5-1-1940

Incidence, etiology and pathology of coronary thrombosis

Wilford J. Deweese
University of Nebraska Medical Center

Let us know how access to this document benefits you
http://unmc.libwizard.com/DCFeedback

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses
Part of the Medical Education Commons

Recommended Citation
https://digitalcommons.unmc.edu/mdtheses/799

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.
The Incidence, Etiology, and Pathology of Coronary Thrombosis

by Wilford J. Deweese

Senior Thesis
Presented to the College of Medicine
University of Nebraska
Omaha
1940
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>History</td>
<td>3</td>
</tr>
<tr>
<td>Incidence</td>
<td>17</td>
</tr>
<tr>
<td>Etiology</td>
<td>28</td>
</tr>
<tr>
<td>Pathology</td>
<td>69</td>
</tr>
<tr>
<td>Bibliography</td>
<td>90</td>
</tr>
</tbody>
</table>
Introduction
The problem of coronary thrombosis has rapidly come to the front as one of the greatest with which medical science is confronted. Not purely because of the number of people who are claimed as its victims, nor because of the prominent careers that are suddenly terminated in this way, nor even because of the terrible suffering often seen during its attack, is this of great interest. But more because of the cloak of mystery that envelopes the situation at present, and the incompleteness of our knowledge, all rendered the more important by the recognition of the probable future with which we are to be faced, in view of the present trends. Heart afflictions are the greatest cause of death today, and are on the increase, and may be expected to continue to do so as life expectancy is increased by modern science. And making up a definite, and apparently rapidly increasing, proportion of this mortality and morbidity is the baffling affliction of coronary thrombosis. Since the treatment is purely symptomatic even if the attack is not immediately fatal, the emphasis must fall on the events taking place before the thrombosis occurs. Why are people, who seem to be in the best of health one minute, dead of a coronary thrombosis in the next? What are the predisposing and the precipitating fac-
ors? What do the victims have in common? How can the condition be guarded against? What is the underlying pathology?

It is in an attempt to evaluate the present status of the knowledge on these aspects that this paper is written. The history is of interest in helping to understand how the present knowledge evolved, and in shedding light on some of the problems that have arisen and which are the cause of confusion at present. Only the incidence, etiology, and pathology are considered here, for they are the aspects that bear on this side of the question.

Coronary thrombosis is defined as a clotting of blood in any of the trunks or branches of the coronary arterial tree, which partially or wholly occludes the lumen of that artery. This may produce immediate death, or, depending on the rapidity and degree of occlusion, infarction of the myocardium, with necrosis of that part of the heart muscle deprived of its blood supply.
History
The occurrence of coronary thrombosis can, in the light of present knowledge, be recognized to have taken place many hundreds of years before the condition itself was in the least suspected. The earliest recorded case in which a fatal attack of coronary thrombosis is inferred is in Homer's "Odyssey", where Menelaus' navigator Phrontis, the son of Cnetor, "dropped dead with the steering oar of the moving ship within his hands," when Phoebus Apollo shed down his gentle darts upon him.(134) But the dispute so characteristic of the whole story of this condition begins already, for another instance is claimed as the first authentic case of coronary thrombosis, which happened nearly six hundred years before Christ.(106) This attack came after an unusually heavy meal: the man refused to let anybody have a bite of his supper especially prepared by his friend, the blacksmith. He proceeded to empty the dish intended for several, and shortly after the engorgement he tumbled off his stool, dead. This was none other than Gautama Buddha, the founder of Buddhism.

The pathological condition itself has a much shorter history, which up until very recently is the history of angina pectoris. For, although angina pectoris dates from the time of Heberden as a clinical condition, its distinction from coronary thrombosis
was long over-looked, and unknowingly included in the syndrome of angina pectoris as an inconsequential detail, if not totally ignored. Thus the present status of our knowledge came from a gradual unfolding of the picture of angina pectoris, in which an actual change in the coronary arteries and the heart muscle came to occupy a more and more prominent part.

The first case of coronary artery disease to be recorded is attributed by Riesman (133) to William Harvey in the first half of the seventeenth century. Harvey also described a case in which he surmised impeded blood flow from the left ventricle into the arteries to have been the cause of heart rupture. The patient was a Sir Robert Darcy, who was afflicted with a distressing chest pain with syncope and suffocation in repeated attacks, and with progressive decompensation. He finally died in an attack, and at the post-mortem examination a rupture of the left ventricle was found which was large enough to admit a finger. The wall itself appeared sufficiently thick and strong, which led Harvey to believe that the rupture had been due to the impeded blood flow. (73)

The story of angina pectoris, and so also of coronary thrombosis really begins with William Heberden, whose first observations were made public in 1768
at a meeting of the Royal College of Physicians in London. He described the picture of angina pectoris as we know it today, a description that remains a classic, and in his last few sentences includes conditions now thought to be those of coronary thrombosis. He is quoted by Fulton as follows: "In one or two persons the pain has lasted some hours, or even days; but this has happened when the complaint has been of long standing and thoroughly rooted in the constitution: once only the very first attack continued the whole night. I have seen nearly a hundred people under this disorder, of which number there have been three women, and one boy twelve years old. All the rest were men, near, or past, the fiftieth year of their age. But the termination of angina pectoris is remarkable. For if no accident intervene, but the disease go on to its height, the patients all suddenly fall down, and perish almost immediately."(46) Heberden believed that these anginal pains were caused by a spasm of the coronary arteries, and makes no mention that they might be due to changes in these arteries.

Jenner in 1772 discovered the connection between sclerosis and angina pectoris, but did not announce it until 1799 out of regard for his friend John Hunter,
whom he did not wish to alarm. For Hunter was suffering from angina pectoris at that time. Due to his consideration, however, he lost priority on his discovery, for Black in 1795 (124) published the connection. Jenner's description of the autopsy is interesting: "I was making a transverse section of the heart near its base, when my knife struck against something so hard and gritty as to notch it. I well remember looking up to the ceiling, which was old and crumbling, conceiving that some plaster had fallen down. But on further scrutiny the real cause appeared: the coronaries were become bony canals." In a letter to a friend of John Hunter's, written in 1778, telling him of his diagnosis of Hunter's condition, a description appears of a post-mortem examination of another person who died of angina pectoris. "...but about three weeks ago, Mr. Paytherus, a surgeon at Ross, in Herefordshire, desired me to examine with him the heart of a person who died of angina pectoris a few days before. Here we found the same appearance of the arteries as in the former case. But what I had taken to be an ossification of the vessel itself, Mr. Paytherus discovered to be a kind of firm fleshy tube, formed within the vessel, with a considerable quantity of ossific matter dispersed irregularly through it. This
tube did not appear to have any vascular connection with the coats of the artery, but seemed to lie merely in simple contact with it."

"As the heart, I believe, in every subject that has died of angina pectoris, has been found extremely loaded with fat, and as these vessels lie quite concealed in the substance, is it impossible this appearance may have been overlooked? The importance of the coronary arteries, and how much the heart must suffer from their not being able duly to perform their function (we cannot be surprised at the painful spasms) is a subject I need not enlarge upon, therefore, shall only just remark that it is possible that all the symptoms may arise from this one circumstance."(96)

In the year that Jenner announced his discovery, Parry is credited with first proposing the theory of ischemia of the heart muscle as the chief cause of the anginal pain.(124) In 1809 Allen Burns did the first experimental work in attempting to prove this theory by ligaturing the vessels of one limb of an animal. He suggested the theory upon which our conception of intermittent claudication is based, speaking of the effect of a tourniquet on the leg, the early fatigue by deficient circulation, and likens that to the inelastic and incompetent coronary arteries.(46)
The magnitude of these conceptions gradually impressed the medical men of the early part of the nineteenth century, for one hundred years ago in his "Goulstonian Lectures" Marshall is quoted as saying that "many facts lead me to believe that the cause of sudden death arises chiefly from interruption of the coronary circulation."(73) In his "Diseases of the Heart" published in 1847, Latham of London (87) believes angina pectoris to be a spasm of the heart. He describes, however, coronary arteries that have been reduced to mere bony tubes, with the dependant heart muscle being very thin and soft, but without being fat. Obstructions of the coronary arteries, however, are not recognized. At about the same time Hope of Edinburgh, in his "A Treatise on the Diseases of the Heart and Great Vessels,"(69) states that Parry, Burns, and Kreysig believe the cause of angina pectoris to be ossification of the coronary arteries. But less than ten years later Stokes, in his work entitled "Diseases of the Heart and Aorta," a book of six hundred pages, devotes eight pages to a discussion of angina pectoris according to the ideas of Heberden, Parry, and Latham. Any foothold that the understanding of the coronary pathology may have gained by this time was rendered the more insecure by his closing
words: "Upon the whole, we may conclude, that the special group of symptoms described as angina pectoris by Heberden, Parry, Percival, and Latham, is but the occurrence, in a defined manner, of some of the symptoms connected with a weakened heart. Obstruction of the coronaries may or may not be present, and is probably not infrequent; but as the cause of angina, its action is remote, and its existence unnecessary."

(46)

In the same year, 1854, as the publication of the above quotation from Stokes, Sir William Gairdner described "a case of ossification of the coronary arteries with tendinous degeneration of the heart."(1) The gap between the clinical picture of angina pectoris and the pathological states at times observed in the hearts seems to have been as wide as ever.

Another interesting aspect of the evolution of this problem is presented by Dobell of London in 1872. (39) In discussing angina pectoris he assents that in the pain of heart affections the neuralgic must always occupy the most prominent place because of its agonizing character. The heavy oppressive pain is by distension of the right auricle obstructing the orifices of the cardiac veins and the venae Thebesii. The dull, heavy pain in the arms he attributes to obstruct-
ed blood return through the subclavian veins.

But suddenly the whole problem was advanced to a position far more near to its ultimate solution by one of the totally unexpected and brilliant steps that have so often marked the progress of medical science. In 1878 appeared an account in "Wiener Medizinische Wochenschrift" by Hammer, a German who had come to the United States after the revolution of 1848. Hammer was called by one of his colleagues to see a patient who was apparently in extremis, and after a consideration of the history, symptoms, and signs told his colleague at the bedside that these symptoms could only be produced by a thrombotic occlusion of at least one of the coronary arteries. The colleague replied, "I have never heard of such a diagnosis in my whole life," and, Hammer writes, "I answered, 'nor I also.'"

A subsequent autopsy showed a thrombus in the sinus of Valsalva which had ultimately completely shut off the lumen of the artery.(46)

After this startling achievement the further advances began to come more rapidly. In the following year Ziegler of Jena published a description of acute and chronic heart infarction, and gave it the name "myomalacia cordis." He also affirmed the ischaemic origin of this condition.(179) Pothergill in his book
(44) considered angina pectoris and sudden death together, and stated his belief that angina pectoris was a state of acute distension of the heart. He described degeneration of the heart muscle, and states, "some commencing imperfect nutrition of the heart must be suspected here." Slight atheromatous deposits in the coronary arteries are described, and the association of the condition of atheroma with angina pectoris is said to be grave.

