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Etiology of coronary thrombosis

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THE ETIOLOGY OF CORONARY THROMBOSIS

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INTRODUCTION

The subject of coronary thrombosis is one about which very little was known until the twentieth century. Disease of the coronary arteries was noted as early as the 17th century but its significance was not truly recognized until the latter part of the 18th century with the death of Hunter who as a sufferer of the disease.

It was in 1912 that the first classification of coronary thrombosis was attempted by Herrick. He pointed out at that time that the symptoms depended on the size of the artery occluded and divided the cases into those in which death was instantaneous, those in which death occurred in a few minutes, non-fatal cases in which symptoms were mild, and severe cases in which death was delayed hours, days, or months, and at times followed by complete recovery.

This paper did not greatly impress the medical profession but from 1920 on papers began to appear in ever increasing numbers and the disease has become one of the most prominent in the eyes of present day medicine.

With a better understanding of the underlying pathology and physiology, the use of the electrocardio-

graph and interpretation of the findings therefrom, the diagnosis has been made much more simple and a more or less clear cut clinical picture has been developed. No longer is coronary thrombosis to be so often incorrectly diagnosed as in the not so far distant past and its clinical differentiation from angina pectoris is fairly well established.

The better understanding of the disease has also brought about better methods of treatment. The prognosis is still very difficult to predict and should the individual recover from his first attack, the occurrence of a second is a probability which he must face and attempt to prevent.

Thus while much progress has been shown in diagnosis and treatment, the outcome is an individual who must spend the rest of his or her days in semi-invalidism. Thus the problem becomes one of considerable economic as well as clinical importance. Little can be done to repair an already damaged heart and the only satisfactory answer to the problem can be found in the establishment of the etiology and an attempt to prevent the occurrence rather than to effect a cure.

The problem of the etiology of coronary thrombosis has shown much less progress than have the other phases

of the condition. The causes suggested are many and varied and it shall be the purpose of this paper to attempt to sum up the more important factors suggested in the literature to date.

INCIDENCE

Cohn and Lingg, (1934), point out that statistical studies show that deaths due to coronary disease are on the increase. These authors as well as Levine, (1933) and others feel that this is at least partly due to the fall in the death rate from infectious diseases. Levine, (1933) feels that the increased frequency is due to the fact that more people now reach the age of forty, when the degenerative processes begin to take their toll. Increased accuracy in diagnosis is also considered an important factor. Cohn and Lingg, (1934) however, feel that the saving from infections in the younger group is not so important as that in the older group where deaths due to circulatory disease are more common. At any rate the infectious diseases have decreased from forty years of age on since 1900 while deaths due to coronary disease have become increasingly more frequent.

Barns and Ball (1932) in a series of 1000 unselected postmortem examinations found 49 cases of infarction or 4.9 percent of all cases coming to autopsy. In 685 cases 40 years or over there were 47 cases or 6.86 percent of the entire series above the age of 40 years.

The majority of cases of coronary thrombosis occur in the latter years of life. Levine (1929) gives the average age in his series of 145 cases as 57.8 years. The following is a chart of the age distribution in the above mentioned series. This distribution is rather typical.

Decade	Number of Cases
30-39	3
40-49	29
50-59	44
60-69	55
70-79	13
80 plus	1
Total	145

Most authorities are in agreement that most cases are between 50 and 70 years of age. Levy (1936) gives the sixth decade as the most dangerous. Conner and Holt (1930) reported that eight percent of their series of 287 cases of coronary thrombosis occurred before the age of 40 and one percent before 30 years.

Coronary thrombosis is much more common in men than in women. Levine (1929) states that in his experience men predominate about 3.3 to 1. This agrees

fairly well with the figures quoted by other authors. Gordon, Bland, and White (1939) in a recent study of 3,400 consecutive postmortem examinations at the Massachusetts General Hospital found that coronary sclerosis was much more common in men up until the age of 70 years. After this age there was no difference in the incidence.

There is no satisfactory explanation to date, for this marked preponderance of coronary thrombosis in males. Levine (1929) suggests as possible factors, the greater amount of physical work that men do, the more frequent use of tobacco by the male, and the difference in general physique and strength.

