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ETIOLOGICAL FACTORS AND PATHOGENESIS IN CORONARY THROMBOSIS

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SENIOR THESIS PRESENTED TO THE COLLEGE OF MEDICINE, UNIVERSITY OF NEBRASKA, OMAHA, 1946.

TABLE OF CONTENTS

INTRODUCTION

In presenting any thesis concerning the coronary arteries, one can add greatly to the reader's understanding of the subject, if he will present briefly the allied topics which help to complete the whole picture. For this reason, I am including rather concise accounts of the Anatomy, Histology, Physiology, and Pathology of the coronary arteries. I have devoted more space to a discussion of the Pathogenesis of coronary arteriosclerosis, atherosclerosis, and thrombosis for these are the fundamental processes by which the etiological factors exert their influence.

Most of the data in the section on Anatomy is taken from the classical work of Louis Gross, who has done the outstanding investigating in this particular field. The sources from which the data was gathered for the other sections, as well as the main body of the thesis, were, for the most part, original articles, monographs, and bound publications by the authors who did the work. Only two textbooks were employed and these were both standard and accepted books.

The etiological factors, themselves, are taken up individually and are arranged, as much as possible, in the order of descending importance. This is, of course, a

subjective matter and the arrangement here-in may differ considerably from that which the reader would deem more appropriate.

While consulting the literature, I discovered a method of presentation in several of the longer articles and books, which seems to have two distinct advantages. The method consists of presenting the evidence and research on the subject and following this presentation by the evaluation, comments and conclusions of the author. It seems to me that two definite advantages to be gained from this method are: 1. The reader may consult only the data presented and arrive at his own conclusions which may be more correct and useful to him than those of the author; or 2, for the sake of saving time and because of faith in the ability of the author, the reader may wish to accept the conclusions presented without having to study all the mass of data. I have, therefore, followed this arrangement in my own presentation. The evidence is presented with only the slightest comment and my personal discussion, evaluation, and conclusions are found in the last section of this paper.

Also included are a table of contents and a complete bibliography which is found at the end of the thesis.

HISTORY

Although the anatomy of the coronary arteries and the fact that they may be affected by disease have been known for some three hundred years, it is only within very recent times that there has come to be any realization of coronary thrombotic processes by physicians. As early as the middle of the seventeenth century, Raymond Vieussens described roughly the anatomy of the coronary vessels and, in addition, noted the diagnostic features of pericardial effusion and gave the first description of aortic insufficiency and mitral stenosis(72). Later, in 1768, William Heberden gave the first clear-cut clinical description of angina pectoris, establishing the condition as a disease entity(72). In 1788, Edward Jenner, working with C. H. Parry, was the first man to associate coronary artery disease with angina and he was able to prove his point when an autopsy revealed ossified and narrowed coronary arteries in the heart of his friend, John Hunter(72). Ten years later, 1799, Parry independently published his findings and beliefs on coronary artery disease in his book, Syncope Angiosa(56).

The first inkling as to treatment of the anginal pain came in 1867 when Lauder Brunton found that amyl nitrite

gave the muchly needed relief of increased blood pressure(56). This was followed in ten years, 1879, by the introduction of nitroglycerine by Murrell for the relief of the patient's discomfort(56). However, it remained for Sir Thomas Brunton, who, noting a rise in the blood pressure in some patients suffering from angina, was the first, 1879, to successfully employ nitrites in the treatment of the condition(72).

The year, 1884, was noted for the publication by Leyden of an excellent description of coronary sclerosis in which he, for the first time, satisfactorily correlated the symptoms, signs, and pathological changes of this disease(43). In the latter part of the nineteenth century, William Harvey presented his case of cardiac infarction in his friend, Sir Robert Darcy. Although he did not interpret this infarct as being due to a coronary thrombosis, from his description of the case it seems impossible that it could have been anything else. After relating the symptoms, signs and the course of the illness in his patient, he describes the autopsy findings and concludes that the huge laceration in the left ventricle of the heart "had apparently been caused by an impediment to the passage of the blood from the left ventricle into the arteries"(78). In recent years, 1903, Josué claimed to have produced

medial arteriosclerosis in rabbits by the use of epinephrine(37).

The history of coronary thrombosis itself is so recent that it falls entirely within the twentieth century. Although credit for their achievement is usually not bestowed upon them, it is really owed to Obratzow and Straschesko, who, in 1910, published the first important and satisfactory account of the clinical features attending attacks of coronary thrombosis. These Russian authors diagnosed correctly two of the three cases they published. They emphasized a triad of symptoms--- severe lasting retrosternal pain, dyspnea and orthopnea, and finally gastralgia. All three of their cases had had precedent angina pectoris. They called attention to many of the features we now recognize as important findings in coronary thrombosis, e.g., gallop sounds, mural thrombi, pale cyanosis, etc. They also noted the different clinical and pathological events that might result depending upon the size of the coronary artery involved(42).

The man to whom credit is usually given for the earliest complete clinical description of sudden coronary occlusion is J. B. Herrick. Although he was not the first, he did make a very important contribution with his publication in 1912 which really brought to

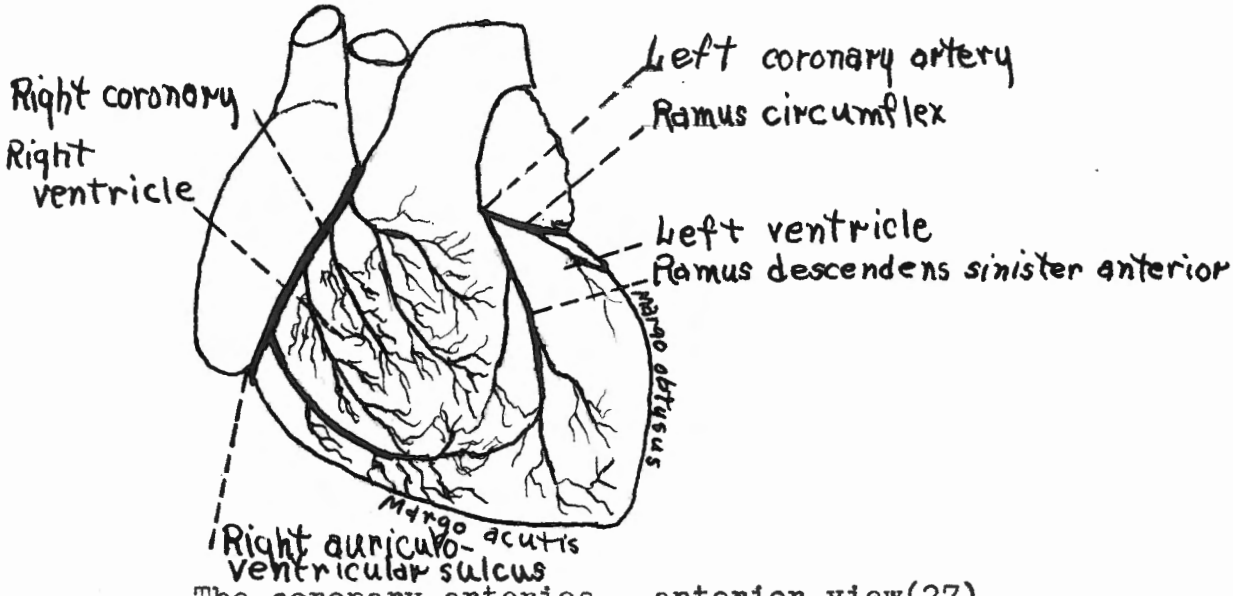
focus the attention of the American Medical Profession on this hitherto obscure condition. He was the first to set down a differential criteria between coronary thrombosis and angina pectoris. He also recognized that the clinical picture was often complex and variable but that it was a definite clinically recognizable syndrome. He further stated that coronary thromboses usually occurred in males who were past middle age and that it was frequently preceeded by anginal pain(32 & 72).

In 1923, Mackenzie published his important work on angina pectoris and coronary thrombosis.

It was not until 1928 that serious attempts began to be made concerning the etiological factors causing this heart ailment. In this year Eli Moschovitz reported four cases of what he called "tobacco-angina-pectoris"(75). Since this time great effort has been expended by many investigators on this problem and it is the purpose of this paper to find just what the status of the problem is today.

ANATOMY

The work done by Louis Gross in 1921 is classical and still the most accurate description of the course and variations in the course of the coronary arteries to be found today. As to methods, he used not only dissections of paraffin injected specimens but also Roentgenograms of specimens injected with slightly viscus suspensions of radiopaque materials. In this manner he was able to outline the courses and anastomoses of even the capillaries.



The coronary arteries - anterior view(27).

Gross describes both superficial and deep divisions of the coronary arteries, the former being the main large branches of the surface of the heart.

He states that the right coronary artery arises

from the aorta below the edge of the anterior cusp and emerges on the anterior surface between the roots of the aorta and the pulmonary arteries. It then passes down the atrioventricular sulcus and continues through the atrioventricular groove as the arteria circumflexa dextra. In its course it gives off branches to both the auricles and the ventricles. Two branches are given off consistently on the anterior surface of the heart and one at the lateral part, ramus lateralis, descends along the Margo Acutus toward the apex. The ramus descendens posterior follows the posterior interventricular furrow to the lower one-third of the ventricle. The right coronary ends in two or three branches which descend over the posterior surface of the left ventricle.

The left coronary artery comes from the Left Anterior Sinus of Valsalva, just below the free edge of the cusp. It then proceeds forward and left and gives off the large ramus descendens anterior sinister which descends along the interventricular furrow around the apex and up the lower one-third of the left ventricle posteriorly and gives off lateral branches to the left and right ventricles.

The other large branch of the left coronary artery is the ramus circumflex sinister, which passes

along the auriculo-ventricular sulcus to emerge from beneath the left auricular appendage. Here it bends downward over the left ventricle and gives off lateral branches especially to the posterior surface of the left ventricle.

Gross(27) next described the deeper division of vessels which he worked out with his Roentgenographic Technique. The deeper vessels are branches from the surface arteries which arrange themselves in a circular manner. From these circular vessels small arteries arise at right angles and pass into the muscle until they reach the subendocardium, where they form a fine network. The ultimate distribution is that of a fine capillary mesh around each individual muscle fiber. Branches pass from the rami descendens of both coronary arteries into the interventricular septum where they anastomose richly. Both coronaries give off branches to the auricles, and to the subpericardial fat, the arteriae telae adiposa cordis.

There may, of coarse, be great variation of origin and distribution of these vessels. For example, there may be two left coronaries arising from the aorta, the lesser one following the course of one of the large branches. The blood supply to the auricles is extremely variable and no typical picture can be drawn.

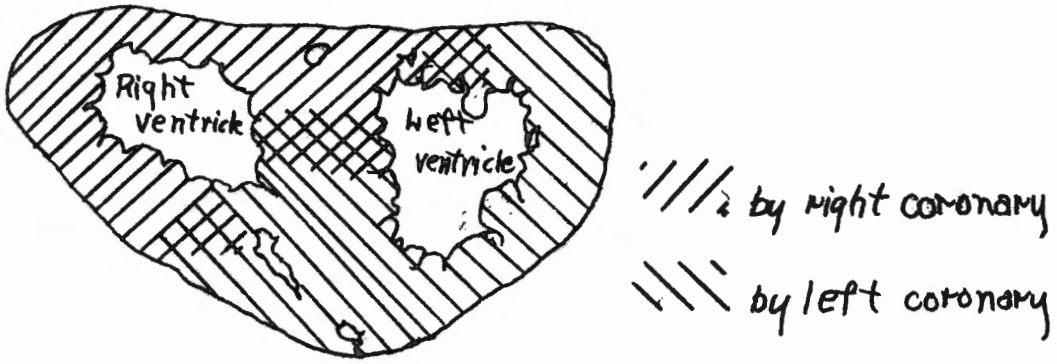


Diagram showing areas supplied by right and left coronary arteries and their anastomotic areas(27).

As to the areas supplied by the coronaries, the right coronary artery supplies the right ventricle with the exception of the left one-third of the anterior wall. Through its rami ventriculares sinistre, is supplied the right half of the posterior wall of the left ventricle and a small strip of the posterior portion of the interventricular septum.

The left coronary supplies the rest of the left ventricle, the small left anterior portion of the right ventricle, and a small anterior strip of the interventricular septum.

There is a large area of junction and overlapping of supply on the posterior wall of the left ventricle,

on the anterior wall of the right ventricle and one in the mid-portion of the interventricular septum.

The blood supply to the sino-atrial node and to the auriculo-ventricular node seems to come usually by way of branches from the right coronary artery. There is no definite and consistent branch to the interventricular bundle.

Because of anastomoses with other branches of the right coronary and with the left coronary, occlusion of the right coronary rarely produces the serious impairments of conduction which one might expect. Also there is some compensatory supply for the inner fibers from the ventricular blood itself. This is believed to come by way of the Thebesian Veins and the subendothelial anastomoses(27).

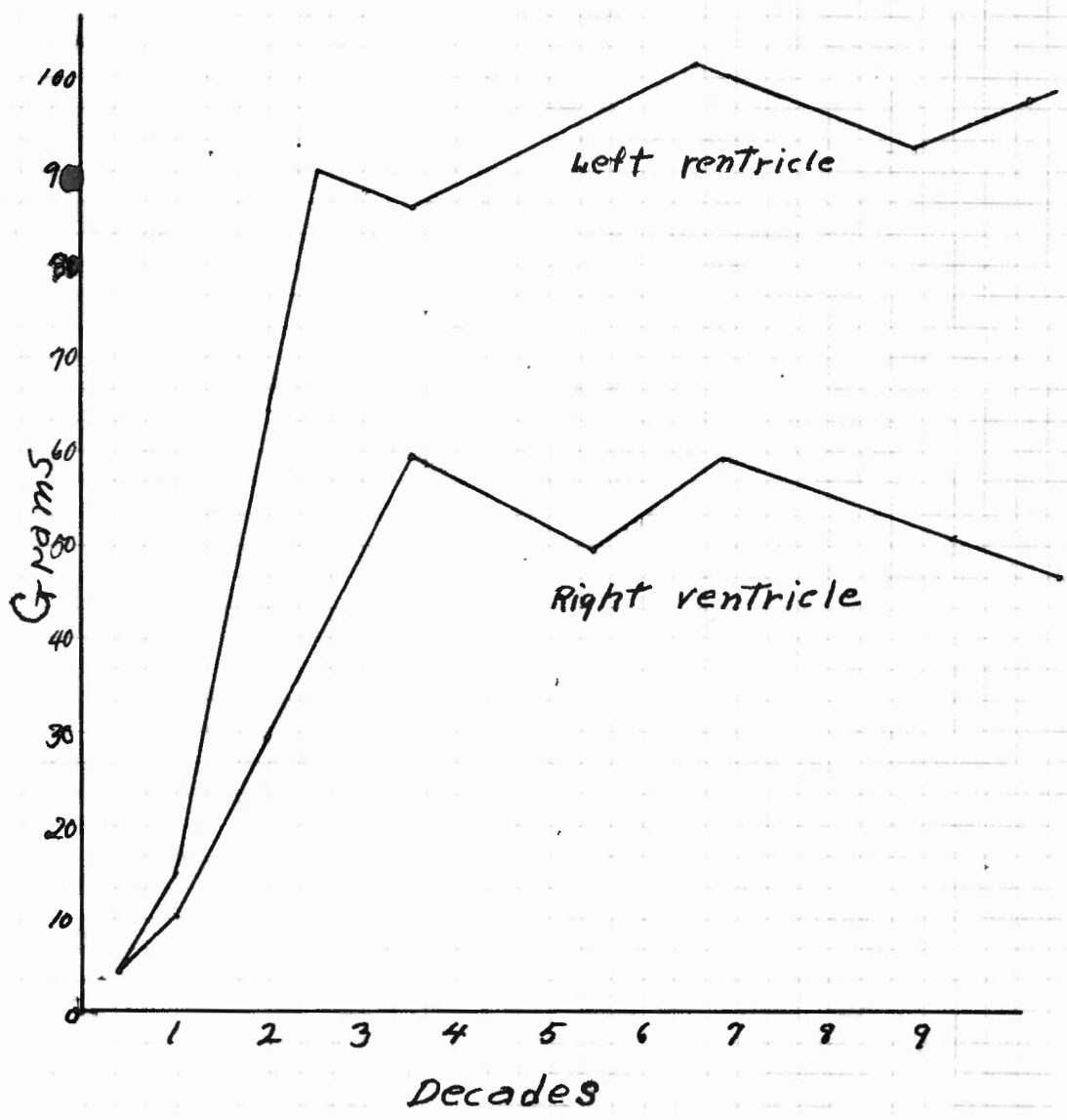
Even a large infarct with much cicatrization will not produce impairment due to the rich interanastomosing of the neuromuscular tissue within the chambers(73).