Just as angina pectoris may be considered as beginning with Heberden in 1768, so coronary thrombosis may be considered to begin in 1878-1880 with the work of these men: clinically with Hammer, and pathologically with Ziegler and Weigert. The latter is usually given the credit as being the expounder of the doctrine of cardiac infarction. (15) "With atheromatous changes of the coronary arteries, thrombotic or embolic occlusions of their branches not infrequently occur. If the closures result slowly, or, more important still, in such a way that collateral channels, even too insufficient for nourishment, exist, there ensues a slower atrophy with disappearance of the muscle fibers, but without injury to the connective tissue." He showed that infarction in the heart was analogous to that in other organs.
In 1881 Cohnheim and von Schultess-Rechberg studied the pathological anatomy of experimental coronary infarction in dogs, and emphasized the conception of the coronary arteries as end-arteries. This conception was advanced by Cohnheim a short time previously, believing that the effect of coronary thrombosis was due to the lack of considerable anastomosis. He concluded that the sudden occlusion of one of these vessels, or of one of the larger branches, such as the ramus descendens of the left coronary, meant death within a few minutes. (35)

Leyden in 1884 wrote a paper on the effects of coronary artery disease. This contained an accurate clinical and pathological account of several cases of coronary thrombosis. (128) Three years later in the Lancet appeared a series of four articles on "Fibroid Degeneration and Allied Lesions of the Heart, and Their Association With Disease of the Coronary Arteries" by Steven of Glasgow. He stated, "Fibroid degeneration generally occurs with widespread degeneration of the arterial system, obviously including in most instances the coronary arteries of the heart. More acute processes occur in the same arterial degeneration or with embolism." Again, "Infarction is by a chronic extensive disease of the coronary arteries, plus a sudden
obliteration of the trunk by thrombosis or embolism." He describes a clot in the coronary vessels at post-mortem, as causing "additional obstruction," and says that cardiac infarction and fibroid degeneration can probably be correctly diagnosed. (148)

Dobell's characterization of the agonizing heart pain as "neuralgic" is contradicted by Hale in his book, "Lectures on Diseases of the Heart," published in 1889. He admits that angina pectoris is regarded by some as an organic disease, but by most as a functional one, and states further that it is not a neuralgia, because the paroxysms are increased by exertion and emotion, and because it is so frequently and suddenly fatal. He mentions rupture of the heart, as taking place even during repose. (57) In the same year Huchard reported on a series of 123 cases of angina pectoris with coronary lesions. (70)

The next big advances in the solution of this problem came in 1896. Marie, in Paris, published a comprehensive pathological study of acute necrosis, scarred infarcts, aneurysm, and rupture of the heart. (100) In the same year Dock is credited with being one of the first to diagnose coronary thrombosis during life and prove its presence at autopsy. He recognized the importance of the pericardial friction rub

-13-
as an aid to diagnosis.(91)

In 1901 Krehl called attention to the possibility of recovery after an attack of coronary thrombosis. He discussed the development of aneurysms of the ventricle, and thought that they were not an infrequent cause of rupture of the heart. He also recognized that the symptoms were more severe in a sudden occlusion than in a gradual one.(83)

Nine years passed until the next milestone was reached, when Obratzow and Stracheska described three cases of coronary thrombosis, of which two were diagnosed during life, and confirmed by post-mortem examinations. These investigators are given the credit for being the first to establish coronary thrombosis as a clinical entity distinct from angina pectoris. (123) But here the solution was not so near at hand as it appeared to be. For what is now recognized as coronary thrombosis continued to be considered severe angina pectoris, or "status angiosis" for another four years or so. And in England, coronary thrombosis as a specific problem was not considered until 1925!(91)

In the same year that Obratzow and Stracheska made their contribution, William Osler gave his "Lumleian Lectures on Angina Pectoris" before the Royal College of
Physicians in London, 143 years after Heberden had appeared before the same society. And, in his second lecture, Osler said: "Had Heberden listened to my first lecture he could have remarked very justly: 'Well! They have not got much ahead since my day.'" (119)

Osler's lectures are evidence of how angina pectoris was still taken to include the whole of the problem. The symptom was divided into three categories: 1) formes frustes (mildest) 2) mild 3) severe. In the severe class were included "a large proportion of all cases of organic change in the arteries, and a liability to sudden death." In discussing the pathology, luetic aortitis and affections of the coronary arteries were the two large headings, and under the latter were: a) narrowing of the orifices b) blocking of a branch with a fresh thrombus ("very common in cases of sudden death in angina") c) obliterative endarteritis, and d) no lesions found. (119)

The present era of investigation really begins with the work of Herrick of Chicago, first published in 1912. (65) He established coronary thrombosis as a clinical entity by a discussion of the clinical features associated with it, and took exception to Cohnheim's belief by stating that large branches of the
coronary arteries can be occluded, at times acutely, without resulting death.

From this time on the literature accumulated rapidly on all of the aspects of coronary thrombosis. Some of the more important advances will be reviewed in the discussion in the following sections.
Incidence
The frequency of the occurrence of coronary thrombosis before the time of its establishment as an entity to be separated from the general condition of angina pectoris can be only speculative. But, even so, the low incidence inferred from the number of angina pectoris cases of some of the early clinicians who have left records on this condition adds to the present-day belief that the incidence is increasing very rapidly. Heberden stated that he had seen "nearly a hundred people under this disorder, (46) yet in 1857, ninety years later, Bamberger in Germany called angina pectoris "one of the rarest symptoms of heart disease," and had seen only six cases when he published his book on heart disease in that year.(19) Austin Flint in the United States, writing in 1870, asserted that he found only fifteen cases of angina pectoris in three hundred and eighty-three consecutive cases of heart disease.(19) However, in 1896, Balfour, a distinguished Edinburgh consultant, wrote that he had seen ninety-eight cases in ten years, though Osler a year later had seen only forty cases of "true angina pectoris."(117) This trend is reflected in the reflected in the registration of deaths as well, for in 1845 out of the 5,171 deaths occurring in Hamburg, Germany, only three were attributed to angina pector-
The present status is in marked contrast to these early figures. And, as has been recognized, is really a triumph for modern medicine. For today heart disease has come to the fore as the chief cause of death, and brings with it a proportion of deaths due to coronary thrombosis. This trend is readily seen in mortality statistics, and summed up in Mackenzie's statement that "one person out of every three having reached the age of forty-five will die of cardio-vascular disease." (98)

<table>
<thead>
<tr>
<th>Death Rates per 100,000 Population in New York City</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Total rate</td>
</tr>
<tr>
<td>Circulatory System Diseases</td>
</tr>
</tbody>
</table>

The inverse proportion between circulatory system diseases and the total death rate is evidence of the fact that more people are living to the age when a proportion of their number may expect to die of cardio-vascular diseases, which is also demonstrated by the following table: (94) (see next page)

But the increased average age and life expectancy is not in any way the whole explanation, as will be discussed later.
Population Age in New York City

<table>
<thead>
<tr>
<th>Age Group</th>
<th>1910</th>
<th>1920</th>
<th>1930</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 15 years</td>
<td>28.7</td>
<td>28.4</td>
<td>24.4</td>
</tr>
<tr>
<td>15-34 years</td>
<td>40.2</td>
<td>37.2</td>
<td>38.0</td>
</tr>
<tr>
<td>35-64 years</td>
<td>28.3</td>
<td>31.3</td>
<td>33.8</td>
</tr>
<tr>
<td>65 and over</td>
<td>2.84</td>
<td>3.11</td>
<td>3.83</td>
</tr>
</tbody>
</table>

In Detroit in 1923 heart deaths in people over thirty years of age represented 314 per 100,000 population, while in 1932 the figure had increased to 364 per 100,000. These figures are higher than for the whole country, for in the same year as the second figures, 1932, Master stated that the heart disease deaths for the United States were 224 per 100,000 population, with a total of two million patients with heart disease.

Hospital post-mortem statistics are interesting when investigated from this standpoint. In the Presbyterian Hospital in New York from 1910 to 1931 there were 126,445 admittances, with a total of 2,877 post-mortems. Of these, 762 examinations showed affections of the coronary arteries. At the Mayo Clinic in 1932, the results of one thousand consecutive post-mortems showed 49 hearts with gross myocardial infarctions, an incidence of 4.9%. Again, in a study of 23,972 autopsies in Minneapolis, 3,872 deaths
were attributed to non-congenital cardiac disease, and of these 928 to fatal coronary disease, an incidence of 4% of all deaths in patients over six months, and 6% of all deaths over forty years of age. (34)

The frequency of the diagnosis of angina pectoris and coronary thrombosis in practice is evidenced by the many series of cases reported in recent years. After remarking on the rarity of the diagnosis by such men as Bamberger and Flint, Boas and Donner report in 1932 that they have seen 225 new angina pectoris or coronary thrombosis cases in less than two years. (19) Master, Dack, and Jaffe report on a series of 522 cases of coronary thrombosis in 1937. (103) At the Mayo Clinic, where coronary thrombosis was first diagnosed in 1915, this condition represented 0.006% of first admissions to the Clinic in 1922, 0.090% in 1928, 0.160% in 1931, and 0.300% in 1933. (170) At the Presbyterian Hospital in New York from 1913 to 1919 clinical diagnoses of coronary disease were made on 0.05% of the hospital admissions. Since 1919 there has been a quite steady increase, until in 1931 the diagnosis was made in 0.8% of the admissions. (94) Yet the significance of these figures is increased by the fact that at that hospital from 1921 to 1931
coronary thrombosis was correctly diagnosed in only 43% of the cases that came to autopsy there. (7)

The significance of these impressions and figures on the increasing incidence of coronary thrombosis is a perplexing problem in itself. How much of the increase is real and how much only apparent? Surely the accuracy of diagnosis, aided by an ever-increasing understanding of the problem and by the modern aids to diagnosis and increased pathological knowledge, plays a very large part here, and probably the major one. But it is not the whole answer. (19) Besides the increasing life span, and the accuracy of the diagnosis, there seem to be other factors entering into this phenomenon, which must be sought in a study of the etiology of coronary thrombosis.

The incidence of coronary thrombosis according to age presents some interesting aspects. It has commonly been believed to be an aspect of the degeneration of the cardiovascular system coming on with increasing age. Thus the majority of cases are seen to occur in the sixth and seventh decades: (103) 61% in one series of three hundred cases (104), 70% in another. (10) The average age is usually from 52 to 62 years. (115) (105) (91) (166) But an ever-increasing number of cases are being found outside of the age group usually
thought of. Of a series of 300 cases, 29% were less than fifty years of age, 61.5% from fifty to sixty-nine, and 28% over seventy years of age. (104) The difference in ages is great, in spite of the high average ages found, and of the fact that people of seventy years of age or over were believed to seldom be afflicted. (9) Large series of cases show age ranges of from 28 to 82 years or, again 27 to 88 years. (103)

Great interest has been taken in coronary thrombosis occurring in younger people in the last few years. One author found twenty proven cases in the literature in patients less than forty years of age, the youngest being twelve. (142) White reports 138 cases less than fifty years of age, of which twenty-one were less than thirty. (163) Another reports coronary thrombosis in a twenty-two year old pregnant woman, believed to be the youngest woman on record with this condition, and of one boy eighteen, another twenty-two, and four males less than thirty, all with coronary thrombosis. (164) Twenty-seven coronary thrombosis patients between the ages of thirty and thirty-nine are reported from the Mayo Clinic. (52) In another survey 208 cases of coronary thrombosis in people less than forty are summarized, (138) while at the University of Michigan
Hospital seven cases of this disease were seen in patients less than thirty-five years of age from 1931, to 1935. (40) Thus it appears that with increasing accuracy of diagnostic methods, and increased knowledge of the signs and symptoms of coronary thrombosis, the diagnosis can be made where it would not have previously been suspected.