There is no definite statistical evidence available at present with which to determine the relative frequency of coronary thrombosis in the different races. However, most authorities agree that the condition is more common in the white race than in the colored.

It has been pointed out by numerous authors that there is an increase in the incidence of coronary thrombosis during the winter months. Spargue (1920) gives this opinion and Mullins (1936) in a study of coronary thrombosis in the New England states found that there were twice as many cases during the months

of December, January, and February as in all the other months of the year together. No attempt to explain this was made.

There is no one occupation in which coronary thrombosis is outstanding in occurrence. It is generally agreed that it is more common among the professional groups and those whose work requires little exercise than among those of the laboring classes who are subjected to greater activity.

Gordon, Bland, and White (1939) in their study of the records of 3400 consecutive post mortem examinations, found that the relative incidence and the degree of coronary atherosclerosis were significantly greater in the 600 patients from the private departments than in the 2800 patients from the general wards. They found that the greatest difference occurred in the middle aged patients, in whom coronary occlusion was twice as frequent in the private group.

ARTERIOSCLEROSIS AND HYPERTENSION

In referring to the etiology of coronary thrombosis, Parkinson, (1932) states that it is a local product of arteriosclerosis. Levy (1932) says, to quote him, "Thrombosis of a coronary artery may be considered as an episode in the natural history of coronary sclerosis, for the thrombus almost invariably forms in a vessel already the seat of atheroma or calcification." Ernstene, (1929) gives arteriosclerosis as the cause in most cases as do the majority of authors. Willius, (1925) states that pathological examination of the hearts of patients dying as a result of coronary thrombosis invariably reveals extensive arteriosclerosis of the coronary arteries. Jones, (1927) states that the sclerotic morbidity is not always wide spread in the arterial system. Not only may the process be localized to the coronary arteries but to only a few centimeters of one of these vessels, or one of the coronary branches may be selected to the exclusion of the others.

There are, however, a definite small group in which sclerosis changes are not present so that it

would seem that coronary sclerosis was not an absolute prerequisite. Levine (1929) feels that small vessel sclerosis was going on in most of the patients in this group.

Both sclerotic changes and thrombosis are most commonly found in the descending branches of the left coronary artery. White, (1931) points out that for this reason the descending branch of the left coronary is often spoken of as "the artery of sudden death", or the "artery of cardiac infarction". Luten, (1931) in searaching for an explanation for the apparent predisposition of this artery to thrombosis suggests the findings of Whitten, (1930) that the arterial branches supplying the left ventricle leave the main stem at right angles and pass directly through the musculature, while those to the right ventricle enter the musculature more obliquely. Whitten believes that this difference in relationship explains the more frequent occurrence of thrombosis in the left ventricle, kinking and consequent vessel wall changes in the main stem, being promoted there by the anchoring effect of the branches.

The fact that sclerotic changes in the coronary vessels, while most common in the middle-aged and old,

are also at times found in younger individuals is of interest. White (1935) states that sclerotic changes are not uncommon in the young and are infrequently found in the first decade.

That coronary arteriosclerosis is an almost constant factor in coronary thrombosis cannot be denied. However, it must be remembered that by no means all individuals who suffer from coronary sclerosis become the victims of a thrombosis. This may be well brought out by a study made by Nathanson, (1925) in whcih on examination at autopsy of 113 cases of coronary disease, an advanced degree of sclerosis was found in all cases. There were 24 of these cases or 21.2 percent in which coronary thrombosis had occurred. This emphasized the point that while coronary sclerosis is undoubtedly an important factor that it must be accompanied by some other condition which is necessary to the production of the thrombosis.

Most authorities are in agreement that hypertension plays a definite part in the etiology of coronary thrombosis. Levine, (1929) states that it is probably the most common single etiological factor. He also states that the occurrence of a sufficient number of cases in which no evidence of hypertension could be found indicates clearly that it is not absolutely

essential. In his series of 145 cases of coronary thrombosis 58 had a deifnite hypertension, that is, a systolic pressure of 160 or over and a diastolic pressure of 100 or over. Evans, Ambler, and Dodson, (1933) in their study of the records of 8,500 autopsies found that arterial hypertension with resultant cardiac hypertrophy characterized a large proportion of the cases of coronary occlusion. They state that 44 percent have a blood pressure of 160/100 or better. Paullin (1921) also lists hypertension as an important factor.

