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Diabetic arteriosclerosis

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DIABETIC ARTERIOSCLEROSIS

by

ROBERT DANIEL WARNKE

Senior Thesis

Presented

to

College of Medicine

University of Nebraska

Omaha

1939
PREFACE

The writer's interest in this subject was first aroused by the death of his maternal grandmother two years ago from diabetic gangrene of the toes. The treatment applied at that time was more or less ineffective in arresting the progress of the lesion. The immediate family had been previously warned that this type of termination was to be expected in patients suffering any length of time from diabetes mellitus.

Curiosity having been stimulated by this experience, recourse was made to the literature and it was found that the majority of patients past the middle of life who have had diabetes over a period of five years, whether controlled or not, developed a cardiovascular complication of the disease, especially marked in the peripheral arteries. This was of a nature of an arteriosclerotic process which obstructed the blood flow through the vessels.

The questions that were stimulated were "what causes this change", "why does it occur", and "what can be done about it to decrease the incidence or improve the condition". It was further found that these questions were the subject of research work
and comment by various investigators throughout the country and progress was being made in understanding and explaining the underlying processes.

The conclusion was reached that this would be a very practical and profitable problem to pursue for detailed study. The literature has been scanned for the various prevailing views as to the cause of the formation of the premature arteriosclerosis and the clinical and laboratory data that support these views. The problem of treatment has also been the subject of considerable reading.

If no other purpose has been served by the compilation of this work, it has greatly clarified the conception of the author as to the production of arteriosclerosis and developed a profound sense of respect and appreciation for the efforts of the research workers and clinical investigators who are endeavoring to further elucidate this problem.
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DEFINITION

The title of the subject in question, arteriosclerosis comes from the combination of two Greek words meaning "hard arteries". Arteriosclerosis is not universally considered to be a disease sui generis; some authors would rather call it a symptom or a group of symptoms which, however, are not specific enough to warrant their collection into a definite disease. Arteriosclerosis is a term loosely used by clinicians to connote changes in the arteries which are characterized by hyperplasia, fibrosis, and degeneration of their walls, and are distinguished in the living subject by a variety of signs and symptoms, due to disturbances in function in the organs of other structures supplied by these arteries.

At the beginning of the twentieth century, clinicians defined arteriosclerosis as a "subacute and chronic disease of the arteries characterized anatomically by increased thickness of the walls of the blood vessels, the initial lesion being for the most part in the middle (muscular) coat, leading not infrequently to calcification of this coat and to the formation of minute aneurysms along the vessels". (44) This definition should be enlarged so as to include all disturbances of the vessel walls as the lesion
at fault, since the process manifests itself by deposits of the most varied kinds which are irreversible and at the climax of the process result in the deformation of the lumen and brittleness of the vascular walls. (15) The onset of the process may be said to begin as soon as toxic influence or physiologic strain have brought about an alteration in the structure or habitual physiology of the blood vessels. (8)

In general it may be stated from the current clinical standpoint the term arteriosclerosis has replaced the less commonly used arterosclerosis and end arteritis. When the arteriosclerotic process is combined with an obliteration of the arterial lumen either by narrowing or by thrombosis, it is qualified by adding the adjective obliterans. When evidence of obstructed flow is present the condition should be described as one of arteriosclerosis obliteratorans, which is the modern designation. If diabetes mellitus is present the proper designation is diabetic arteriosclerosis obliterans. (10)

In this thesis only one type of arteriosclerosis will be considered and that is the one complicated by the presence of diabetes mellitus.

The complete relationship of diabetes to associated pathology was not known at the beginning of the twentieth century and diabetes mellitus was said to be an abnormal condition of the economy characterized by an excessive secretion of urine containing
glucose, due to derangement of the glycogenic function of the liver or to defective metabolism of the normally produced glucose, or both; associated at times with evident lesions of the nervous system, at times with morbid changes in the pancreas and at times with undiscoverable lesions. (82)

The present opinion defines diabetes as an inheritable constitutional disease characterized by glycosuria and hyperglycemia which result from subnormal insulin production by the islets of Langerhans in the pancreas; and, therefore, an abnormal limitation of the functional capacity of these endocrine organs and of the ability of the body to utilize glucose. Sufficient depressions of the rate of glucose utilization lead to secondary disorders of the fat and protein metabolism. The disease is further distinguished, especially in the middle and later decades of life, by disease of the arteries (arteriosclerosis) and a variety of other manifestations not directly related to the characteristic anomaly of the glucose metabolism. (90)
HISTORY

Though printed records of lesions of arteriosclerosis first appear in the works of the anatomists of the sixteenth century, proof that the disease has existed from early times was disclosed by Shattocks (75) study of the mummy of Amenhotep II and that one of the most widely known of all the ancient royal Egyptians, Menephtah, the reputed Pharaoh of the Hebrew exodus, who seems not to have died in the Red Sea as conventionally taught. Good microscopical sections revealed typical advanced sclerosis with extensive deposition of calcium phosphate. Other discoveries in the body indicated that Menephtah was an aged man at the time of his death; his aortic changes seems to have been the usual one seen in senility.

Ruffer's (68) observations on mummies dating from the eighteenth dynasty (about 1575 B.C.) to the twenty-seventh dynasty (1575 A.D.) showed that the arterial damage encountered differed in no way from the degenerative arteriosclerosis of today. This has significance, since any agency brought forward as a cause of arteriosclerosis must meet the test of possible availability during a period of at least thirty-five centuries. (39)

The medicine of ancient Egypt recorded in the
"Therapeutic Papyrus of Thebes", one of the earliest records of the history of medicine written in 1552 B.C., the knowledge, beliefs, and practices of that age. A superficial knowledge of anatomy was possessed as is evidenced by the skillful practice of mummification. Knowledge of the arteries of the body can be assumed from this passage: "There is in the heart a vessel leading to every member of the body. If the physician places his finger on the head, neck, arms, hands, feet or body, everywhere he will find the heart, for the heart leads to every member, and speaks in the vessels of every member".

During the third and fourth centuries B.C. the center of culture was at Alexandria. The medicine of that time was based upon that developed by the ancient Greeks. Because Herophilus was the first individual who regularly dissected the body of man and studied it systematically, he is known as the "Father of Anatomy." Herophilus carried forward the work of his teacher Praxagoras in distinguishing between arteries and veins. He was the earliest physiologist; the first to study the rhythmical tides produced in the arteries by the beating heart. He mastered the pulse beat in health and illness comparing its variations to the musical scale. Erasistratus, a con-
temporary and colleague of Herophilus at Alexandria duplicated and surpassed the former's work on the heart and vascular system. He knew the veins and arteries communicated through invisible orifices (synanastomoses) which are now called capillaries and that the pulse progresses as a regular occurring wave down the arteries.

The torch of knowledge was passed from one center of culture to its successor. Aretaeus, one of the Greek physicians in the time of height of Roman medicine described diseases in a vivid manner. He is the author of the first systematic account of diabetes. He correctly called it a species of dropsy, and describes the patient's fiery thirst, his imperative desire to pass water, his dry mouth and parched skin. "It is a wonderful malady" he says, "a melting down of flesh into urine". (63)

In the second century there appeared in Rome the best educated and most gifted physicians of the second century and of the centuries to come, Galen. Today, whoever speaks of anatomy pays tribute to Galen; many names of muscles suggested by him are still retained at the present time. The moderns have made little changes in his osteology. The science of blood vessels was the weakest point in the Galenic structure of anatomy, but even here he built better
than his contemporaries for in opposition to the prevailing views of the age, he proved that the arteries convey, not air, but blood. He was the first to describe, with some correctness, the aorta, the jugular vein, and the three coats of the arteries. (11) Galen recognized that the pulse was hard in some individuals and soft in others.

A superstitious reverence for the dead confined both the Greeks and the Arabians to the dissection of Apes and Quadrupeds; since the medicine of Rome was borrowed from the Greeks, the more solid and visible parts were known in the time of Galen, and the finer scrutiny of the human form was reserved for the microscope and the injections of the modern artists.

Galen's teaching consisted of facts mixed with hypotheses and conjectures. Everything was catalogued and explained. There did not seem to be any problem for medicine left to solve. The influence of this doctrine was to cause a darkness of medical knowledge to fall over Europe which was not lifted until after the Renaissance.

The first great anatomist who dethroned Galen was Andreas Vesalius. The advancements which were made were due to the fact that he himself made the dissections. Enthusiasm was aroused among his contemporaries; a textbook was written, and man as nature formed him was given to the medical profession and a more accu-
rate and complete knowledge of all the systems of the human body was evolved.

A quiet unassuming young English physician, William Harvey began the study of physiology of circulation. His little quarto, "Anatomical Exercise on the Motion of the Heart and Blood in Animals" was published in 1628. From experimentation in vivisection a new thought fermented in his mind, "I began to think whether there might not be a motion, as it were, in a circle." Harvey was able to demonstrate this discovery and in the face of much diadetic opposition maintained his position and changed the outlook of medicine in general and especially added much impetus toward the advancement of the knowledge of the cardiovascular system in particular. (63)

His references to arteriosclerosis were brief and at this early period no one seems to have thought the subject worthy of exhaustive investigation. Harvey did mention the difficulty of transmission of "the pulsific faculty" in arteries thickened and hardened with calcareous material. (15)

Modern methods of study follow in passive fashion the history of the development of the microscope. Leeuwenhoek, a seventeenth century scientist, contributed much to knowledge of biological sciences by his manufacture and use of crude microscopes. During this
time the viewpoint concerning the dissection of man had changed. Anatomy had become a fundamental science. Thebesius described the arteries and venules. (89)

During the period of modernization of medicine the clinician who added most to the advancement of cardiovascular knowledge was Laennec. In 1816 a young woman consulted Laennec about heart trouble. It was impossible for him to listen to the heart directly so he rolled a cylinder of paper and applied it to his ear and the larger end to the patient's heart. This was the first stethoscope. This one advancement stimulated interest in the pathology of the heart and its vessels. (63)

It was not until late in the eighteenth century that Giovanni Morgagni indicated that the aorta was frequently involved in a degenerative process. From this time on the advancement of knowledge was notable for the appearance of a number of important treatises on the physiology and pathology of the vascular system. In a lengthy treatise by Morgagni, on "The Seats and Causes of Disease", the lesions of arteriosclerosis were accorded a consideration more extensive than in any preceding publication. Minute descriptions of the lesions abound throughout the whole classic work. These descriptions are valuable chiefly for
their length, minute detail, clinical correlation, and exposition of associated pathological lesions, such as aneurysms, enlargement of the heart, and pain in the chest. (15)

The term "arteriosclerosis" was used by Lobstein in 1883. Some names of those individuals who have made important contributions to the study of this disease are Mahomed, von Basch, Huchard, Thoma, Marchard, Jores, and others. (20)

The first accurate histological description of arteriosclerosis of the arterial system was made by the foremost pathologist of the last century, Virchow. His conception of the formation of the atheromatous processes, (imbibition theory) has withstood the melting processes of additional research and advanced study and at the present time with a few additions and modifications is still the most acceptable conception of formation early arterial disease. It now is the basis for future study in that line. (5) With Virchow's studies of arteriosclerosis, which included recognition of the association of fatty substances with the lesions, clinicians began to consider seriously for the first time the clinical implications of the disease. (37)

To show how recent the development of the knowledge of factors of diabetic pathology influencing
vascular disease is, Warfield, in a comprehensive book on etiology of arteriosclerosis published in 1908, failed to mention diabetes having any etiological relationship to arteriosclerosis. (84)

Much has been learned of the development and untoward effects of arteriosclerosis and of its part in the decay of the human body. Yet to this day the etiology of arterial thickening is obscure. The association with certain anomalies of metabolism, such as gout, obesity and diabetes, has been stressed and in such cases uncertainty has always existed as to what was cause and what was effect. The etiological role of diabetes has been in question being considered both as a cause in the young and a result in the old individual. (15)
ETIOLOGY

The etiological factors present in the production of diabetic arteriosclerosis obliterans are extensive in number and varied in their influence upon the blood vessels. Such predisposing causes as obesity and hypertension are present in the production of generalized arteriosclerosis as well as being important in the consideration of diabetic arteriosclerosis. The evaluation of their causal role here is extremely difficult. Faulty food metabolism, especially that of the lipoids has an important etiological effect in the production of arteriosclerosis. These arterial changes are premature, occurring earlier than in normal patients as will be shown in the consideration of incidence and duration of the disease.