The ratio of males to females among the victims has long been interesting. There were only three women included in almost one hundred angina pectoris patients that Heberden saw. Yet present-day proportions differ greatly from this. Of a series of 555 coronary thrombosis victims, there were 432 males and 123 females (103): in another of 400 cases, an even one hundred were women. (115) That the incidence in women tends to be later than in men is demonstrated by an average age of fifty-two for the males and of fifty-five for the females in the last series. That women tend to be less afflicted than men earlier in life, and more in later years has been established. (36) In young adults men exceeded women by a ratio of three to one, and in middle age the ratio was decreased to two to one, while over seventy years no significant difference was present. (53) Another found that in the seventh decade the occurrence in women exceeded that
in men by nearly twice, but that sudden death by coro-

The conception of the occupational incidence is

The conception of the occupational incidence is just at present undergoing a profound change. Coronary thrombosis was long called the "physician's disease," and was believed to be due to the strain imposed on the doctor by his profession. It is considered to be "peculiarly frequent" amongst physicians of many races and generations, and to have destroyed some of the finest men in this profession. That this may not be unfounded is evidenced by a recent article, where the obituaries of 3,345 physicians appearing in the Journal of the American Medical Association in 1935 are examined. Heart disease took 1,345, or 40.5%, and of these 220, or 16%, died of coronary thrombosis. This is accompanied by the statement that the medical profession leads all others in deaths from this cause. Osler said that angina pectoris was an affliction of the better classes, and was not often seen except in private practice. This aspect of the problem has been examined very critically in the last few years, with interesting results. Boas speaks of the belief that coronary thrombosis occurred among the well-to-do, among people of the business and professional
world "who work with their brains at high pressure," and then gives the results of a series of cases among Jewish workers in the garment industry in New York where the incidence was exceptionally high: 11.1 per 1000 cases of sickness. (19) They compare this with an incidence of 4.2 per 1000 cases in consultation practice, 2.3 per 1000 in general practice, and 0.6 per 1000 in hospital and dispensary practice.

Master classified his series of 522 cases of coronary thrombosis by occupations, with the following results: (103)

<table>
<thead>
<tr>
<th>Occupations</th>
<th>Cases</th>
<th>Per-cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workers and laborers</td>
<td>196</td>
<td>37.5</td>
</tr>
<tr>
<td>&quot;White collar,&quot; office workers</td>
<td>52</td>
<td>10.0</td>
</tr>
<tr>
<td>Store workers</td>
<td>26</td>
<td>5.0</td>
</tr>
<tr>
<td>Business men</td>
<td>52</td>
<td>10.0</td>
</tr>
<tr>
<td>Professional people</td>
<td>41</td>
<td>7.8</td>
</tr>
<tr>
<td>Housewives</td>
<td>117</td>
<td>22.4</td>
</tr>
<tr>
<td>None, or retired</td>
<td>38</td>
<td>7.3</td>
</tr>
</tbody>
</table>

From this they assumed that occupation played little or no part, since the disease was common in all strata of society. Another such series gave rather similar results, where 44.2% of cases of coronary artery disease occurred in foremen and skilled workers, 39% in men of the professional and executive
groups, and then came manual laborers, clerical workers, semi-professionals and minor executives, housewives, retired or unemployed, and, lastly, students. (94) While these results seem quite conclusive they are not without opposition, for it has been observed that occlusions in groups of private patients are still twice as numerous as those of similar groups of ward patients. (53) And strain of occupation, as in professional men, is still considered by some to be one of the major factors in the production of this condition, as will be discussed later on.

The racial variations in susceptibility to coronary thrombosis have awakened interest, and are worthy of mention. It has been stated that it is uncommon in the negro, and especially in negro women, but that no race is immune. (3) Out of ninety-four hearts with a major coronary artery occlusion studied by one investigator, however, one-fourth were from negroes. (113) Angina pectoris and coronary thrombosis are almost unknown among the Chinese. (73) The condition has at times been noted to occur with a relatively greater frequency, especially in the younger age groups, among the Jews. (19)(163)

Coronary thrombosis shows a greater occurrence in the winter months than in the summer months. This
seasonal incidence is in accord with the mortality of deaths from cardio-vascular disease in general, and was observed over a three year period in Philadelphia. During this time 133 acute seizures of coronary thrombosis were noted in 131 patients, with the result that forty-seven attacks were found to have taken place in the three winter months, twenty-six in the three spring months, twelve in the summer, and forty-eight in the autumn months. (178) This is supported by another report of four hundred cases where nearly twice as many initial attacks occurred in the months of December, January, and February as in the summer months (115).
Etiology
The etiology of coronary thrombosis is at the present time a point of contention for the medical world, and at the same time one of its most important and interesting problems. That it is largely speculative is evidenced by the multiplicity of the factors which have been and are being emphasized as possible predisposing or exciting causes, which have been suggested and investigated in the hope of finding a tangible clue. This appears to be the most important part of coronary thrombosis, both to the people at large who may be affected and to the physician, for at present it seems to be the aspect from which the most benefit may be derived. It is a dreaded and devastating affliction, whose next victims cannot be foretold, and which, once having struck, can at present only be combated with symptomatic measures. Thus an understanding, if only partial, of the causes of coronary thrombosis would be the greatest achievement in its management, by aiding in preventing a condition that, once having occurred, can only be so ineffectively treated, and whose prognosis rests so completely with fate. In this paper it will only be possible to deal briefly with the various etiological aspects encountered in the literature, and the sequence will in general represent the popularity of
the factor with the writers.

Marie in 1896 stated that coronary thrombosis was never spontaneous, but was always due to disease of the artery. (100) This represents the general conception at present, for arteriosclerosis is given as the underlying pathological lesion in the coronary arteries in the majority of reports. It is said to be as invariable accompaniment in post-mortem examinations in some series of cases. (138) (97) In this respect angina pectoris and coronary thrombosis have a common background, and are both steps in the progression of coronary arteriosclerosis, which may lead to coronary occlusion and death without either of them occurring. This coronary sclerosis is believed to provide the setting on which a thrombosis may, but will not always, be superimposed. In 762 proved cases of cardiac deaths, coronary artery sclerosis was found to be by far the most common disorder, being present in 97%. (95)

In a study of 5,060 consecutive autopsies at the Mayo Clinic, coronary and aortic sclerosis were investigated, particularly with respect to age. 870, or 17.2%, were found to be free of sclerosis, the proportion varying inversely with age. None were found to be free in the age groups from seventy to one hundred years. Slight sclerosis was found in 2,759 (54.5%),
moderate in 991 (19.6%), marked in 378 (7.4%), and
extreme sclerosis in 62 (1.2%). This was all found
to be in proportion to age, in the moderate to severe
groups were included 33.6% of the males of the series,
and 18.8% of the females.(169) That arteriosclerosis
is, in general, proportional to the age is demonstra-
ted by this series, but that marked individual varia-
tions may be encountered is well known. Some middle-
aged people are quite free, while some young adults
present quite definite findings, and arteriosclerosis
has been found in children as young as two years.(138)
(163) The relative incidence of the vessels involved
in arterial disease has been studied by Brooks.(22)
In a survey of four hundred consecutive cases of art-
erial sclerotic disease, 368 showed serious disease of
the visceral trunks. The coronary arteries were pre-
dominantly affected, being involved in 270 of the 368
cases, and the writer believed this to be due to the
increased work demands thrown on these arteries when
disease of the other usual distributions exists.
Brain arteries were the next in frequency, being aff-
ected in 132 cases, and the renal arteries third, with
81 showing sclerosis.

But, admitting that coronary arteriosclerosis is
the most common etiological factor, there are several
aspects of the problem that remain puzzling. How to account for the increase in coronary thrombosis in recent years is a question. There has been an undoubted rise in atheroma and arterio-sclerosis, but not enough by any means to account for the great increase in cases of coronary thrombosis.(32) The answer for this must be sought among other causes. Again, the incidence of occlusion does not parallel the extent of coronary sclerosis.(97) Some hearts examined with thrombi in the coronary arteries present very little or no sclerosis of these arteries. And if the association were proportional, the arteries most involved in one process should be also the most involved in the other. But arteriosclerosis has been found to be equal in extent in both the right and left coronary arteries, while it has long been established that the left coronary is more frequently involved in thrombosis than the right, and that infarcts are uncommon in the right ventricle. (4)(7)(11) One series showed occlusions to have taken place one hundred times in the left coronary as compared to twenty-nine in the right, and sixteen multiple, in hearts that had about the same degree of sclerosis in the right and left coronaries.(4) In a detailed study of 900 fatal cases of coronary sclerosis 523 showed practically equal severe involvement of both the
right and left coronaries. Of the balance 367 showed a less amount of sclerosis in which the left coronary was involved more than the right, and only ten where the right was involved more than the left. Of these 900 cases, coronary thrombosis occurred in 419, with a distribution as follows: 301 in the left coronary artery alone, ninety-one in the right alone, and twenty-seven times in both. From this the discrepancy does not appear to be so great.\(^{(34)}\) However, one investigation of the increasing fat deposit in the coronary walls with increasing age found that the anterior descending branch of the left coronary artery called the "artery of sudden death" because of the frequency of thrombosis there, was the first vessel affected in the early decades, while the right coronary artery did not show any regular deposits until the fourth decade, and the posterior descending branch not until the seventh.\(^{(163)}\) The fat deposition and fibrosis were believed to come more in regions of particular stress. Another factor in the location of thrombi may be that arteriosclerosis appears to progress with diminishing severity from the larger to the smaller branches, and to be confined to the superficial vessels. Significant sclerosis of the penetrating myocardial vessels is stated to be the exception rather than the rule.\(^{(113)}\)
That the increasing sclerosis is not accompanied by an increasing incidence of coronary thrombosis in the higher age groups has been remarked upon. As stated above, sclerosis was found to be universal above seventy years of age, and yet coronary thrombosis is uncommon above that age, and occurs at an average age of nearly ten years less. In a study of 700 patients seventy-five years of age or over, 385, or 55% had clinical evidence of heart disease. Of these 381, or 98.9%, had hypertension or coronary sclerosis, 172, or 44.7%, having coronary disease. But in spite of this high percentage of sclerosis, there was only one case of coronary thrombosis, an incidence of 0.3%.

This is believed to be due to the increased anastomoses between the branches of the coronary arteries with advancing age, so that collateral circulation is more readily established. From another aspect, however, the relationship is borne out better by the difference between the sexes. 80% of the cases of marked arteriosclerosis occur in men, which is approximately the same as for attacks of coronary thrombosis. In women, arteriosclerosis occurs on an average of about ten years later than in men, so that more of the women with coronary thrombosis come in the later age groups than do the men. In the seventh decade 8% of the cases of coronary thrombosis in men occur, as
against 17% of the attacks in women. (172)

The cause of arteriosclerosis will then be in a measure the cause of coronary thrombosis, when it is understood. (81) A full discussion of this is outside the realm of this paper, but some of the factors will be referred to in the further discussion of the causes of coronary thrombosis. British writers discuss atheroma separately from arteriosclerosis in discussing the causes of coronary thrombosis, and state that it is the commonest primary lesion. (1) (32) It is not apparently held distinct by the American investigators, but included with arteriosclerosis. The pathological aspects of these will be discussed in a later section.