Brill (1938) is of the opinion that hypertension is of somewhat doubtful significance. He bases his opinion on the fact that hypertension is slightly more common in women than in men. Levine (1929) also brought out this point to some extent. He mentions that of the 58 cases with hypertension in his series of 145 cases, 19 were women. Conner and Holt (1930) and Berger (1936) give the incidence of hypertension as about 25 percent to 34 percent of their cases. Musser and Barton (1931) state that exaggerated hypertension plays no part in the etiology.

It is quite probable that both extremes of opinion are represented here and in the absence of

more accurate data it can only be said that hypertension probably plays some part in the etiology but its importance as a factor cannot at present be definitely stated.

The following chart from Allan (1934) gives some idea of the occurrence of hypertension in coronary disease.

Incidence of Hypertension in Coronary Occlusion

Author	Number of Cases	Number with High B. P.	Percentage with High B.P.
Levine, Brown (1929)	145	58	40
Connor, Holt (1930)	287	97	34
Parkinson, Bedford (1928)	100	49	49
White, Bland (1931)	200	50	25
Reisman, Harris (1934)	83	49	59
Meakins, Eakin (1932)	50	24	26
Boaz, Donner (1918)	171	71	42
Evans, Ambler, Dodson (1933)	72	32	44
Total	1108	430	39%

BODILY BUILD, WEIGHT, AND HEREDITY

Levine (1929) gives the typical patient as a well set person, womewhat overweight, often of considerable physical strength who enjoys unusually good health. Such persons have usually been, during their youth, active in athletics.

Glendy, Levine, and White (1937) in a study made comparing 100 patients under 40 with coronary disease and 300 healthy persons past the age of 80 found that the young group were for the most part sedentary in habit, exercising very little while the majority of the old group exercised considerably to well beyond middle life.

The great majority of authors are in agreement as to the part played by heredity in coronary disease. Levine (1929) states that it is of considerable etiological significance. The same author in 1933 says of biological selection, "The latter factor cannot be lightly dismissed, for the very same individuals who succumb to coronary artery disease in the second half of life are apt to be those who were attractive, strong, energetic, both mentally and physically, and able to succeed in early life in competition with

their fellow men or women. They would, therefore, be more apt to marry and have children to perpetuate their builogical tendencies, including a vulnerable vascular system." Bancker (1933) says, "Poor cardio-vascular heredity is the most important single factor involved in the etiology of this disease."

Musser and Barton, (1931) point out the conclusions of numerous men that heredity is an important factor and separate coronary thrombosis into two distinct groups. The first group is made up of elderly individuals who are the possessors of a well marked sclerosis of the arterial tree as a whole and in whom the etiological factors are those of arteriosclerosis in general and represent largely the effects of senescence.

The second group is made up of men, who, in most cases have not yet passed the sixth decade of life, who do not have generalized arteriosclerosis, who may have relatively slight but never exaggerated hypertension, who have been singularly free from past infections and who give a history of coronary occlusion in several members of their family.

It has been previously mentioned that the typical case is of a robust or definitely obese nature. Glendy

Levine, and White (1937) in their study found that nearly 70 percent of the young group were robust in build or distinctly fat, whereas 83 percent of the old group were of average build or had been thin or lean for most of their lives.

Goldsmith and Willius (1937) in a study of the habitus of 300 individuals who had coronary thrombosis found a mean deviation of plus 6.7 percent from the average weight for height and age. Fifty-two percent of the group were overweight, 25 percent were normal, and 23 percent were underweight.

Bulmer, (1932) points out statistical studies which show, among other things, that degenerative disease of a fatal nature in the heart, arteries, kidneys, and liver are 2½ times commoner in the obese than in the standard weights and 3 3/5 times commoner than in the underweights.

Dublin, (1930) in a review of insurance statistical studies found that all ages combined, men of normal weight in the study had a death rate of 80 per 100,000 from organic heart disease. For underweights this figure was 65 per 100,000, or only 80 percent of that for the normal group. For all overweights, the rate was 121 per 100,000 or 50 percent in excess of

that for normals and nearly double the rate among underweights. Moreover, whereas the death rate from heart disease is quite stable in underweights it goes up with increasing weight among the overweights. The death rate from angina pectoris was 14 per 100,000 in underweights, 16 among normals, and 35 among the overweights. Here again the death rate increased markedly with increase in rate.