Anastomoses exist between the right and left coronary arteries both in their capillary and precapillary distributions. Anastomoses exist between the branches of each coronary artery. Anastomoses exist between the the coronary arteries and vessels from the adjacent and attached organs. Anastomoses in the heart are universal and abundant.

In the young adult heart, the anastomotic channels are all in active function and for that reason cannot act as entirely adequate compensatory agents. Nevertheless, when occlusion does occur there is some compensation so that the area of infarction is smaller than the corresponding vascular area occluded. Further, if the occlusion be slow and the circulation be good, sufficient dilitation of the anastomosing vessels can occur to preserve most, if not all, of the musculature. When the obliteration occurs in the heart of an older individual, the greater abundance of patent and free anastomoses, as well as the well-developed arteriae telae adiposae, can often amply supply the affected area so that no infarct will occur. Thusly, the age of the individual is of prime importance.

The author has demonstrated that fetal valves contain musculature and blood vessels. These both regress as age advances but may both still be present in the infant. Relatively few normal adult heart valves show a vasculature, the frequency being somewhat greater than the persistence of muscle strands.

It is shown that in the course of development form birth to senility there is a great increase not only in musculature and function of the left ventricle as compared with the right but also in its vascular



Graph demonstrating the absolute increase in weight of the right and left ventricles as age advances, and the relative preponderance of the left ventricle over the right ventricle (27).

supply and anastomoses. Also there is a normal and progressive increase in the amount of subpericardial fat and in the arteriae telae adiposae. This has been definitely shown by both Injection and Clearing Technique and Injection and Roentgen Technique. So that we see the heart, as age advances, preparing itself to better withstand the arteriosclerotic vascular changes which are to come to it; hence, too, the thrombotic processes.

As old age approaches, due to the lag in the right-hearted-vascular development, the individual comes into the period of dangers due to right-hearted insufficiency and failure. Because of the stagnation of blood in, and the relative anoxia to, the pulmonary tissue, one sees a great incidence of pneumonia in the aged. So we may say that, barring thrombotic coronary accidents, a man is really only as old as his right coronary artery, the left side having compensated through the years(27).

HISTOLOGY

The coronary arteries proper are arteries of the muscular type. The intima contains the usual endothelium, the subendothelial tissue, and the inner elastic membrane(12). The media consists of numerous layers of concentrically arranged smooth muscle fibers, but is unique in these arteries in that it is divided by a thick fenestrated membrane into an inner and an external layer(47). The tunica externa or adventitia is a connective tissue layer which sometimes contains scattered bundles of longitudinal muscle fibers. It passes over into the surrounding connective tissue without sharp boundaries. This layer contains many longitudinal elastic fibers, which are particularly numerous toward the media, where they are grouped as the external elastic membrane. The nerves and vessels ramify in the externa(12).

The extent of the vascularity of the walls of the coronary arteries varies from the most minute local network, composed of but a few injected capillaries, to arborescences which occupy all of the coats of the vessels. Many of the vasa vasorum of the coronaries have demonstrable intimal orifaces. That is, minute openings through the intimal layer directly into the

blood stream of the coronary artery. By means of dilitation of the vasa vasorum and their interanastomoses with each other and with the lumen of the artery, a shunt may be formed around an occluded portion of a vessel(87).

Parasympathetic plexuses from the Vagus are abundant in the media of the medium and smaller sized coronary arteries and the muscle fibers of the myocardium. Stimulation of the Vagus causes coronary artery constriction by liberating Acetylcholine at the synapse and nerve endings(29). It is also now believed that sympathetic fibers terminate in the media of the coronary arteries, having arrived by means of the Cardiac Nerves.

Another unique characteristic of the coronary arteries is that they have developed a layer of unstriped muscle and cellular subendothelial fibrous tissue. This is without a circulation of its own, depending for nutrition on imbibition through the endothelium. That the buffer layer in the coronary arteries is a response to the unusual stresses which these vessels are called upon to bear seems highly possible(40).

According to Reisman(66), who differs with Gross on this point, the coronary arteries are end-arteries in the sense that there is no anastomosis between them, but a capillary communication exists and is capable of considerable expansion. It is on this basis that one

can explain survival after slow occlusion of a fairly large branch of either coronary artery(66). Gross(27), on the other hand, claims to have definitely shown precapillary anastomoses constantly and actual anastomoses between the smaller branches of the coronaries quite frequently. He cannot ascribe to the belief that the coronaries are end-arteries. Gross' idea is the prevalent one today.

We may sum up the histological characteristics by stating that the coronaries have a highly vascular adventitia, a highly elastic and muscular media, a well defined intima, and have so specialized themselves that they are better able to perform their particular function than any other arteries in the body(87).

PHYSIOLOGY

The physiology involved in the fomation of thrombi in the coronaries is still unsettled but numerous theories are advanced, some of which have rather sound foundations. Hueper(35) believes that in the physiological senescing process, the lesions of atherosclerosis are related to an ageing of the colloids, which undergo dehydration, and to an increasing affinity of the vascular tissues thus changed and made denser to metabolic waste products like cholesterol and calcium salts. This leads to impaired nutrition, degeneration, necrobiosis, and thrombosis. Boyd(11) claims to have demonstrated the fact that an arteriosclerotic plaque may suddenly undergo an acute degeneration associated with inflammation and that thrombosis, in this case of the coronary arteries, may be the result. According to Nelson(52) coronary thromobósis is based on the inflammatory process with cellular infiltration and fibrous repairative processes. Hueper(36) now believes that the arteriosclerosis is due to a variation in tyrosine metabolism which, in turn, produces endocrinic vasotonic agents causing the sclerosis. Leary(40) believes that there is a cyclic character of the arteriosclerotic process for he frequently found a comparatively recent lipoidosis in the smaller branches

of the coronary arteries as compared with advanced ones in the larger branches. Further, some of his experimental rabbits had received no cholesterol for five months before their death.

Since the normal intima is not vascularized, while the pathological intima is, it would seem that vascularization is a response to, rather than a cause of, inflammatory or atherosclerotic change. It is capable, nevertheless, of maintaining and increasing the intimal fibrosis and, since it leads to intramural hemorrhage, it is important(52). There are two factors leading to intramural hemorrhage: (1)Softening, by atheroma, of the supporting stroma; and, (2)High intracapillary pressure(58). In 350 cases of coronary thrombosis, these men observed multiple fresh coronary occlusion in 11. The striking observation was made that all of these multiple fresh coronary occlusions occurred in the presence of shock lasting from 8 to 288 hours. Such multiple thrombi were not observed in any of the cases where shock was not present(9).

White(82) believes atheromatosis to be due to some obscure metabolic abnormality which causes fat to be laid down in the intima in such amounts that it cannot be taken up again quickly; and that its presence excites a reaction of fibrosis and, in older

individuals, atheromatous abscesses and calcification. Raab(65) refers to arteriosclerosis as a condition caused by a "damaging agent" of unknown nature. He asserts that the following facts show that epinephrin, sympathin, and similar substances play an outstanding role in the development of arteriosclerosis and atherosclerosis:

1. In animals, repeated injection of epinephrin hydrochloride produces severe medial changes in the arteries, analogous to those found in human arteriosclerosis.
2. In rabbits, experimental cholesterol lipoidosis of the intima was found to be greatly enhanced by injection of epinephrin and other lipoid extracts of the adrenals.
3. Epinephrin is absorbed by arterial tissue in vitro.
4. Repeated implantations of adrenal tissue causes vascular changes similar to arteriosclerosis.
5. Arteriosclerosis and arteriolosclerosis, including nephrosclerosis, are common in persons with tumors of the adrenals, even in infancy and youth.

> 6. The heart muscles of most persons who have died from "hypertension" and "arteriosclerotic" heart disease were found to contain abnormally high concentrations of epinephrin and of epinephrin-like substances.

Furthermore, Raab states that the lowest values for the deposition of epinephrin-like material were found in the arteries and kidneys of youths and infants; the highest, in those in the sixth and seventh decades of life. He also was able to show that sclerotic aortas contained high concentrations of adrenalin-like material more frequently than normal aortas.

De Takats(19) claims that, in general, any injury to the intima is another big factor in thrombus formation. This coat may be injured by contusion, stretch, rupture, burns, or frostbite.

It is well known that shock constitutes one of the most prominent clinical features of coronary thrombosis. A series of cases presented by Blumgart(9), however, suggests that in the case of multiple fresh occlusions the reverse may be true, i.e., shock due to non-cardiac conditions, or occurring occassionally as a consequence of congestive failure, may secondarily precipitate multiple fresh occlusions. He states that the following

factors operate in shock to cause multiple fresh coronary thrombi: (1) Dehydration, (2) Decreased blood volume, (3) Oxygen unsaturation of the arterial blood, (4) Impaired nutrition and increased permeability of the blood vessel walls due to toxemia, (5) Other physical and chemical changes in the blood, (6) Stasis of the blood flow, and (7) Lowered blood pressure. Phipps(64) agrees that dehydration due to increased viscosity of the blood is an important factor.

In his article, Hutcheson(37) says that considering the type of pathology upon which coronary thrombosis depends and considering the usual history preceeding the attack, it seems unlikely that exertion or any other cause of accelerated blood flow has any bearing whatever on the occurance of thrombosis. On the contrary, it appears to him that slowing of the circulation rather than acceleration would promote clotting. This is in accord with the view of de Takats(19) and Luten(44), who, however, insists that in addition there must be a change in the character of the blood.

Certain other physiological characteristics should be mentioned, most prominent of which is a questioning of the general belief that a fall in blood pressure is associated with coronary occlusion and a

rise in blood pressure with angina pectoris. Weiss(80) has found the exact reverse to be true. He observed that in the early painful stages of an attack of coronary thrombosis a rise in blood pressure is not at all unusual. This he believed to be due to the pain, the excitement, and the apprehension of the patient and the oppression of the occlusion which probably initiated pressor reflexes which, in turn, caused the rise in pressure. This was also aided by the vasoconstrictive phenomenon of the shock. He cited three cases in which the blood pressure, during the first one-half hour and before relief of the pain, rose from normal to 150-200 systolic and from normal to 100-120 diastolic.

It is now definitely believed that the gastro-intestinal symptoms are due to stasis of blood in the gut wall. This causes atony and distention of the wall and secretory failure(54).

Jones(39) believes that the pain in obstructive coronary disease is due to vasospasm. He bases this on the fact that so many patients suffer pain of angina with few, if any, signs of serious cardiac changes. The present view, however, is that the pain is due to anoxia of the myocardium.

Any discussion of the physiology of any type of coronary disease would not be adequate without a

few ideas concerning the regulation of the coronary circulation itself. The work of Anrep and Segall in 1926 not only laid the foundation for our present knowledge but is still essentially correct. They(2) showed that in the denervated heart, only the arterial blood pressure regulated coronary circulation. In the innervated heart, due to a nervous reflex through the Vagus, an increase in cardiac output is accompanied by an increase in the coronary flow. This effect disappears after section of the Vagi. Section of the Vagi is followed by an increased coronary flow and stimulation of the Vagi results in decreased coronary flow. There are shown to be vasoconstrictor fibers to the coronaries through the sympathetic fibers of the Cardiac Nerves and the Stellate Ganglion.

It is shown that a rise in cerebral blood pressure decreases the coronary flow and a decrease in cerebral blood pressure increases coronary flow. Adrenaline injected into the cerebral circulation will produce the former effect and in the cardiac circulation will produce the latter effect(with an increase in heart rate). It is shown that large doses of Atropine (7 mgm) will prevent the action of the Vagi both on heart rate and coronary flow(2).

They(2) demonstrated that cerebral anemia increases coronary flow very markedly through the sympathetic fibers, for it failed to produce this increase when both Stellate Ganglia were removed.

PATHOLOGY

In this study it is necessary not only to know what the pathology of infarction is, but also, where it is, i.e., where one may expect to find the lesion located. Barns and Ball(3), in a series of 48 autopsied cases, found that in 28 instances, infarction occurred in the region supplied by the anterior descending branch of the left coronary artery; as compared with 20 instances in which it occurred in the region of the left ventricle supplied by the right coronary artery. He then concluded that the designation of the anterior descending branch of the left coronary artery as "the artery of coronary occlusion" was no longer justifiable. Stroud(72) observed that infarctions of the lateral and posterior walls of the left ventricle are commonly represented by a more patchy fibrosis than that observed with this type of lesion of the anterior wall. He believed that rupture occurred more often with infarctions of the anterior and apical walls of the left ventricle than when the infarctions occur elsewhere in the myocardium.

The actual pathology of myocardial infarction and repair was studied in detail by Willius(85) who proclaimed that at autopsy, a recently infarcted area

will be clearly demarcated and confined to the region supplied by the obstructed artery. At times, the infarct is hemorrhagic and stands out in clear relief from the surrounding myocardium. The myocardium is often the seat of a patchy, diffuse, fibrotic process. Associated with a recent infarct there is, at times, evidence of an old, slowly developing or chronic infarct, manifested as a thinned out, cicatricial area, usually the result of a gradual obliterating atherosclerosis. Histologic study of a recent infarct reveals acute necrosis of the muscle bundles with segmentation and fragmentation of the fibers. The muscle is often granular in appearance, and an infiltration of polymorphonuclear leukocytes usually occurs. An area of localized pericarditis over the infarct may be present, but rarely is the amount of pericardial fluid appreciably increased. White(83) follows the same description but brings out the fact that repairative processes begin almost immediately and, after a few weeks or months, a fibrinous scar results. During this process of repair, there is a thinning and weakening of the ventricular wall which may result in an aneurysm and rupture. Sometimes lime salts or even bone are laid down in the old necrotic area. White(55) stresses the fact that a

collateral circulation is being set up even as the occlusion is forming but that this collateral circulation is never as effective as its predecessor. At times one finds an unexpected and apparently unexplained site of infarction. This is really due to the fact that the artery supplying this area has been previously occluded but has been overlooked, and the collateral vessel supplying this area has now become occluded.

The pathology is not constant but depends upon the completeness of the occlusion. "It may be only a simple ischemia without any structural change; it may be a slight fatty degeneration, localized or general, with a later light fibrotic change; or there may be complete necrosis."(83). The factors involved are time, collateral circulation, and the size of the artery involved. White(83) believes that the thebesian veins are of uncertain value as collaterals.

In the extreme case when both coronary arteries are occluded, a collateral circulation may still be established. This circulation takes place through the thebesian orifaces and, by way of the pericardial circulation, through anastomoses with the internal mammaries and the nutrient arteries to the lungs(81).