A second important etiological aspect of this problem, and one closely associated with arteriosclerosis, is hypertension. Levine states that a previous hypertension is probably the most common single etiological factor in coronary thrombosis. (91) In his 145 cases, fifty-eight had a blood pressure greater than 160 mm. systolic or greater than 100 mm. diastolic, with an average pressure of 191/110. In another series of seventy-five cases of coronary thrombosis 70% were hypertensives. (101) In contrast, out of 287 cases studied by Conner and Holt, only 33.9% were classed as hypertensives, and they concluded that high blood pressure had no more re-
lation to coronary thrombosis than did low blood pressure. (36) Phipps believes an underlying hypertension is present in 20% to 40% of the cases of coronary thrombosis, and that this condition is responsible for from 6% to 10% of the deaths of hypertensives. (128)

Again, out of 419 patients with fatal coronary thrombosis 220 had hypertension and 199 did not: certainly not a significant difference. These were taken from a larger series of 900 cases of fatal coronary sclerosis, which gave nearly the same ratio: 410 with hypertension and 290 without. (34) The authors, however, state that hypertension is the most common suggestive etiological factor in coronary sclerosis, but admit that it is seen to be lacking even in severe cases. Of the 300 cases of coronary thrombosis reported by Goldsmith and Willius, hypertension was established in eighty-three. (50)

Hypertension is believed to play a more important part in coronary thrombosis in women than in men, (91) and it is considered probable that occlusion takes place in women only when hypertension is present. (101)

Yet in a series of 923 fatal cases of coronary sclerosis eighty-eight females had hypertension and sixty-seven not: relatively little more than among the males, where 326 had hypertension and 442 were not so affected. (34)
This is rather unexpected, for hypertension is about twice as common among women as men. The exact data on this subject is difficult to obtain, for often a markedly elevated blood pressure returns to normal limits very shortly after the attack of coronary thrombosis occurs. If the patient is first seen at that time he may be recorded as a non-hypertensive, but his previous condition may be deduced from retinal sclerosis, or from cardiac hypertrophy. Of Levine's series, only six patients were absolutely known to have had normal blood pressure previous to their attack: the rest must be placed in a questionable group. (91) But, as he says, there are a sufficient number of patients who at no time have had hypertension to establish that it is not an absolute prerequisite.

The mechanism by which hypertension may affect the onset of coronary thrombosis is not clearly understood. Thrombosis is usually thought of as occurring when the circulation is less brisk than normal. High blood pressure increases the work of the heart, and so taxes the coronary blood supply to it. A relative insufficiency of blood from this cause could give angina pectoris, or death from the insufficiency, but would not be expected to give a thrombosis. In its association with sclerosis, as a cause of sclerosis perhaps, its
effect would be more obvious. A new light has been shed on this problem by the work of Paterson, which will be discussed under the pathology of coronary thrombosis. His work on capillary rupture and intimal hemorrhage as a causative factor admits of the increased blood pressure being an agent in promoting the rupture of the capillaries.

Another oft-mentioned etiological factor of coronary thrombosis, and also one to be thought of in connection with arteriosclerosis, is diabetes mellitus. In so far as it is accompanied by early atherosclerosis and arteriosclerosis, it would be expected to appear as a significant cause. Levine considers that diabetes is second in etiological importance only to hypertension. He states that large numbers of diabetics eventually develop coronary artery disease, and make up a fair proportion of the coronary thrombosis victims. These are especially the elderly mild diabetics, who have reached the stage of marked vascular changes. That the diabetes is an actual cause, however, is not altogether certain, for their age at death is not essentially different from those dying from this affliction without diabetes. It may be that this is merely the type of individual having the vulnerable vascular system. In Levine's
series of 145 cases of coronary thrombosis, thirty-four, or 23.4%, had glycosuria or diabetes. The average age of these at their attack was 58.1 years, while that of the entire group was 57.8 years. However, one-third of the diabetics were females, while only one-fifth of the entire group were. In another series of 287 cases of coronary thrombosis, twenty-eight, or 10.2%, had diabetes. (36) It is interesting to compare with this the group of Jewish garment industry workers mentioned before, where only eight of 171 cases had diabetes. This was attributed to their youth, since 84% were below 50 years, pointing out that some other factor was responsible here. (19) Of the 522 cases of coronary thrombosis reported by Master et al, twenty were receiving insulin regularly, and they concluded that no relationship was established here as had been noticed regarding insulin and angina pectoris. (103)

Four years ago the results of an investigation inspired by this accepted association of diabetes mellitus and coronary thrombosis were published. Here twenty-one patients with coronary thrombosis, ranging in age from thirty-four to seventy-six years, were studied from the standpoint of sugar tolerance. All tests but three were done within two weeks of the coronary closure, and all known diabetics and those who had
shown any glycosuria at any other time than during the acute stage of the coronary thrombosis were excluded. The results throw a new light on the part diabetes was believed to play in this process, for of this group 71% gave evidence of an abnormal sugar tolerance. Of those examined within two weeks all showed an abnormal curve. After an interval of time 67% presented normal sugar curves. They believed the hyperglycemia and glycosuria of the acute stage of coronary thrombosis to not be dependant on a latent diabetes, but rather on a disturbance of the vegetative centers of the brain. Edema of the medulla and pons has been demonstrated in patients with coronary closure who died early in their attack, and the same has been produced in dogs by coronary ligations. (129) If these results represent the true picture the association of true diabetes with coronary thrombosis is probably so low as to be of very little significance. There may be another aspect, however, for in some cases attacks of coronary thrombosis appear to have been precipitated by hypoglycemia of insulin administration to diabetics. (108)

The factor of heredity has been often considered in studies of the underlying causes of coronary thrombosis. This is believed to be by the familial ten-
dency to a type of vascular system that is peculiarly susceptible to disease of one type of another. Levine believes that this is the most important of all of the etiological factors, and suggests that it may be due to variations in the anatomical pattern of the coronary vessels tending to be inherited as are other bodily configurations, and tending to place excessive strain or tension upon the arteries. He cites three brothers whom he had seen, all of whom died of acute coronary thrombosis during the sixth decade of their lives, and believes that this and the many other instances noted are much more than mere coincidence. (93) This opinion is supported by other reports in the literature where the family history was investigated from this aspect. In one series of 300 cases of coronary thrombosis, that of Goldsmith and Willius, a family history of some type of cardiovascular renal disease was found in 55%. (50) Of these, fifty-seven had some member of their immediate family die of cardiovascular disease, and eighteen had both parents die of heart disease. Cerebral hemorrhage was established specifically in the families of fifty-two, and coronary thrombosis in fourteen. Other authors state that the heredity factor, the inherited tendency to vascular disease, is a most important etiological factor.
The age at which the attack of coronary thrombosis occurs appears to be influenced by the factor of heredity. Heredity is given as a factor in 27% of cases by one author in discussing the problem in general, but as a factor in 65% of cases of a series all under forty years of age reported by Goodson and Willius. In this connection it has been noted that coronary artery disease and thrombosis can be classed in two major groups. The first is in the late middle age or elderly group of patients, where it is merely a phase of the general syndrome of arteriosclerosis, typical of that age, the heart involvement being but an incident in the whole picture. The second group is in younger people, especially young vigorous men thirty-five to fifty years of age, with few indications of peripheral artery disease but with a peculiar tendency to degenerative changes in the coronary vessels. They may have an essential hypertension, but the heart is the only part of the body showing significant pathology. It is in this latter type that heredity seems to play the major role, for this is the type that often presents the marked family history of sudden death, presumably by coronary occlusion. These cases are often singularly free of
past infections, but this affliction seems to be more malignant in them than in the others. Even if the hereditary factor were no stronger in the younger than in the older, however, the family histories would be expected to present more positive findings in the younger group since a smaller proportion of them would be taken by other afflictions before their coronary disease progressed to a fatal termination, and since their deaths would be more likely to be remembered in the family. That other factors are at work is indicated by the fact that while the average age of the population is increasing, the incidence of coronary thrombosis is relatively increasing in younger persons.

Closely linked with heredity in the discussion of coronary thrombosis is the factor of body build, but here again there is no general agreement on the part it plays. One is struck by the similar wording but opposite conceptions expressed, where equally qualified authorities state that "obesity plays a role," and "obesity plays no role," in the causation of coronary thrombosis. This was investigated at the Mayo Clinic in 300 coronary thrombosis patients, with interesting results. At time of their admission to the Clinic, thirty of these patients
were 30% over-weight, as against thirty-nine who were more than 15% underweight. This shows a significant difference in the question of obesity as related to coronary thrombosis, but even more so are the results of a survey of the average weights of those same patients before their admission to the Clinic. In their normal condition fifty-five were more than 20% over-weight, and only seven more than 20% underweight, while 123 were more than 10% over-weight as against thirty-seven being more than 10% under-weight. (50) From this it can well be concluded that coronary thrombosis occurs more in those who are over-weight than in the under-weight, a conclusion supported by the observation that it rarely occurs in the thin. Insurance statistics have shown that after forty years of age vascular disease is the most common cause of death, and that of normal insurance risks over forty years of age those who are from 20% to 40% over-weight have an increased mortality of 30% to 80% respectively in the following decades. (91)

Apart from mere weight, coronary thrombosis seems to occur more in the shorter, well-set, stocky type of individual. These are the people who are often of considerable physical strength, and who have been vigorous and muscular and have done hard physical work. (91)
These, of course, are also the people who are apt to be over-weight, and to be afflicted with hypertension.

Also closely allied with heredity is the possible factor of nervous sensitivity. It is not thought of as being the usual accompaniment of the physical type described above, but is nevertheless often mentioned as an etiological factor. A hyper-irritable nervous system is believed by some to predispose to coronary thrombosis, and as support is mentioned its being so rare among the Chinese, a race renowned for their calm. This is probably also inferred from its frequent occurrence among prominent men, who have succeeded by virtue of their nervous driving energy. The same might be said for its seeming greater frequency among members of the Jewish race. The causes of angina pectoris and those of coronary thrombosis are usually considered to be the same, as will be discussed later, and nervous tension is admittedly a large factor in the former. But the part it may play in coronary thrombosis as distinct from angina pectoris is obscure. This is supported by the work of Boas and Donner on their group of Jewish industrial workers. They found the same high percentage of coronary artery sclerosis and coronary thrombosis in their patients under fifty-one years as they did angina pectoris without physical
or electrocardiographic findings. Since they diagnosed myocardial degeneration and coronary thrombosis only on objective evidence they concluded that the high incidence which they found cannot be explained by an increased nervous sensitivity of these patients, and that it had no apparent relation.(19)

The problem of infection as an etiological factor in coronary thrombosis has complicated the problem even more. Any discussion of the causes of phlebitis and embolism deals with the effects of infection, and this is included in discussions of coronary thrombosis in the same manner. It may also exert its effect through being one of the possible factors in arteriosclerosis, but here we are treading on very insecure ground. As a more immediate etiological agent its part is much disputed. In 1928 Boyd published an article on this phase of the subject in support of infection as a cause of coronary thrombosis. He believed that underlying arteriosclerosis was the basic lesion for the formation of a thrombus, but since coronary arteries may remain sclerosed for years without thrombosis taking place there must be some mechanism that eventually incites the deposition of platelets and fibrin. In two cases examined by him, he believed the mechanism to be clearly in evidence, due to finding the remains of the onset