Under the age of 45 the death rate from organic heart disease was 18 per 100,000 for underweights, 25 for normals, and 30 for overweights. At ages 45 and over, when the actual rates are much higher, the mortality among the overweights from this cause was 58 percent in excess of the normal and nearly twice the rate among the underweights. Extreme overweights had, in fact, a death rate more than twice as high as that prevailing among the underweights.

Niehaus and Wright (1939) in discussing the part played by obesity in cardiac disease are of the opinion that it is an important etiological factor through its added burden and frequent association with hypertension and coronary sclerosis. Goldsmith and Willius, (1937) in their study of 300 cases of coronary thrombosis found that the individuals who had

hypertension tended to be more overweight than did those who had a normal blood pressure.

Hartman and Ghrist (1929) in a study of the relation of blood pressure and weight in 2,042 consecutive registrants at the Mayo Clinic, found that there was a definite elevation of blood pressure with increase in weight.

Beall, (1924) placed fat in the role of a parasite and he feels that the load placed upon the body by the presence of surplus fat is a very important factor in the occurrence of heart disease. He estimates that each pound of fat contains about 4,500 feet or 5/6 of a mile of blood vessels and that therefore a person who is 30 pounds overweight carries 25 extra miles of blood vessels through which the heart must pump blood. He points out the extra load placed on the organs of digestion, excretion, and circulation by such an extra amount of tissue. He feels that by the added strain placed upon the vital organs by such a burden they are worn out long before their expectancy under normal conditions.

The frequent association of abesity with diabetes also brings up the possibility of factors of a metabolic nature. The future will probably feveal much on this subject.

DIABETES

Blotner (1930) states that diabetes and angina pectoris have been recognized as clinical entities for many years, yet not until the latter part of the 19th century was the occurrence of the two in the same patient commented upon. Since that time there have been frequent reports on the incidence of coronary sclerosis as a frequent pathological finding. Blotner (1930) presents a clinical study of thirty-five cases of diabetes with coronary artery disease. He points out that coronary sclerosis occurred in 45 percent of all diabetic cases necropsied in the Peter Bent Brigham Hospital. That the incidence was greater in diabetics than in non-diabetics was shown by the occurrence in 21 percent of the latter group above the age of 40. Wolferth (1937) states that the incidence of acute occlusion is high in diabetics. Evans, Ambler, and Dodson (1933) state that coronary thrombosis is frequently associated with diabetes but that coronary cases with diabetes do not die earlier than those without diabetes. In Levine's (1929) series of 145 cases of coronary thrombosis there were 34 or 23.7 percent in whom glycosuria was found or where it was

definitely known that diabetes had existed previously. Nathanson (1932) in an analysis of 100 autopsies on diabetics found an incidence of 41 percent of severe coronary disease. Above the age of 50 the incidence was 52.7 percent as compared with 8 percent in an even larger series of non-diabetics of the same age. He states that the frequency of coronary disease is almost as high in the female as in the male.

In Enklewitz' (1934) series of 100 diabetic patients past the age of 40 years, 34 showed coronary thrombosis and 45 showed coronary sclerosis. He expresses the opinion that both coronary thrombosis and diabetes in individuals over 40 years of age are manifestations of degenerative vascular disease.

Warren (1930) states that in addition to the atheromatous type of involvement, fibrous thickening of the intima frequently occurs in the diabetic.

Levine (1932) mentions the fact that in recent years attention has been called to the occasional precipitation of an anginal attack by the injection of insulin and points out that following the injection there is an increase in the work of the heart of about 25 percent. He further states that a temporary glycosuria may be present, disappearing after the first

several days of the attack.

Raab and Rabinowitz (1936) found that in non-diabetics whose sugar tolerance was studied within two weeks of their occlusion, there was a high percentage of the group who showed an abnormal sugar tolerance. They also point to numerous cases in the literature in which patients with no previous history of diabetes suddenly developed a marked elevation of blood sugar with glycosuria following coronary thrombosis. In most cases this persisted for several weeks and then dispapeared. They attempt an explanation on the basis of a distrurbance in the vegetative centers of the brain.