Osler stated that arteriosclerosis is a common complication of diabetes. He has also suggested that it has some etiological significance in the production of the disease as the pancreatic artery may be greatly narrowed by arteriosclerosis. Woodyatt has regarded arteriosclerosis to be a causative factor in the production of diabetes by the formation of organic lesions (atrophy of the pancreas, central nervous system lesions, etc.). He further points out that the arterial disease
of diabetics is often most marked in the mildest cases and absent or insignificant in the most severe forms seen in younger subjects, and can scarcely be viewed as a causative factor in the majority of cases so it appears to be an effect rather than a cause. (90)

From the clinical standpoint, it is convenient to recognize that arteriosclerosis is commonly associated with: (1) intoxication and infections, (2) old age, and (3) hypertension; but because of the very slow development of arterial changes, it is extremely difficult to prove conclusively a definite cause-and-effect relationship between infections, intoxication, senility, or hypertension, on the one hand, and sclerotic changes in the arteries on the other. The association of arteriosclerosis with gout, diabetes, or Bright's disease lends suspicion to the belief that there is a well defined relationship between the metabolic disturbance and the diseases of the arteries. The influence of the metabolic factors concerned, carbohydrate, protein, and fat, are extremely multiple and vague. (20)

It seems probable that certain circumstances predispose the arteries to damage. The onset of both diabetes and arteriosclerosis shows marked individual variability. Osler has early observed "the onset of what
may be called physiological arteriosclerosis depends, in the first place, upon the quality of arterial tissue (vital rubber) which the individual has inherited, and secondly upon the amount of wear and tear to which he has subjected it". (56) This may influence both the incidence and the severity of the arterial disease. Goodridge feels that in many instances, there seems to be a definite inherited factor. (20)

Incidence and Duration

Arteriosclerosis is becoming an increasingly important problem in the management of diabetic patients. In the last decade among Joslin's patients arteriosclerosis has risen three-fold in importance and coma has dropped to less than one-third of its former incidence as the cause of death of the diabetic. The reason for this is that the use of insulin has prolonged the life of the diabetic and increased the duration of the disease so that the patients live to develop arteriosclerosis. The average age of death in diabetes in the Maunyn period was 44.8 years, the average age of death in diabetes since Banting's Epoch is 54.2 years. Fifty years is the age in which diabetes develops most frequently in women, fifty-one years in men. The average duration of diabetes before insulin period was 4.7 years
and this was not long enough to determine if arteriosclerosis would develop. Recent figures give the present average duration of the disease to be 8.9 years. (31)

It was known at the beginning of the twentieth century that arteriosclerosis sooner or later presents itself in almost every case of diabetes mellitus. Tyson suggested then that in some instances at least it was the direct result of the irritating qualities of the blood since it was so often found in young subjects as well as in older persons in whom, of course, it may have been due to other causes, operating in the old. (82)

Studies of young diabetic children reveal frequent occurrence of arteriosclerosis of the low pressure type. The blood pressures were normal or below normal but the diagnosis was made by finding increased resistance of the radial and brachial arteries to palpation and the presence of tortuosity of the peripheral vessels. (2) A group of fifty young diabetic patients, of an average age of 23.4 years and duration of the disease of 6.9 years, was studied by Shepardson to determine the incidence of arteriosclerosis as evidenced by the roentgen ray and 36 per cent gave roentgenologic evidence of vascular disease. (76)

After the third decade of life arteriosclerosis is
increasingly frequent in diabetics and is found with great uniformity in middle aged and elderly subjects. (90)(57) The following table modified from Rabinowitch (62) gives the incidences of cardiovascular disease among 500 diabetics according to age:

<table>
<thead>
<tr>
<th>Age period</th>
<th>Total number diabetics</th>
<th>Number cardiovascular cases</th>
<th>Per cent</th>
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<tr>
<td>0-10</td>
<td>4</td>
<td>0</td>
<td>0.0</td>
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<tr>
<td>11-20</td>
<td>14</td>
<td>4</td>
<td>28.6</td>
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<tr>
<td>21-30</td>
<td>34</td>
<td>5</td>
<td>14.7</td>
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<tr>
<td>31-40</td>
<td>67</td>
<td>33</td>
<td>49.2</td>
</tr>
<tr>
<td>41-50</td>
<td>124</td>
<td>91</td>
<td>54.7</td>
</tr>
<tr>
<td>51-60</td>
<td>158</td>
<td>106</td>
<td>67.1</td>
</tr>
<tr>
<td>61-70</td>
<td>80</td>
<td>59</td>
<td>73.7</td>
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<tr>
<td>71-80</td>
<td>18</td>
<td>14</td>
<td>77.8</td>
</tr>
<tr>
<td>81+</td>
<td>1</td>
<td>1</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>500</td>
<td>313</td>
<td>62.6</td>
</tr>
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The effect of increasing duration of diabetes upon the arteriosclerosis is more apparent now than a few years ago. As a general rule, regardless of the youth of the patient, a diabetes of five years or more duration will produce arteriosclerosis or some degree. The longer the duration of the diabetes, the more extensive will be the arteriosclerosis and the
higher will be the percentage of death due to some form of arteriosclerosis. (69) Joslin finds that if the duration of the diabetes is less than five years, arteriosclerosis leads to 30 per cent of the deaths, if five to nine years, to 44 per cent, if ten to fourteen years to 63 per cent, if fifteen to nineteen years to 60 per cent and if thirty years or over to 68 per cent. (30)

Hypertension

The consensus of opinion of various authors, John (29), Joslin (31), Root and Sharkey (65), Schwartz (74), is that the blood pressure is higher in diabetics than in normal individuals of the same age, and hypertension occurs more frequently in diabetics. This relationship has been known for some time. Purdy in 1904 called attention to increased arterial tension as being a frequent symptom of diabetes mellitus. It was explained then that this might be reasonably expected as the glucose is an irritant which may readily excite vasomotor tension, which in turn is a natural fore­
runner to endarteritis and arteriosclerosis. (82) More recent studies by John of series of cases of diabetes showed the blood pressure was the same as in normals below and including the fourth decade; above this age
the incidence of high blood pressure was greater in diabetics. (29) Diabetes precedes hypertension in the majority of cases. In a recent review of cases under observation by Root and Sharkey for 18 years the blood pressure rose from normal to a level above 150 mm. of mercury in 16 per cent of the cases, and in 50 per cent rose over 10 mm. of mercury. Among a series of diabetics followed to death hypertension occurred in 54 per cent. (65) A comparative study of 243 diabetic cases and 938 non diabetic cases were made by Schwartz. Blood pressures ranging from 171-260 mm. of mercury occurred in 13.2 per cent of diabetics as compared with 4.9 per cent of non diabetics. The greatest percentage of hypertensive cases was found in diabetics between the ages of fifty and sixty. In the whole life span systolic pressures above the 150 mm. mark were recorded in 30.4 per cent of the diabetic series and only 15.6 per cent of the non diabetics. (74) Recent reports of Steiglitz indicate that diabetes of itself does not promote hypertension but it is attributable to the coincidental etiological factors such as age and obesity. (80) There is a certain liability of obese individuals to develop hypertension findings but many do not. Hartman and Christ analyzed the blood pressures of 2,000
consecutive patients, equal numbers of males and females. They found the blood pressures of the overweight group to be about 12 per cent higher than those in the underweight group. (24)

Obesity

It has been consistently apparent that there is a predominance of obesity in diabetics. The etiological significance of this fact in the production of arteriosclerosis is not readily evident. Studies show 91 per cent of diabetic patients are overweight and 82.9 per cent more than 10 per cent overweight when their diabetes begins. The amount of obesity increases up to the fifth decade. (47) Joslin finds that 70-80 per cent of persons with diabetes are or have been obese. Arteriosclerosis, obesity, gall stones are undoubtedly more common in diabetics than in non diabetics. It is much more likely that all of these are the results of the metabolic disturbance, particularly the disturbance in fat metabolism than that they are in any sense a cause of the disease. (10)

It appears without much question, relying upon clinical investigation of Beck (7) and others that the hypertension associated with obesity in diabetic patients is due to the obesity per se and is not an etiological factor in production of diabetes by causing an
arteriolar sclerosis of the pancreatic vessels. In early cases it has been shown that there is a development of diabetes long before any arterial disease is noted so it can be inferred that diabetes hastens the development of arterial disease. (7) It is undoubtedly the interrelation of both the obesity and hypertensive factors that produce increased physiologic strain on the vascular system.

Hypercholesterolemia

The coincident presence of diabetes mellitus and arterial disease has been observed to be more marked among obese patients. The influence of hyperglycemia on obese patients is such as to hasten pathological changes in the arteries largely through the inadequacy of complete fat catabolism. Westphal has reported that in 71 per cent of patients with high blood pressure, a hypercholesterolemia occurs and that in primary hypotension there is frequently an associated decrease in blood cholesterol. The responsibility of this change in blood lipid content has been laid to the liver and a fall in blood pressure with diuresis is reported to follow administration of cholic acid. Other investigators find no such parallelism. Glaser has demonstrated in eight subjects that excitation of the sympathetic
system by injections of epinephrine is followed by excess of cholesterol in the blood. The hypocholesterolemia may therefore by as much the result of vegetative nervous system stimulation associated with hypertonia of the arterioles as the cause thereof. Whether or not changes in blood cholesterol content are of etiologic significance in the production of hypertension preceding arteriosclerosis is very uncertain. (80)

Race

Not much study has been made upon the influence of race and physical characteristics, except obesity, in the incidence of the appearance of arteriosclerosis. The influence of race appears to have a definite effect upon the arteriosclerotic mortality in diabetes. Thus it is decidedly more prone to be a factor in Jews. Of Jewish deaths 54.2 per cent were due to arteriosclerosis, in contrast to 43 per cent for non Jews. The percentage of arteriosclerotic deaths in Jewish women was 58.9 per cent as contrasted with 42.8 per cent for non Jewish women. (32) This parallels the increased incidence of diabetes in Jews in which 1.3 per cent manifest the disease whereas only 0.5 per cent of non Jews ultimately show signs and symptoms of diabetes mellitus.
Localization of Lesions