-45-
of acute inflammatory changes within an arterioscleratic plaque at the site of deposition of the fresh thrombus. He suggested that the cause was circulating toxins from the infections that had been present in those patients: acute bronchopneumonia in one and suppurative localized peritonitis in the other. (20) These findings were supported just a few years later by expressions from other authorities that acute infections may increase the chances of thrombus formation. (9) Focal infections were held to be of vast importance. (32) (73) In 1935 eighty-eight cases of coronary thrombosis were reported, in which forty, or 45%, showed definite evidence of gall bladder disease. (166) This association had also attracted the attention of Campbell of Belfast, who a year later stated that gall bladder infections are most commonly found with coronary thrombosis, and described several cases supporting this contention. He also gave cases where such attacks of occlusion had occurred following influenza, phlebitis, pneumonia, carbuncle, cystitis, and pyelitis. He believed that these infections were related to the attacks of coronary thrombosis, and that they should be eliminated if possible in the hope of averting any such cardiac tragedy. (32)

At about the same time Karsner wrote on the vascular disease accompanying general infections, dis-
cussing the intimal thickenings which predispose to thrombosis that may result from such infections.(78) This was confirmed a few years later by Rae of Toronto, who stated that the vascular lesions in general infectious diseases may be degenerative, inflammatory, or proliferative, and that involvement is fairly general. The histology of these is not different from that of rheumatic fever, which will be discussed below.(130)

That these opinions are not universally held, however, becomes quickly evident. Luten in 1931 stated that there was little evidence that infection, acute or chronic, contributed toward thromboses, except in rare instances.(97) More positive was Levine, who decided that infectious diseases play no role whatever. In fact, it was noticed that often coronary thrombosis patients had been singularly free from infections.(91)(116) Focal infection was believed to play no part by Lloyd in 1934(96). More recently, in a careful study of 522 cases of coronary thrombosis, a significant association of infection was not established. It was found in 1.9%, of which nine cases had acute upper respiratory infections the week before, one case had erysipelas, and one had bronchopneumonia. (103) This opinion was supported by that of Goodson and Willius.(52)
Infections more specific have been considered as possible etiological factors. Within the last two years endarteritis has been listed among the causes, and a coronary arteritis is claimed to be recognized as a cause of coronary thrombosis, especially in younger people, with increasing frequency. \(68\)(156) As a cause of this, rheumatic fever has been frequently mentioned. Two of the greatest authorities in this field, Levine and Herrick, a decade ago believed that rheumatic infections were not related to subsequent coronary thrombotic attacks, and remarked on the rarity of coronary disease and thrombosis in these patients. \(67\)(91) This was thought to be probably true of even the younger rheumatic patients with aortic insufficiency who may have attacks of angina pectoris. More recently, however, the arterial lesions of rheumatic fever have been carefully studied in this respect, with interesting results. Karsner in 1934 studied post-mortem fifty-six hearts, all of which showed Aschoff nodules or typical rheumatic inflammation. All of these showed edema of some part of the arterial tree, and fibrinoid was found in all cases. Necrosis was found in these in proportion to age: 4\% in the first decade, 50\% in the second, 75\% in the third, and in 100\% thereafter. Intimal thickening was believed to be
usually cellular, but sometimes ocellular. The cells were believed to not come from the elastica interna, but possibly be endothelial or sub-endothelial cells, or fibroblasts. He concluded that rheumatic fever may produce arterial lesions like those of any other infectious disease, and predispose to fibrosis of the coronary artery tree early in life, and to what appears to be precocious coronary sclerosis. This is probably a chronic inflammation, but has not been shown to be dependent upon the acute degenerative and inflammatory lesions. (78) This work was supported three years later by that of Rae of Toronto, who concluded that inflammatory involvement of the coronary arteries in rheumatic fever is common, with the acute myocardial state, the main coronary arteries being involved inconstantly. She found varying intimal thickening, polymorphonuclear infiltration, destruction of the elastica, narrowing of the lumen, and occasional thrombosis. The ultimate result is fibrosis and premature coronary sclerosis.

These results appear to be of significance in the etiology of coronary thrombosis, especially in the light of the ultimate fibrosis and early sclerosis. But Gross in an extensive study arrived at a different conclusion. He studied the records of the 3,264 post-mortems performed at the Montefiore Hospital in
seventeen years, and found thirty instances of coronary arteriosclerosis and rheumatic valvular disease together, and incidence of 0.91%. The problem, then, was one of pure coincidence, or if coronary sclerosis was a degenerative lesion superimposed on damage by rheumatic fever. The combination of the two lesions occurred earlier in the females, with an average age of fifty-seven, and ranging from twenty-nine to ninety-one years. The right coronary artery was involved in seventeen cases, the right more than the left in three, and both the right and the left in thirteen cases. The increased frequency of the involvement of the right here may be by hypertrophy of the right ventricle secondary to mitral stenosis. Fourteen of the cases, nine females and nine males, had a history of angina pectoris. He concluded that there was no proved etiological proportion between the initial valvular lesion and the subsequent coronary artery sclerosis, and that the coronaries of young patients with rheumatic fever are usually free of arterioscleratic changes. Such patients were found to live to about the same age as do arterioscleratic patients, and the rheumatic fever has usually run its course before the period of degenerative heart disease. That the rheumatic process appeared to neither predispose or prevent the degeneration of the
coronary arteries was suggested by the finding of several with severe coronary sclerosis and insignificant associated rheumatic valvular lesions, and vice versa. Gross also concluded that coronary thrombosis was relatively rare in patients with rheumatic valvular disease. (54)

Syphilitic infection is another factor to be considered in the etiology of this condition. This is, however, probably the result of the whole problem being considered under angina pectoris for so long, where the frequent and well-known partial or even complete closure of the orifices of the coronary arteries by luetic aortitis would naturally be thought of. While one author states that 6% of coronary sclerosis is due to arteriosclerosis, thus allowing syphilis to definitely enter as a cause of coronary thrombosis, this opinion is not generally held. (96) Most believe that luetic processes very rarely, if ever, invade the coronary vessels, involving them at their orifices only. (1) (147) In addition, it is demonstrated that lues is no more frequent in patients with coronary artery disease than without it, and that it even seems rare for cases of cardiovascular syphilis to be complicated by coronary thrombosis. (32) (94) Conner and Holt found an incidence of 14.2% of luetic infections
in their series of 287 cases of coronary thrombosis, but state that most of the early cases had no evidence of luetic infection and believe it not a factor.(36) Levine found positive serology in three out of eighty-nine cases, noting that the average age of these three was forty-five years, thirteen less than the average, but stating that it was rarely an underlying factor. (91)

A few other diseases have been offered as contributing causes of coronary thrombosis, which may be briefly mentioned here. Thrombo-angiitis obliterans appears to be the causative factor in a very small proportion of cases. Two of these, aged thirty-six and thirty-eight, were present in Levine's series.(91) Two others are reported by Sclar that were shown at autopsy to be Buerger's disease of the coronary arteries. He states that there is a definite relationship, that one-third of the victims of Buerger's have coronary artery pathology, and that one-half will die of a visceral vascular accident.(137) Periarteritis nodosa has been reported as the cause of coronary thrombosis in two cases, fifteen and twenty-one years of age.

Gout has been mentioned as a cause of coronary thrombosis, in view of its relationship to arterial
change. This early arteriosclerosis may involve the coronaries as well as any other arteries of the body. (18)(41)(93) The infrequent incidence of the disease itself, however, requires it to play a very small part in the picture of coronary thrombosis: Levine found only one case with a positive history of gout in his series of 145 cases. (91)

Polycythemia rubra and nephritis are mentioned as possible causes by one author, but have received very little recognition. (134)

The part played by all types of stress and strain in the predisposing and precipitating causes of coronary thrombosis is one of the many battlegrounds of medicine. When all painful afflictions of the heart were angina pectoris the onset of the pain with activity, excitement, or anger was repeatedly demonstrated, as was its disappearance with the cessation of such activity or emotion. Such a relationship is definite at present with angina pectoris, but as far as coronary thrombosis is exemplified by the description of Winslow's: "The common type in the male is the able, energetic, over-worked man, laboring under high tension and responsibility, not rarely robust, in the prime of life, and often foremost in the business and professional world." (172) These are surely the cases
which attract the most attention when they occur, and this is probably the reason for the seeming preponderance of this type of individual among the victims of coronary thrombosis. But many articles written in the last few years state that the incidence is higher among doctors, lawyers, business men, and captains of industry, and that long physical effort, undue mental strain, and psychic trauma are now-a-days among the most important causal factors. Allen believes that mental and nervous strain, with large responsibilities, play a far greater part in the development of this condition than in all of the other diseases mankind falls heir to. This contention seems to be supported by the seasonal incidence referred to in the previous section, where the greatest occurrence of acute coronary thrombosis and of cardiovascular deaths in general coincides with the greater stress imposed on individuals by the colder months.

Activity as a precipitating factor of attacks of coronary thrombosis, as well as a predisposing factor, is of great interest, and one that is quite unsettled at present. The stories of the middle-aged men who suddenly drop dead with "heart attacks" while golfing, shoveling snow, or doing some other ordinary activity are of almost every-day occurrence in the newspapers,
and are familiar to everyone. This relationship was long taken for granted, but recently has been under considerable suspicion. Fitzhugh and Hamilton studied one hundred patients who had died of coronary occlusion or met death in angina, on whom sufficient information concerning their previous activities could be obtained from their families. The private physicians were often questioned directly. These investigators were impressed by the frequency of unusual events in these stories, and believe that these fatal attacks are not usually haphazard in their occurrence but are usually preceded by extraordinary departures from the usual and reasonable habits of living. Their results are best summarized in a table:

<table>
<thead>
<tr>
<th>Significant Events</th>
<th>Times Occurred in 100 Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unusual and violent physical exertion</td>
<td>24</td>
</tr>
<tr>
<td>Unusual Physical exertion</td>
<td>31</td>
</tr>
<tr>
<td>Unusually prolonged usual exertion (undue fatigue)</td>
<td>44</td>
</tr>
<tr>
<td>Persistance in activities which had repeatedly produced angina</td>
<td>6</td>
</tr>
<tr>
<td>Travel</td>
<td>33</td>
</tr>
<tr>
<td>Emotional strain</td>
<td>13</td>
</tr>
<tr>
<td>Alcoholic excess</td>
<td>5</td>
</tr>
<tr>
<td>Gorging</td>
<td>16</td>
</tr>
<tr>
<td>Starvation</td>
<td>3</td>
</tr>
</tbody>
</table>
Acute infection 6
Surgical operation 4
Medication 2
Suicide 1
Unusual sex activities 1

They conclude that not more than one case in five failed to show such significant information, and that usually these causes were preventable. (43)

That this is not be any means universally accepted is quickly seen in the literature. Levine states that while athletes seem to succumb to vascular disease early in life, mental tension seems to be of minor importance. (91) In the section on "Incidence" it was shown that coronary thrombosis is by no means confined to those occupations where the strain is the greatest. (19) (94) (103) The precipitating causes are no more agreed on. Phipps studied the precipitating causes of 437 cases of coronary thrombosis, and found physical stress in the form of exercise present in only 13%, and that 60% of the cases showed no relation at all to physical stress. He expresses great doubt concerning the causal relationship between physical stress and coronary thrombosis. (128) Clawson found only 10% died of work or during effort. (34) In a careful analysis Master et al found in their series of 522 cases of coronary throm-
bosis that 72, or 13.6%, occurred during ordinary mild activity, 28, 5.3%, during moderate activity, and 11, 2.1%, during unusual or severe exertion: a total of 21%. They conclude that the occupation at the time of the attack is a coincidence. (103)

Last year, however, Paterson, by means of serial sections through the coronary arteries of patients dying of thrombosis showed that hours or even days often elapse between the inception of the thrombus and the time when complete occlusion, with the resulting cardiac pain, occurs. The age can be judged from the organization present in the clot. He concludes from this that "to eliminate physical exertion or emotion as a factor in coronary thrombosis, the activities of the patient should be investigated not only for the few hours prior to the attack but for many days previously." (127) Two cases are cited of sudden death with no previous history, where microscopic sections showed new and old portions of thrombi, where the organization of the old part indicated that it was at least three days old. From his pathological studies on the rupture of intimal capillaries as a cause of coronary thrombosis he believes that there is reason to believe that physical and mental states producing a temporary hypertension cannot be excluded as pre-
cipitating factors of coronary thrombi. These internal capillaries arise from the arterial lumen directly, as will be explained later, so that they are not protected from increased blood pressure by a long chain of arteries and arterioles. Thus exertion, or emotion, which may elevate a normal blood pressure to 160 or 180 mm. of mercury may produce the rupture of these intimal capillaries, producing a thrombosis.