Blotner (1930) states that the sudden lowering of the blood sugar concentration by insulin may be dangerous for the elderly diabetic patient with vascular disease. Such a patient is likely to have coronary sclerosis as part of a generalized arteriosclerosis and the sudden lowering of the blood sugar may induce thrombosis and a fatal outcome.

Dublin, (Levy, 1936) states that the disturbance of fat metabolism in diabetes is probably the important factor in the diabetic tendency to arteriosclerosis. Brill (1938) states that hypercholesterolemia arising

from overdosage or other causes, although of probable importance in coronary artery disease, cannot be regarded as of exclusive etiological importance. Cruickshank (1931) is of the opinion that both coronary thrombosis and glycosuria are more probably the result of a common cause (vascular degeneration) rather than that glycosuria is an etiological factor in coronary thrombosis. Nathanson(1925) suggests the possibility that in a certain percentage of cases a degree of pancreatic artery sclerosis sufficient to produce diabetes may occur with coronary disease.

That diabetes is commonly associated with coronary thrombosis is definitely agreed upon by most authors. The importance of the underlying metabolic factors cannot as yet be determined. Many authorities feel that these factors are of extreme etiological importance while others feel that the occurrence of diabetes and coronary thrombosis together merely indicates a type of individual with a vulnerable vascular system. (Levine, 1929)

SYPHILIS

There is considerable difference of opinion among the various authors as to the role of syphilis in the etiology of coronary thrombosis. White, (1931) discusses a type of coronary disease due to syphilis, in which the lesion is primarily in the media but the intima eventually becomes involved also and the lumen of the vessel is ultimately narrowed and at times occluded. He makes no mention of sudden occlusion from this cause. Stroud (1932) and Bancker (1933) feel that syphilis is a definite etiological factor.

Levine (1929) states that syphilis is rarely an underlying factor in the causation of coronary thrombosis. This is in agreement with McKeen (1926) White and Bland (1931) and others. Of the 145 patients in Levine's series, 89 had Wasserman tests and of this group only 3 showed positive. Similar results were obtained by Applebaum and Nicolson (1935). In their series of 168 cases they found ten cases which were due to syphilis with a moderate degree of aortitis. In 9 of these cases, occlusion of one or both coronary orifices was caused by the luetic process in the aorta and in one case the main trunk of the right coronary

vessel from the orifice down to the bifurcation was occluded by a thrombus. In this case the vessels were free from sclerosis.

Conner and Holt, (1930) in their series of 274 cases found 39 cases of proved or probable syphilis or 14.2 percent. Levy, Bruenn, and Kurtz, (1934) in a survey of the clinical and pathological records of 762 cases of coronary disease found the incidence of syphilis to be 13.4 percent and concluded on this basis that syphilis is no more common among patients with coronary disease than in any unselected group of cases.

Warthin, (1930) states that syphilis of the coronaries involves most frequently the smallest intermuscular branches; only rarely are the main divisions the seat of active syphilitic lesions. In the small vessels of the adventitia showing perivascular infiltrations and fibrosis, resulting eventually in obliteration. Sclerosis of the intima invariably results and syphilis must be regarded as one of the causes of coronary sclerosis as it is of aortic sclerosis.

After studies of the findings of 1289 autopsies between 1919 and 1929 he concludes that : (1) Active syphilitic lesions of the larger coronary branches are

infrequent. They rarely produce occlusion of the vessel or lead to thrombosis or myocardial infarction; (2) Arteriosclerosis of the coronaries, coronary occlusion, coronary thrombosis, myocardial infarction and angina pectoris are more frequent in the latent syphilitic than in the non-syphilitic. Syphilis predisposes secondarily to coronary and aortic sclerosis and their resultant cardiac pathology.

TOBACCO

The question of tobacco as an etiological factor in coronary thrombosis has, for quite some time been a point of considerable controversy. The increasing use of tobacco makes the question of considerable importance.

