, Huchard, and Olsen. This group included 283 cases. They found coronary diseases in 50.1%, while no coronary changes were found in 49.9%. But this was undoubtedly a macroscopic study and limited to a study of only the coronary arteries, not mentioning the cardiac muscle. (36)

Then Dr. Harlow Brooks collected autopsy records, without regard to angina pectoris or heart disease. The average age being 45 years. In 398 cases with all kinds of causes of death, he found coronary disease in 270, or 73.3%. So he concludes that angina pectoris is not dependent on coronary pathology since such a high percent present coronary disease, without all having angina. (37) Desportes examined many bodies over 50 years of age and found coronary atheroma at least as common in women as in men. Thoree says "Life is often prolonged with both coronaries closed, and yet without anginal pains." But he gives no specific incidence. But Dr. Samuel West reports a case in which one coronary is stopped and the other orifice so minute no blood could have traversed it, to get to the heart, yet there were not anginal pains. Sir Clifford concludes "That disease of the coronary arteries does

not set up angina, is an axion founded on universal experiences." (36)

So we are forced to turn away from disease of the heart, aorta and coronary arteries as the etiology of angina pectoris and look for other reasons.

Physiology has shown that there must be a proper balance between energy taken in and energy expended. The heart muscle receives its nourishment by means of the coronary arteries mainly as stated earlier in this paper, but a great amount comes through the endocardium by the Thebesian vessels. The reason that makes one sure that angina pectoris is associated with the heart, although the attack lacks all the physical signs, as pulse change heart rate and regularity, and B.P. changes, only pain, and anxiety being present, is the electrocardiographic changes the same as found in coronary thrombosis. H.L. Otto did experimental work on dogs. He put a ligature around the right coronary artery and inversion of "T" wave and fusion of "S.T." waves resulted. On ligating the left coronary artery he found an increase of the "T" wave. (22)

Dietrich was able to show by animal experiments, that the characteristic electrocardiograph changes occur when a misproportion is created between the volume of the blood passing the heart and activity of this organ, it is immaterial whether the misproportion is due to limitation of the blood flow with normal activity of the heart or to an increased cardiac function with a failure of adjustment of circulation. The charact-

eristic changes consist of a negative final fluctuation and the S T interval; they serve as an expression of an insufficiency supply of O<sup>2</sup>.<sup>(5)</sup> This was proved by subjecting animals to air poor in oxygen.

Buechner, Franz and von Lucadow and Walter performed experiments on rabbits. These rabbits were forced to run in an electrically driven cylinder after having been subjected to an acute anemia which injured the entire circulation including the coronary circulation. It was pointed out by various investigators that the electrocardiographic characteristic of the major coronary infarct, namely, a negative ST and T, especially in the first and second leads, were seen to appear temporarily in short attacks of angina pectoris. With the study of the rabbit under the same conditions. Duchosal and Luthis electrocardiograph, which writes in ink, with an electromagnetic oscillograph was used at first, later one with an electrodynamic oscillograph for the purpose of longer excursions. The results were as follows. The mere withdrawal of 1/5 of the total blood caused a negative ST and T waves to appear in the electrocardiogram for about one hour. When the anemic animals were forced to run the typical changes appeared regularly in the first lead, immediately after the strain, and sometimes in the second lead. The changes returned to normal within 24 hours. Next normal animals were taken and forced to run until they were exhausted, and the regular ST and T waves appeared but only remained from 3 to 10 hours. On examining the hearts

(11)

multiple necrosis or young cicatrical areas were found.

In attacks of angina pectoris in the human similar changes occur as reported by Feil and Siegee. They tell of 2 cases while during an anginal attack there were inversion of the ST waves and a return to normal following the attack. (21) Of a 104 patients study by Eppinger and Levine only 20 cases showed a normal curve during an attack, the others being characteristic. (14)

So from the above discussion we may assume that the cause of angina is a disproportion between the volume of blood passing through the heart and the activity of the organ. The foremost explanation today is that of anoxemia, due to a circulatory deficiency. The fact the  $O_2$  properly administered relieves the pain in coronary thrombosis gives a basis. Rothchild and Kissin assume that pain in angina pectoris arises from a localized sensitive area which is affected by a number of stimuli. They noticed that in some cases pain appears only at the beginning of effort, and if the same patient starts slowly, he develops no pain. So they assume that the patient is unable to "Shift Gears" quickly enough. That there is too sudden a nutritional demand by the myocardium and so initiates the pain. They also noted that cold acting as a peripheral vasoconstrictor, often caused many anginal patients to develop pain. And so it is with many patients who develop a coronary thrombosis during an anginal attack, are relieved of their anginal pain following it. This they say is the result of the