The localization of arteriosclerosis has been studied for all fatal cases. The heart was the most frequent site, 19.1 per cent of the total mortality, next the legs 13.2 per cent as evidenced by gangrene, far less the brain, 7.2 per cent, and least of all the kidneys 4-7 per cent. Sex made no essential difference in the distribution of the arteriosclerosis. If one compares the localization of the arteriosclerosis for the different epochs, Naunyn, the Allen, and the Banting, it will be found that the percentage of deaths due to arteriosclerosis in the brain remains constant while that of the heart and peripheral arteries increases at the expense of the kidneys. (32)

Allen and Crisler studied the effect of the intraarterial injection of papaverine hydrochloride, acetylbetamethylcholine chloride and histamine phosphate on the peripheral cutaneous temperature. The temperature of the fingers in all instances rose to a much higher level than did that of the toes. This occurred regardless of the location of the injection, whether given in both femoral or in the brachial artery or whether given intramuscularly or intravenously, when papaverine was given. The lower extremities seem to be relatively
refractory to such vasodilating drugs. They believe that the refractoriness of vasodilatation of the lower extremities is intimately associated in some, as yet unexplained way with the much higher incidence of chronic occlusive arterial diseases in the lower extremities as contrasted to their incidence in the upper extremities. (3)

Hyperglycemia

Schwartz advances the opinion that hyperglycemia per se is not particularly harmful in the diabetic in the production of arterial damage. Hyperglycemia varying from 160-500 mg. per 100 cc. of blood is no index to the degree of arteriosclerosis found. It merely indicates the presence of disturbance of faulty carbohydrate metabolism. (74)
DIAGNOSIS

The detection of the presence of arteriosclerosis and arterial damage is comparatively easy in advanced stages of the process but presents difficulties when it is desired to make an early diagnosis. All methods of diagnosis may be used to determine the presence of arteriosclerosis; palpation, percussion, auscultation, and observation, are very valuable here. Various laboratory methods have been suggested for studying the conditions of the arteries and the capillaries. In patients who do not present sufficient symptoms and signs to recognize a pathological change, the laboratory may help greatly in confirming or detecting evidences of impaired circulation. Among these tests may be mentioned: (1) calorimetric studies, including skin temperature readings and heat loss in the extremities; (2) the oscillograph; (3) skin reactions to histamin; (4) roentgen ray; (5) intradermal wheal test; (6) intraarterial injection of opaque solutions followed immediately by roentgenography; (7) capillary microscopy. (36)

History

The first method of approach to a diagnosis may readily be by means of the history. A careful hist-
ory, special emphasis being placed on the presence of complaints of claudication, cramps in the calves of the legs, coldness in the feet, numbness or pain in the extremities, will lead to the suspicion of impair-ment of circulation. A history of trophic ulcers or focal gangrene may also be significant in making the diagnosis. (36)

Criteria for Diagnosis

Definite criteria or standards should be main-tained by which an accurate diagnosis of arteriosclerosis can be made in diabetes. These points have been suggested by Joslin to be of value in the recog-nition of the process:

(A) by physical examination of vessels, four grades:

1. The arteries are palpable; 2. the arteries roll under the examining finger; 3. the arteries are tortuous; 4. the arteries are beaded or pipe stemmed.

(B) Evidence from autopsies: (1) (a) calcification with or without bone formation, either medial or intimal. (b) fibrous thickening of intima; hya-line degeneration of intima--intima approximately twice or more thicker than normal; (2) arteriosclerosis of atheromatous type, if they presented in addition to the fatty change (a) either pro-liferative or atrophic changes of a local char-
acter in the elastic laminae, or (b) cellular necrosis.

(C) Evidence from fatal cases: The term arteriosclerosis has been taken to include all deaths under the headings (1) arteriosclerosis and gangrene and (2) all deaths from gangrene. (31)

By using a combination of all methods of diagnosis; clinical examination, ophthalmoscopic examination of the fundi, X-Ray of the feet, and X-Ray of the heart, the incidence of diagnosis approaches very nearly that revealed by careful autopsy examination. But the methods used singly or in combination of two do not give nearly as high an incidence of diagnosis. There are four suggestive signs of arteriosclerosis, namely, (a) thickened radial vessels, (b) hypertension, (c) enlargement of the heart, and (d) accentuation of the aortic second sound. These, when found together, form a picture which is pathognomic. Singly, however, they have their limitations. All of these findings at times are misleading and difficult to elicit and are not to be relied upon to a great extent. (61)

Observation

Careful painstaking examination of the extrem-
ities is exceedingly important, and in a vast majority of cases this method alone may permit diagnosis of a definite impaired circulation. In preparation for examination the patient should be in bed with no obstructing clothing and with both limbs bared to mid-thigh. On general observation there may be noticed a pale waxy appearance of the skin, loss of subcutaneous fat, and atrophy of the muscles of the foot and calf of the leg. These findings indicate faulty insufficient blood supply to the extremities. (49)

When the circulation of the extremity is impaired it is not strange that the nutrition of the foot and toes becomes so deficient that atrophy of the tissues may result. In examining diabetics' feet, the observer should note whether or not the skin is of normal thickness and elasticity, and also whether the subcutaneous tissue is normal. This can be done by picking up the skin on the dorsum of the foot between the thumb and forefinger. The thinness and glossiness of the skin and the difficulty encountered in trying to pick it up between the fingers will be noted. The subcutaneous tissue may be absent and the skin so atrophic as to be parchment-like and stretched tightly over the tendons. The
toes are thin, stiff and the skin over them is apt to show more atrophy than is found on the dorsum of the foot. The bones too share this atrophy. The toenails are worthy of close observation for when atrophy of skin and subcutaneous tissue is present, they are small and greatly thickened. They are usually brownish in color and lack any transparency.

When the atrophic findings are marked the inference can be drawn that the circulation is impaired by occlusion of the large vessels and there are few anastomotic vessels. (55)

Color Changes

Color changes are usually present if the circulation is deficient. The foot of good color, particularly if most of the color is maintained whether the foot is elevated or dependant, is a foot with good circulation, even though it is impossible to palpate any pulsation in the dorsalis pedis artery. If the foot when elevated assumes a death-like pallor rapidly and then when returned to the horizontal position regains its usual color very slowly, the circulatory disturbance is probably extensive. When the foot is placed in the dependent position the more normal the color the better
the circulation. The color change may be localized or extensive involving merely the tips of the toes or extending midway up the thigh depending on (a) the level at which the larger vessels are occluded, (b) the degree of their occlusion and, (c) the amount of collateral circulation developed. (49)

Pickering has suggested a simple test depending on color changes in the foot. A sphygmomanometer is placed on the thigh. The leg is elevated to the upright position and blood allowed to drain out for a period of four or five minutes. The cuff of the sphygmomanometer is then inflated to above systolic blood pressure and the leg lowered to the horizontal position. The circulation is cut off for a period of a few minutes. When the pressure in the sphygmomanometer cuff is suddenly released, one notes the rapidity of the hyperemic blush that travels down the leg. In obstructive vascular disease it is very slow and patchy in distribution. (58)

Local Lesions

The presence of any local lesions should be determined. There are some lesions which are prognostic signs of impending gangrene. These early signs include rose spots, scars, pigmented areas, blebs,
ulcerations, and small areas of focal gangrene. The rose spots are small pink or erythematous areas usually seen on the legs and sometimes on the feet. They are presumably due to some pathologic changes in the minute vessels and seem to indicate recent activity. They may last for weeks. Ultimately they change to pigmented areas and in time are replaced by small scars. Scars are frequently seen on the legs in these cases of impaired circulation. Bullae may be found on the toes or on the feet. They vary in size from 1-3 cm. and usually develop over night and as a rule painless and have a tendency to become purple and be followed by local gangrene. These blebs are most likely due to a recent and more or less rapid occlusion of the smaller vessels. (36)

If gangrene is present, it is important to note whether it is definitely demarcated or whether it is a diffuse process. It is particularly important to note whether the infection is localized in the form of an abscess or of an osteomyelitis of a phalanx, or whether the local evidence of infection is slight compared to the extensive infection along lymphatics or along the veins of the foot. As a rule the foot with localized pus or osteomyelitis in the absence of
gangrene is a foot with fairly satisfactory circulation. Otherwise localization of the infection would not have taken place. (49)

Palpation of Vessels

Determination of the presence or absence of pulsation in the peripheral vessels is essential to an understanding of the character of the vascular system of a given leg. A foot may be apparently normal without palpable pulsation in any of the arteries below the femoral at the groin. Such a highly developed, collateral circulation, however, is very uncommon. In general, the diabetic patient with a pulseless foot lives in the shadow of impending gangrene. The three arteries of the leg that are normally palpated are the dorsalis pedis, the posterior tibial, and the popliteal arteries.

The dorsalis pedis artery is clinically the most important of all the peripheral vessels of the leg. Except in rare anomalies it can be palpated in every normal individual. This artery lies just lateral to the extensor longus hallucis tendon and is best palpated between the proximal ends of the first and second metatarsals. It is sometimes variable in its course and often difficult to feel, particularly if
the lumen is narrowed, the walls rigid, and the tension low. It may be felt readily on one day and with difficulty or not at all on the next. There are, moreover, other factors which interfere. The twitching of a tendon may be difficult to distinguish from the pulsating of the artery of the patient and that of the examiner. (49)

The posterior tibial artery is more difficult to feel and is of much less clinical importance than the dorsalis pedis. It is located by allowing the tips of the fingers to rest in the hollow behind or below the internal malleolus. If present, pulsations can usually be felt, except in the presence of edema.

The popliteal artery is at times difficult to feel particularly in a large leg. It generally lies on the outer side of the midline in the popliteal space, and usually found between the midpopliteal region and the external hamstrings. (49)

By palpation, too, the temperature of the two feet should be carefully compared, likewise that of the various levels of each extremity. A sufficiently accurate indicator for clinical use is the palm of the hand. The examiner starts at the mid-thigh and carefully passes the hands down toward the toes. Normally the temperature change should be
gradual from the thigh to the toes and no definite point that shows a sudden change. The more sudden the arterial occlusion and the less extensive the development of collateral circulation, the more definite the point of abrupt temperature change will be. (49)

Arterial Measurements

The problem of arteriosclerosis may also be investigated by measuring the degree of vascular sclerosis in terms of arterial elasticity or arterial rigidity. The arterial elasticity or arterial rigidity can be evaluated by determining the rate at which the pulse wave is propagated through the arterial tree, in as much as it is not possible to measure arterial elasticity directly on the living subject. Since the velocity with which the pulse is transmitted along arteries depends on the elasticity of the vessel walls, one can obtain an index of the degree of arterial rigidity or arterial elasticity by determining directly the velocity of the pulse wave in living man. Bramwell and Hill (11) after mathematical treatment of the equation relating the velocity at the front of the pulse wave to the coefficient of volume elasticity, have shown
that the velocity of the pulse wave is a direct function of arterial elasticity. Thus an increase of velocity of the pulse wave implies an increase in arterial rigidity or conversely, a decrease or arterial elasticity. By employment of an optical recording apparatus the velocity of the pulse wave through the aorta and iliac vessels (velocity of the aortic pulse wave) and through the brachial, radial, and carotid vessels (velocity of the radial pulse wave) was studied on normal cases and on 21 diabetics and results indicated young diabetics have a higher radial pulse wave velocity than the normal of that age group. The values for the transmission of the aortic pulse wave did not indicate any significant changes from the normal. The conclusion from this type of test is that the diabetic state either initiates early or accelerates the development of premature arteriosclerosis in the young adult.(23)

The oscillometer may be used as a means of determining the site of obstruction of vessels of the leg. Theoretically the amplitude of the oscillations reflects the amplitude of the pulse. When a large vessel is narrowed by thrombosis or the wall stiffened by sclerosis and calcification, the oscillations
become greatly reduced and the level at which this change is observed may be regarded as the level at which the obstructing process is effective.