Master, Dack and Jaffe, (1937) in a study of a group of 272 males with coronary thrombosis found that about 70 percent of the group were smokers. Of these 38.6 percent were heavy smokers, 21 percent moderate smokers and 9.6 percent light smokers. They conclude that these figures do not differ from those of society in general enough to be of any significance and they feel that tobacco has no influence on the occurrence of coronary thrombosis.

Reisman (1923) (1934) feels that tobacco is a factor of importance in the etiology of coronary thrombosis. Niehaus, (1939) also feels that it is of considerable importance. Glendy, Levine, and White (1937) in their study of 100 patients under 40 years with coronary disease, and 300 healthy persons past the age of 80 found that tobacco was used in a greater quantity and by a greater number in the young group, the incidence being 93 percent, which exceeds even the high incidence

in the general population.

Recent statistical studies by Pearl, (1938) show a definite increase in the death rate after the age of 30 in heavy and moderate smokers. He concludes from these studies that smoking definitely impairs the duration of life.

The following chart from the studies of Short and Johnson (1939) is of interest:

Symptoms, Findings and Averages for Smoking and Non-Smoking Groups

Symptoms and Findings Circulatory System	Non-Smokers No.	%	Smokers No.	%	% Increase or Decrease
Palpitation	14	2.8	54	4.2	Plus 50%
Precordial Pain or "stress"	28	5.6	125	9.7	Plus 73%
Dyspnea on Exertion	24	4.8	148	11.5	Plus 140%

No significant variations in blood pressure, pulse rate or weight was found in the two groups.

Segal (1938) made studies of the effects of cigarette smoking on the electrocardiographic tracing and lits the following changes:

1. An increase in the heart rate.
2. A lowering and at times an inversion of the T-wave.

He points out that these changes in the T-wave do not necessarily mean a coronary insufficiency but

probably represent a reaction of the heart to increased work. He adds that even though these changes do not mean coronary spasm, yet the increased heart action without the benefit to the body that exercise as a whole produces can do no good and probably does harm over a period of time.

Hines and Roth (1938) found that cigarette smoking produced an elevation of the blood pressure in the majority of individuals tested by a standard smoking test. The excessive rises in the blood pressure from smoking occurred only in the patients who had evidence of an inherently hyper-reactive vascular system as measured by the cold pressor test. The effect of smoking tobacco on the blood pressure, however, is not due entirely to a non-specific stimulus acting on a hyper-reactive vascular system but is the result at least in part, of some element in the tobacco smoke which produced vasoconstriction.

Trassoff, Blumstein, and Marks, (1936) report the results found in a group of patients whom they subjected to skin tests in an attempt to show a possible allergy to tobacco in the production of thrombo-angiitis obliterans and coronary disease. From the results of this experiment they concluded that while it is theoretically

plausible that hypersensitiveness of the vascular system to tobacco is the mechanism in thrombo-angiitis obliterans and coronary artery disease they do not believe that such a theory is justifiable at the present time.

MISCELLANEOUS

Acute infections and foci of infection are of little importance as etiological factors in coronary thrombosis in the opinion of the majority of authors. Luten (1931) states, "Opinion at present is not altogether in agreement upon the matter, but those who report large series of cases find little evidence that infection, either acute or chronic, contributes toward precipitating thrombosis except in rare instances". This is in agreement with Wearn (1923) Levine (1929) Evans, Ambler, and Dodson (1933) and others.

Some authorities attach much more importance to infections as a possible factor, however. Campbell, (1936) is of the opinion that infections play a definite part in the production of coronary thrombosis at times. He sites numerous cases in which coronary thrombosis occurred following gall bladder infection, influenza, infected teeth, etc.

Herrmann (1937) states that occasionally there seems to be a definite relationship to an acute general infection such as influenza. Gwyn (1927) sites two cases of his own in which coronary thrombosis occurred

during the course of acute bacterial infections. He feels that since thrombosis occurs in so many different arteries in the course of the various infections, it stands to reason that the coronaries must suffer in some proportionate degree, and he further states that since the existence of acute thrombosis in arteriosclerotic coronary arteries has been recognized it is important that the question of acute cardiac incidents in infections be approached, keeping the possibility of coronary thrombosis in mind.