sensitive area being replaced by fibrous tissue. With these observations and explanations they set out to confirm them. They started out to investigate the effect of gradually induced anoxemia. For this two groups of persons were chosen. They chose 46 cases, the first were controlled cases, that is first normal individuals with no history of precordial pain and no symptoms referable to the heart. Second individuals without precordial pain, but subjective complaints related to the circulatory system, with objective evidence of cardiac disease, and third individuals having a history of pain in the left chest not due to impaired coronary circulation, but diagnosed spondylitis, brachial neuritis, rheumatic conditions etc. The second group was the individuals with true anginal attacks. This group they divided as follows. First individuals with a history of precordial pain and with objective evidence of myocardial disease as enlarged heart, hypertension, harsh systolic murmurs and dilation or sclerosis of the aorta. Second individuals with a history of precordial pain, but with slight or no evidence of myocardial disease. (23) They then constructed an apparatus which by means of soda lime they controlled the CO<sub>2</sub> and also by rebreathing the air. The patients were told nothing about what to expect and ask only leading questions after the test. The results were as follows; None of the control group developed pain. Of the 26 patients suffering from angina pectoris, 18 developed precordial pain during induced general anoxemia, and 8 did not. But the experiment

was not continued beyond the point of evident discomfort, so they think the S would have developed symptoms if the experiment had continued. It was found that pain did not appear until the oxygen level was down to 7%, one went to 5.9% before pain appeared, while the S did not get down below 8% of oxygen. (23)

Dietrich and Schwiegk assume anoxia as cause of angina pectoris and this was brought out by exposing anginal patients to a negative pressure on air poor in oxygen. (25) With the fore

going experiments it seems rather evident that angina pectoris is caused by anoxemia of the cardiac muscle. Just how this condition is brought about, is the next consideration. That pain in angina pectoris is produced by the same modus operandi as in coronary thrombosis has been shown in this paper, to be generally accepted. Parkinson states that "the claim that the coronary arteries are the source of anginal pain seems today well nigh uncontested." (26) The question is whether it is caused by a spasm of the artery or by partial occlusion.

Spasms are in the body, as have been seen in ocular vessels, with the ophthalmoscope. The result of spasm is evident in Raynard's disease, and as it can be felt in intermittent claudication as shown by a case reported by Lauda. He had one patient that had intermittent claudication in his left leg which gradually increased in intensity for two years until on admittance to the hospital, he began to complain of precordial distress. On the third day after admittance he had a violent sub-sternal pain, and two days later he died. (9) This seems



to show the spastic tendency of the vascular system.

Gulengritz and Jaraslow attempted to show by experiments that the pain is a result of a coronary spasm. They used dogs, and used the blood pressure as an indication of pain. Sensations of pain originating in the heart are carried to the central nervous system by way of either the pressor or depressor nerves; a moderate stimulation is carried through the pressor system while intense stimulation travels through the depressor system producing a diminuation of the peripheral blood pressure. In previous experiments they found that sensation of pain in the liver and kidneys is caused not by contraction, but by dilation of the corresponding ducts. This being a theory as advanced by Wenckebrach and upheld by Kutschera. They believe that pain originates by the dilation of the aorta or the first portion of the coronary arteries. While they do not say that spasm is not present, they claim that the spasm causes a stasis and this in turn dilates the portion of the artery proximal to the spasm and so pain results. So they claim that an increase in pressure can produce the necessary dilation to cause pain. (2) But this opinion is held only by a few. Gubergritz and Jarsolow followed the opinion of most authors in that the heart<sup>pain</sup> is located along the descending branch of the coronary artery. They then ligated this artery as from the atrio-ventricular septum because of important nerve nodes located there which might interfere with the results of the experiments. (4)

The peripheral blood pressure was determined before,

during and after ligation and thus the presence or absence of pain could be detected. A dilation of blood vessels was produced in one series of experiments by the introduction of a thin cannula into the ligated blood vessel above the ligature and injection of a physiologic saline solution through this cannula; thus a dilation of the proximal portion of the blood vessels. In the second series of experiments two ligatures, five to six centimeters from one another, and a cannula introduced between them, this being done to prove stasis was not the cause of pain, but that the constriction from the ligature plus proximal dilation was the cause. The experiments were performed on 14 dogs a cannula was introduced into one of the femoral arteries and connected with a Kymographion. In a number of cases artificial respiration had to be employed, and this interfered some with electrocardiographic records. Then saline solution was introduced very slowly and dilation of the vessels was only moderate and did not produce changes in the blood pressure immediately but the motor effect took place a few seconds after injection with a fall in blood pressure. It could not have resulted by changes in the myocardium, as the time was too short for sufficient change to take place. This latent period tending to prove participation of the nervous system. The considerable fall of blood pressure shows that evidently the sensation of pain is transferred by the depressor system. They conclude that the coronary arteries are the site of anginal pain, but that the dilation and not the spasm was the cause of the stim-

ulation. ~~But~~ they agree with the spasm concept and explain it that the spasm causes a dilation proximal to the constricted area. Kutschera and Aichbergen found a dilation of the proximal portion of the coronary vessels in many autopsies of individuals that died of angina pectoris. They further say that a lesion of the myocardium may cause pain but not of the intensity of a true angina pectoris. Involvement of the coronary arteries will produce pain only if the artery did not lose its elasticity and ability to dilate. <sup>(14)</sup> This seems to point out

that severe atheroma and sclerosis of the coronaries cannot cause pain because they have lost their elasticity. Katz says the pain of angina pectoris is due to a spasm of coronary arteries ~~is~~ ischemia, the latter being attributed to a reflex spasm of the coronary vessels dependent on an increased irritability of nerves and nodes in the walls of these vessels. The nervous system may exert an influence on the lumen of the coronary vessels directly. <sup>(3)</sup> This view is also upheld by Bosco.