With a lack of correspondence between activity and attacks of coronary thrombosis, it was noticed that a large proportion of these attacks came on at rest. Luten in 1931 remarked on the almost invariable absence of effort in the onset of thrombosis, and decided that the conspicuous association of rest cannot fail to be significant. (97) In Clawson's series of 923 cases of fatal coronary sclerosis, 75% died while at rest, and he suggested that the fall in blood pressure during rest may aid in thrombus formation. (34) In the series of Master's, 41.3% of the attacks began while the patient was asleep or resting, while 36.9% occurred during mild or moderate activity or walking. These figures are the more significant when it is considered that one-third of the day is spent in sleep and one-fifth resting in addition, as compared to one-half of the day spent in mild activity. (103)
Luten attempts to explain the high incidence of attacks occurring while at sleep by the fact that coronary flow is proportional to diastolic pressure, since it is during diastole that the coronary arteries receive their blood. Thus the coronary thrombosis may be aided by the diminished coronary flow during sleep, when the diastolic pressure and systolic output gradually decrease to a low point around four o'clock in the morning. Also, the coronary flow varies with the cardiac output through a vagus reflex mechanism. (97)

Associated with the conception of strain as an etiological factor is the significance of trauma. Psychic trauma has been mentioned previously. (73) Master found only one case apparently due to trauma (a fall on the chest) in his series: an incidence of 0.2%. (103) It is rarely mentioned in the literature, but Herrmann believes that it has not been given due emphasis. (68)

Another closely allied factor often considered is that of operations as exciting agents in coronary thrombosis. Of Phipps' series, twenty-six, or 6% of the total cases, appeared to be precipitated by surgery. (128) In White's group, 22 cases, or 4.1% occurred after surgery. (103) He believes that this may repre-
sent a true relationship, for the attacks usually occurred within three days post-operatively. And thrombosis cases are "extremely rare in medical services:" he had seen only four in the past seven years. The reports of occlusions following surgery mention all types of operations and anesthesias. In a study of heart conditions in surgical patients, Hamilton decided that hearts failed in two ways: congestive heart failure and anginal heart failure.\(^{(60)}\) DeSanto believes post-operative coronary thrombosis a definite group, in which trauma or the operations acted as predisposing factors. The site is always one of previous vessel damage, and changed blood constituents may be a factor.\(^{(38)}\) Several cases are reported by various authors, who give some suggestions as to possible connections between the operation and the coronary thrombosis.\(^{(107)}\)(\(^{(110)}\))(\(^{(131)}\))(\(^{(161)}\)) Among these are the increased blood pressure by the epinephrine used with novocaine for injections, the fall of blood pressure post-operatively, and a case with slow pulse and drop in blood pressure from beta-eucain poisoning.

The use of tobacco has been much considered as a possible etiological factor in coronary thrombosis, and its excessive use is often listed as such. Nicotine

-60-
has been proven to cause peripheral vascular constriction, and from this it seems possible that it may similarly cause coronary constriction, and thus predispose to coronary thrombosis. It is known to cause anginal pains, presumably by this mechanism. (138) White in his private practice encountered fourteen cases of coronary thrombosis in patients less than forty years of age, all of whom used "considerable" tobacco. (163) He cites the case of an eighteen-year-old male who was made to feel badly and slightly dizzy by the inhalation of tobacco smoke, and who, during this, showed in the electrocardiogram inversion of the "T" waves, as is seen in thrombosis. Riesman states that one-fourth of the victims of coronary thrombosis are heavy smokers, (134) while Levine states that tobacco is one of the few acquired differences between the sexes, and should be suspected of playing some role in view of the difference in incidence between the sexes. (91)

The use of tobacco in 364 patients with coronary thrombosis has been carefully studied by Master, Dack, and Jaffe, with enlightening results on this problem:

<table>
<thead>
<tr>
<th>Use of Tobacco</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers</td>
<td>84(30.8%)</td>
<td>88(15.5%)</td>
</tr>
<tr>
<td>Use of Tobacco</td>
<td>Angina Pectoris:</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>None</td>
<td>Slight to</td>
<td>Much to</td>
</tr>
<tr>
<td></td>
<td>moderate</td>
<td>excess</td>
</tr>
<tr>
<td>Cases (750 total)</td>
<td>346</td>
<td>221</td>
</tr>
<tr>
<td>Per-cent</td>
<td>46.1</td>
<td>29.5</td>
</tr>
<tr>
<td>Controls:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (750 total)</td>
<td>279</td>
<td>220</td>
</tr>
<tr>
<td>Per-cent</td>
<td>37.2</td>
<td>29.3</td>
</tr>
</tbody>
</table>

"Light" was taken as up to five cigarettes, or one cigar, or one pipeful of tobacco a day; "moderate" as six to fifteen cigarettes or two to four cigars or two to four pipefuls a day, and "heavy" as over sixteen cigarettes, or five cigars, or five pipefuls a day. Thus one-third of the males, and practically all of the females were non-smokers, and the proportion of heavy and moderate smokers did not differ from society in general. They concluded that tobacco exerted no influence. (103)

A similar survey was carried on by White and Sharber on 750 patients with angina pectoris and 750 people picked at random as controls. Their results are as follows:
From this data they decided that neither the use of nor abstinence from tobacco plays an important part in the genesis of angina pectoris, but that it may precipitate attacks. (162)

Harkavy in a study of hypersensitivity to tobacco in vascular disease found that in a series of one hundred cases of coronary artery disease and 140 with thrombo-angiitis obliterans a total of twenty-five had family and personal histories of allergy. This was comparable to the findings in two hundred unselected normal control smokers investigated from the same point of view. Positive histories were obtained in 33% of the young patients with coronary artery syndrome, however. (62)

Alcohol has also been suggested as a causative factor of coronary thrombosis, but has very little supporters, and is usually believed to not be related. (73)(134) Master et al investigated this as they did the use of tobacco, with similar results:

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-drinkers</td>
<td>145 (51.4%)</td>
<td>93 (95.9%)</td>
</tr>
<tr>
<td>Light or occasional</td>
<td>93 (33%)</td>
<td>4 (4.1%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>33 (11.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Heavy</td>
<td>11 (3.9%)</td>
<td>0</td>
</tr>
</tbody>
</table>
From this they decided that alcohol not only had no part in the etiology of coronary thrombosis, but that it actually may protect, since only 4% of their cases were heavy drinkers. Only one attack took place following a drinking bout.\(^{(103)}\)

The lower-than-average proportion of heavy drinkers is illustrated also by White and Sharber's study of their 750 cases of angina pectoris:

<table>
<thead>
<tr>
<th>Use of Alcohol</th>
<th>None</th>
<th>Slight to moderate</th>
<th>Much to excess</th>
<th>Great excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases(750)</td>
<td>483</td>
<td>259</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Per-cent</td>
<td>64.4</td>
<td>34.5</td>
<td>1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Controls:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases(750)</td>
<td>463</td>
<td>224</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>Per-cent</td>
<td>61.7</td>
<td>29.9</td>
<td>8.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The use of alcohol plays no important role in the etiology of angina pectoris, and may act to prevent or relieve the attacks.\(^{(162)}\)

Another of the many possible causative factors rather frequently mentioned is that of food. This has been considered as being related to this problem in several different ways, one of which is the act of eating or the digestion of a heavy meal. Luten has been impressed by the frequency with which the precipitating
cause seems to be related to the gastro-intestinal tract. He quotes from Levine, on coronary thrombosis: "it frequently occurs during rest, while sitting quietly in a chair at the dinner table, or during sleep,"(91) and from Parkinson and Bedford: "many patients are aroused from sleep by the pain, or are seized with it while sitting quietly at rest, after a meal."(123) He believes that this may be due to a reflex coronary vasoconstriction through the vagus nerve coming from the gastro-intestinal tract. He also cites two cases where occlusion followed immediately the drinking of a cold fluid. The apex of the left ventricle is separated from the fundus of the stomach only by the diaphragm, and it has been observed that cold drinks may produce inversion of the T wave of the electrocardiogram in lead III.

Excess food has been given as a factor in coronary thrombosis.(138) It's action is thus believed to be from a mechanical standpoint, causing pressure on the heart.(3) Again referring to the investigation of Master et al, twenty-eight, or 5.3%, of their cases of coronary thrombosis occurred during or after a meal. They found that no more attacks accompanied a heavy meal than a light one, and that in a few instances came with the first mouthful of food taken, or with
a cold drink. Walking after a meal was followed by an attack in only five cases. The attacks therefore seem to be just coincident with the taking of food, and the theory of etiology by a full stomach or one dilated with gas appears unfounded. (103) This conclusion is supported by White, who states that diet has no relation to incidence. (163)

Diet, however, over a period of time, may have a relationship to coronary thrombosis in an entirely different way. A decade ago Mills published results of his investigations which may have far-reaching effects. He showed that the intake of protein produced an increase in the blood coagulability, and that there was a lack of this effect with carbohydrate or fat. This effect was related to the increased rapidity of platelet clumping and lysis, and that rather strenuous exercise or adrenalin injection may produce similar results. A possible explanation for post-operative thrombosis is also introduced, which often appears as the patient is put on a full diet and allowed out of bed. The platelets are severely decreased during fevers and parturition, but soon begin to increase, and reach a peak of nearly twice normal in about eight to eleven days. (110) The effect of protein on clotting factors was supported by Bancroft and Stanley-Brown. (5)(6)
Diet may also affect coronary thrombosis by promoting arteriosclerosis, as has been observed in those with poor cholesterol metabolism. Leary speaks of the importance of this, remarking on the fact that cholesterol is all derived from ingestion, being especially found in milk and eggs, and that man is the only animal that eats milk and eggs throughout his lifetime, and the only one that dies in early life of atheroma of the coronary arteries, and in later life suffers almost universally from atherosclerosis. (89) The high-fat diets used in the treatment of diabetes were also noticed to produce early arteriosclerosis. (88)

Food allergy is mentioned as a possible cause of coronary thrombosis by one writer. (68)

In summary, then, it may be said that at the present time the etiology of coronary thrombosis is mainly that of arteriosclerotic and atheromatous changes in the coronary arteries, and that this may be present as a usual accompaniment of advancing age or as a more malignant form in younger people involving the coronaries particularly. But thrombosis is not proportional to sclerosis in the higher age groups, probably because of a more adequate collateral circulation. Hypertension has not been found to be very
closely associated, but the recent work of Paterson suggests how this may be directly related. Diabetes appears to play a small but definite part, and heredity and body type and obesity are important. Nervous sensitivity, occupation, and class in society have been shown to be much less important than formerly believed. Lues, rheumatic fever, and infections in general play a small part of the whole picture, as do thromboangiitis obliterans and gout. Activity seems to have very little, if any, relation to attacks of coronary thrombosis in the most thorough studies to date, as does the use of tobacco or alcohol. Post-operative thrombosis seems to form a small but definite group, and diet may be of significance through its effect on arteriosclerosis and on clotting factors.
Pathology
Distribution of Coronary Arteries

Adapted from Spalteholz. (146)
Branches of Right Coronary Artery

1. Arteria adiposa dextra.
2. Ramus ventriculi dextri anterior.
3. Ramus marginis acuti.
4. Ramus ventriculi dextri posterior.
5. Ramus suli longitudinalis posterior.
6. Ramus ventriculi sinistri posterior.
7. Ramus ventriculi sinistri posterior accessorius.
8. Ramus atrialis dexter anterior.
9. Ramus atrialis sinister posterior.