Some authors list rheumatic fever as an important etiological factor. Slater (1931) presents three case histories in which following attacks of acute rheumatic fever the patients suffered attacks of coronary thrombosis as diagnosed on the basis of symptomotology and electrocardiographic findings. Applebaum and Nicolson (1935) report one case of rheumatic pancarditis with thrombotic occlusion of both coronary arteries.

Gross and Oppenheimer (1936) state that in their opinion coronary thrombosis is relatively rare in patients with rheumatic valvular disease. At necropsy they found that the coronary arteries of young patients with rheumatic heart disease showed strikingly little evidence of arteriosclerotic change. They believe that

the most important reason for the infrequent association of rheumatic fever and arteriosclerotic heart disease is that the rheumatic patient has usually succumbed to his heart disease before the period of degenerative heart disease comes on. Rheumatic fever per se, does not, in their opinion appear to predispose to coronary arteriosclerosis.

In a discussion of the prophylaxis of coronary disease, Swann, (1936) considers as one group those individuals with a minus basal metabolic rate of minus 5 to minus 10. He points out that hypothyroidism is rather constantly associated with an increase in blood lipoids, the degree of hypercholesterolemia being roughly proportional to the diminution in the basal metabolic rate. He also points out that this group are rather sluggish physically, tire easily, and are prone to show slight substernal oppression or pain after exercise.

Hall, Ettinger, and Banting, (1936) describe experiments carried out with dogs in which they attempt to show that an upset in the equilibrium or physiological balance between the sympathetics and parasympathetics were possibly important etiological factors in coronary thrombosis. By the use of repeated injections of acetyl choline, they were able to produce clinical degradation

with severe myocardial and coronary artery damage, the damage being found in those areas most richly supplied by vagal post-ganglionic fibers.

PRECIPITATING FACTORS

Boyd, (1928) states that little attention has been paid to the immediate changes which precipitate the deposition of thrombus. It is evident that a coronary artery may remain sclerosed for years without thrombosis and there must be some mechanism which eventually incites the deposit of platelets and fibrin.

Berger (1936) defines thrombosis as "a pathological process which infers the formation of a clot within the heart or within a blood vessel during life." He states that it is the resultant of certain essential factors acting individually or in combination. These essential factors he lists as follows:

1. Changes in the blood stream.
2. Changes in the vessel wall.
3. Changes in the blood.

Luten (1933) states that except in cases of embolism, thrombosis ultimately depends on a lesion in the vessel wall. He lists as possible contributory factors, (1) a slowing of the circulation, and (2) a change in the character of the blood and states that therefore, in the presence of sclerosed coronary arteries, any influence which might lessen the coronary

flow or anything which might change the blood itself so as to make it more easily coagulable might conceivably precipitate occlusion. He does not feel that the mere increase in the need for oxygen, unaccompanied by diminution of coronary flow favors occlusion, nor does increased oxygen want when accompanied by increased coronary flow, both of which effects may produce an anginal attack.

Anrep and Segal (1926) find that in the denervated heart, coronary flow is regulated entirely by the mean level of arterial pressure, principally by the diastolic level. As the diastolic pressure rises coronary flow increases and vice versa. In the innervated heart, however, diastolic pressure change, while important, is not the only regulatory factor. In the heart-lung-brain preparation they found that the flow varies also with variation in cardiac output. It is independent of the strength of contraction. This variation in coronary flow with systolic discharge they attribute to a reflex mechanism through the vagus. When the vagi are cut, volume flow no longer varies with change in output. Stimulation of the peripheral end of either vagus then diminishes coronary flow. These authors reach the conclusion that constrictor

fibres are carried by the vagus, and dilators by the sympathetics. They suggest as possible factors in the diminution of coronary flow the following:

1. Lowering of the diastolic pressure.
2. Lessening of the cardiac output.
3. Coronary constriction by vagus stimulation.

Stoll (1933) called attention to be rather common occurrence of coronary thrombosis during or following a hearty meal. He suggests several factors as possibly contributory to the cause at this time. The coronary circulation, due to vessels already diseased, is definitely impaired though symptoms may have been lacking. As the stomach becomes distended, the position of the heart changes somewhat and as a consequence the already impaired circulation may be further embarrassed. They suggest that it may also be that the postprandial dilatation of the capillaries of the splanchnic system that accompanies digestion is associated with a diminution of blood flow in the coronary arteries thus favoring thrombosis. Moreover, they feel that the leukocytosis and platelet increase that accompany digestion possibly favor clotting. This is in agreement with the opinion of Luten (1936). Luten also sites two cases of his own in which the evidence of occlusion

immediately followed the drinking of cold fluid, and considers the possible mechanisms here as (1) reflex coronary constriction, and (2) the direct effect of the cold upon the heart. Werley (1925) suggests a possible food allergy basis as responsible in the cases whose onset is associated with eating.