As to the thrombi and their organization and canalization, it is an interesting characteristic that they tend to extend in both direction to, but not beyond, the next adjacent large branch of the vessel occluded. Winternitz(87) observed that these large branches are frequently found to be connected by one or a network of adventitial vessels, thusly establishing a by-pass or collateral circulatory system and avoiding, not only myocardial infarction, but also, all cardiac symptoms in many cases. Winternitz(87) describes the mechanism of organization of a thrombus in the lumen of a vessel as characterized by the disintegration and digestion of the blood elements and by the growth into the clot of capillaries and fibroblasts, together with many mononuclear phagocytes. The lumen, he states, may thusly become filled with connective tissue. The collateral adventitial circulation is then established, but should the collateral circulation to parts of the thrombus, vessel wall or surrounding tissue prove inadequate, calcification of the blood and necrotic tissue may occur to further complicate the picture.

There are other pathological events which accompany coronary thrombosis. Definite gross cardiac

hypertrophy was found to be present in 88 per cent of his cases by White(83). He believed that this was due to the effects of the infarction alone. It averaged an increase in weight above the estimated normal of about 132 grams. Bartels(4) found the same to be true in his series of 47 autopsied cases of coronary thrombosis in which he found cardiac enlargement in 37 of the cases. Other results of coronary occlusion are small patchy fibrous areas in the myocardium, localized pericarditis when the epicardium is involved in the infarct, and mural thrombi and embolism and death when the endocardium and subendocardium are involved(61).

Not all myocardial infarctions must have been preceeded by thrombotic processes. Blumgart(8) has presented evidence that temporary ischemia may cause irreversible myocardial change, and if the ishemia be of sufficient duration, myocardial infarction will result. It may be of the same character and degree as that which occurs after permanent and complete coronary occlusion. This, then, is the explanation of the sudden deaths with angina pectoris not accompanied by coronary thrombosis.

PATHOGENESIS

It is in the study of the pathogenesis that probably the closes approach has been made to the solution of the problem of the etiology of coronary thrombosis. Huepер(35) gives a good general view when he states that the mechanism in forming of the atheromata and arteriosclerotic plaques is an interference with the oxygenation and nutrition of the vascular walls. This then leads to the various degenerative and proliferative vascular changes and "is the fundamental causal mechanism regardless of the nature of the etiological agent".

The classical work done in the field of pathogenesis was by Timothy Leary(40). His idea is that, in young men aged 25 to 55 years, there occurs a fibrous reaction in the subendothelial layer of the coronary artery. The nutrition of the new fibrous tissue is dependent, in its early stages, on imbibition from the blood circulating in the lumen. Ultimately, as the fibrous layer increases, there is a capillary circulation formed in the more central layers. As the fibrous tissue continues to increase, the circulation becomes inadequate and a cresentic layer of necrosis results which affects the layer fartherest from the lumen or next to the media.

This necrosis cuts off the capillary circulation from any connection with the outer wall of the vessel or the vasa vasorum. There is a small amount of lipoid cell infiltration, a marked inflammatory reaction with lymphoctic infiltration, and the formation of the thrombus. It is conclusively demonstrated that the endothelial necrosis leads to the thrombosis. Very little calcification was found in these arteries.

In older men, usually over 47 years of age, the formation of an atheromatous cavity or "abscess" begins by the laying down of masses of lipoid cells with a minimal amount of supporting fibrous tissue. The partitions between the cells are slender strands of reticulum. These massive accumulations of cells are dependent on imbibition for their nutrition, even when, in some cases, vasa vasorum have penetrated through the media. As a result of the hazard to the nutritive supply, necrosis tends to occur, cholesterol crystals are formed as a result of ester splitting, and the space occupied by the dead cells is converted into a cavity filled with living and necrotic cells, detritus, cholesterol crystals, and fluid. This is the atheromatous abscess, which is not inflammatory in any sense. There is a total absence of bacteria and inflammatory cells. This

atheromatous cavity will then rupture into the lumen of the vessel and secondary thrombus formation occurs in most of the cases. Rupture may occur from the lumen into the atheromatous focus and secondary thrombi form, or death may result simply from coronary insufficiency.

White(83) agrees with Leary but adds that calcification occurs in the abscesses and this makes them brittle so that they break or ulcerate and give rise to the secondary thrombi. Page(55) adds that the flow which is slowed by the sclerotic processes causes an increased systolic effort and increased pressure in the arteries. This will then cause a degeneration and ulceration of the endothelium over the atheroma or cause a hemorrhage by bursting the vessels in the vascular base of the sclerotic area.

Hemorrhages from the rupture of minute vessels in the vascularized arteriosclerotic walls of the diseased coronaries, alone or associated with other changes in the vessel walls, may precipitate coronary thrombosis. The wall will show focal thickening and a dark red hemorrhage, which extends through the intima to the lumen. There is much vascular granulation tissue and fibrin deposition in this area(60). Winternitz(87) concurs to this opinion but adds that an acute exudative

process alone in a thickened intima may be enough to precipitate a thrombus. Or either one of the above processes of themselves may completely close an already narrowed lumen without the formation of a thrombus.

Paterson(58) again states very definitely that, as many intimal hemorrhages occur with complete patency of the adjacent lumen, there must be another factor acting to cause the formation of the thrombus. This factor he believes to be stasis, as caused by sclerotic narrowing of the vessel distal to the thrombus, which has been so frequently observed by Clark and others. Nelson(52) found exactly the same thing true and was further able to demonstrate an intact endothelium.

As to the mechanisms in the formation of the hemorrhage, it may arise as result of the formation of a small arterio-venous fistula and tearing of the intima of one of the vessels. This tearing produces bleeding and the production of a small clot which is enlarged greatly upon contact with blood in the main artery(87). It is considered that the most important factors concerned in the production of intramural coronary artery hemorrhage are weakening of the capillary wall and sudden raising of the intracapillary blood pressure(52). As to the mechanism back of the weakening

of the capillary wall, Leary(40) contributes some interesting information as a result of his experiments with cholesterol forced feeding in rabbits. He was able to show the initial lipoidosis in the coronary, the first stage in the process of atherosclerosis. This was found to be the same as in infants who died with congenital heart anomalies. At autopsy of a rabbit in the second stage of the process, the characteristic lesion showed a moderate abundance of lipoid cells and a subendothelial fibrous lesion. This same thing was found in a blue-baby, a mongolian idiot who died at one month, and in a boy who died at 14 years of age. As the fibrous tissue ages, secondary fatty metamorphoses arise, and necrosis of the intima may occur. This was found by Leary in both his experimental rabbits and in humans. In both, the fundimental character of the lesion was similar in all respects.

Werley(81) asserts that substances absorbed from the intestine go into the blood stream. The quantity and kind of material passing through the vascular tubing must exercise some effect upon its walls, "just as a road must be affected by the kind of traffic that goes over it". That arteriosclerosis begins in the intima seems to bear up this point.

He apparently has, however, no idea what-so-ever as to the nature of this substance.

It is stated that one must consider an increased reactivity of the vascular endothelium to injuries of bacterial and of toxic nature. Thus, it has been possible to sensitize the vascular endothelium experimentally with bacterial protein or split products of protein. Such an intima is in a state of vulnerability and responds with fibrinous exudate at the slightest provocation, thus giving the initial impetus for thrombosis. The author(76) presents four cases of coronary thrombosis which manifested symptoms of food allergy and states that the thrombi were possibly formed on this basis.

Blumgart(9), in support of his shock theory, presents the fact that multiple fresh thrombi were found in widely different parts of the coronary system and he believes that this indicates that they were precipitated by conditions affecting the heart generally, rather than by factors restricted to one localized area of the coronary arterial tree.

It is easily demonstrated that at each point of penetration of a coronary artery the vessel becomes more or less fixed and some buckling occurs. Here are regions of increased stress and favorite sites for arteriosclerosis(86).

ETIOLOGICAL FACTORS

ARTERIOSCLEROSIS AND ATHEROMATOSIS

Parkinson (56), writing in the British Medical Journal gives a quite unique, yet sound, view of the causal problem between arteriosclerosis and coronary thrombosis. He writes: "In considering certain points of especial interest, I would first refer to the aetiology of coronary thrombosis, which is a local product of arteriosclerosis. The most practical point of view of arteriosclerosis is to consider it common to all of us as we age. In some it arrives early, in others late, but it is inevitable. It is unfortunate when it is premature or situated in the vital arteries of the heart or brain. As we do not know the fundamental cause of arteriosclerosis, we must likewise admit that we do not know that of a coronary thrombosis. Yet our ignorance of the primal cause need not deter us from seeking for secondary or accessory causes which may favour a local exacerbation of the arterial disease". Though written in 1932, this statement of the problem, I believe, still is accurate today.

Levy (43) believes that thrombosis of the coronaries is simply 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. Nathanson (57) found an advanced degree of coronary sclerosis in all 24 of his cases of thrombosis and he, therefore, regards it, not as a separate

clinical entity, but merely as a complication of coronary sclerosis. Wearn (78) found some degree of arteriosclerosis in every one of his 19 cases of thrombosis. He therefore believes, as does McKeen (48), that the factors which lead to arteriosclerosis play a direct part in causing thrombosis and cardiac infarction. Ernstene (23) presented a series of 9 cases, all males from 55 to 73 years of age. Arteriosclerosis was the principal cause in all. None evidenced syphilis or rheumatic fever. Five had dyspnea and four of these had angina. One had moderate myocardial failure at the time of the onset of the thrombosis. Two had auricular fibrillation prior to the onset of thrombosis (this was rare). From this series he concludes that arteriosclerosis is the most common cause of occlusion, that extensive thickening of the walls of the coronary arteries may occur without producing signs or symptoms, that the pain of the thrombosis may be the first symptom of cardiac derangement, and that the severity of symptoms may be proportional to the size of the infarcted area.

By far the most important cause of coronary thrombosis is arteriosclerosis. Klotz, Lloyd, and Herrick (71) give the following sequence of events: 1. endarteritis, 2. atheroma, 3. calcification, 4. stenosis, 5. thrombosis, 6. infarction, and 7. myofibrosis. This process may be prevented or interrupted by collateral circulation. Hutcheson (37) and Smith (69) support the view that thrombosis, in the large majority of instances, is

the end result of atheroma affecting the coronary vessels. Nelson (52) found that of 11 vessels in which occlusion was due, in part at least, to intramural hemorrhage, 10 showed the presence of advanced coronary atherosclerosis. Jones (39) aptly expresses the thought that "in the structure most necessary for the maintenance of life, insidious arteriosclerosis aims to end existance. Nature seems more accurate in death than in birth production".

Phipps (64), in his series of 235 cases, found that arterisclerotic heart disease preceded coronary thrombosis in only 20% and wondered whether there were not more factors involved in thrombosis than simply coronary sclerosis. It is said that, although the usual ultimate cause of occlusion is sclerosis of the vessel wall, secondary factors must frequently contribute to produce the thrombosis for many patients with extensive vessel change never experience clinical occlusion (44). Page (55) explains that coronary atherosclerosis may be complicated by thromotic occlusion whenever the conditions for intravascular clotting, namely, slowing of the stream of blood and endothelial denudation, are fulfilled. Flow is slowed by sclerotic obstruction and increased tissue pressure due to increased systolic efforts; the epithelimm may degenerate over an atheroma, forming an ulcer (40% of cases), or may be suddenly burst by hemorrhage form the vascular base of a sclerotic area

(60% of cases). Herrick (33) states that stagnation and platelet changes in the blood are necessary, in addition to sclerosis, for the production of a thrombus. Variations in systemic blood pressure is another important factor which must be considered.

Leary (40) definitely believes that calcification is a much later phenomenon in the coronary arteries than in the aorta. "From the standpoint of etiology of coronary thrombosis it is of little significance".

I would like to quote briefly from Paul White (83), 1944, so that it may be compared with the quotation from Parkinson written in 1932. White states: "The cause of atheroma of the coronary arteries, as well as that of arteriosclerosis in general, is unknown. Faulty cholesterol metabolism, local arterial strain or overwork, hypertension, infection, allergy, endocrinopathy, and heredity are among the many factors suggested but none has been proved or even found consistantly". We are able to understand from this that the situation today is approximately the same as it was 12 years ago except that Parkinson's advice is being followed and the subsidiary factors are being sought out and brought to light.

Sutton (73) believes that complete occlusion is most likely to occur in individuals with an extensive coronary sclerosis although it may be found on an almost isolated arteriosclerotic patch. The thrombosis definitely depends on the rough-

ing of the coronary intima by the sclerotic process (66).

Paterson (59) states that the softening due to the atheromatous degeneration in the coronary wall allows the pressure of the blood within the capillary to dilate its walls to the extent that rupture occurs and thrombus formation then follows. Intimal hemorrhage almost invariably occurs into these softened plaques in which the rigidity of the supporting stroma has been destroyed.

The present idea and hope is that atherosclerosis is a disease and not the inevitable consequence of age. Hutcheson (37) believes this to be true since he finds it appearing in the young and acting in a highly selective manner in its localization.

HYPERTENSION

Paterson (59) presents a quite logical explanation of why hypertension is believed to be important in causing coronary thrombosis. He states that as the intimal capillaries lie in direct communication with the lumen of a large artery rather than being buffered by a series of arteries and arterioles, the pressure in the artery is the pressure in the capillaries and it is not surprising, therefore, that a temporary or permanent elevation in blood pressure can dilate and rupture these delicate vessels leading to intimal hemorrhage and thrombosis. In his series of 186 cases of coronary thrombosis, he found that intimal hemorrhages were more than five times as frequent in hypertensives (60%) as in non-hypertensives (11%). Allen (1) found an incidence of hypertension as high as 73% in Carolina and showed that this checked with the figures of other men in his state. Paterson (58), in 1925, stated that 50% of his cases of coronary thrombosis had hypertension prior to the onset of the occlusion. Phipps (64) found it in 20 to 40% of his cases and stated that 6 to 10% of hypertensives die of coronary thrombosis. White (84) found antecedent hypertension in 34% of his 200 cases of thrombosis, Goldsmith (25) in 28% of his 300 cases, and Smith and Weiss (69) state that the coexistence is very frequent. Hypertension is statistically supported as a contributory factor to coronary artery disease

and a very common precursor of coronary thrombosis (24). Barns (3) found hypertension in 31% of his cases.

Tice (74) is less enthusiastic about the idea and explains that, although coronary thrombosis is frequently associated with hypertension, it occurs commonly with a normal or low blood pressure. Parkinson (56) also states that it is present in a fair proportion of cases, although it is in no sense an essential part of coronary thrombosis.

Wearn (78) was able to find no direct relationship between hypertension and coronary occlusion in his series of 19 cases, only 3 of which had high blood pressure prior to the onset of the occlusion. He believes that this possibility deserves further investigation, however.

Blumgart (9) believes that hypertension and valvular disease increase the work of the heart so that, combined with shock, multiple fresh coronary thrombi result. He again emphasizes the importance of shock in the originating of the thrombotic process.

SEX

There is very little doubt but that coronary thrombosis shows a predilection for the male sex. The range of incidence is, however, quite interesting. Hutcheson (37), in a 50 case series, found it in 90% males and 10% females. White and Bland (84), in a series of 200 cases, in 1931, found 85% males and 15% females affected. White (83) showed that there was no increasing incidence in females, for, in 1928, he found it in 40% of females, while, in 1936, he found it in only 15% of females. Barns and Ball (3) found that 18% of their cases were women and 82% men. Sprague (71), in a series of 1,824 cases, found 23.4% females and 76.6% males. Parkinson and Bedford (57) found 13% females and 87% males in an 83 case series. Wearn (78) found it in 48% females and 52% males in his series.

White (82) asserts that the male sex is overwhelmingly the victim in early life. Tice (74) states that men are the victims 4.5 times as frequently as women. McKeen (48) and Parkinson (56) simply state that coronary occlusion is more common in men than in women.

A possible explanation for the above discrepancies is offered by the investigation of Gordon, Bland, and White (26), which was done in 1939. They found, by an analysis of 3,400 cases varying in age from 0 to 100 years, that in the youth and younger adult, coronary thrombosis occurs in the male 3 times

as frequently as in the female; in middle-age, it was 2 times as frequent in males as in females; while at 70 years of age and over, there was no significant sex difference in the occurence of coronary changes.