Branches of Left Coronary Artery

10. Arteria adiposa sinistra.
11. Arteria septi ventriculorum.
12. Ramus collateralis descendens anterior.
   12' Ramus primus.
   12" Ramus secundus.
13. Ramus ventriculi sinistri anterior.
15. Ramus ventriculi sinistri posterior.
16. Ramus atrialis sinistri anterior.
17. Ramus atrialis sinistri posterior.

-69-
The condition of coronary thrombosis is important only because of a perversity of nature, which leaves the most important muscular structure in the body so dependant upon its blood supply being intact, and so helpless when a part of that supply is cut off. For the major portion of the heart is enclosed within two almost frictionless surfaces, between which there is usually no connection outside of their reflections, with direct continuity with the rest of the body only at its base. The walls of the great vessels, the fat, nerves, and the lymphatics here provide only a minimum degree of continuity with other structures, and thus the heart is deprived of its most important compensatory property, that of being able to establish a collateral blood supply adequate to meet an emergency. If such a collateral blood supply were available to preserve the heart for the first few moments, hours, or days after a serious coronary accident, the story of coronary thrombosis would not be the tragic one that it is.

The usual distribution of the coronary arteries and their branches is easily shown by the accompanying diagram. Galen is accredited with being the first to describe and name the coronary arteries, while Harvey described them more fully, and pointed out their mission.
The three regions usually affected by occlusion of a coronary artery are described briefly by Barnes. The anterior descending branch of the left coronary artery, the "artery of sudden death," supplies the anterior portion of the left ventricle and the apex, and the anterior two-thirds of the interventricular septum, and gives off a few branches to supply a narrow zone of the anterior portion of the right ventricle. The circumflex branch of the left coronary supplies the left one-third to one-half of the posterior region of the basal three-fifths of the left ventricle. The terminal portion of the right coronary artery usually supplies the posterior one-third of the interventricular septum and posterior basal portion of the left ventricle.

The histology of the coronary arteries has been studied in the attempts to shed light on this problem. These arteries are muscular in type, relatively poor in elastica. They differ from other muscular arteries in having a layer of unstriped muscle and subendothelial fibrous tissue. Soon after birth the lamella elastica interna splits, and connective tissue elements further develop internally to the latter. This subendothelial layer is without a circulation of its own, but depends for nutrition on imbibition through the endothelium. This layer is considered as a buffer.
layer, developed even in early youth in response to stress in these arteries, and has been found to occur especially in the proximal portion of the left coronary artery.\textsuperscript{(89)} Some believe the connective tissue elements here already constitute early stages of sclerosis, since fatty changes not infrequently occur in them, but they are by Gross, Epstein, and Kugel thought to be normal.\textsuperscript{(55)} The deposit and formation of calcium salts, lipoid crystals, blood vessels, and inflammatory cells are considered abnormal.

The larger coronary vessels present an adventitial layer of meshed connective tissue which increases in density with increasing age. These fibers are mainly circular, especially in the inner layers. The media, of smooth muscle, also contains elastic elements scattered among the muscle fibers, more toward the outer layers. The intima is at birth a single elastic lamina covered with flat endothelium. The subendothelial layer, described above, takes on greater proportions with increasing age, with a relatively greater increase of connective tissue elements in the inner portions, until the intima eventually becomes thicker than the media. Areas of discontinuity appear in the layers, and the limiting borders become hard to define.\textsuperscript{(55)}
The anastomoses between these branches of the arterial system of the heart were long considered to be so insignificant that the arteries could be classed as end-arteries. It is becoming increasingly evident that such communications do exist, in a degree not before realized. Herrick in 1912 in his original article believed that large branches of the coronary arteries could be occluded, at times acutely, without resulting death, at least not immediate death, and stated that anastomoses between these vessels had been shown by clinical histories, animal experiment, and anatomic study to be of considerable degree.(65) In 1918 Fred Smith, working on dogs, remarked on their survival after extensive coronary artery ligations, the variations in the extent of the lesions produced by obstruction of the same vessels, and the small size of the infarct often seen after ligation of a large artery. He concluded that while the degree is variable, there often must be a fairly free communication between branches of the right and left arteries, or between smaller branches of the same artery.(143) Wearn in 1928 showed that the capillary supply of the heart was very rich, averaging one capillary per muscle fiber in the ventricular walls and papillary muscles, which is about twice the number of capillaries in skeletal
muscle, and that the anastomoses between these capillaries were very numerous indeed. (158) This belief was supported more recently by Saphir et all, who, in a series of thirty-four cases, found that in all cases of coronary thrombosis with infarction at least two branches of the coronary arteries to the area were involved, and in cases of infarcts where only extreme narrowing of the coronaries was present, at least three main branches were involved. (135)

But the nutrition of the myocardium may be maintained in another way. In 1704 Vieussens described collateral circulation in the form of small vessels leading from the heart chamber into the myocardium, (155) and three years later Thebesius described the channels from veins to cardiac chambers that now bear his name. (154) These vessels are believed to be the remains of the intertrabecular circulation of the embryo, and in human hearts some have been found to drain capillaries, and some to drain coronary arteries and veins. It has been estimated that as much as ninety per-cent of arterial blood may escape by way of the Thebesian vessels. (159) The part that these may play is unproven, but it has been demonstrated that bismuth and bacteria may enter the coronary system in the beating heart by way of the Thebesian vessels. (135) Scott
gives these vessels the credit for maintaining circulation to the heart in cases where the orifices of both coronaries have been completely obliterated by luetic aortitis. (139)

The third possibility for collateral circulation is through extra-cardiac anastomoses. Langer in 1880 described the coronary arteries anastomosing through their branches with vessels of the mediastinum, parietal pericardium, diaphragm, and hila of the lungs. (85) (86) Smetana a decade ago showed anastomoses between the vasa vasorum of the aorta and the coronary arteries. (141) Recently Beck and Tichy have shown by injections of dye that the vascularization of the myocardium was slight from the collateral bed, the Thebesians excluded, and sometimes almost completely absent if coronary circulation was normal. The blood vessels, though, grow into the myocardium when it has need for more blood, such collaterals being demonstrable in three weeks. (14) Hudson injected coronary arteries at post-mortem with carbon particles, and found extra-cardiac branches of the coronaries emerging at the root of the aorta, the base of the pulmonary artery, around the pulmonary veins and the ostia of the superior and inferior venae cavae and in the intervascular pericardial reflections. These went to the parietal pericardium,
the diaphragm, the hila of the lungs, and the mediastinum, trachea, and esophagus. (71) Pericardial adhesions may also carry collateral channels. (113) That these play at best a very small part in acute occlusions, however, is evident.

The "standard" site of coronary thrombosis is in the anterior descending branch of the left coronary artery, which earned it the title of the "artery of sudden death." Of Wearn's nineteen cases described in 1923, sixteen occurred in this place. (157) Parade stated that this was the site of thrombosis in 85% of the cases. (122) Saphir found the area one centimeter long starting two centimeters from the origin of the anterior descending branch the area most often involved. (135)

The degree of predominance of this site for the location of thrombi has not been entirely agreed upon, and recently has been closely examined. In 1928 Parkinson and Bedford found the right coronary involved in eighteen cases, and the left in thirty-seven, of which the main vessel was involved in three, the anterior descending branch in twenty-four, and the circumflex in ten. (123) Barnes and Ball found twenty-eight cases of infarction in the area of the anterior descending branch as compared to twenty in that of the right coro-
nary in their series. Master in 1937 found that in 140 cases acute coronary thrombosis of the left and right arteries or their branches occurred with equal frequency. Two years later he reported on 150 cases, in which thrombosis took place in the left anterior descending branch in sixty, or 40%, in the left circumflex artery in thirty-four, or 23%, and in the right coronary in fifty-six, or 37%.

The reason for the predilection of thrombosis to particular parts of the arterial tree is not easily understood nor well agreed upon. In spite of some opinions that there is no proportional variation in the sclerosis of the coronary arteries, as discussed before, other studies have shed light on this problem. The occlusion is usually at one place only, there being no evidence of a widespread thrombotic tendency. Monckeberg recognized the region two centimeters from the bifurcation of the left coronary artery as the seat of the severest sclerotic changes of the coronary system. Kirch called it the "Lieblingsstelle," or place of predilection. Wolkoff conducted an extensive study on coronary arteriosclerosis, and found the left to be more involved than the right, and the changes to be more pronounced in the distal portions. Hebel believed the sclerosis was found more at points
of division because of the pressure exerted there, and that it was also more severe in portions attached directly to the myocardium.