The oscillometer gives no information regarding the extent of the collateral circulation. For this reason, as well as the fact that the oscillometer readings are affected by the force and character of the cardiac contractions, it has not been found, up to the present time, to be of great practical value except as an aid in the early diagnosis of arterial occlusion. (49)

Roentgenological Diagnosis

Roentgen ray examination of the extremities is an accurate method of judging the presence of calcium in the vessel walls. It is more reliable than clinical methods in the diagnosis of vascular calcification. Statistical study of groups of cases show roentgenographic evidence of calcification of the vessels was present in the legs of 53 per cent of a large group of patients selected at random. Almost twice as many diabetic patients showed calcification of vessels in the legs than did non-diabetic patients of the same age group. The incidence and degree of vascular calcification increased with the
age and with the duration of the diabetes and was much higher than in non-diabetic patients. (52)

The technique of X-Ray examination of the extremities is somewhat detailed. The legs and feet are chosen for study instead of the arms because the vessels of the legs show evidence of sclerosis earlier than do those of the arms. Calcification is not always seen in the aorta even when the process is moderately advanced in the vessels of the legs, perhaps partly because of the fact that it is more difficult to detect calcification in the aorta.

Care must be exercised in the detection of calcified vessels. Flecks of calcium may escape the eye unless carefully sought. One must guard against the shadows not infrequently seen in the region of the ankle which simulates a calcified vessel. These shadows are probably due to tendon sheaths.

The patients are classified according to whether the degree of calcification of their vessels was (1) slight, (2) moderate, or (3) advanced. Patients whose vessels are visible for only a short distance and are not well outlined by calcium for a considerable portion of the course. In the third, or advanced group, are placed the patients whose large arteries are visible as an almost continuous calcium shadow and in whom at least some branches are calcified. (52)
It is important to realize that a roentgen-ray plate of a leg is of little value in determining the blood supply to a foot. It may be helpful in showing calcification of vessels not otherwise demonstrable. Extensive sclerosis, however, may be present without any evidence of gangrene, and moreover, a conservative operative procedure such as amputation of a toe, can frequently be done with roentgen-ray evidence of extensive calcification of the dorsalis pedis artery and larger vessels to and above the knee. (49)

Bowen and Koenig who introduced the procedure of X-ray plates of the extremities in the diagnosis of arteriosclerosis find it of very much value. Arteriosclerosis in their opinion is not necessarily generalized and may involve one region or organ more than another. The arteriosclerosis in long standing diabetes is of the senile type, i.e. calcification of the walls, so that the artery feels beaded to the palpating finger. These vessels are visual on roentgen ray plate before becoming discernable clinically. The diagnosis of early arteriosclerosis of the lower extremities which is difficult to make in any way but by X-ray is of considerable importance in the prognosis and management of vascular conditions when combined with diabetes. (9)
Since the introduction of roentgen ray films of the extremities as a diagnostic procedure, their use has become very extensive. More recent investigators question their value. An understanding of the pathology of the vessels of the lower extremities in arteriosclerosis makes one very skeptical of the value of roentgen ray films as a means of demonstrating vascular obstruction. Medial calcification is a very prominent feature seen in any section of these arteries. It is so massive that a ring of lime encircles the tube. It is this massive calcification that the roentgen ray plate reveals; however, the obstruction to the circulation is not due to medial calcification but rather to the process known as intimal thickening. The collagenous material that fills in the lumina of the artery and obstructs it does not throw a roentgen ray shadow. If medial calcification and intimal thickening always occurred together, the roentgen ray shadow showing calcified arteries would be of great value. But this is not the case. Lansbury and Brown (38) studied the relationship of the calcification of peripheral arteries in the presence of absence of occlusion. They found 65 per cent of normal men past the age of fifty showed calcification of the peripheral arteries compared with 85 per cent
incidence of arteriosclerotic individuals of the same age group. Their conclusion was that the presence of calcification did not give significant information as to the presence of an occlusive process. (55)

Skin Reactions

Estimation of the adequacy of circulation of the feet and legs may be done by the histamin reaction. The technique is as follows: The patients are placed flat on their backs with legs extended. Areas of normal skin are cleansed with alcohol and after complete evaporation, a drop of histamin acid phosphate, 1:1000 dilution, is placed on the surface. With a sharp needle the skin is pricked seven times through the drop, the pricks forming a circle about 5 mm. in diameter, the needle going well in the skin but not deep enough to draw blood. Usually one test is placed above the knee, one about six inches below the patella, a third six inches above the ankle, and a fourth on the dorsum of the foot. The resulting reactions are roughly sketched at two and a half, five, ten, and fifteen minute intervals after initiating them. The reactions normally resulting resemble mosquito bites; first a red spot appears, followed and obliterated by a sheal, surrounded by a redden ed area (flare) several cent-
imeters in diameter; a sensation of itching accompanies the reaction.

The normal reaction is complete (both wheal and flare present) within five minutes and the reactions on the foot closely resemble those on the leg and the thigh, the distal usually appearing a little slower and being a little less well formed than the proximal. Evidence of diminished circulation in the feet consists of delay in appearance and imperfect development of the reaction of the foot, while the reaction above the knee remains normal.

In a series of 100 unselected diabetics under treatment, the response of the skin of the lower extremities to histamin under standard conditions indicated 32 per cent had a normal circulation of the feet, in 34 per cent the circulation was somewhat impaired, in 34 per cent markedly impaired. (79)

The intradermal salt absorption test is also used to determine the lowest level of adequate circulation and appears to be reliable. Intradermal injections of 0.2 cc. of a physiologic solution of sodium chloride solution are made at 3 inch intervals on the inner aspect of the leg from the ankle to the upper third of the thigh, the rate
of absorption of the resulting wheals being used as an index of the adequacy of the circulation of each level. When the circulation is normal the rate of absorption is slow and the wheals persist for an hour or more. When the circulation is impaired the rate of the absorption of the wheals is uniformly increased from above the knee downward to the ankle; some of the wheals are completely absorbed at the end of five minutes. The circulation is usually regarded as adequate at and above a given level if the wheal at that level is half of its original size at the end of an hour after the intra-dermal injection was made. (48)

Cholesterol Level

There is a disturbance of cholesterol metabolism in diabetes mellitus with a relatively high concentration of this substance in the blood plasma. The high cholesterol content of the blood plasma is an etiological factor in the production of the arteriosclerosis of diabetes so that the finding of an increased cholesterol content of the blood is of value to the diagnostician in determining the probability of the presence of diabetic arteriosclerosis in the individual patient.
This table modified from Rabinowitch (62) gives the plasma cholesterol levels in different conditions:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Average Cholesterol mg. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes with symptoms</td>
<td>242</td>
</tr>
<tr>
<td>Accidentally discovered diabetes</td>
<td>212</td>
</tr>
<tr>
<td>Potential diabetics</td>
<td>166</td>
</tr>
<tr>
<td>Non diabetics</td>
<td>150-160</td>
</tr>
</tbody>
</table>
PATHOLOGY

In the human body there are two important main types of arteries that become involved in arteriosclerosis: The elastic arteries, such as the aorta, the iliac, and carotid arteries; and the muscular arteries, such as the posterior tibial, or brachial, in which the development of the muscularis very often over shadows that of the elastic laminae. This muscular type is encountered chiefly in the peripheral and splanchnic arteries. The arterioles also are of the muscular type.

One of the first contemporary classifications of arterial lesions was that of Warfield. He listed lesions of true arteriosclerosis to be of three types. (1) the focal or nodular; (2) the diffuse; and (3) the senile. In general, the changes were thought to be of a degenerative disease; as age increased there was an increase in the strain upon the vessel walls and the elastic tube fortified itself by the connective tissue thickening of the intima and to a lesser extent of the media. Finally degenerative changes consisting of local areas of coagulation, necrosis, and calcification, especially marked in the deep layers of connective tissue thickening of the intima and in the muscle fibers of the media, resulted com-
Completing the process. (84)

Development of Types of Sclerosis

The process just described does not accurately portray the true picture of the various types of arteriosclerosis. In non-diabetic individuals the vascular pathological changes that are encountered are fairly closely correlated with the different types of vessels. The atheromatous plaque is the characteristic arteriosclerotic lesion of the elastic arteries. This may present several forms, all of which are presumably related and represent various stages in the process of atheromatous degeneration.

The first stage is the so-called atheromatosis of puberty, characterized by fine yellowish subendothelial streaks of spots, particularly about the orifices of the intercostal arteries. The plaques are translucent and slightly raised. The elasticity of the vessels is normal. Microscopic examination shows the swelling and loosening of the intercellular substances of the intima, chiefly in the deeper layers, with the deposition of minute fat droplets. These, among the fibrillae, consist chiefly of cholesterol ester. The fatty infiltration here is far more marked in the intercellular substance than in the cells themselves. As the process develops, more and
more of the intima is involved, until finally the endothelium is reached. These changes are apparently reversible.

The next step is the development of true arteriosclerosis or atherosclerosis which is fundamentally the same. However, there has been a more marked swelling and hyaline changes of the ground substance of the intima with infiltration of lipoids and new formation of fibrous tissue, which in turn becomes hyalinized. Beneath the hyaline connective tissue there may or may not be an enormous mass of atheromatous material. Finally, necrosis of the tissue cells occurs with decomposition of the cholesterol esters to the characteristic needle-shaped cholesterol crystals and fatty acids, which sooner or later combine with calcium. These calcium soaps become the calcareous or even bony plaques formed in the atheromatous regions. As the plaque becomes larger and reaches nearer the surface, the blood stream may sweep away portions of the pultaceous material, forming the familiar atheromatous ulcer. Aschoff emphasized that the lipid content of the plasma does not cause the atheromatosis but influences the character of the atheromatosis plaques by determining the degree of fatty infiltration of the hyalinized ground substance.
The second great type of arterial change is that seen in the muscular vessels. Here medial calcification, the Monckeberg type of sclerosis, predominates. This lesion is entirely distinct from the atheromatous process which we meet in the elastic vessels and is restricted to the muscular vessels. Intimal change is negligible and the lumen remains intact or is even actually widened.

The initial change is the deposit of granules of calcium in the connective tissue stroma about the muscle cells. This calcification gradually becomes more and more abundant finally surrounding and causing atrophy of the smooth muscle cells. It is sometimes difficult to tell whether the particles of lime are outside or within the muscle cells, which may be necrotic. Any leukocytic reaction is extremely rare. Not infrequently organization of the calcified mass may take place with resultant formation of bone, which may even contain marrow in the more advanced cases. Through secondary intimal injury, thrombosis may occur. (35) (20)

There is little if any relationship between the occurrence of this type of arteriosclerosis and the atheromatous, although occasionally the two forms
may coexist. In the smaller arteries there may be thickening of the intima with or without the deposit of lipoids. When this intimal change is at all marked one is justified in considering the possibility that the patient from whom the vessel was removed may be diabetic.

The third great type of arterial change is that known as thrombo angiitis obliterans, or Buerger's disease. This type usually occurs in young adults. Here thrombosis, organization of the clot, and subsequent partial recanalization of the thrombosed vessels are the outstanding features, followed by shrinkage of the walls and the resultant reduplication of the elastic laminae. Calcification is absent as is deposition of lipoids. There is usually a very sharp distinction between the fairly normal appearing adventitia and muscularis and the obliterated fibrosed lumen.