AGE

That coronary thrombosis is seen more frequently at advanced ages is an undisputed point. There are those, however, who absolutely deny that age is a factor in the production of this disease.

Parkinson (56) states that cardiac infarction is seen most commonly in patients over 45 years of age, though it is by no means unknown between 30 and 45, or even below 30. It is a disease of the late middle aged as well as elderly. Sprague (71) states that senescense is statistically supported as contributory to coronary artery degeneration. Wearn (78) and McKeen (48) state that, almost without exception, coronary thrombosis occurs in patients over 40 years of age, being most common in the sixth and seventh decades of life. From his series of 50 cases, Hutchinson (37) was able to agree that the highest incidence of coronary thrombosis was in the sixth decade of life. Tice (74) concurs that sixth and seventh decades are the most dangerous but there are cases seen in the third decade. He adds, however, that 90 per cent of cases occur after 50 years of age.

Levine (42) found that in his series of 150 cases the average age was 57.8 years. Blumgart (9) placed the average somewhat higher, 65 years, with a range of from 59 years to 69 years. A chart, as compiled by Barns and Ball (3), might serve

well to illustrate graphically the age factor.

Age Groups	0-19	20-39	40-59	60-79	80-99
Subjects examined (Total 1000)	144	171	390	277	18
Infarction	1	1	24	22	1
% of Infarction	.7	16	6.2	7.9	5.6

Distribution of cases and incidence of infarction by scores of life (3).

There is another school of thought to be considered in the problem of age and coronary thrombosis. Paul White (82) expresses his belief that we can no longer say, with a shrug of our shoulders, as we are wont to do in the case of patients with angina pectoris or coronary thrombosis in the seventh and eighth decades, "that the coronary disease is but a natural result of old age and steps in to prevent a long senescent invalidism". Though age is a factor in that more coronary thrombosis is found in the middle-aged, still, at the present time, we are finding a much greater proportion of coronary artery disease among younger age groups. He presents 4 cases under 30 years of age, 21 cases under 40 years of age, and 138 cases under 50 years of age. Werley (81) supports White's statement that age, per se, is not a cause of coronary sclerosis and thrombosis. Jamison (38) (38) reported in 1925 that the youngest case on record was in a boy 18 years old but today cases have been reported even in infants.

The processes operating in old age to bring about the thromboses are atheromatosis and sclerosis of the coronary

arteries which are "but part and parcel of the process of growing old" and are not preventable (69). Paterson (59) agrees with the above statement and explains the lowered incidence in very old people by the fact that these atheroma have calcified and support the walls of the intimal capillaries to avoid dilitation and rupture. Leary (40) explains the mechanism operating to cause the atheromatosis and sclerosis as being the development of an inefficiency of the cholesterol metabolism. Paterson's (59) idea is that capillary intimal weakness and inelasticity due to age leads to intimal hemorrhage and thrombosis. Enkelwitz (22) believes that diabetes in the sixth and seventh decades is an important cause of thrombosis.

More people are reaching adult or senescent years of degenerative vascular changes, so naturally there are more coronaries to be affected with the lesions that favor thrombosis (33 and 71). Sprague (65) states that more coronary thrombosis will appear in younger age groups because of the tension factors in American life.

In 1931 White (84) found, in a series of 200 cases, that: the first attack of coronary thrombosis occurred before the age of 51 in one-third of cases, and in three-fourths of cases before the age of 61 years. He concluded that it is a disease of early middle life rather than elderly life. In 1944, he published a series of 461 cases showing the age of onset of coronary throm-

bosis with myocardial infarction:

Below 30 years of age	.7%
30 to 40 " " "	3.5%
40 to 50 " " "	17.4%
50 to 60 " " "	36.6%
60 to 70 " " "	30.8%
70 to 80 " " "	10.2%
over 80 " " "	.9%

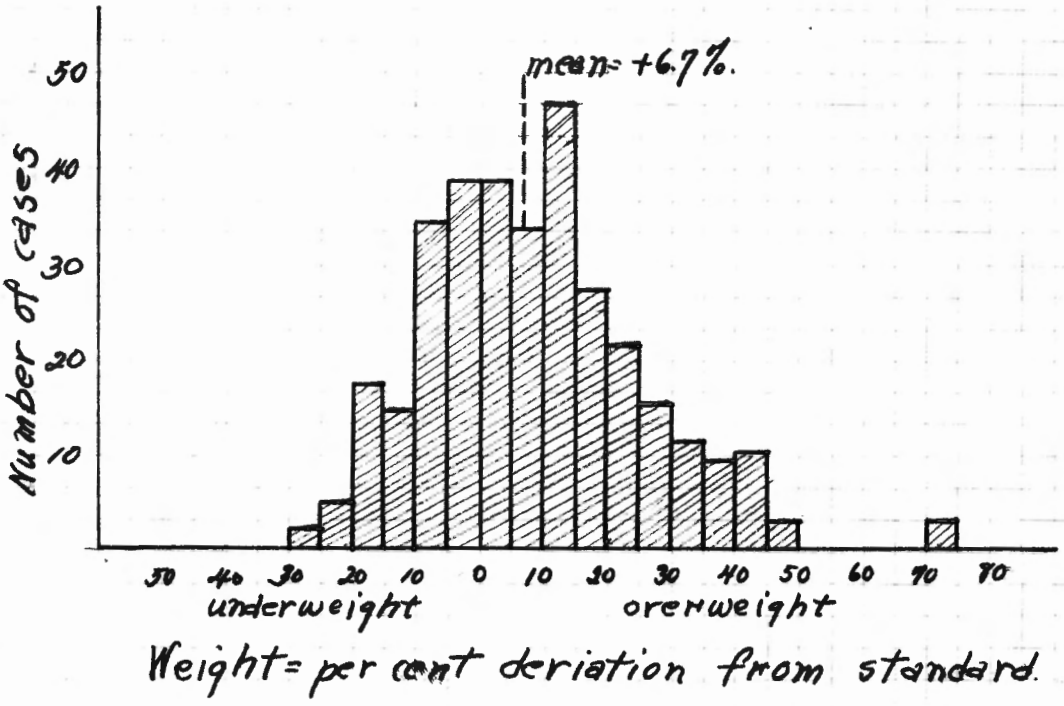
The youngest patient in this series was 22 years of age; the oldest, 81. The average age was 56.2 years (83).

WEIGHT

Although thin people can have hypertensive and coronary disease, Stroud (72) believes these conditions are much more prevalent in the obese. He adds that more people are refused by insurance companies for obesity than for any other one condition. Goldsmith and Willius (25) state that the occurrence of overweight in more than 50% of their 300 cases is significant in showing obesity causes a predisposition to coronary thrombosis. They present the following graph of 300 cases between the ages of 40 and 80 years which they studied at the Mayo Clinic (Graph 1).

Niehaus and Wright (54) state that obesity has long been recognized as a handicap to the cardio-vascular system and that degenerative disease of the heart, arteries, and kidneys are 2 1/4 times more common with the obese than with those of normal weight and 3 3/4 times as frequent as in the underweight. It is claimed that a reduction in weight of 35 pounds reduces the load on the heart by 20%.

Beall (5) draws the following interesting analogy: "Fat is a parasite and a fat person is as truly a host to a parasite as is an oak tree full of mistletoe. Fat was formerly of great potential service to its possessor, supplying food in time of famine. But civilization has now banished this need and fat has become a curse to its possessor. A man of 50 years with 50 pounds of excess flesh has reduced his life expectancy by 50%".



Graph 1 - Showing weight deviation from standard in 300 cases of coronary thrombosis between the ages of 40 and 80(25)

White (82) points out that though very few of the old men and women are fat the same is true of the young coronary cases. This is not only true but also brings to mind the fact that obesity is surely not the only cause of coronary disease.

As to the cause of obesity, Bulmer (14) believes that the majority of cases fall into the constitutional group and that the probably cause is the failure of the weight-regulating mechanism in the Hypothalmus. He also suggests "carbohydrate addiction" as a factor.

It is well recognized that obesity leads to hypertension and hypertension to atheromata which result in coronary thromboses. This was brought out by Hartman and Ghrist (31) using the data on their series of 2,042 consecutive registrants at the Mayo Clinic in 1929 and is in agreement with the views of Levine (42)and Levy (43).

Goldsmith and Willius (25) present the following table showing the relation of the weight of the patient to the family history of cardiovascular disease and the value for blood pressure:

	Patients	% of Pts.more than 5% underweight	% of Pts.whose wt. was normal 5 lbs.	% of Pts.more than 5% overwt.
Family History of C-V disease	165	23.03	24.84	52.13
No family Hist.of Cardio-Vascular disease	135	25.19	23.70	51.11
Hypertension present	83	15.66	25.30	59.04
Normal Value for blood pressure	217	27.19	23.96	58.85

Relation of weight of Patient to Family History and value for blood pressure (25).

HEREDITY

Most authorities definitely believe that there is a family tendency to sclerosis of the coronary arteries with angina pectoris and coronary thrombosis. Sprague (71), Tice (74), and Blumer (7) support this view and the latter author finds that 18% of his cases give a definite history of coronary disease in relatives. He also cites the case of a Mr.B. whose father, two uncles, one aunt, and one brother all died with symptoms which were clearly either angina pectoris or coronary thrombosis. Levine (41) has seen three brothers all of whom died of acute coronary thrombosis during the sixth decade of their lives and it seems to him as if the original tissue or structure which the individual had at birth must be particularly susceptible to ordinary wear and tear. Cooley (16) reports two cases in a mother, aged 83, and her son, aged 62, who was quite obese.

Musser (50) suggests that there exist two distinct clinical divisions of coronary occlusion: the one, the occlusion that occurs in old individuals, which is merely part and parcel of the general syndrome of arteriosclerosis and in which those various indefinite, vague, and irregular pathogenetic factors operate which are presumably responsible for the arteriosclerosis and which exhibits a general sclerosis of all the vessels of the body. On the other hand, there exists a

certain group of individuals who die at a relatively early age of coronary thrombosis. These individuals do not have hypertensive heart disease. They have not had arteriosclerotic heart diseases as ordinarily conceived, nor peripheral arteriosclerosis, but they do possess a peculiar liability for generative changes in the coronary vessels and they show a peculiar and marked familial tendency to sudden death, which death, of course, occurs presumably as a result of the cardio-vascular accident of coronary thrombosis. It is in this type of individual that this catastrophe occurs when they are under 60 years of age; usually they are people who have always had excellent health, who have never had syphilis or rheumatic fever or other severe infections and who have led active, busy lives. He presents the case of Mr. W. who was an active, healthy, hardworking, professional man who died of coronary thrombosis in his forties. A first cousin died of "angina pectoris" just past 50. Three other cousins died of coronary thrombosis at an early age. One grandfather and one granduncle died suddenly, possibly of coronary occlusions.

Stroud (72) hopes that by studying the family tree we may be able to pick out those children who are potential coronary cases and steer them through life so that they avoid most of the other etiological factors and escape coronary occlusion.

Leary (40) believes that early death due to coronary thrombosis is due to the inheritance of a poor cholesterol

Metabolism.

White (82) states that, in general, the question of ancestral longevity and inheritance is undoubtedly important. He shows by his histories that it is of fundamental importance to have long lived ancestors. He further states that he does not believe that heredity exerts a definite action of the occurrence of coronary thrombosis except in so far as there may be an inheritable predisposition to certain diseases which favor the occurrence of presenile coronary artery disease, especially diabetes, xanthomatosis, and hypertension (83).

There are those who are less favorable toward the view that there is an heritable role in coronary thrombosis. Goldsmith and Willius (25) were unable to show an inheritable factor by means of their data and Wearn (78) found only one ancestral coronary death in his whole series of 19 cases. He dismissed heredity at once.

DIABETES

It is said that Diabetes is a factor in coronary thrombosis. Sprague (71) found Diabetes in slightly less than one-fourth of his cases of thrombosis and states that Levine found it in slightly more than one-fourth of his cases. Levine (42) states that among the distinct disease entities that are etiologically related to coronary thrombosis, Diabetes is second in importance only to a previously existing hypertension. Enklewitz (16) presents a series of 594 cases:

	Diabetic	Non-diabetic
Number of cases	74	520
Number with coronary thrombosis	23	77
% with coronary thrombosis	31%	16%

From this he concludes that coronary thrombosis occurs twice as frequently in the diabetic as the non-diabetic patient.

Others have found diabetes much less frequently as a causative factor. Blumgart (9) found it in only 12.5% of his cases and White (84) in only 10% of his 200 cases. McKeen (48) states that it is infrequently found as a causative factor.

Cooley (6) definitely asserts that Diabetes is not a causative factor and presents a series of 188 cases in support of his view:

	Diabetic	Non-diabetic
Total no. of cases	92	96
Average age	58.5	60
No. with occlusion	26	71
50- (No.of cases	63	70
69 (No.with occlusion	20	55
yrs.(Average age (occlusion)	61	61
(Males (occlusion)	13	45
(Females (occlusion)	7	10
(% females	35	18

He finds, however, that it did occur twice as frequently in diabetic women (16).

The mechanisms involved mostly are centered around cholesterol metabolism. The function of the Pancreas is related to the level of plasma cholesterol. There is unanimity of opinion regarding the frequency of hypercholesterolemia in Diabetes Mellitus and a certain parallelism exists between the level of blood glucose and cholesterol and the severity of the disease. Diabetes is associated with atherosclerosis and several authorities have found that diabetic persons have a significantly greater incidence of angina pectoris and coronary thrombosis (67). This is also the opinion of Hueper (35) and Leary (40) who adds that the condition is aggravated by the relatively high fat diet which is used in controlling Diabetes.

Enklewitz (22) introduces a rather novel view of Diabetes when he remarks that he prefers to regard Diabetes in people past the age of 40 years as a manifestation of degenerative vascular disease. By so doing, he minimizes the metabolic disorder and stresses the condition of the vascular tree. If Diabetes of middle age is interpreted as clinical evidence of

generalized arteriosclerosis affecting the arterioles of the Pancreas, it is reasonable to expect that a large number of diabetic patients will also have coronary artery disease. Tice (74) and Stroud (72) also recognize the increased incidence of arteriosclerosis and thrombosis in Diabetes and the latter author expresses the belief that Insulin may reduce the incidence of vascular disease.

Another theory as to the action of diabetes in causing coronary thrombosis is proposed by Campbell (15). He believes that many cases of coronary thrombosis in diabetics are due to the increased incidence of infections sustained by diabetics rather than to degenerative vascular changes. He presents one case due to infective agents and two cases due to degenerative vascular changes in diabetics.

OCCUPATION AND NERVOUS TENSION

The impression exists quite generally among members of the Medical Profession and others that coronary thrombosis is a terminal event reserved for the business and professional groups. This idea receives support from some eminent authorities. Stroud (72) states that the long hours of nervous tension and mental concentration with inadequate relazation and too few vacations, probably play a definite part in the coronary syndrome. This is the reason so many physicians have coronary thrombosis.. Tice (74) believes that the wear and tear due to the tension and strain of life in the last few years is observed to be a plausible and logical explanation of the increase in coronary thrombosis. Over 80% of Blumer's (7) cases of coronary thrombosis gave a definite history of exertion or emotion immediately preceding the onset of the attack. Paterson (58) explains that excitement and exertion, by raising the pressure of the blood in the capillaries of the coronary wall, leads to their rupture and subsequent thrombus formation. Many of his patients gave a history of unusual physical exertion or excitement many hours or days prior to the onset of the attack and during this interval the thrombus was forming and enlarging. Hutcheson (37) presents the following list of occupations in 50 cases of coronary thrombosis:

Retired	5
Professional men	9
Business men	18
Farmers	5
Laborers	2
Bookkeepers	3
Automobile Salesmen	3
Housewives and Mothers	5
	50

As to occupation in a series of 50 Coronary Thromboses (37).