Barnes, in this country, agreed that the disproportionate sclerosis at the orifices of the secondary trunks may increase the occurrence of coronary occlusion, and that sclerosis increases the tortuosity of the vessels. White stated that fat deposition and fibrosis were more in regions of particular stress. This was supported by the work of Leary, who studied the left coronary artery in cases of congenital heart disease, where unusual stresses would be expected in the effort to overcome the developmental faults. He found the earliest atherosclerotic processes in the left coronaries of these hearts. This sclerosis of the coronaries he considers as of two types: one a fibrosis leading to narrowing, a reaction of youth, and the other a collection of lipid cells with a tendency to atheromatous necrosis, a lack of the reaction of youth. He also suggested that the curve in the first part of the left coronary and its descending and circumflex branches may increase this stress, and noted that the right coronary was quite straight and had no early large branches. Moritz writes that coronary thrombosis is
commonly confined to the superficial vessels, since significant sclerosis of the penetrating myocardial vessels is the exception rather than the rule, and cites Karsner's statement that arteriosclerosis appears to progress with diminishing severity from larger to smaller branches. (113) Saphir found no relation between the gross lesions in the larger branches and the histological changes in the arterioles, for these often showed no noteworthy changes in the presence of marked arteriosclerosis of the larger branches. Only a few sections showed arteriolar intimal thickening. (135) Wearn, though, found the finer branches frequently closed by sclerosis. (157)

The mechanism by which thrombosis is produced has been studied extensively. Following Marie's statement that thrombosis never occurs in a normal artery, the pathological changes in the arteries have become of great interest. Intimal changes are thus believed necessary for the formation of a clot, but other more marked changes are usually present. Coronary sclerosis is usually extensive and has produced marked narrowing, but the exceptional case may show only very slight fibrotic changes, and apparently the roughened or injured intima is sufficient to allow thrombosis to occur, by forming a point of attachment and impeding
Klotz and Lloyd list the pathological events as taking place as follows: endarteritis, atheroma, calcification, stenosis, and thrombosis. The fatty substances are laid down in the structure of the intima by the action of especially adapted mononuclear phagocytes. Little or no fat lies outside of these cells, but with their degeneration the fat comes to lie free and some of it seeps into the collagen of the elastic and connective tissue fibrils. At the same time overgrowth of the subendothelial connective tissue forms a plaque over the surface of the original fatty deposit. This is the beginning of the atheromatous structure associated with the ever-present chronic endarteritis. These authors also describe the development of similar lesions after a primary endarteritis accompanying acute infections, where secondary degeneration of a proliferative reaction takes place. Leary agrees with these steps of development, and adds that the fatal issue is most frequently due to the part of the intima of the artery outside of the plaque undergoing necrosis as its nutrition, which is by means of imbibition from the lumen, is cut off. This fibrous or fibrinous necrosis extends to the endothelium, and when endothelial necrosis takes
place thrombosis is precipitated. In older people the connective tissue response to lipoid cells is lacking, and more massive necrosis takes place. (89) This is the atheromatous "abscess" formation, discussed by the English and Canadian writers as the most common primary lesion. (1)(126)

The rupture of these sclerotic or atheromatous areas is not necessary for a fatal termination, for the process may continue until the coronary artery lumen is obliterated without a thrombosis taking place. In one series of 150 deaths by progressive stenosis in this fashion, seventy-eight were found to have superimposed thrombi. (4) Thus thrombosis may be considered to be an episode in the progress of sclerosis. (95) The impeded blood flow due to the stenosis, and the resultant eddying, are important contributory factors to thrombosis, as has been shown by the study of aneurysms. (6) Thrombosis has been found to occur where there are eddies, and to be lacking where a rapid flow was maintained.

Another possible mechanism has recently been investigated, and offers great promise. Leary described the development of a capillary circulation from the lumen of the artery directly to supply areas of the fibrous tissue whose nutrition had been cut off as
their increased thickness reduced the process of their absorption directly from the arterial stream. These capillaries were distinct from those of the vasa vasorum, being cut off by the necrotic area. More recently Paterson has studied these in detail, and observed their rupture with a resulting intimal hemorrhage in cases of coronary thrombosis. No evidence of vascularization of the intima of the coronary arteries was observed in children or in young adults, even in the presence of endarteritic plaques where branches of the vasa vasorum could be shown to be more numerous. In older people with atherosclerosis of the coronary arteries without thrombosis, proliferated capillaries in the inner one-third of the intima internal to the site of the atheroma were not infrequently present. In almost every case of coronary thrombosis the atherosclerotic intimal thickening was marked, and proliferated intimal capillaries close to the lumen at the site of the thrombosis was seen in thirteen out of the sixteen cases examined. Intimal hemorrhages were found in nine cases of atherosclerosis without thrombosis, and nine of the cases with occlusion at the sites of the thromboses. The hemorrhage was believed to result directly from the rupture of the capillary walls, dependant on blood pressure, the strength and elastic-
ity of the capillary walls, and the rigidity of the supporting stroma. The latter factor is believed to be the most important. Here the capillaries were seen to be dilated through the softened areas, and their lumina to be small where they crossed dense hyaline tissue. In a later article he describes these nine cases in detail, as studied by serial cross-sections. (126) The endothelium was intact over the hemorrhage in four cases, and the capillaries were seen to be dilated as they entered the atheromatous focus where the hemorrhage had occurred. In thirty-one cases of intimal hemorrhage without thrombosis, intimal erosion was often seen, apparently due to diminished nutrition attendant on capillary rupture and retrograde thrombosis. In two of the cases the massive intimal hemorrhages compressed the already narrowed coronary lumen. In this article a series of thirty-seven recent cases of coronary thrombosis were reported, of which thirty-two presented intimal hemorrhages at the site of the occlusion. In four of these the intimal hemorrhage was on one side only, and in these the thrombus was attached at the same side at a point overlying the hemorrhage. Paterson concluded that if proper stagnation and eddying exist at a point in the coronary system, capillary rupture
with its sequelae occurring in the same region may precipitate a thrombosis. This might be effected by a diffusion of blood and thromboplastic substances from the intima into the lumen, by a necrosis of the intima, or by a retrograde thrombosis from the capillary back to the arterial lumen where it could form a nucleus for further thrombosis. Some of the hemorrhagic areas showed some inflammatory reaction.

The lesions described by Boyd in his discussion of the two cases of apparent inflammatory etiology of coronary thrombosis are strikingly similar to these, and are probably of the same origin with the mechanism unrecognized. (20) Winternitz also describes the independent capillary circulation of the intima when irritative, obliterator, or morbid processes are present, and found them to anastomose with the rich adventitial plexus. He states hemorrhage to be one of the more common manifestations of this vascularity. (173) The nature of the "fibrinous necrosis" has been more thoroughly investigated by Clark et al in its relation to thrombosis. This "fibrinoid" is found in the walls of affected arteries, and elsewhere, and in its staining resembles fibrin. It is believed to be important in the etiology of thrombosis, and is often an accompaniment of atherosclerosis and luetic
aortitis. They believe, though, that its origin is from partially organized surface deposits of fibrin, and that it is not the result of necrotic changes. It may be due to the rarefaction of the covering layer of an atheroma permitting penetration of plasma and fibrinogen but not of formed blood elements. Either of these changes may form the base for an occluding thrombus.(33) Wartman describes forty-one cases of coronary occlusion, of which six were by intramural hemorrhage alone, and fourteen by intramural hemorrhage plus thrombosis.(156)

Since Weigert the pathology of cardiac infarction has been quite well understood. The damage resulting from a coronary thrombosis depends on the completeness of the closure, the rapidity with which it takes place, the caliber of the occluded vessel, the extent of the anastomoses, and the condition of the heart muscle.(139) That the time is of great importance is demonstrated by the survival of the heart with both of the orifices of the coronary arteries gradually but completely occluded by luetic aortitis.(14)(139) While closure in humans is usually complete when examined post-mortem, the significance of the degree of closure has been demonstrated by animal experimentation. It has been found that a normal dog can withstand a re-
duction in size of about one-third of both coronary arteries in one stage.\(^{(14)}\) Also on dogs it was found that ligation of one of the two main branches of the descendens was not fatal, and that primary ligation of the descendens as near its orifice as possible, but below the septal branch, produced no marked cardiac disturbance. Ligature of the circumflex in twenty-three dogs produced moderate temporary disturbance in eighteen, and serious disturbance in five, of which two died. Dogs recovered from the circumflex ligation withstood ligation of one, and often both, main branches of the descendens, but promptly died of cardiac standstill when the main trunk of the descendens was ligated less than twenty-five mm. from its orifice.\(^{(109)}\)

In the human the fatality of the different types of occlusions may be inferred from the post-mortem statistics of their occurrence, given above, but have not been tabulated as such to date.

The extent of the anastimoses is believed to be responsible for the differences in mortality in the different age groups, the anastimoses increasing with age. This also may explain the greater proportion of bilateral occlusions in the older age groups. Moritz found 13% of the occlusions in patients thirty-one
to forty-five years of age were bilateral, and the immediate mortality of all of the occlusions in this group to be 80%. From forty-six to sixty years sudden death followed 65% of the attacks, of which 16% were bilateral. In the cases sixty-one to seventy-five years of age sudden death followed only 35% of the attacks, and 24% of these were bilateral.\(^\text{(113)}\)

The condition of the heart muscle tends to have the opposite effect. The extent to which this may be effective is indicated by the fact that the immediate mortality of coronary thrombosis in young adults is much lower than that in older adults, at least in some series.\(^\text{(46)}\) In one, of twenty-three cases under forty years of age, there was no immediate mortality.\(^\text{(115)}\)

Smith in his early dog experiments noted that the infarcted area was of much greater extent in the endocardial and subendocardial regions than in the subpericardial or in the body proper of the myocardium.\(^\text{(143)}\) This has been observed in human cases also, by Smith and others since, and also that the infarcted area is usually less that the total area supplied by the artery.\(^\text{(123)}\)

The process of infarction of the heart muscle when its blood supply is thus cut off is well known,
and need only be briefly reviewed here. First is a congestion and swelling of the involved area, with a granular appearance of the muscle fibers. Red cells are extravasated, and polymorphonuclears infiltrate from the surrounding tissue. The cloudy swelling of the muscle fibers proceeds to granular and hyaline necrosis, and is accompanied by a varying amount of necrosis of the connective tissue elements. The border is injected, and there may be extensive hemorrhage into the neighboring muscle. The infarct may be mottled with areas of hemorrhage, or be completely hemorrhagic. (12) (15) (34) (77) (123) (135) (174)

The process of necrosis is at a maximum from the fourth to the twenty-first days, and cardiac rupture, if it is to take place, generally occurs within two weeks. The connective tissue proliferation begins at the end of the first week, but is not striking until the third week, and does not become firm for eight weeks. (91)

Infarction is confined almost entirely to the left ventricle and the interventricular septum, but sometimes involves the right ventricle as well. (12) (102) This is due to the distribution of the vessels described before.

The heart muscle shows very little if any tend-
ency toward regeneration. Kaufmann described attempts at regeneration in the vicinity of myocardial infarcts, believed to be indicated by finding the so-called muscle giant cells close to the infarcted portions. It is believed that this must be a foreign-body giant cell reaction, for no evidence of actual regeneration has been observed. Apparent hypertrophy of the muscle fibers in the vicinity has been viewed as a compensatory reaction.

The complications and further changes that may take place are outside of the announce realm of this paper. For when the infarction has taken place the damage has been done, and the further pathology or course of events is not important in the understanding of the problem of the occurrence of coronary thrombosis.
Bibliography


12. Barnes, Arlie R. "The Electrocardiogram In Myo-


24. Bundesen, H. N., and Falk, J. S. "Low Temperature,


29. Ibid. 214:644 March 26, 1936.


38. De Santo, D. A. "Operation and Trauma as a Cause


61. Hammer, A. "Ein Fall von thrombotischem Ver-


110. Wills, Clarence A. "Relation of Protein Diet to Thrombosis." Annals of Surgery 91:489 April, 1930.

111. Monckeberg, J. G.; Henke; and Lubarsch. "Handbuch


119. Ibid. 1:839 March 26, 1910.

120. Ibid. 1:973 April 9, 1910.


136. Ibid. 10:762 August, 1935.


-101-
149. Ibid. 2:1205 December 17, 1887.

150. Ibid. 2:1255 December 24, 1887.

151. Ibid. 2:1305 December 31, 1887.


169. Willius, F. A.; Smith, H. L.; and Sprague, L. J. "A Study of Coronary and Aortic Sclerosis." Proceedings of Staff Meetings of Mayo Clinic 8:140 March 1, 1933.


174. Wolff, Louis, and White, Paul D. "Acute Coro-
nary Occlusion." Boston Medical and Surgical Journal 193:13 July 1, 1926.