He did his work on aerophagia, in relation to angina pectoris and he concluded that it is a reflex of the vegetative nervous nature. <sup>(17)</sup>

The influence on the lumen of the coronary arteries was thought to be hormonal. Shwarzman supposes that the musculature activity, produces a hormone, which enters the blood stream and prevents spasm of the coronary arteries, but in disease of the somatic muscle this hormone is lacking and so the spasms occur. <sup>(32)</sup>

Bridges also advances a new metabolic theory that increased blood uric acid is the cause of angina pectoris.

So he took patients with angina and found the uric acid to be 4.7 mg. per 100 cc as against 3.1 mg. per 100 cc in the normal person. He treated nine cases with salicylates in a watery solution, these cases were not selected only as far as having as angina pectoris. In these cases studied all received relief, some complete in as short as 8 days, as the uric acid dropped to normal limits. He thinks uric acid is not the sole factor but the disease is a metabolic disturbance. (38)

Klemperer was able to show that reflex spasms of the coronary arteries of psychic origin may produce myocardiac lesions caused by local ischemia. (3) Gibson says, "True angina pectoris results from reflex, vasomotor, neurasthenic, and hysterical cases is now beyond the region of a doubt. (34) Lian speaks of functional angar, and he divides it into reflex angar which may be considered as a result of aerogastria, cholethiases thoracobrachial neuralgia, then his neurotic angar and toxic angar due abuse of nicotine etc. (16) Schmidt theory is that angina pectoris is result nerve involvement, and calls it the vasomotor-neurogenous theory. His argument is the presence of first painful points in angina pectoris, located in the areas of the 1st to 5th dorsal vertebrae and left brachial plexus is sensitive to touch. Second he finds a certain analogy between angina pectoris and other neurologic conditions as neuralgia of the trigeminus nerve or sciatica. (1) Neither of these observations seem to be upheld by other men except Rudnitskiy, who says the vasomotor component of Schmidt's theory cannot be dan-

ied.

In assuming that coronary spasms are the cause of angina recent surgical treatment has been employed, on this basis. It is based on an interruption of the paths along which in the anginous attack, the stimulations originating from the heart and give rise to pain and anxiety. It has been found that the most important paths course in the cardiac rami over the stellate ganglion to the spinal cord. At the ganglion a separation of rami communicantes from eight cervical to 4th dorsal, blocks efficiently and without difficulty the transmission of impulses. The stellate ganglion and the important motor fibers passing from it to the heart are left intact. <sup>(4)</sup> But this has merely the same effect as a cardotomy for the relief of pain, but it is doubtful if it cures the site of trouble in the heart. With the cause of angina pectoris as a result of anoxemia, which is quite definitely proven, attention has been turned these last few years to thyroidectomy for heart disease. This procedure was started in 1932 in Boston by Blumgart and his coworkers. The principle is based on the fact that the rate of metabolism is governed by the thyroid gland, although this is still questionable. So if the thyroid were removed, the metabolic rate is lowered; with the lowering of the metabolic rate there is a diminished demand for oxygen by the tissues; if the oxygen requirements are lessened the demands on the circulation are diminished. While a damaged heart cannot carry the full circulatory load of normal metabolism, it maybe able to carry

(4)  
 the complete load of a lowered metabolism. Cutler and Schnitker report 29 cases which had a total thyroidectomy for angina pectoris since Dec. 1932. Of this series 21 patients in whom the postoperative period of observation was from two and one-fourth months to 16 months, showed improvement. The amount of relief was gauged as follows; 47.6% improved from 90-100%; 66.6% improved from 75-100%; 90.4% improved over 50% and only 9.5% improved less than 50%.  
 (42)

Mixter, Blumgart, Herman and Berlin report 75 cases of angina pectoris treated by total thyroidectomy showing quite similar results. (41) It has been found by these men, that all thyroid tissue must be removed if permanent hypothyroidism is to be present and a lowered metabolic rate result. So in attempting to draw any definite conclusion it is going to be quite difficult. A few things seem certain. Pathological changes in the aorta and coronary arteries is not the cause of angina pectoris as autopsy records show, but may be a complicating factor. With the brilliant work recently done on anoxemia it seems to me to leave little question that this is the cause of anginal pain. As to how this condition is brought about there still seems to be a question. It seems since pathological changes do not cause angina pectoris, then it must be a functional condition. The only avenues left would be metabolic, hormonal, nervous, or coronary spasm. Yet little evidence has been advanced to uphold the hormonal and metabolic theories. So this leaves only the coronary arteries and

their nerve control. I believe that the general trend of most authorities is leaning toward the theory of coronary spasm as I have previously quoted, as the fundamental cause of angina pectoris, whether this condition be of local origin or from nerve control has not been worked out as yet.

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