There are many men and there is much evidence that disputes the general idea of occupational incidence of coronary thrombosis. It is believed by many that excessive or prolonged physical effort or excitement plays practically no part in the production of coronary thrombosis but that certain people are born with a "spasmogenic aptitude" which predetermines their span of life. Supporting this view are Stroud (72), Hutcheson (37), Master, Dack, and Jaffe (45), and Sprague (71).

Wearn (78) refutes the idea that coronary thrombosis is reserved to the professional and big business groups. Rather, he found in his series of 19 cases; clerks, machinists, housewives, and even one "Christian Science Healer". Master, Dack, and Jaffe (45) compiled the occupations in 522 cases of coronary thrombosis and concluded that it occurs in all walks of life and in all occupations:

Occupation	Number	Incidence
Workers & laborers	196	37.5%
Store workers	26	5.0%
White collar & Office workers	52	10.0%
Business men	52	10.0%
Professional people	41	7.8%
Housewife	117	22.4%
None or retired	38	7.3%

Occupation in 522 cases of Coronary Artery Thrombosis (45).

There are those who find that rest is at far greater fault than exertion. Hutcheson (37) observed that 76% of his patients were at rest (sitting or reclining) when the onset of the attack began. Phipps (64) found that 60% of his patients' attacks occurred during rest and believed it due to slowing of the coronary circulation. He presents the following table showing the precipitating causes of coronary thrombosis in 437 cases:

	Cases	Approximate %
Physical Stress	98	23
Exercise	57	13
Surgery	26	6
Gen.infection	15	3
Moderate or unusual exertion (43 cases within 1 hr. p. o.)	77	18
After eating	54	12
Digitalis	3	5
Epinephrin	5	1
Insulin	22	5
Resting		
Dehydration	27	6
Primary anemia	3	1/2
Malnutrition	13	3
"No cause"	68	65
Larval	11	2
Sleeping		
"No cuase" (Bad dreams)	36	8

Precipitating causes of Coronary Thrombosis in 437 cases (64).

Herrick (33) relates that the ceaseless wear on the Intima the coronaries, their constant subjection to extreme active and passive stress and pressure, their unusual kinks and tortuoisities may help to explain why the coronaries are more often the seat of arteriosclerosis and thrombosis than the other arteries. Yet he

cannot understand why an artery that is almost never quiet should so readily develop thrombi. This leaves us with a problem of considerable magnitude, at present, unanswered.

MANNER OF LIVING

White (82) believes that coronary thrombosis is more common among city dwellers than those who live in the rural areas due to the stress and tension of city life and the lack of exercise. Later, while working with Gordon and Bland (26), he compared 3,400 patients at the Massachussetts General Hospital. 600 of these were private patients and 2,800 were general ward patients of menial income and of the laboring type. The reasons for hospitalization and causes of death were comparable in all; all were males; and all were between the ages of 20 and 80 years. They arrived at the following conclusions:

1. The general level of coronary atherosclerosis in the private patients in all age groups was consistently greater than in those from the general wards.
2. The incidence of occlusion in those aged 20 to 40 was very much higher in the private than the general ward cases.
    a. Narrowing of vessels was higher in private patients of this age.
3. In those 41 to 60 years of age, coronary occlusion was twice as great in the private group as in the ward group.
4. Im the 61 to 80 year group, the preponderance was less strikingly in favor of the private patients, but

but was still significant.

These findings are in general agreement and support the clinical impression.

Herrick (33) stated, in 1931, that strenuous life may cause arteriosclerosis and hypertension but that it is not definitely known whether it has anything to directly with coronary thrombosis.

Tice (74) relates that in Osler's day it was commonly believed that social status played a part in the etiology of coronary thrombosis. Today, however, we find occlusions in the members of all strata of society so that this theory is no longer teneable.

Master, Dack and Jaffe (46) compiled a record of the factors associated with the onset of 452 attacks of coronary artery thrombosis:

	Attacks	Incident
Rest	94	20.8
Sleep	86	19.0
Walking	81	18.0
Mild Activity	61	13.5
Moderate Activity	21	4.6
Unusual or Severe Exertion	4	.9
Trauma	0	0
During or after a Meal	22	4.8
Excitement	25	5.5

Factors Associated with Onset of 452 Attacks of Coronary Artery Thrombosis (46).

It is recognized that periods of excitement or emotional stress are quite common occurrences during one's life. So the value of 5.5% seen in the above chart is so low that it can indicate only coincidence. The same may be said for mild activity

fof mild activities (conversing, dressing, sitting, etc.) are far too numerous and routine to account for only 13.5% of the cases (46).

ANGINA PECTORIS

That angina pectoris and coronary thrombosis are frequently close traveling companions most any physician of today will admit. Dry (21) states that angina may sometimes occur as prolonged attacks of pain when occlusion has not occurred but is pending. After three or four such "prodromal attacks" of angina, the patient is seized by an attack which bears all the hallmarks of acute coronary thrombosis. Yet acute thrombosis is frequently the first sign of coronary artery disease and is often brought on by some unusually heavy exertion.

Hutcheson (37) found that in 50 cases of coronary thrombosis, 14 patients had previously been treated for angina pectoris and 18 more had had milder attacks of precordial pain. This gave Hutcheson 64% of cases preceded by angina which corresponds quite well with Luten's (44) 62% and with Blumgart's (9) 62%. The last named investigator also found in all cases but one, accessory collateral channels were demonstrable and showed the presence of old areas of narrowing or occlusion.

Parkinson (56) finds that in slightly more than one-half of his cases of coronary thrombosis there were preceding symptoms of the Anginal Syndrome. He gives a broader definition to angina pectoris when he states that it is the clinical syndrome due to coronary sclerosis or spasm or even slow thrombosis. Phipps (64)

is in agreement with the figures given by Parkinson for the frequency of angina pectoris.

Allen (1) considers Angina Pectoris and Coronary Thrombosis together because the pathology is usually the same—coronary sclerosis, and because a majority of coronary occlusions are preceded by angina, and in most cases of angina, coronary occlusion eventually takes place. He has further shown that the incidence of hypertension in both is the same. Levine (42) believes that coronary thrombosis is the end result of previous angina pectoris and that the great majority of patients have had definite angina pectoris antedating the attack of coronary thrombosis. Sprague (71) concurs.

Barns (3) found that only 10% of patients would give a history of previous angina pectoris.

DIET

There are many authorities who firmly believe that errors in diet cause coronary sclerosis and thrombosis. Werley (81) says, "What goes into the stomach gets into the blood and exercises its influence on the intima". Leary (40) believes that any metabolic agent capable of producing atherosclerosis must have been an article of diet from early times, since atherosclerosis has been found in the Egyptian Mummies. Cholesterol is the stable ground work of the cytoplasm, it is not synthesized in the body, and the supply must be ingested. The most urgent demands come for it at times of most rapid cell division. For this reason egg yolk is provided for the embryo and milk for the infant.

Man is the only animal that ingests eggs and milk throughout its lifetime. Man is also the only animal which dies in early life from coronary sclerosis, and which acquires atherosclerosis almost universally in advanced life. The cholesterol must be in lipoid combination to be soluble, and these lipids were isolated in abundance from athersclerotic aortae (40). Hueper (35) reemphasized this theory again in 1941.

Paul White (82) has been unable to bear out the truth of this theory in his studies and he discards it. Shaffer (67) in comparing 100 peptic ulcer patients on the high cholesterol

Sippy Diet with 500 patients on normal diet, found that only 9% of the ulcer patients showed evidence of coronary artery sclerosis and thrombosis while 10.5% of the control group did. He came to the conclusion that the nutritional role of cholestrol in the genesis of human atherosclerosis, arteriosclerosis, and thrombosis is of doubtful significance unless there is an associated endocrinopathy.

Another factor in diet is protein. Stroud (72) believes it may have an effect on occlusion because a deficiency will result in increased capillary permeability.

It is suggested that undernutrition may be a factor in cardiovascular disease but that, unless very marked, it does not play an important role. This does not assume vitamin deficiency states of which Vitamin B is the most important to the myocardium (54). Phipps (64) concurs that malnutrition is a factor. Herrick (33) states, however, that whether changes in food, in the air we breathe, especially in our large cities with their automobile and factory fumes, may have an influence, is a matter of surmise and that more facts must be known (33).

As to the quantitative side of diet, it is believed that excess food and exercise have a definite but limited bearing on the formation of atheromata and, hence, thrombi and occlusion (74). Luten (44) believes that the reflex vasoconstriction of coronary arteries by the gastric distention of eating, upon occasion, does lessen the coronary flow enough to

cause angina or to precipitate thrombosis. He showed that electrocardiographic changes occur following visceral stimulation. He quoted numerous instances of thrombosis occurring in relation to meals, either during the meal or just following. He further showed that the ingestion of cold fluids caused electrocardiograph changes, diminution of the coronary flow, and probably thrombosis of small arterial branches supplying the under surface of the apex. This was due to the fact that the cold was transmitted from the distended stomach, through the diaphragm, to the cardiac apex (44).

Master and his group (45 & 46) deny that the ingestion of food initiates any attacks of coronary thrombosis and that the relation to meals is merely coincidental. Hutcheson (37) is inclined to agree with Master for he found a relationship to meals in only a few of his 50 cases.

ENDOCRINE DISORDERS

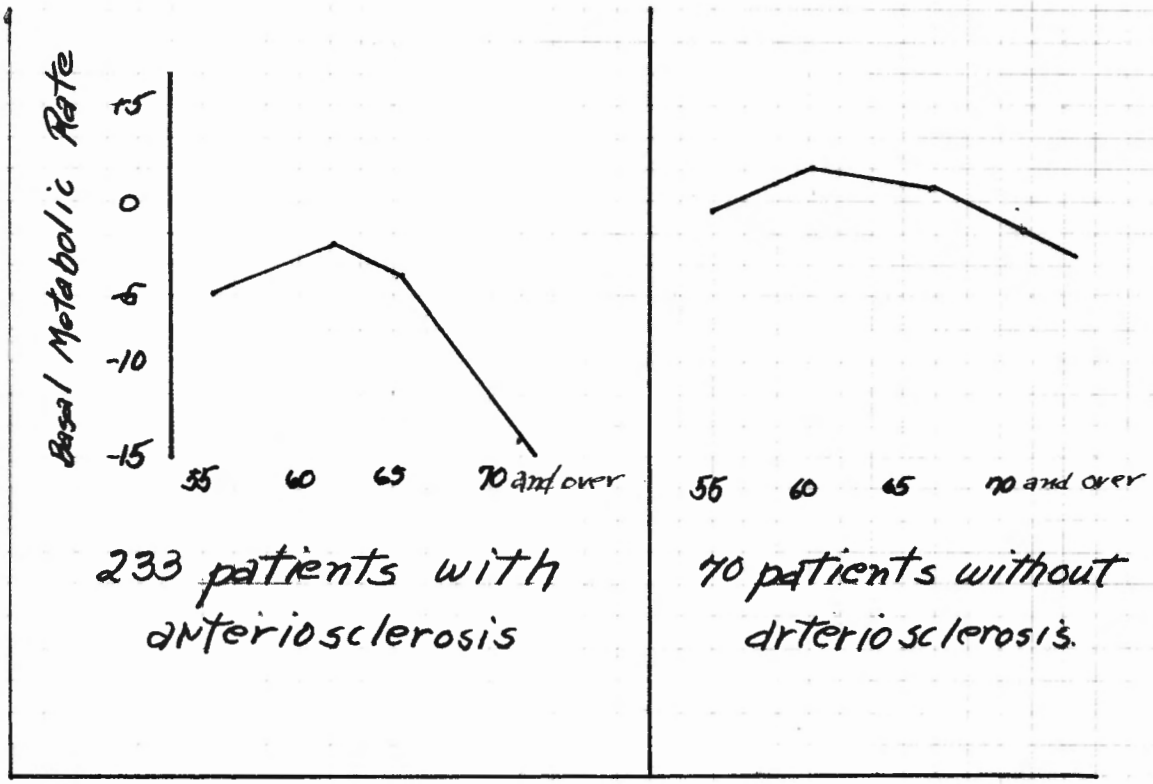
It is stated that the relation of hypercholesterolemia, especially when associated with lipemia, to the increased incidence of atheromatosis and thrombosis in inherited and acquired endocrine disturbances in man is definite (67).

Experiments on rats have demonstrated that an increase in calcium has no effect on arteriosclerosis unless it is accompanied by hyperparathyroidism or by massive dosis of ultra-violet light (35).

Bruger and Rosenkrantz (13) state that after the age of 55 years, the thyroid gland begins to slow down in function, change in structure, and the basal metabolic rate drops. Also after this age, that arteriosclerosis steadily increases. That the incidence of hypometabolism in subjects 55 years or older is greater for those exhibiting arteriosclerosis than for those without arteriosclerotic manifestations. That when rabbits were fed potassium iodide, thyroxin, or thyroid substances, simultaneously with cholesterol, aetherosclerosis of the aorta was inhibited. They conclude, then, that it is conceivable, though of course far from proven, that the receptivity of the vascular tree to the deposition of lipids may vary inversely with the activity of the thyroid gland. This idea receives support from some renowned men such as Cooper, McCarrison, Leary (40), and Phipps (64), but also a great deal of

opposition from such men as Hunt, Warren, and Page (55). The authors (13) concede that there is no single factor producing arteriosclerosis, on the contrary, the problem of its pathogenesis is a complex one. They present a chart showing the correlation of individual basal metabolic rates with age in 303 patients(Graph 2).

Hyperthyroidism is not found as a frequent causative factor of coronary sclerosis and thrombosis (48).



Graph 2 - Correlation of individual basal metabolic rates with age in 303 patients(13)

BLOOD CHANGES

As was stated earlier in this paper, it has long been felt that other factors beside arteriosclerosis operated to cause the formation of thrombi. One of these factors, which has been suggested, is changes in the blood. Herrick (33) believed that the following changes were contributory factors: (1) sluggishness of the blood current, (2) qualitative and quantitative physical and chemical changes in the blood, (3) variations in its viscosity or its content of albumin, and (4) alterations in the number of platelets and their fragility.

Doles(17), by means of prothromin determinations, claims to have shown a shortened prothrombin time with an increased tendency to thrombosis in cases of acute occlusion. While Ewing (24), as a result of his experiments, found that the interval between the appearance of fibrin and the formation of a solid clot was 7.4 seconds in 14 control (non-thrombotic) patients, while in the group of 16 thrombosis patients, the interval was 13.2 seconds. He claims that this difference was to be significant when analyzed by the T-test of Fisher. This apparently means that the blood of the thrombotic patients did not form a solid clot so readily as did that of the controls. He presents the following chart showing the results of his experiments:

Determination	Seconds Max.	Min.	Mean	Mgm.% Max.	Min.	Mean	No.of Cases
Prothrombin Time	19.7	16.2	17.4				
Plasma Clotting time							
Appearance of fibrin	95	80	83.3				14
Formation of Clot	100	86	90.7				controls
Serum Calcium				7.4	10.8	9.9	105
Prothrombin Time	19.8	16.8	17.9				16
Plasma Clotting time							thrombosis
Appearance of fibrin	91	78	82.2				
Formation of Clot	110	81	95.4				
Serum Calcium				13.2	11.5	10.2	10.9

Plasma clotting time and serum calcium of controls and cases of thrombosis (24)

De Takats (19) believed that changes in the clotting mechanism affected the tendency to thrombosis. He measured the tendency for coagulability of the blood of thrombotic patients and found it to be increased. He cited the following factors as contributing to this increase: (1) postoperative state, (2) acute thrombosis, (3) Buerger's Disease (acute phase), (4) Polycythemia, (5) severe burn and sudden dehydration, (6) acute hemorrhage, (7) severe trauma, (8) adrenal stimulation (anxiety or fear), (9) digitalis (toxic doses), and (10) carcinomatosis. Campbell (15) adds to this list gallbladder infection and relates two theories for its method of operation: (1) the presence in the blood of an increased amount of bile salts, bile pigments, and other substances in acute gall bladder attacks which is said to be injurious to the heart muscles; and (2) the infected gall bladder acts as a septic focus. He presents 10 cases of gall bladder di-

sease with, or followed shortly by, coronary thrombosis and states that the frequency of their occurrency is highly suggestive of a relationship.