Still a fourth type of vascular change is met with in the smallest of the arteries and the arterioles, the so-called obliterative endarteritis. This usually appears as a hyaline thickening of the intima. Hyaline changes in the elastic laminae are undoubtedly of great importance. Obliteration of the lumen may be practically complete.
Peripheral Arteriosclerosis

In the diabetic individuals, which is the type in which interest here is centered, the atheromatous type of lesion is the outstanding one. The others may be present but if there is one thing that should lead us to suspect that an artery in a given case comes from a diabetic patient it is when we find the intimal type of involvement in the muscular arteries, either alone or superimposed upon the medial calcification. Arteriosclerosis of the intimal type may be considered to be present if there is local thickening and hyaline change of the intima with lipoid infiltration, the presence of cholesterol crystals or the presence of calcified deposits. These changes are practically always accompanied by fraying or reduplication of the internal elastic laminae. As a result of pathological changes the arteries lose their elasticity and become hard, rigid and tortuous. In the smaller vessels, proliferation of the intima may so narrow the lumina as to cause complete obliteration. (85)

Studies of gross pathological changes in the arterial channels of diabetic legs which have been amputated were done by Henderson. The findings were visualized by injecting metallic mercury into the popliteal artery and taking roentgenograms of the entire leg below the knees. The mercury was intro-
duced at approximately systolic pressure so that a rough approximation of physiologic conditions were produced. After a study of the roentgenray plates, the leg was dissected at strategic points and the arteries studied directly. The order of involvement of the arteries seemed to be posterior tibial, peroneal, and anterior tibial.

Basing the inferences on the pertinent data found, these statements are to be considered important:

1. Diabetic arteriosclerosis starts as a patchy affair.
2. It may sometimes occlude a major vessel so rapidly that adequate collateral circulation can not develop to prevent gangrene.
3. It may sometimes progress slowly, accompanied by the development of good collateral circulation, and eventually involve most of the major vessels in a diffuse process. At this stage it either resembles or is identical to non-diabetic or senile arteriosclerosis.
4. In the slowly developing cases the collateral vessels though never able to deliver a normally rich supply of arterial blood to the part, seem often to be sufficient to keep the patient symptom free or to diminish only slightly his activity and comfort if infection is avoided. In these cases and in the early
ones as well, infection seems to be the precipitating factor. (27)

The factor of the blood supply and nutrition of the vessel walls themselves figure prominently in the pathological lesion of arteriosclerosis. Special staining and clearing have shown blood capillaries running through all coats of otherwise unchanged human vessels. Their origin is traced from three separate sources, the adventitia, the region of the orifices of branches and directly from the lumen of the vessel.

The response of the vessel walls to injurious agents is manifest through the capillary bed by exudation and proliferation. Exudation may include serum and cellular elements, and be further complicated by the precipitation of fibrin. Proliferation consists of new formation of blood vessels and connective tissue elements, including fibroblasts and many varieties of mononuclear cells.

If the intramural hemorrhage be large absorption and organization may be incomplete, and the residuum remain as a necrotic focus, and be potent contributing factors in formation of atheroma. There is extensive collescence of lipid materials and cholesterol crystals and deposits formed.

Calcification of the lesions of the artery wall
is not a process which differs from calcification elsewhere. The primary requisite, necrotic tissue, preferably rich in lipoids is found in abundance in the vessel wall.

Arteriosclerosis is not "degeneration or the inevitable concomitants of age". With increased knowledge of the activity of these endocrine glands, their association with, and indeed, their control of growth, it may well be ascertained that the size of the vascular bed, including the vasa vasorum, is dependant on their activity. The association of the pancreatic hormone with phenomena has not been directly shown but likely exists. (89)

Coronary Sclerosis

Contrasted with that picture found in the peripheral arteries, examination and histological study of coronary vessels in 31 diabetic hearts showed no change that differentiates it from a non-diabetic heart with well developed coronary disease.

In both cases, microscopical sections showed well developed intimal thickening. This intimal thickening consisted mainly of an increased amount of loose connective elastic tissue elements, collagen, and the deposition of lipid materials. There were no qualitative differences found either in the different
vessels of the same case or in the vessels of the different cases. Neither were there found any significant differences in the vessels obtained from the hearts of different age periods or changes that would be characteristic of the severity or duration of the diabetes. However, there seemed to be a qualitative difference inasmuch as the longer the duration of the diabetes and the older the patient, the more marked were these changes. In the non-diabetic patients the extent and character of the intimal sclerosis and the deposition of lipid material differed in no way from those found in the diabetic hearts. (40)
PATHOLOGICAL PHYSIOLOGY

There are various faulty organic processes at work in the diabetic individual, which contribute either singly or in combination, to produce arteriosclerosis. Whether the increased prevalence of arteriosclerosis in diabetes is due to the disease itself or to methods of treatment of the disease, the importance of the problem is such that it cannot be disregarded. Altered physical factors; improper protein, carbohydrate, and fat metabolism; presence of obesity, hypertension, and hypercholesterolemia; all may be at fault. Shields Warren has observed, "I have yet to see at autopsy a diabetic, or read the autopsy of a diabetic, whose disease has lasted five years or more, free from arteriosclerosis regardless of age.....The diabetic has not only more than his share of arteriosclerosis but it falls to his lot ten of twelve years earlier than to the non diabetic. (85)

Physical Factors

Physical factors underlying the activities of the vascular system are subject to a number of variables: thickness of the vessel wall, its diameter, the distensibility, mode and frequency of branching
and relation to surrounding tissues, viscosity of the blood, the control exercised by the autonomic nervous system, and endocrine regulating mechanism. (89)

The structure of the vascular system determines the influence of the various factors upon it. The adventitia, media and subendothelial portion of the intima serves one elementary purpose; the preservation of the integrity of the lumen and endothelial lining but must be accompanied by the maintainance of a degree, of resiliency sufficient to sustain the diastolic blood pressure. (89)

The adventitia has two outstanding characteristics of considerable value; it is very vascular which is important in the development of collateral channels when the lumen of the vessel is narrowed and it has high tensile strength to prevent it from breaking.

The media of the arteries has elastic and collagenous tissue, also muscular fibers. The muscular arteries are very prone to undergo medial change ending in calcification without involving either the intimal or adventitial coats, whereas this type of change is uncommon in the larger elastic arteries, aorta, subclavian, iliac, etc. The property of distensibility
and contractibility is largely resident in the medial coat. This distensibility is gradually lost with increasing old age, but only coincidentally related to arteriosclerosis as the change is the same in an arteriosclerotic as in the same age group who is not sclerotic. (89)

The intima layer is composed of a layer of endothelium the function of which is to maintain a smooth unroughened surface which will not affect or impede the passage of the blood stream. It is this portion of the peripheral arteries that become involved to the greatest extent in the pathologic lesion which is typical of diabetic arteriosclerosis, the atheromatous formation followed by sclerosis of the media.

Protein

Arteriosclerosis is a functional disorder of the individual cells of the body and that function is dependant upon biochemical changes. Protein is acknowledged to favor the onset of arteriosclerosis. Bishop's belief is that arteriosclerosis arises when the cells of the body become sensitive to particular proteins and that these proteins create irritation, something in the nature of a mild anaphalaxis and if this is continued over
a long period of time the result is changes in structure which constitute the disease known as arteriosclerosis. Protein molecules were all considered to have a poisonous group and it is these split products of the protein molecules, whether formed by enzymic digestion or as a result of intestinal putrefaction, that are absorbed and carried through the blood stream. They exert their irritating properties here before being excreted and thus the main etiological factor is intrinsic and due to "auto intoxication". (S) The unrestricted diet of the untreated diabetic contains an excess of all varieties of food, protein carbohydrate, and fat. Protein intake is as much important as is lowering the carbohydrate and fat. (31)

Influence of Acid-Ash Diet

High protein diets with their excessive acid-ash, such as were formerly used in the treatment of diabetes, may have been partly responsible for the arteriosclerotic changes. The factor of acidosis may be important by means of its influence upon the intima of the blood vessels. The artificial production of arteriosclerosis in laboratory animals has long occupied the attention of many investigators both in this country.
and abroad. Some have succeeded in producing arteriosclerosis in animals by feeding them diets high in cholesterol containing foods. Newburgh and his various collaborators have successfully demonstrated that the human picture of arteriosclerosis can be reproduced in animals by the prolonged feeding of excessive quantities of protein. He suggests the chemical composition of the protein molecule and the type and arrangement of the amino acids may determine and produce the changes. (73) The incidence of arteriosclerosis is twice as high as in controls when acid ash foods such as meat, fish, egg, cereals and bread are fed to laboratory animals. (17)

Carbohydrate

Carbohydrate does not have any function in the production of arteriosclerosis except if taken to an excess so as to produce obesity. A persistent hyperglycemia is an abnormal finding and in time tends to produce pathological changes in the vessels. It is difficult to estimate how much noxious influence hyperglycemia might have in producing arteriosclerosis because patients with high hyperglycemia have succumbed early in the course of the disease to coma.
Joslin's opinion is that a hyperglycemia up to 0.25 per cent is not particularly harmful to a diabetic provided the urine is sugar free, since this proves the sugar is being utilized as food. (31)

High Fat Diet

A high fat diet may influence the production of arteriosclerosis in two ways; the effects of the lipoids themselves, and the increased cholesterol production. Anitschkow believes that the endothelial lining of the arteries is freely permeable for lipoids and various colloidal substances dissolved in the plasma, and that these are adsorbed by the interstitial chromotropic substance of the walls, especially of the intima, and on the surface of the elastic fibers. His views as to the primary importance of this lipoid filtration in the genesis of arteriosclerosis receive support by the marked tendency to severe arteriosclerosis in diabetics with their high lipemia and cholesterolemia. (15) The opposing view is subscribed to by Warren. He suggests that the lipoids are not the first wave of the assault. They are the reinforcements that consolidate the gains made by the attacking force. The normal intima is not disturbed by fat but given an abnormal intima, atheromata
will develop in proportion to the amount of fatty substances present. (85)

In a group of fifty young diabetics, patients of Shepardson, the average age being 23.4 years and the duration of the disease being 6.9 years, 36 per cent already gave roentgenologic evidence of vascular disease. Neither the severity of the disease nor the presence of associated pathologic changes can be considered as a pathogenic factor in the development of arteriosclerotic changes and the duration is important only because the causative factor must act over a reasonable length of time before its effects are manifest. In this group of patients the average values of blood cholesterol were markedly lower than heretofore obtained, and paralleling the reduction in lipemia, the incidence of arteriosclerosis was found to be greatly reduced. The addition of insulin therapy has resulted in a marked lowering of blood lipoid content. The parallel reduction in the incidence of arteriosclerosis apparently necessitates the assumption that altered fat metabolism is the morbid factor in the development of vascular disease in association with diabetes mellitus. (76)

**Presence of Cholesterol**

The influence of circulating metabolites in the
blood and anatomic changes in the vessels themselves can hardly be separated. So far as arterial hypertension is concerned, the roles of glucose, salt, quanidine the potassium-calcium ratio and of peptones in the blood are still not clearly defined. The effects of circulating hormones from the pituitary and adrenals, while definite, do not seem to explain more than a small portion of the cases. Other substances, such as cholin compound, histamine and pancreatic extracts, such as "padutin" have temporary effects upon blood pressure. The one substance found both in the blood and in the blood vessel walls with which, experimentally, typical atherosclerotic lesions can be produced, is cholesterol. It is sometimes found in increased amounts in cases of hypertension. It is not the height of the cholesterol in the blood, but the degree of saturation which is important. In hypertension the serum is often over saturated with cholesterol even though the concentration in milligrams per 100 cc. is normal. Thus it is the relation between the cholesterol and the colloids of the serum together with the affinity of the cells of the arterial wall for cholesterol which determines the deposition. (65)
Cholesterol is an alcohol, a hydro-aromatic secondary alcohol, possessing the power of uniting with fatty acids to form esters. It is relatively insoluble, its best solvents being the fat solvents. It is relatively resistant to the action of enzymes of animal, vegetable or bacterial origin. Cholesterol is found in every animal cell. In the animal body it is closely associated with the fats, being found in the unsaponifiable residue following extraction by fat solvents.