The occurrence of coronary artery obstruction due to pressure from a calsified nodule in the myocardium, as reported by Niehaus, (1935) should be considered as an occasional factor in the production of thrombosis.

De Santo (1934) sites four cases of coronary thrombosis following surgery in three cases and head trauma in the fourth. He concludes that there is a small though definite group of cases in which the operation or violent trauma result in the arterial occlusion in vessels that are the site of a chronic degenerative process. Master, Dack, and Jaffe, (1938) site thirty-five cases of coronary occlusion occurring post-operatively at Mount Sinai Hospital, this number being about 5.6 percent of the total number of cases occurring at this hospital in a six year period. He lists as possible factors, surgical shock attended by diminution of blood volume and a drop in blood pressure

tachycardia, dehydration and infection.

Phipps (1936) in discussing contributory causes calls attention to the fact that in about 60 percent of his series of 235 cases the onset occurred during rest with no preceding physical stress. Hutcheson (1932) points out that periods of rest tend to further decrease the coronary flow and thus are more apt to bring about a thrombus formation.

Hutcheson (1934) also mentions the tendency of atheromatous placques to rupture or ulcerate. This is further discussed by Leary, (1934) who describes the rupture of an atheromatous "abscess" into the lumen of the coronary vessel as the immediate cause of thrombosis. He bases this on his finding of a defect in the intima at the site of thrombosis and the presence of atheromatous material within the adjoining thrombus. He explains the presence of intimal hemorrhage as due to the back flow of blood through the defect in the wall at the site of rupture of the "abscess".

Boyd, (1928) discussed two cases in which he felt that the mechanism was clearly in evidence. He states that an atheromatous placque may lead to sudden thrombosis whether it be situated in the aorta or in

a coronary artery by reason of the onset of an acute inflammatory change within the placque. He states that the causes of the acute inflammation which may occur in atheromata is obscure, but that his two cases suggest vascular injury about the placque, possibly from circulating toxic material derived from an extensive infection as one source. He also describes hemorrhage within the intima near the site of thrombus which he considers due to the rupture of the vasa vasorum due to the inflammation.

Paterson (1938) points to the intimal hemorrhage, per se, as a causative factor in precipitating thrombosis. He found 32 cases out of 37 to show some degree of hemorrhage. He feels that given the proper conditions of stagnation and eddying of blood at a point in the coronary system, capillary rupture with its sequelae occurring in the same region may precipitate thrombosis. He also feels that capillary rupture may initiate thrombosis of a coronary artery by diffusion of blood from an intimal hemorrhage into the lumen, by necrosis or erosion of the intima from damage to its capillary blood supply or by retrograde capillary thrombosis. He states that any or all of these factors may operate to produce the thrombosis.

CONCLUSION

The content of this paper shows that at present as in the past the subject of the etiology of coronary thrombosis is still in a very controversial state. It is generally agreed by most authors that it is the result of degenerative changes in the vascular system, either localized or general plus certain, as yet undetermined, contributory or precipitating factors. That diabetes seems to play a definite part in the etiology cannot be denied. However, whether this is on the basis of the diabetic tendency to atheromatous changes, or to certain metabolic disturbances, or both, remains to be determined.

It is apparent that the overweight individual is much more apt to develop cardiovascular pathology than one who is normal or underweight. This fact is certainly worth keeping well in mind, although the reasons for it are as yet unknown. Heredity is without doubt a factor of importance.

The present status of the question has been well summarized by Herrick (1931) who states that at present there are certain gaps in our knowledge of coronary artery disease, these being the cause of arteriosclerosis

and thrombosis. He urges the cooperation of the practitioner of medicine, the pathologist, the experimental physiologist, the pharmacologist, and the student of electrocardiography.

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