PHYSICAL TYPE

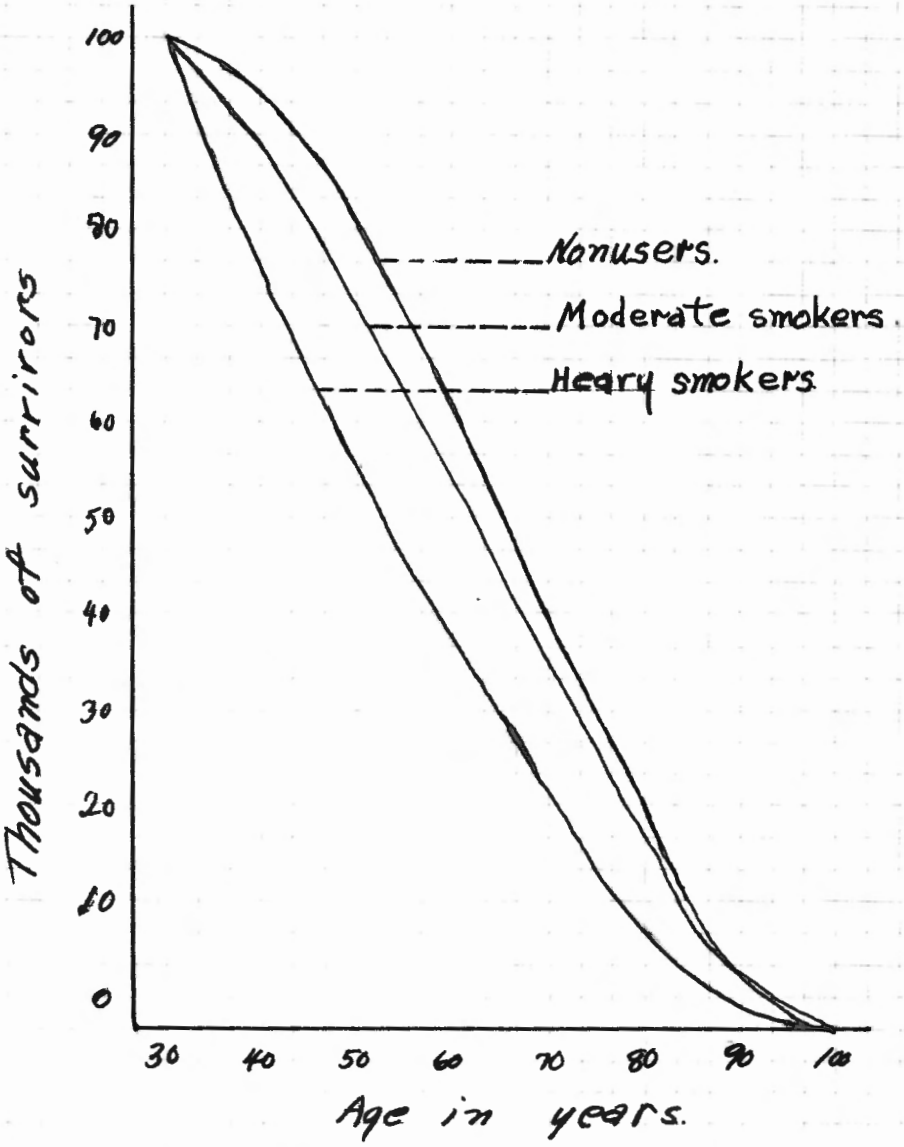
Levine (42) believes that there is a characteristic type of constitution belonging to those patients who are afflicted with disease. The patient is usually a well set person, somewhat over weight, often of considerable physical strength who enjoyed unusual good health. Such persons often have indulged in vigorous physical effort either in the form of sports or in their ordinary work, and, when they have not, they were apt to feel that they had more than the average physical strength even if they were not accustomed to use it. This does not apply to the very aged, of course. Tice (74) gives a similar description and states that persons of normal weight or underweight definitely do not develop coronary occlusion as frequently as do the above described types.

Goldsmith and Willius (25) found absolutely no consistency whatsoever as to body type in their study of their collection of 300 cases. They found, rather, that all body types and temperaments were well represented.

TOBACCO

There is as much disagreement as to whether tobacco is an etiological agent of coronary disease as there is with any problem in medicine. Considerable evidence can be found both pro and con on the matter and opinions vary from one authority to the next.

Paul D. White (82) has now reversed his view and believes that tobacco is a definite etiological factor. He found that all his younger cases of coronary thrombosis used considerable amounts of tobacco. Tice (74) states that it is a definite etiological cause of vascular degeneration. Phipps (64) believes that it acts through sensitivity, while Hueper (35) believes that the harm is due to the fact that nicotine causes mobilization of adrenalin and medial spasm, increased blood pressure, and arteriosclerosis. By injections of alcoholic extracts of tobaccos, Harkavy (30) was able to demonstrate this hypersensitiveness to tobacco in a 37 year old patient with coronary thrombosis. The delayed allergic response manifested itself as an acute dermatitis. Pearl (62) presented a graph showing the relation of tobacco smoking and longevity of 6,813 white males over the age of 30. They were picked entirely at random and the only selective factor used was the amount of tobacco smoked. There were 2,094 nonusers, 2,814 moderate users, and 1,905 heavy smokers. (Graph 3).



Graph 3 - Death age in tobacco smokers(62)

To determine the effects ot tobacco smoking on the vascular system, Hines and Roth (34) conducted a series of Standard Smoking Tests on patients and then ran controls on these patients with unlighted cigarettes. Their results were:

1. A considerable rise in blood pressure occurred after smoking the first cigarette and a further rise after the second.
2. A parallel was found between the response to the smoking test and the Cold Pressor Test. Those who responded excessively to the Cold Pressor Test responded excessively to the cigarettes, i.e., high diastolic and systolic rise.
3. In those who had little response to the Cold Pressor Test, the diastolic response to the Smoking Test was about the same but the systolic rose considerably more.
4. Patients with hypertension had a much greater rise in systolic and diastolic pressure than normal patients.
5. There was little or no rise of blood pressure in the control tests.
6. Those who showed the greatest rise in the Smoking Test had evidence of an inherently hyperactive vascular system as shown by the Cold Pressor Test.

From this it is seen that tobacco may be a factor in the development of arteriosclerosis and why the pain of angina

is lessened by not using tobacco (72).

The reason, then, why people will continue to use tobacco, even though there is such a good possibility that it does cause coronary artery disease, is interesting. Pearl (62) explains it as being due to certain purly hedonistic elements of behavior which are present in human beings, as well as lower animals, and which frequently override reason and common sense. For this reason, though people know that tobacco smoking is definitely deleterious, they will continue smoking and rationalize their behavior by saying that the keen pleasure outweighed the relative (in their view) smaller harm. Thusly, tobacco smoking is an extremely complex behavioristic problem rather than a simple physiological matter.

Wearn (78) and McKeen (48) were unable to find any history of excessive use of tobacco in their cases of coronary thrombosis and they concluded that it was not a causative factor. Blumer (7) finds that in his coronary thrombosis cases:

1. 34% didn't smoke
2. 37% smoked not more than 20 cigarettes per day.
3. 29% smoked more than 20 cigarettes per day.

As compared with a cross-section of the general population:

1. 34% non-smokers
2. 33.3% moderate smokers
3. 32.7% heavy smokers.

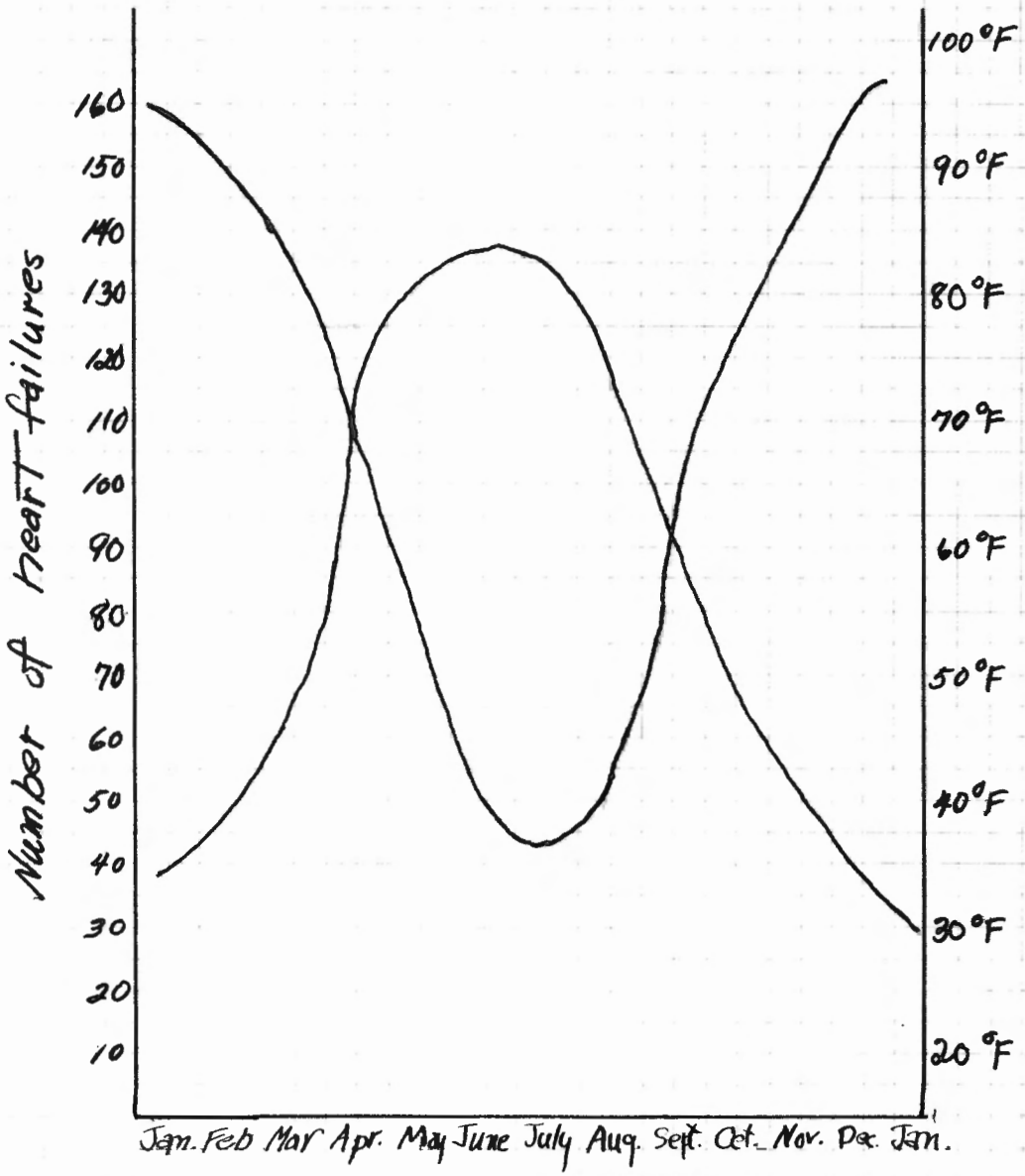
From this he is forced to conclude that the use of tobacco has nothing whatsoever to do with coronary occlusion, in spite of the new hypersensitivity theory. Master, Dack, and Jaffee (45 & 46) made similar observations on two separate occasions and

arrived at the same conclusion. Trasoff, Blumstein, and Macks (75) state that although it is theorectically plausible that hypersensitiveness of the vascular system to tobacco is the mechanism in thrombo-angiitis obliterans and coronary disease, their studies failed to uphold this concept.

SEASON AND CLIMATE'

Bean and Mills (6) present data to show that there exists a marked seasonal swing in the frequency of coronary occlusion attacks. He shows that they are almost twice as frequent in winter as in summer in the Temperate Zones. He presents several theories as to the cause of this: (1) Increased temperature of the body and increased metabolism due to Upper Respiratory Infections in winter; (2) With stormy weather, temperature fluctuations produce a strain by little known vaso-motor reflexes; (3) Certain forms of voluntary activity also increase in the cold; and (4) external temperature is believed, of itself, as it drops, to cause a rise in the body's metabolic rate. He also observes that there is little heart disease in the tropical and subtropical countries as compared with its severity in the middle temperate zones. They present the following graph showing the frequency of heart failure and mean temperature level (Graph 4). Paterson (59) holds the same view and believes that it is due to a decrease in the average blood plasma Vitamin C concentration in the winter months and increased capillary fragility and intimal hemorrhage.

Hutcheson (37) found that in his 50 cases, no patient gave a history of exposure to cold at, or immediately preceding, the time of the attack. Sprague (71) believed that season had no relationship to the incidence of coronary thrombosis. He was supported in his contention by Master and his associates (45 & 46)



Graph 4 - Relation between frequency of heart failure and mean temperature level(6)

who found the incidence of attacks from October to April (Autumn-Winter season) was 51.2% and from April to October (Spring-Summer season) was 48.8%, a difference too small to be significant.

Master, Dack, and Jaffe (46) found that the incidence of attacks during the day differed little from that during the night and, therefore, they concluded that exertion played little part in the initiation of attacks. They presented the following chart and decided that there was too little difference to be significant:

	Attacks	Incidence
7 a. m. - 1 p. m.	94	30.7%
1 p. m. - 7 p. m.	68	22.2
7 p. m. - 1 a. m.	60	19.6
1 a. m. - 7 a. m.	84	27.4
7 a. m. - 7 p. m.	162	53.0
7 p. m. - 7 a. m.	144	47.0

TOXIC AND FATIGUE FACTORS

It is generally agreed and supported by statistics that toxic and fatigue factors are contributory to coronary sclerosis and thrombosis (71 & 81).

As to the mechanism of action, it is suggested that toxic states alter the blood platelets and lead to thrombosis (76). Another mechanism suggested is that these states act on the wall of the intimal sinusoids, weaken them, and lead to intimal hemorrhage, when accompanied by transient increases in blood pressure (52). Paterson (59) adds that there is a local inflammatory process set up which weakens the intima and leads to the local hemorrhage and thrombosis.

CARDIO-VASCULAR FACTORS

It is rather surprising to find coronary thrombosis associated with so many other cardio-vascular diseases when one has been under the impression that the victim of this disease is usually the hale and hearty individual who has never been sick a day in his life. But, as we shall see, such is the truth.

In a series of 235 cases, Phipps (64) found previous attacks of coronary thrombosis as the most frequent etiological factor in coronary thrombosis. He found an incidence of 38%. White and Bland (84) found multiple attacks in 33% of their 200 case series. Barns and Ball (3) found 18% of multiple attacks; Hutcheson (37) found 14%; and Blumer (7) found that 5% of his patients gave a history of thromboses elsewhere in the body preceding their current attack of coronary thrombosis.

Luten (44) found that heart failure with the attending shock and diminution of the coronary flow led to coronary thrombosis while Blumgart (9) found that shock led to multiple coronary thrombi and death. Shock in the latter instance was due to coronary thrombosis in two cases.

Vascular allergies as seen in Periarteritis Nodosa, Buerger's Disease, nicotine, and ringworm infections act to cause thrombosis by injury to the Intima (19). One of the most common sites of periarteritis nodosa is the coronary arteries

and here it is almost uniformly fatal (71).

The frequency of precedence by angina pectoris has already been mentioned.

Thrombo-angiities boliterans is frequently followed by an attack of coronary thrombosis (71).

Sprague (71) believes that vasomotor instability is statistically supported as contributing to coronary artery degeneration.