Cholesterol and certain of the compounds have physical characteristics that permit of tracing the substance to a degree in the tissues. In the ester form seen in the arteries, cholesterol occurs in drops which stain like fats with the sudans and which are anisotropic. Under the polariscope they exhibit dark maltese crosses, producing a tetrad-like appearance. The solid crystals are doubly refractive. The cholesterol esters in the surface lipoid cells of aortic lesions are evidently in very unstable equilibrium, since in tissues that are stained or fixed they are precipitated out thus giving a means of identification. (39)
The function of cholesterol in the human body is believed to be a conveyor of fats, it appears to serve as an insulating medium in the myelin sheaths. Cell membranes are believed to be rich in cholesterol and phosphatides, which control cellular permeability and membrane equilibrium. In this relation it is known that cholesterol is an active antihemolytic agent.

From every viewpoint, cholesterol is one of the most important substances present in the body. That man can synthesize cholesterol is probable. The indications are that he does not, all of the cholesterol which he needs being ingested. Milk, eggs, and pork fats are the important sources in the human diet. The presence of cholesterol in large amounts in spores, seeds, pollen ova, and sperm has been referred to as indicating specific needs for the embryo for this substance. Egg yolk, which is rich in cholesterol, is intended for the embryo. Milk is intended for the infant. Man is the only animal that dies in early life from coronary sclerosis and acquires atherosclerosis almost universally in advanced life. (74)

Rabinowitch has shown by laboratory study and statistical analysis of a large number of known cases of diabetes that there is an increased amount of plasma
cholesterol in arteriosclerosis which is constantly higher than normal. The duration of the disease, the age of the patients, type of treatment were all considered and the summarization of the evidence makes it appear reasonable to conclude that excess blood cholesterol is an important etiological factor in the production of arteriosclerosis in the young diabetic. When the cases were grouped according to age, the average cholesterol of those with cardiovascular disease was 46 milligrams higher than that of the group with no detectable vascular disease. Expressed as percentage difference, the average cholesterol in the cases with cardiovascular disease was about 20 per cent higher than those in which no vascular changes were found by very careful general physical examination, examination of the fundi, roentgen ray examination of the lower extremities for calcification of the arteries, and roentgen ray examination of the heart. (62)

Chemical analysis for the cholesterol content of a portion of the aorta of a young man, age 27, who died of coronary disease after having had comparatively mild diabetes for the previous eight and one-half years was done by Cullinan and Graham. Treatment had been with insulin and a low carbohydrate-high fat diet (C. 25,
The results of the analysis showed the cholesterol content to be 5.832 per cent which shows the affected aorta in this case to contain about nine times as much cholesterol as a portion of a normal aorta of the same age. (16)

A series of chemical analysis for cholesterol is reported by Lehnherr. The examination of twenty-five diabetic aortas, twenty-five non diabetic aortas and six children's aortas showed that the changes were similar in the diabetics and non diabetics, but that there was a greater deposition of lipoid, a more marked change in the lipid allocation (increased proportion of the total lipid as cholesterol and a diminished proportion of the total lipid as fatty acid and as phospholipid) and a higher calcium and phosphorus content was 8.07 gr. per cent in diabetics as compared with 4.8 gm. per cent in non diabetics. (41)

Menne, Beeman, and Labby state that atheromatous lesions always contain cholesterol, whether in herbivorous or in omnivorous animals. The process in man is comparable with that seen in animals. Any conditions which lowers metabolism in man or animals will result in abnormally increased amounts or altered states of cholesterol in the blood and will further
its deposition. They believe this to be the essential factor in the production of arteriosclerosis. The disease does not develop in those conditions which tend to deplete the blood of cholesterol. Two essential factors in the production of atherosclerosis are hypercholesteremia and mechanical stress. Once the infiltration of the substance into the tissue spaces and the lymphatic chains of the vessel wall is begun, its accumulation there will serve to produce a vicious circle of destruction, absorption and defensive regeneration. (51)

That it might not be the insulin producing portion of the pancreas that is at fault in the production of high cholesterol levels is shown by the work of Samuelson. He has used insulin free pancreatic extract in cardiovascular arteriosclerosis manifested by angina pectoris of precardial pain and intermittent claudication in peripheral vascular diseases. Before treatment the average cholesterol level was 275 mg. per 100 cc. An average dose of 5 cc. was used and within an hour following injection there was a lowering of plasma cholesterol of 40 mg. per 100 cc. and it did not return to its former level for about 24 hours. Some clinical improvement accompanied the lowered cholesterol level. The blood sugar level remained unaffected. (71)
Production of Atherosclerosis

As atherosclerosis is studied a general resemblance to other metabolic diseases, especially diabetes is seen. As in diabetes, marked variations in susceptibility are evident in the experimental animal and seem to exist in man. As in diabetes the inheritance of a weak cholesterol metabolism appears to lead to early death from coronary sclerosis. There are families in which coronary disease is the standard form of death. As in diabetes, advancing age with growing inefficiency of the cholesterol metabolism is associated with more frequent manifestations of the disease. Finally a familial inheritance which seems to be dependent on a general inferiority of the metabolic systems may manifest itself in individuals of such a family in the form of diabetes, obesity, arteriosclerosis, gout or combinations of these. (39)

Atherosclerosis can be produced readily in the rabbit by overwhelming its weak cholesterol metabolic system by feeding excess cholesterol. The same procedure, i.e., the overwhelming of the cholesterol metabolic system, was unintentionally carried out in human beings by the use of high fat diets in diabetes, in the decade 1930 to 1930, and the results were just as definite as
those obtained in the experimental rabbit. It was rea-
soned that fat could be substituted for carbohydrates
and thus spare the inefficient carbohydrate metabolism
in diabetic patients. The reasoning was good. Unfortun-
ately the simplest method of increasing fat was to add
cream, butter, and eggs, all wholesome foods but potent
sources of cholesterol, to the dietary. The effects of
the excessive cholesterol diet manifested itself in an
increase of arteriosclerosis, even in children, and xan-
thomas were more common in the skin. (39)

The method by which the lipid reaches the intimal
layers of the arteries is still questioned. Warren
believes that edema of the intima occurs with stretch-
ing and swelling of the endothelium. This could well
favor the introduction of foreign material. The high
sugar concentration and the great fluctuation in sugar
concentration in the blood of persons with diabetes
could possibly lead to swelling of the intimal ground
substance through changes in the osmotic pressure and
thus favor lipid imbibition. (85)

The atheromatous process is the fundamental one
in production of arteriosclerosis and the most accepted
explanation of the process is that one advanced by
Asgaard.
In the earliest stages, there appear on the posterior wall of the aorta very fine yellow streaks or spots, which are opaque and not at all elevated. The longer the process lasts, the more distinct does the process become. Other changes which may be recognized macroscopically are not seen. Outside of these changes the aorta is normal. (5)

Microscopically the atheromatosis begins as a peculiar fatty change in the elastic stria terminalis, in the deep layers of the intima. This fatty change consists of a granular deposition of choleseterin esters in the cement substance of the elastic fibers which compose the stria terminalis. The entire process can be interpreted only as a sort of loosening and swelling of the cement substance with a simultaneous deposition of fat droplets. As the process continues it extends to the surface until it reaches the endothelium where the affected area begins to swell at the surface.

The fat deposited has been demonstrated to consist of cholesterol esters. Since this can not arise from a transformation or decomposition of the elastin or collagen of the intima, it must be derived from an infiltrative process. The only source for such an infiltration is the blood plasma itself. This nourishes the
inner layers of the vessel wall through a kind of imbibition stream. The condition necessary for an increased invasion is a loosening of the tissue elements. This is intimately associated with physicochemical changes present in the blood stream. However the fact that the process begins just at the origin of the intercostal arteries indicates that mechanical factors permit an easier inflow of blood plasma. The fact that these deposits develop in a line parallel to the direction of the blood stream supports this conception. There is a second factor that must be present before atheromatous plaques may appear. This is sufficient concentration of lipoids, especially of cholesterol esters in the plasma. From plasma of low cholesterol content no deposition of lipoids will occur, even though mechanical conditions are favorable. (5)

The localization of the atheromatous patches in the intima is explained by the existence there of particular circumstances favorable to swelling precipitation. Thus the elastic stria terminalis is the first densely woven membrane that the invading stream of plasma meets, and it serves as a filter. In it the elastic fibrils are separated by a molecular change in the cement substance. This slowing of the imbibition
stream allows the precipitation and absorption of the lipoids. When the tissue cells and the intracellular substance become overloaded with lipid substance, necrosis occurs. In the necrotic tissue there is progressive splitting up of lipid elements in particular. The cholesterin ester decomposes, the cholesterin is freed and crystalizes out. The fatty acid forms soaps, the most important of which is the calcium soap since this leads to calcification of the atheromatous deposit and develops the picture of atherosclerosis. (5)

Relationship of Hypertension

The frequency of hypertension in diabetes is common, 39 per cent of a series of 500 of Kramer's cases showed a blood pressure over 150 mm. of mercury. Much discussion as to cause has been offered. Some have maintained a common etiology of diabetes and hypertension is present. Others suggest that the factor of obesity causes both hypertension and diabetes. A further suggestion is that the hypertension causes the diabetes. In this survey the correct causal position of hypertension in diabetes is important in evaluating the effect upon the production of arteriosclerosis.
The presence of hypertension in diabetes may be attributed to various factors: The pathogenesis of these conditions is practically the same. The factors which tend to bring about an increase in blood pressure are usually thought to include errors of diet, (metabolic disturbances), mental unrest (prolonged mental strain), wear and tear, endocrine disturbances, low grade infections and nephritic conditions. The causative factors responsible for the development of diabetes may be briefly enumerated as follows: neurogenic, embracing prolonged mental strain, constant worries and nervous shock, endocrine disturbances, hereditary influences, race, acute and low grade infections, dietary indiscretions, and obesity. The same conditions which have brought about hypertension, may eventually produce diabetes. (34)

Schwartz insist that no direct relation exists between hypertension and diabetes. However hypertension may be a indirect factor in the causation of diabetes. Prolonged hypertension may cause arteriosclerosis involving the vessels of the pancreas and cause a disturbance in the internal secretion of the pancreas and result in diabetes. The reason that there is so many hypertension patients among diabetics is be-
cause the disease occurs more frequently among women than among men and hypertension is also more common in women. (74) There appears to be a period of arterial hypertonia for a variable length of time before the appearance of glycosuria and other clinical signs of diabetes. As a general fact the hypertonia continues for several years after the onset of glycosuria and then decreases in proportion to the length of time the patient gets further away from the clinical onset of the diabetes. (46) The role of inherited constitution has been emphasized in relation to hypertension. The predisposition to diabetes is also inherited as a Mendelian recessive characteristic and possibly a tendency toward vascular disease is also inherited in the diabetic. (65)