Goldsmith and Willius (25) obtained a family history of cardiovascular disease in 165 or 55% of the 300 cases in their series. This, they believed, showed that there is a definite relation between it and coronary thrombosis.

It is rather remarkable that coronary thrombosis so rarely occurs in hearts with fibrillating auricles, (23).

NEUROLOGICAL FACTORS

Boaz and Donner (10) are inclined to believe that the nervous system plays a secondary role in the genesis of the syndromes of coronary artery disease, and that some unknown factors are more fundamental.

The capillaries are better able to stand a mild persistent hypertension than sudden transient increases in pressure such as are induced by emotion, exertion, or other factors of a similar nature (52). Paterson (59) explains this on the basis of intimal capillary rupture, intimal hemorrhage, and thrombosis.

The opposition believes that coronary thrombosis rarely appears during unusual effort or excitement. Of 81 cases, coronary thrombosis occurred in none during unusual exertion. 40% occurred while the patient slept or was in bed and in 32% more there was no relationship to exertion. The intimate relationship of the onset of coronary thrombosis and rest, especially during sleep in the early morning must be significant. This is precisely when diastolic pressure is lowest and systolic output smallest (44).

Master, Dack, and Jaffe (45) present the following list of attending events in 530 attacks of coronary thrombosis and, from it, conclude that exertion and excitement have nothing to do

with the precipitation of attacks of cornorary thrombosis:

1.	Rest	115(21.7%)
2.	Sleep	104(19.6%)
3.	Walking	95(18.0%)
4.	Ordinary mild activity	72(13.6%)
5.	Moderate activity(except walking)	28(5.3%)
6.	Unusual or severe exertion	11(2.1%)
7.	Trauma	1(.2%)
8.	During or after meal	28(5.3%)
9.	Excitement (mental or emotional)	27(5.1%)
10.	Post-operative	22(4.1%)
11.	Infection	10(1.9%)
12.	Gradual onset with angina	9(1.7%)
13.	No definite onset	8(1.5%)

Attending Events in 530 Attacks of Coronary Thrombosis (45).

DRUGS

It is well to know the effects of drugs on blood coagulability and thrombus formation because, not infrequently, one must administer to a thrombotic patient. A sad situation might develop from unwittingly giving a drug which has the effect of increasing the blood's coagulability.

Adrenalin, by causing a paroxysmal hypertension, will exhaust the media of arteries and lead to arteriosclerosis. It may also lead to a restricted vaso-hypertonia which is not reflected in the general blood pressure (35).

It is important to realize that digitalis given either in large or small doses increases the effectiveness of the coagulative mechanism and reduces the clotting time (20 & 64). This was shown to be true by de Takats (20) using the Heparin Tolerance Curves on four patients and numerous dog and cat experiments. He believed it acted by mobilizing prothrombin from the liver. He states that, when using digitalis in Auricular Fibrillation or the Thrombotic Vascular States, it is expedient to run daily Heparin Tolerance Tests to establish and govern the maximum digitalis dosage with a minimum of thrombotic and embolitic effects. Another undesired effect of digitalis is that it causes vasospasm resulting in impaired oxygenation and nutrition and regressive changes in the walls of the arteries. These walls then take up more metabolic waste products such as cholesterol and

calcium and become sclerotic (35).

The Hypotonic-hypotensive agents produce, by an excessive dilitation of the vascular walls, a compression and collapse of the vasa vasorum, a slowing of the blood flow and a lowering of the blood pressure, causing, thereby, a stagnant anoxemia in the vascular wall and an impaired gaseous exchange between the blood and surrounding vascular tissues. This causes a proliferation of the Intima and absorbing by the Media of various metabolic waste products and athero- and arteriosclerosis. The length of the effect varies with the size of the dose. Such substances are: (1) Histamine, (2) Acetylcholine, (3) The nitrites, (4) Carbonmonoxide poisoning in repeated doses, and (5) Lowered atmospheric oxygen in excessive exposure. This fact explains the sudden deaths from coronary thrombosis and diseased coronary arteries observed recently in comparatively young patients (35). Hall (29) produced sclerosis, thrombosis, and infaction of the myocardium in dogs by repeated injections of 500 cc of 1:10,000 Acetylcholine bromide intravenously every 24 hours.

Blumgart (9) believes the nitrites act to cause thrombi through producing peripheral vascular collapse.

Insulin apparently bears no relation to coronary thrombosis. Further investigation is required (46).

Paterson (59) makes the assertion that capillary weakness and inelasticity due to avitaminosis C leads to intimal hemorrhage and coronary thrombosis. He presents a series of 455 cases of

coronary thrombosis 81% of which showed a concentration below 0.5 mgm % of Vitamin C.

Heuper (35) produced a rapid and severe arteriosclerosis in both dogs and rats by giving excessive amount of Vitamin D.

Morton and Burger (49) state that an excess of Vitamin K does not result in an increase of thrombosis. They also found that there was no demonstrable effect on the prothrombin times, hematoorit determination, and clotting times after giving Vitamin K. Even after scratching the Intima with a hooked needle, the incidence of thrombosis was not significantly increased. They present the following result of this experiment:

Group	No. of veins	Positive for Thrombosis	% of positive
Vitamin K	97	37	38.0
Control	89	29	33.0

Comparison of results in 27 dogs given Vitamin K and 25 used as controls (49).

They further found the following incidence of thrombophlebitis in parturient women with and without Vitamin K:

Group	No. of deliveries	Cases of Thrombophlebitis	% of Thrombophlebitis
Vitamin K	700	1	0.14
Controls	5,728	28	0.48

Incidence of Thrombophlebitis in Parturient Women in the University of Virginia Hospital (49).

This is definitely contrary to our beliefs and findings as to the effects of Vitamin K on the coagulation time.

Should one have erred and administered a drug with coagulent properties, there is still a possibility of preventing thrombus formation by the use of heparin or dicoumeral. This is

borne out by the experiments of Solandt and Best (70) who found that by the Intra-arterial injection of sodium ricinoleate into the coronaries of dogs, they were able to produce, in most cases, a thrombosis of the injected vessels or one of its large branches. When the animal was heparinised before the injection of the sodium ricinoleate and during the period of observation, the formation of thrombi and the resulting infarct, was in large part, prevented. They further showed that heparinisation for 72 hours is sufficient for intimal healing. The results of their experiments are given in the two following tables:

Dog No.	Large Artery Thrombosis	Myocard. degeneration	Coronary Thromb. with Myo. infarct
1	yes	yes	yes
2	"	"	"
3	"	"	"
4	partial	"	"
5	yes	"	"
6	no	"	"
7	yes	"	"
8	partial	"	"
9	"	no	no
10	yes	yes	yes
11	no	"	"
12	yes	"	"
13	"	"	"

Sodium Ricinoleate injection of coronary Artery without Heparin (70).

Dog No.	Large Artery Thrombosis	Myocard. degeneration	Coronary Thromb. without Myo.Deg.
1	no	no	no
2	partial	"	"
3	"	"	"
4	no	"	"
5	"	"	"
6	"	yes	yes
7	"	no	no
8	yes	"	"
9	no	"	"
10	"	"	"
11	"	"	"
12	"	"	"

Sodium Ricnoleate injection of Coronary Artery in Heparinised Dogs (70).

RACE

There exists today very little well established factual information on the racial aspect of coronary artery disease. This is due, in a great measure, to the difficulty of separating heredity and environment.

Boaz and Donner (36), in a study of 615 Jewish industrial workers in New York City, found that 57 had coronary thrombosis and 171 had diseases of the coronaries, which was an incidence of about 35%. The incidence of diabetes in the group was only 4%. Hedley (36) found a somewhat higher mortality from coronary occlusion among Jews in Philadelphia than among gentiles, but he related this to a high incidence of diabetes mellitus among the Jewish people.

Hueper (36) shows that there is apparently a race conditioned tendency of the American Negro to develop certain types of arteriosclerosis at an earlier age and to a higher degree than the Whites under similar conditions. This he believes due to the stress and tension resulting from attempts at adjustment to the new and complex life into which the negro was transplanted from his simple native environment.

It was shown that among Mexican Indians hypertension, angina pectoris, and coronary thrombosis show a low incidence, while arteriosclerosis is not much less frequent than among the Whites. Hueper (36) then concludes that there is little

connection between race and coronary thrombosis. Sprague (71) concurs and presents the following summary of 200 cases:

Race	No.of cases of coronary thrombosis
English	135
Jewish	29
Irish	23
French	4
Italian	2
Dutch	1
Spanish	1
Turkish	1
	200

OTHER DISEASES

Blumer (7) is emphatic in his belief that infection, even minor infection, as an exciting cause of thrombus formation in the coronaries, is much more important than has generally been stated. 10% of his patients gave histories of infection and usually the relationship between the infection and the development of the coronary occlusion was so immediate that it was impossible to believe that the infection could not have been responsible for the thrombus. He reminds us that thrombosis elsewhere is not infrequently of infectious origin and that many probably coronary occlusions followed the flu or grippe in the 1918 epidemic. Nelson (52), Turnbull (76), and Boyd (11) agree, and, the last author adds that infection acts by means of causing an acute inflammation of the atheromatous plaques and the subsequent deposition of the thrombus then follows. Sutton and Lueth (73) add their support and suggest that the process is not due to changes in the vessel wall alone but also to changes in the chemical constitution of the blood and its physical properties such as viscosity and lowered tension.

In 1931, Herrick (33) stated that the relation of infection to coronary thrombosis is still an open question. The problem needs further study.

There are those who report large series of cases

and find that there is little evidence that infection, either acute or chronic, contributes toward precipitating thrombosis, except in rare instances (44). Master, Dack, and Jaffee (46) found that in only 2.2% of their cases was there any evidence of infection preceding the attack. Wearn (78) found that infection did not cause a single case of thrombosis in his 19 cases. Sprague (71), White (82), McKeen (48), and Master, Dack, and Jaffe (45) all state that there is no experimental evidence for the causative role of infections and that the theory of their being etiological factors is out-moded.

Slater (68) reported three cases of acute rheumatic fever which, during the course of the disease, developed acute coronary closures. The walls of the larger branches of the coronaries were found to be involved by the rheumatic virus producing a rheumatic coronary arteritis. The closure was usually due to thrombi but in some was due to edema. Werley (81) believes that the only infection which decidedly increases the frequency of atheromatous arteries is rheumatic fever. Stroud (72) states that it is debatable whether frequent infections, especially streptococcal, contribute toward more rapid development of arteriousclerosis. The main point in favor is the pathological picture of the coronaries seen in children dying of rheumatic fever in the first decade of life. It is probably true that thrombotic occlusions of small coronary branches frequently

occur as a result of rheumatic arteritis, but not a major vessel; the question is still unsettled (79).

Rheumatic fever has its adversaries. Sprague (71) points out that it affects the coronary arteries only very rarely and then either by means of the Aorta or aortic regurgitation or the involvement of the coronary ostea. It does not cause degenerative coronary artery changes leading to thrombosis. Wearn (78) found it in only one of his 19 cases and concluded that it was not a factor. White (83) cannot believe it to be a factor.

Some cases of coronary thrombosis may give a history of a previous infection, such as, pneumonia, carbuncle, cystitis, or pyelitis. These, as etiological factors of venous thrombosis are well known, and they are frequently associated with coronary thrombosis as a complication of Phlebitis (15). Winternitz (87) asserts that the involvement of the wall of a vessel secondarily by an acute supperative reaction secondary to an infective process, is frequently the cause of thrombus formation. De Takats (19) blames especially the pneumococcal and virus pneumonias, malaria, and bacterial endocarditis.

As mentioned previously, it is believed by some men that influenza is a potent etiological factor in coronary thrombosis. Gwyn (28), in 1927, expressed surprise that more records showing coronary thrombosis occurring during acute infections, especially

influenza, were not published and he believed that many had been and were missed in diagnosis. He presented two such cases of his own, one in a man 46 years of age and one in a woman 35. Campbell (15) described four such cases of coronary thrombosis just preceded by acute influenza and stressed that myocardial changes are common as sequelae of influenza. Sutton and Lueth (73) also reported a case of coronary thrombosis as a complication of influenza.

Another rare factor is periarteritis nodosa. It was here found that the coronary arteries were most frequently involved with nodules and afterward showed small aneurysms. Thrombosis of the artery was common and afterward a more or less extreme myocarditis was present (73).

Hueper (35) states that it is conceivable that degenerative arterial disease may be the end-result of repeated allergic reactions causing an impairment of the nutrition of the vascular walls by medial spasm in connection with the formation of films, which are composed of allergen-immune body complexes, covering the intima. He believes that it is on this basis that infectious and bacteriotoxic agents act to cause thrombosis.

PRESSURE FROM SOURCES OUTSIDE THE VASCULAR WALL

Niehaus (53) presents a most unusual case. It is that of a man of 42 years who displays a quite typical case of myocardial infarction due to coronary occlusion.

Autopsy showed an infarct of the entire left ventricle except for a three centimeter strip along the septum on the posterior wall. The left ventricle was markedly dilated.

There was a calcified nodule the size of a grain of wheat lying just at the upper margin of the left ventricle. It was placed with its long axis at right angles to the ventricular wall. One end could be palpated just below the anterior cusp of the mitral valve and slightly to the left of the juncture of its anterior and posterior cusps. The other end projected through an attenuated layer of ventricular wall at the auriculo-ventricular junction, so that it pressed against the left coronary artery and thereby obstructed it. At this point the intima of the left coronary was deep red. Distally the vessels were empty.

Apparently, with dilitation and fibrillation of the ventricle, sufficient pressure was exerted on the coronary artery to obstruct it completely.

SYPHILIS

The highest incidence of syphilis found in coronary artery disease was reported by White and Bland (84) in 1931. They found a 14% rate of occurrence in 200 cases. This figure was much higher than is generally recognized and White later lowered this per cent greatly.

The general view of syphilis as to frequency and mechanism of operation was expressed by Warthin (77) in his article in The American Heart Journal in 1930. He believes 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 latter, the process is usually of the nature of a periarteritis, the small vessels of the Adventitia showing perivascular infiltrations and fibrosis, resulting eventually in obliteration. Sclerosis of the Intima invariably results. Myocardial infarction is but extremely rarely the result of a pure syphilitic involvement of the coronary arteries followed by thrombosis. This was found in 1 autopsy in 1,289. 4 autopsies in the same series showed thrombosis on an arteriosclerotic basis due to syphilis. This is in agreement with the findings of Campbell (15), Hueper (35), and Parkinson (56).

By 1944 White (83) had come to the conclusion that

syphilis as an etiological factor in coronary disease was very rare. He stated that the Media was involved first, then the Intima, and then, the thrombus was formed. Others who concurred with his view were Tice (74), McKeen (48), Barns and Ball (3),and Sprague (71).

Werley (81) found that syphilis showed no increased frequency in those who had coronary artery disease as compared with the general population. Wearn (78) found no syphilis in his series of cases. Both concluded that syphilis was not a causative factor of coronary thrombosis.

TRAUMA

Trauma from external sources is a rare cause of coronary thrombosis although not so infrequent in other parts of the vascular tree. Perry and Allen (63) present several cases of acute arterial thrombosis following blunt injury to patients and they blame it on tearing of the Intima.

Vance and de Santo (18) believe that there exists a small but definite group of cases in which operations or violent trauma result in the occurrence of arterial thrombosis in vessels that are the site of chronic degenerative processes. They are unaware of the exact nature of the precipitating factor. They present four autopsy cases of coronary thrombosis, all of which occurred within a short time after operation. Master, Dack, and Jaffee (46) found the rate of post-operative thromboses to be 6.8% as compared with 0% on the Medicine Wards.

Sprague (71) cannot agree that trauma plays a part in coronary thrombosis.