Study was made of a group of patients exhibiting the obese-hypertensive-hyperglycemia syndrome by Musser and Wright. The average increase of blood pressure in the obese patients were 12 degrees for men and 22 degrees for women over a control group of non-obese patients. Statistical studies appear to show a frequent association of obesity and diabetes or arteriosclerosis or both. Some 80 to 90 per cent of diabetic patients appear to be or were over weight before the diabetes began.
Diminished sugar tolerance was found in the obese patients. The fundamental basis for the syndrome seems to be obesity with its diminished sugar tolerance, and with the overweight condition there is an increased blood volume, cardiac output, and an elevation of blood pressure and finally arteriolar sclerotic changes which intensify the blood pressure. (53)(87)

Rosenbloom feels that the hypertension in diabetics is secondary to other changes. He analyzed the findings of 140 cases of diabetes mellitus and in everyone in this series where there was present a high blood pressure there could be demonstrated that an existing nephritis, arteriosclerosis or aortitis was present. He concluded that a high blood pressure in diabetes was due to a chronic nephritis, arteriosclerosis or a cardiac hypertrophy and not the cause. (67)

Enklewitz prefers to regard diabetes in people past the age of forty years as a manifestation of degenerative heart disease. The reasons expressed in support of this suggestion are: It has never been satisfactory proven that abnormal metabolism favors or hastens the production of atherosclerosis; it was not proven that experimental cholesterol atherosclerosis
represents human arteriosclerosis; the rarity of young protracted diabetics developing coronary sclerosis; and the inability of the advocates of premature arteriosclerosis to agree among themselves as to the incidence of arteriosclerosis in young patients as diagnosed by the X-ray. Further evidence is the high percentage of abnormal sugar tolerance curves in the aged and senile patients who show no other evidence of diabetes but rather signs of failure of the other organs of the body. The opinion is expressed that both coronary thrombosis and diabetes in individuals over the age of 40 years are manifestations of degenerative heart disease. By so doing, the metabolic disorder is minimized and the condition of the vascular tree properly stressed. (19)
SYMPTOMS

The appearance of the pathological lesions are so gradual and the onset of the arteriosclerosis is so insidious that the symptoms of the process are so very few and relatively unimportant compared with the serious ofness of the condition.

Pain

Pain is the most important single symptom of arteriosclerosis. Careful questioning may reveal a history, sometimes years before, of pains in the lower legs, especially when walking and of such severity that the patient had to stop or sit down until they disappeared. Such a history of intermittent claudication suggests a period of interference with the normal blood supply to the legs and, if no longer present, indicates the establishment of a fairly extensive collateral circulation rather than a cure of the disease. The location, character, and intensity of the pain associated with the lesion is of utmost importance. There may be less pain than one would expect from the extent of the local process or the pain may be all out of proportion to the external lesion. In general, it can be said that the longer the duration, the more constant and severe the pain, the
poorer the prognosis so far as the viability of the
limb is concerned. (49)

More often than the pains of claudication the
patient complains of fatigue after walking short dis-
tances. Shooting pains, numbness, and burning are also
complained of by the arteriosclerotic, particularly at
night. (55)

Neuritis

Peripheral neuritis often occurs with advanced
arteriosclerosis. In fact, the loss of vibration sense
over the toes is to be expected. This is the earliest
change in the peripheral neuritis that accompanies art-
eriosclerosis. Later there is a loss of pain, and still
later loss of touch. (55)

Hyperesthesia is common in arteriosclerotic gang-
rene with or without an open lesion. Some patients can-
not bear the touch of the bedclothes and the slightest
touch with the examining finger is extremely painful.
On the other hand hypoesthesia is frequently seen par-
ticularly with a foot of good color with fairly extens-
ive arteriosclerosis but usually good pulsation in the
dorsalis pedis artery, (49)
COMPLICATIONS

An analysis of the pathological conditions causing death of diabetic patients since 1930, showed that diabetes was solely and directly responsible for death in 6 per cent of the cases; the remainder being due to degenerative complications, coronary sclerosis, nephritis, apoplexy, and gangrene, and infections, or the consequences of operations. (88) (85) Of the arteriosclerotic complications coronary disease accounted for 30 per cent, apoplexy 10 per cent, gangrene 8 per cent, and all other infections 12 per cent. (85)

Coronary Disease

The essential cardiac lesion of diabetes is coronary sclerosis. Other types of cardiac disease are of relatively rare occurrence. This was recognized as early as 1904 by Tyson who remarked that the involvement of the coronary arteries by sclerosis may account for the cardiac asthma and angina pectoris which are found occasionally in diabetes. (82) In a recent analysis of 100 autopsies upon diabetics there was found an incidence of 41 per cent of severe coronary disease. Above the age of 50 years the incidence was 53 per cent compared with 8 per cent in an
even larger series of non-diabetics of the same age. The frequency of the coronary disease is almost as high in the female as in the male. The incidence of coronary disease is higher in patients with gangrene than in uncomplicated cases. (54)

Raab and Rabinowitz have found some non-diabetic coronary findings that may confuse the diagnosis of the condition and increase the statistics in favor of coronary disease in diabetes. In all of their recent cases of coronary thrombosis in non-diabetics there was an abnormal response to the sugar tolerance test. The glycosuria and hyperglycemia of the acute stage of coronary thrombosis was not dependant on latent diabetes but due to a transient disturbance of the vegetative centers in the brain. (60)

Gangrene

Gangrene signifies the death of microscopically visual portions of the body. It is one of the most serious complications of diabetes, both from the nature of the lesion itself and from the wide path it opens to septic invasion of the body.

Gangrene is merely a localized manifestation of systemic pathology caused by a generalized degeneration of the whole vascular tree. The underlying vascular change affects all the vessels of the body from the
thoracic aorta to the finest radicles but is most marked in the peripheral arteries especially those of the lower extremities. The non gangrenous parts of the vascular tree are still in a state of compensation but with a small margin of safety. The systemic reaction of arteriosclerotic gangrene is considerably more important than the local reaction. Certain definite factors, extent and duration of the gangrene, the presence of a systemic febrile reaction before operation, the site of amputation, the development of recurrent gangrene, and infection or slough of the stump materially affect the mortality rate.

The extent of the gangrene has a two fold significance. It bears a direct relationship to the degree of vascular occlusion, and it also is an index of the duration of the process. Since arteriosclerotic gangrene is known to travel slowly, it may reasonable be assumed that a patient who has gangrene confined to one toe or several toes either has less vascular occlusion or a disease of shorter duration than a patient who has gangrene involving the whole foot. Delay in treatment, either due to the hesitancy of the patient to present himself to the surgeon for care or on the part of the surgeon in attempting to practice conservatism, greatly increases the mor-
The mortality rate.

It is entirely reasonable that the exciting cause of the gangrene should definitely influence the mortality rate and spontaneous gangrene should carry a higher death rate than the traumatic variety. Many patients whom trauma is the exciting cause have an adequate peripheral circulation in spite of their disease. The trauma is accidental and extrinsic. The general condition, therefore, is better, and they have a correspondingly greater chance of survival than the patients whose gangrene has developed spontaneously as a result of the disease. (83)

There are two clinical groups of gangrene recognized: (a) That in which the condition is primarily due to deficient circulation; (b) that in which the condition is primarily due to infection. The most dangerous cases are those with deficient circulation and a superimposed spreading infection. Although the infection may be the predominating factor and is the precipitating cause of death in many of these cases, it is the fertile soil provided by diabetes and imperfect blood supply which makes them so prone to develop blood stream infection. (49)

The symptoms and signs of infection and gangrene are not marked. Even with very extensive in-
volvement very little temperature or tissue reaction is present.

A variety of lesions, rose spots, scars, scarlike depressions, blebs, and small areas of gangrene may be found on the extremities of diabetics. These are not necessarily new developments in this disease but their significance has not been sufficiently emphasized.

These are observed among diabetics who are past middle life, who have a tendency to persistent hyperglycemia and who clinically present evidences of impaired circulation in the extremities.

Almost invariably when the lesions are present, a history of circulatory impairment such as pain, coldness, cramps in the legs, and such findings as pallor of the feet, absence of dorsalis pedis pulsation and sclerotic changes of the vessels are obtained.

The appearance of the lesions, their subsequent course and the presence of symptoms and signs which are definitely associated with circulatory disturbances, all seem to favor the theory that the lesions are the results of pathologic changes in the smaller vessels.

Some of the patients who presented these lesions in one form or another, later developed gangrene on
a larger scale. This development, together with the assumptions that the lesions are evidences of arteri­ial changes, leads to the suggestion that they be looked upon as early warning signs of impending gan­grene. (35)

Trauma is the most important factor in the actual precipitation of gangrene. Trauma need not be extensive but occurs in many forms. Careless paring of a corn or callus, injury to the toe when caring for the nail, failure to care for a small blister, ill fitting shoes, all have been guilty of production of the lesion. In the majority of these cases the result would be of relatively little consequence if infection did not set in. It is the infection secondary to some minor trauma which undoubtedly is the deciding fac­tor as to whether gangrene shall or shall not develop. Trauma due to chemicals is of importance. Frequently a minor injury over zealously treated with strong tincture of iodine becomes a process of great impor­tance. (49)

Differences of opinion are expressed concerning the influences of climate. Exceedingly cold weather seems to put added insult on the already deficient circulation and predisposes to the gangrenous lesion.
Vasodilation of the smaller vessels of the lower extremities occurs when the body and upper limbs are warm and in the normal individual vasoconstriction when the body is cold. Every effort should be made to keep the collateral paths dilated in the arteriosclerotic. It is not only important to keep the limbs warm but the whole body should be protected. (55)

Sex is probably an important factor in the etiology of gangrene only as men are more exposed to trauma than are women. The average age of onset of gangrene is 64 years. The incidence as to decade is as follows: (49)

- 40 to 50 years: 3.8 per cent
- 51 to 60 years: 25.4 per cent
- 61 to 70 years: 55.7 per cent
- 71 to 80 years: 15.2 per cent

All cases of gangrene in diabetic patients, except some of embolic or infectious origin depend primarily on arteriosclerosis. The vascular process precipitating gangrene is nearly always preceded by a gradual narrowing of the lumen of the vessels by the arteriosclerotic process predominantly involving the intima. The reaction of the extremity to such arterial occlusion is: (1) The formation of extensive collateral circulation in an attempt to reestablish
circulation to the part, in many cases utilizing the portions of the longer vessels which are below but not completely occluded by the thrombus. The gradual development of this occluding process allows the collateral vessels to become fairly well opened before the extremity is forced to depend entirely upon them for this blood supply. This period of reorganization is frequently suggested in the patient's history by cramps in the legs on walking, running or climbing stairs which disappear after rest. (2) The onset of gangrene; if the occlusion has been more or less sudden or so high that too much blood supply is shut off at one time gangrene of one or more toes will develop. It is in such a foot where the collateral circulation has not developed that clinically a definite level of sudden temperature, and usually color change, can be demonstrated.