Hueper (35) and White (82) believe that mechanical trauma and stress on certain portions of the coronary arteries do play a minor role in the promotion of degenerative arterial disease. They believe that it acts, not by tearing the Intima, but by means of fluctuations in the vascular tonicity or in the hydrostatic pressure acting on the blood circulation of the vasa

vasorum and, thereby, upon the nutrition and permeability of the vascular walls. This then leads to the deposition of antheromata at the points of stress.

EMBRYOLOGY AND CONGENITAL ANOMALIES

It is recognized that the proximal inch of the left coronary artery and its descending branch is the favorite region of localization of coronary atherosclerosis in its most extreme form. This is the standard site of coronary thrombosis. It is probably due to the quite sharp curve which this part of the vessel takes in its descending course. Moreover, a large branch of the left coronary artery, the Circumflex, arises near the oriface at right angles to the main vessel. The right coronary artery, which is much less commonly involved in severe arteriosclerosis and thrombosis, changes direction only slightly from its origin, is relatively straight throughout most of its length and gives off no large branches in its proximal portion. Even on a normal embryological basis, points of stress appear to be factors in the formation of thrombi.

Leary (40) believes that under the handicap of developmental faults in the heart, the burden thrown on the myocardium in its effort to keep up a circulation causes unusual stresses on the coronary arteries, with resulting lesions and thrombosis. Musser (50) believes that these aberrations of the coronary arteries may run in families and lead to thrombosis.

White (83) states that a simple thickening of the elastic hyperplastic layer of the Intima may occur even in the normal evolution of the coronaries and that this may lead to a

relative myocardial ischemia. However, he and Sprague (71) both agree that congenital anomalies of the coronary arteries are rare and cannot be held responsible for chronic coronary disease or thrombosis.

Herrick (33) propounded an interesting question in 1931 when he asked whether thrombi actually occurred more frequently in the coronaries than in other arteries of the same size. If so, was it due to the tortuosity and twisting of their course, or, did it only appear so because infarcts in other organs were not attended by such dramatic clinical manifestations, hence, many went wholly undiscovered.

ALCOHOL

Alcohol is not a causative factor in the production of coronary thrombosis. In fact, some authors believe that it exerts a protective influence against the formation of thrombi.

McKeen (48) makes the conservative statement that excesses in alcohol are not found as frequent causative factors in thrombosis. Wearn (78) found no history of excessive use of alcohol in his series of 19 cases and decided that it is not a cause of coronary thrombosis.

It was found that among those males who had coronary thromboses, 52% never drank alcohol, and only 4.5% were heavy drinkers. Only one attack followed a bout of drinking. These figures are approximately the same as those for the general population. Masters (46) believes alcohol is without significance. Blumer (7) investigated the problem in a bit more detail but arrived at exactly the same result and conclusion as Masters, except that he believes that moderate doses of alcohol are often of benefit to patients who have had coronary occlusion. Masters (45) in 1937, evaluated the incidence of alcohol drinking in 379 patients and found that:

	Male	Female
Nondrinkers	145(51.4%)	92(95.9%)
Light or occasional	93(33%)	4(4.1%)
Moderate	33(11.7%)	0
Heavy	11(3.9%)	0
	282	97

These figures are approximately the same as for the general population, hence, he concluded that alcohol has no significance in the causation of coronary thrombosis. He was also unable to produce sclerosis or thrombosis by the continued and prolonged injection of alcohol into experimental animals.

To White (83) it appears that the heavy indulgence in alcohol over many years has a protective influence against the ill effect of coronary disease.

Stroud (72) makes the following novel assertion:

> "It is a great comfort to know that no one has been able to prove that alcohol plays a part in this condition. In fact, alcohol in moderate amounts is probably good for the individual past middle life. It will often relieve the angina pain."

COFFEE AND TEA

Coffee and tea are unique in that they are two factors which have not at some time or other been accused of causing coronary thrombosis.

In his series of 19 cases, Wearn (78) found no history of excessive use of coffee or tea and states that they are not a cause of coronary thrombosis. Stroud (72) believes that, unless coffee and tea are used to a great excess, they are not factors in producing either arteriosclerosis or symptoms of angina pectoris.

COMMENTS AND CONCLUSIONS

The anatomy of the coronary arteries is well established. Whether or not one believes that they are end-arteries, one has to admit the existence of cross-communications between them. These were shown by Gross and were borne out by clinical evidence.

The Physiology, Pathology , and Pathogenesis are presented quite briefly in the early part of the thesis. Part of this material is now well established and accepted; part of it is still new and highly controversial. This latter part will be discussed and evaluated in connection with the etiological factors with which it is related. Unnecessary repetition can thusly be avoided.

By far the most important cause of coronary thrombosis is arteriosclerosis and atherosclerosis. Many believe that the thrombosis is simply a complication of the arteriosclerosis and not a separate clinical entity. There are, however, a large number of patients with advanced arteriosclerosis who never experience a thrombosis. It seems likely, then, that there must be other secondary factors, which in the presence of the sclerosis, are able to initiate the thrombotic process. As to the cause of the atherosclerosis, the theory of Timothy Leary concerning

the faulty cholesterol metabolism resulting in hypercholesterolemia seems the best offered to date. This theory combined with the intimal hemorrhage theory of J. C. Paterson will explain a great majority of the thromboses in older individuals. In younger patients, Leary's fibrous reaction theory seems quite consistent with the pathological findings and may again by coupled with Paterson's theory. We must admit, however, that the cause of arteriosclerosis in humans has not been definitely proven or even found consistently in all cases.

It is quite generally agreed that hypertension is a factor in the production of coronary thrombosis and Paterson's theory concerning intimal capillary rupture presents a logical explanation of the process. It is not, however, necessary that hypertension be present for the thrombosis to occur.

There is very little doubt but that coronary thrombosis shows a predilection for the male sex. The preponderance of males is placed in a range of from 90 per cent to 52 per cent. In patients over 70 years of age there is little difference in the per cent of males and females affected.

It had previously been thought that coronary thrombosis was a disease of the aged. However, it is

shown that the calcification of the coronaries supports the intimal vessels so that this disease in people past 65 years is not common. Most arteriosclerosis is found in the sixth and seventh decades of life and this is the age of highest incidence of coronary thrombosis. This leads one to believe that the slowly developing inefficiency of the cholesterol metabolism with advancing age is an underlying factor. The upset cholesterol metabolism leads to the formation of "atheromatous abscesses" in the coronaries and the formation of subendothelial hemorrhages. This view is also supported by the high incidence of arteriosclerosis and thrombosis in young diabetic patients.

It seems well established that obesity leads to coronary thrombosis either directly or indirectly. By indirectly, one means that obesity leads to hypertension, heart strain, and arteriosclerosis which, in turn, leads to coronary thrombosis. The direct mechanism is probably the hypercholesterolemia of Leary.

Due to the fact that coronary thrombosis has so recently been recognized as a clinical diagnosis, the medical records do not extend back far enough into the patient's ancestry so that one can definitely show an hereditary factor in this disease. However,

there does appear to be a definite tendency on the part of members of certain families toward coronary artery disease. Some believe this to be on the basis of an inheritance of a defective coronary anatomy, or an inefficient cholesterol metabolism, or, even, certain diseases which predispose to coronary thrombosis.

Diabetes is a factor in thrombosis. Most authors find an increased incidence of coronary disease among their diabetic patients. Leary's theory is applicable here for the pancreas is related to the level of plasma cholesterol and most authorities agree that there is a hypercholesterolemia in diabetes mellitus.

Long hours of nervous tension and mental concentration with inadequate relaxation and too few vacations do play a part in the causation of coronary thrombosis. This is the reason that most authorities find a preponderance of business and professional men affected with this disease. Many men are now finding a large number of thromboses in laborers and store workers, but there is a far greater number of laborers and store workers to be affected than there are big business and professional people. Therefore, a few laborers who are born with the "spasmogenic aptitude" of Stroud could make up a fairly large segment of the total number of coronary thromboses and still be only

a very minute per cent of the total number of laborers and store workers. While an equal number of cases among the big business and professional group would be fully 50 per cent of these individuals. We must surely admit today, however, that coronary thrombosis cannot be ruled out or in on an occupational basis.

The general impression that coronary thrombosis is reserved for the big business and professional classes is no longer teneable. There is, however, a preponderance of the cases occurring in these two classes. Yet today more and more cases are being recognized among farmers, and skilled and unskilled laborers. It is no longer wise to advise a patient that changing from an occupation involving considerable mental strain to one of a more tranquil nature will insure him against the occurrence of a coronary thrombosis.

The reasons for believing that thromboses, which occur at rest, are really caused by exertion will be stated in a later part of this section.

Angina pectoris is very frequently associated with coronary thrombosis because, in the older patient, the underlying pathology is the same--arteriosclerosis. The patient who has anginal attacks is a likely candidate, in the not too distant future, for a coronary thrombosis

in over 50 per cent of the cases. Some include coronary thrombosis in the Anginal Syndrome.

Some prominent investigators believe that the ingestion of a high cholesterol diet over a long period of time does have a bearing on the formation of atheromata, especially in the presence of endocrine disorders. Leary has shown this to be true in his experiments. The patient is usually one who ingests large amounts of eggs, milk, and other high cholesterol foods and is overweight. Protein deficiency has nothing to do with thrombosis. Vitamin C deficiency may be a factor. Ingestion of large quantities of food, causing gastric distention and reflex vasoconstrition of the coronaries with resultant slowing of the rate of flow of the blood, is a nice theory but is not well borne out be clinical statistical evidence.

A high cholesterol diet, combined with hypothyroidism is found to be predisposing to atherosclerosis. It is also known that the incidence of hypometabolism in subjects 55 years or older is greater for those exhibiting arteriosclerosis than for those without arteriosclerotic manifestations. Hyperthyroidism is not a factor. Hyperparathyroidism, with a high calcium intake, increases the rapidity of arteriosclerosis.

It seems that, in spite of the work of Ewing, there must be some change in the blood which is a factor in coronary thrombosis. This may be a temporary increase in the coagulability which Ewing missed. No doubt alteration in the platelets and rate of flow are factors and variations in the blood's viscosity probably is a factor. The fact that heparinization is so effective in preventing thrombotic processes is definitely significant.

It is shown in the thesis, that, although coronary thrombosis is more frequent in the well set, somewhat over-weight type of patient, it is by no means restricted to this type of individual. To rule out the diagnosis of coronary thrombosis on body type alone would be a great mistake.

It is recognized that in certian peripheral vascular diseases, such as Buerger's Disease, tobacco smoking is definitely harmful. It also is known to increase the pain of angina pectoris. Certainly the use of tobacco is not beneficial to a coronary patient, especially one who reacts strongly to the Cold Pressor Test or is hypertensive. The factor of hypersensitivity also enters into the problem as well as the mobilization of adrenalin which is believed to lead to medial sclerosis. Moderate and heavy smoking have a marked effect in some

patients and none in others. Those affected have their coronary accident before 60 years of age. In those patients over 60 years of age, tobacco is not a causative factor.

Although climate does exert an influence on the incidence of coronary thrombosis, data was presented showing that season and time of day have no marked effect. Convincing evidence is presented on both sides of this controversial issue. Master, Dack, and Jaffe refuse to accept climate, season, or time of day as etiological factors. However, the majority of clinicians and authors believe that more thromboses occur in the winter time than in the summer months.

Toxic and fatigue factors are apparently contributory to coronary sclerosis and thrombosis. Various mechanisms are suggested, the most logical of which is that these agents set up a local inflammatory process in arteries beset by degenerative changes.. This inflammatory process weakens the intima and leads to the local hemorrhage and thrombosis.

Of all the cardio-vascular diseases which lead to coronary thrombosis, coronary thrombosis, per se, is the worst offender. Peripheral vascular collapse,

the vascular allergies, and vasomotor instability are all shown to be complicated, at times, by coronary thrombosis. The relation of angina pectoris has been discussed previously. A family history of cardio-vascular disease was found in 55 per cent of 300 cases by Goldsmith and Willius.

Neurological factors operate only on the basis of vasospasm of the coronaries as explained previously in connection with gastric distention and sudden transient elevation of the blood pressure rupturing the intimal capillaries. It has been shown that the highest per cent of thromobses occur at rest. One should remember that a thrombus does not form in a few minutes and that the capillaries may have been ruptured during the excitement or exertion and the thrombus only have reached sufficient size to become manifest sometime later when the patient is at rest or has retired. Also, the additional factor of a slowed coronary circulation occuring with rest will add to the speed of the thrombus formation once it is started.

The experimental evidence in regard to various drugs is presented briefly in the body of the thesis. Most of the drugs, except digitalis, are not used over sufficient periods of time to cause any noticeable effects. In certain patients it might be well to run

periodic Heparin Tolerance Tests so that their coagulative mechanism can be controlled. I believe that Morton and Burger failed to demonstrate the effect of Vitamin K because no Vitamin K deficiency existed in their subjects before the administration of the drug. Had this deficiency existed, their results would have shown a decreased prothrombin and clotting time.

Except for a slightly higher incidence in Jewish people, there is no relation between race and coronary thrombosis. Even in the Jewish people this is probably due to a higher incidence of diabetes and arteriosclerosis in general.

The evidence that infection is an agent in thrombotic processes in general leads one to the conclusion that infectuous agents may be involved in coronary thrombosis. Rheumatic fever is the outstanding offender and even this is rare. Allergic insult to the coronary intima is a new idea which is gaining more support and is believed by some to be the mechanism by which the bacterial and toxic agents exert their influence.

A coronary occlusion due to pressure from a calcified nodule outside the vascular wall was definitely demonstrated at autopsy.

Syphilis is only very very rarely a cause of coronary thrombosis, mainly, because syphilis only very rarely involves the coronaries themselves. It was found in only 1 autopsy in 1,289 cases. When it is present, it causes a periarteritis.

Evidence was presented suggesting that the ceaseless wear on the intima of the coronaries, and their tortuous course may play a minor role in the etiology. The authors were uncertain, however, why thrombi form here and not in the proximal aorta and heart valves which are also sites of considerable strain. Herrick is at a loss to explain why the coronaries, which are almost never quiet, should so frequently be the seat of sclerosis and thrombosis.

Trauma, as resulting from operations, and local stress and strain on certain parts of the coronary tree probably does play a minor role in the causation of coronary thrombosis. These cases are, however, rather rare. The mechanism involved is a reduction of the blood flow in the vasa vasorum of the coronaries and a resulting impairment of the oxygenation and nutrition of the vascular walls. This leads to increased permeability of the vascular wall and deposition of atheromata at the points of stress.

It is doubtful whether embryological and congenital anomalies of the coronaries have anything to do with the vast majority of cases of coronary thromobsis. Surely the valves of the heart and aorta are under as great stress and strain as the coronaries, yet thrombosis in these areas is believed to be due to stasis rather than stress. Beside, the right coronary, which is relatively straight, is now found to be affected by the thrombotic processes in about one-third of the cases. It is true that with faulty cardiac development enough strain may be thrown on the coronaries to injure the intima faster than it can be repaired.

All agree that alcohol is not a causative factor in coronary thrombosis. Some think it beneficial when used in moderation.

Coffee and tea are not etiological agents.

We find that we do not know definitely the etiology of coronary sclerosis and thrombosis. Of all the etiological factors discussed, the most consistently that any one is found present is 90 per cent. What of the other 10 per cent? No factor has definitely been proven to cause the sclerosis and thrombosis. We are coming to believe that it is a disease and not the inevitable result of the aging and degenerative

processes and that there may be ways of preventing it. The term "ways" is used because it is believed that there is always a multiplicity of factors involved.

Considerable progress has been made in working out the underlying mechanism of the atheromatosis and thrombosis. The Cholesterol Theory of Leary and the Intimal Hemorrhage Theory of Paterson are unquestionably the best offered at the present time. They can be combined and will logically explain the modus operandi of every etiological factor implicated and, in the future, they may be accepted as the physiological basis of coronary thrombosis.

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