If the patient's extremity has developed a fairly adequate collateral circulation it is able to carry on with a narrow margin of safety for years. If, however, a minor injury occurs, or a break in the skin becomes infected, thrombosis of the small but important vessels may result and gangrene appear. Local resistance, diminished by a scant blood supply
and diabetes, is insufficient to localize the process, especially if the offending organism is a streptococcus, and lymphangitis, phlebitis, or even septicemia may result. (49)

Cardiac Collapse

In the presence of sclerosis of the coronary arteries the available supply of carbohydrates, as of other substances, to the myocardium may be reduced to an inadequate level because of insufficiency of the coronary circulation. This result is even more apparent when deficiency of the coronary circulation is associated with a disturbance in metabolism affecting the utilization of carbohydrates, as in diabetes mellitus. Hypoglycemia occasionally results from the use of insulin even though caution is exercised regarding the dosage. In individuals with a damaged myocardium, during periods of hypoglycemia, various disturbances in the cardiac mechanism, such as premature contractions, auricular fibrillation, dropped beats, bundle branch block and pulsus alternans occur.

The deleterious action of insulin on the heart is probably not due to a direct toxic action on the myocardium but is probably related to the supply of carbohydrate that is readily available to this organ.
The function of insulin is its ability to cause the storage of carbohydrate in the tissues of the organism. It may be supposed that the damaged myocardium stores dextrose only with difficulty, then the lowering of the blood sugar by insulin will decrease or remove the heart's source of dextrose supply without at the same time stocking up the myocardium with its carbohydrate needs for the interim. Insulin is not in itself harmful to the elderly diabetic patient with cardiovascular disease but in the patients receiving insulin, the carbohydrate supply to the damaged myocardium is of the greatest importance. (73) (42)
PROGNOSIS

Physicians can not conquer old age but they can conquer premature old age and the damage which arteriosclerosis produces is preventable. The diabetic patient can be protected from gangrene as he formerly was of coma. The diets are gradually approaching the normal, while diabetic symptoms are held in abeyance by insulin and exercise to the diabetics should live about as long as the average individual. While it is yet too soon to say, never-the-less the hope is justifiable that today the only diabetic to develop premature arteriosclerosis may be the neglected diabetic. Arteriosclerosis is so prevalent that it may be considered almost a physiological accompaniment of old age. The absolute prevention of arteriosclerosis in diabetic patients is an ideal that will probably never be attained; the prevention of premature arteriosclerosis is attainable. The diabetic has not only more than his share of arteriosclerosis, but it falls to his lot ten or twelve years earlier than to the non-diabetic. This premature arteriosclerosis must be prevented. (32)(85)

One of the most constant characteristics of the high carbohydrate diet is an immediate and sustained decrease of plasma cholesterol. Since Rabinowitch has
shown that hypercholesterolemia is an intimate causal factor in the production of arteriosclerosis a regime that controls the diabetes and maintains a high carbohydrate-low caloric diet should greatly decrease the incidence of cardiovascular disease in the young diabetic. This type of diet seems not to have any bad effects.

Joslin observes that "diabetic children are precocious in height, weight and mentality; the offspring of diabetic mothers tend to be large; our cardiac specialists give glucose for angina pectoris, our surgeons depend upon glucose; when the blood sugar is low, diabetics and this applies to non diabetics also, are mentally sluggish and faint. Our blood sugar may rise normally after meals to an extent we should term a diabetic blood sugar if taken before a meal. I wonder if a little hyperglycemia now and then may not be a good thing." (62)(32)

The outlook is always bad in cases of arteriosclerotic gangrene of the diabetic type. As a rule the patients are advanced in years. The arteriosclerotic process is intense. The vitality seems to be diminished, both by virtue of the condition of the vessels, as well as by the general systemic condition of the patient. In spite of the best conservative treatment, failure to heal even
a small ulcer is common, and extensive subacute phlegmonous formation is to be expected in many of the cases. Even when a line of demarcation has developed, the spontaneous sequestration of the part and spontaneous healing is only to be regarded with a degree of hope in those cases where but a small part is involved, such as a toe or a part of a toe. (12)
PROPHYLAXIS

Those diabetics past fifty years of age especially those with arteriosclerosis, will do well to elevate the feet while sitting. Legs should not be crossed for long at a time. Circular garters which compress the blood vessels to the legs should not be worn. Frequent shifting of the position of the legs will help promote circulation. Some daily form of exercise is desirable. Walking is the best form of exercise for the adult. Swimming, golf and riding may be indulged in. (72)

The position of the resting limb in all forms of obstructive arterial disease is of importance. When the foot is in the horizontal plane it will be noted in arterial disease that there is a marked variation from the normal color. Any color disturbances seen must be interpreted as attesting a circulatory insufficiency in this position. Such limbs are not to be allowed to stay, during their period of rest, in the horizontal position, but somewhat depressed just enough to bring about color evidences of circulatory activity. The angle at which the normal color returns is determined by trial and is to be the position of rest even while sleeping. Ischemia is almost as harm-
ful as is continued stasis caused by prolonged standing or walking. A position of elevation universally regarded as harmless must be avoided because of its depleting effect. (12)

A list of rules that must be carefully observed to minimize the chance of developing trophic disturbances and gangrene are of practical importance. First, walking for great distances should be avoided, particularly if there is a history of intermittent claudication, cold extremities, previous attacks of gangrene, or trophic disorders, together with the objective findings by the physician pointing to impaired circulation, such as ischemia, pulseless vessels, or erythromelalgia. Second, exposure to cold with possible frost bite is dangerous; even moderate degrees of cold are poorly borne. Third the wearing of tight shoes should be carefully shunned. Whenever possible, a sojourn in a warm climate will be found beneficial. Fourth, all manipulations, such as cutting corns, callouses, ingrown toenails, bunions, should be left to a physician or surgeon, for the beginning of trouble is often traceable to the manipulations of a pedicure. Fifth, the smallest injury should be scrupulously cared for by a competent surgeon. Sixth, daily cleansing of the feet,
with more than ordinary care, and the use of a sterile
dusting powder should be insisted upon. Seventh, tob-
acco and alcohol should be indulged in with great mod-
eration or not at all. (12)

The vasoconstricting action of smoking has been
thoroughly demonstrated clinically and experimentally.
For this reason it is advisable to prohibit completely
the use of tobacco in all forms of peripheral arterial
disease. Fortunately this is not as great a problem in
diabetic arterial occlusion as in other forms of art-
erial disease. (70)

Proper Diet

There are those who believe that the high carbo-
hydrate diets prevent the occurrence of arteriosclerosis.
It is generally admitted that one hundred grams of
carbohydrate is the least that the diabetic patient
should have. But the statement that from two hundred
and fifty to four hundred grams of carbohydrate a day
is necessary to prevent arteriosclerosis has not yet
been proven. The probability of hyperglycemia and
glycosuria make these high carbohydrate diets a source
of danger to the diabetic. Until proof is brought
that high carbohydrate diets do prevent arteriosclerosis,
one can say that the moderate amounts of carbohydrates and fat with constant control of the blood sugar offers the diabetic the best insurance against formation of arteriosclerosis and development of gangrene. (55)
TREATMENT

The treatment of arteriosclerosis is not exceeding productive of results because of the nature of the processes that are present. The lesions are for the most part irreversible and any improvement is by producing compensatory changes rather than altering the pathology that is already present. Some of the means of treating the disease are by using methods of enhancing the circulation by postural methods, application of suction-pressure to the extremities, diathermy, and hot air to the affected parts. Dietary treatment is an important consideration. Consideration of the problem of coronary sclerosis and its treatment may be of value. The management of the diabetic gangrenous extremities whether conservatively or by surgery is a related consideration. The uses of insulin and pancreatic extracts have been practical in the treatment of the arteriosclerosis.

Methods of Enhancing the Circulation

Certain passive exercises may be of value in inducing hyperemia or rubor in the affected limb and therefore be therapeutically beneficial in increasing the blood supply. This therapeutic measure, if carried out daily for a sufficiently long period of time, is
of greater value in improving the circulatory conditions and in increasing the blood supply than any other mechanical or thermal means available.

The procedure is as follows: The affected limb is elevated with the patient lying in bed, to form 60 to 90 degrees above the horizontal, being allowed to rest upon a support for from 30 seconds to 3 minutes, the period of time being the minimum amount of time necessary to produce blanching or ischemia. As soon as blanching is established, the patient allows the foot to hang down over the edge of the bed for from 2 to 5 minutes, until reactionary hyperemia or rubor sets in, the total period of time being about 1 minute longer than that necessary to establish a good red color. The limb is then placed in the horizontal position for about 3 to 5 minutes, during which time an electric heating pad or a hot water bag is applied, care being taken to prevent the occurrence of a burn. The placing of the limb in these three successive positions constitutes a cycle, the duration of which is usually from 6 to 10 minutes. These cycles are repeated over a period of one hour, some 6 to 7 cycles constituting a seance.

The number of seances cannot be categorically stated but should vary with the case. In a general
way they should occur at least 6 to 7 hours a day, that is, every alternate hour during the daytime. During the hours of rest, heat is applied continuously in the form of an electric pad, hot water bag, hot air apparatus, or electric lamp.

The length of time of its application may require modification according to the manner in which the procedure is borne. In some cases pain induced by elevation may necessitate a diminution in the period of elevation. It is not possible to lay down hard and fast rules as to the exact application of this method in any given case. Its employment should be varied according to the requirement of each and every clinical stage and the patient's response. The most reliable immediate measure of the efficiency of the method is the change in color in the leg, the disappearance of trophic disorders, and the subjective state of the patient. All these should govern the treatment qualitatively.

Suction and pressure therapy has been used in the treatment of patients with peripheral vascular disease. The treatment can be instituted in hospital or outpatients presenting the symptoms and signs of arterial occlusion. During the treatment the patients sit or recline in bed. The affected extremity is inserted
into an aluminium chamber and lays in the horizontal plane upon a pillow in the bottom of the chamber. The thigh, protected when necessary by a layer of gauze bandage, is encircled at a point approximately six inches above the knee by a rubber cuff with two leaves, one sealing during pressure, the other sealing during suction. A layer of adhesive tape is applied to each cuff to keep the rubber in close contact with the skin. Suction amounting to between 80 and 120 mg. of mercury is applied for 25 seconds alternating with positive pressure of 40 to 80 mm. of mercury for 5 seconds.

In general when rest pain is severe or when ulcers have not yet begun to heal, the affected extremities are exposed to suction and pressure for one to two hours twice daily. After rest pain diminishes somewhat and after ulcers have begun to heal, the duration of treatment is reduced to one or two hours at first once daily and then three times weekly and finally to one of two hours once weekly. Out patients with relatively mild symptoms may be treated for periods of one or two hours three times a week or less.

The results of the treatment show that cyanosis is usually diminished; symptomatic improvement is sometimes observed, however, without significant change in skin color. The rest pain of ischemia is usually
abolished during actual use of suction and pressure and gradually becomes less severe in the intervals between exposure to the pressure variations. Ulcers, enlarging or indolent under ordinary conservative treatment, usually begin to heal soon after suction and pressure therapy is instituted. Intermittent claudication becomes in general milder and exercise tolerance is definitely increased.

Suction and pressure therapy appears to be a worthwhile addition to the other conservative methods of treating peripheral vascular disease. Good results can be obtained even when organic obstruction has advanced to the stage in which arterial blood flow can no longer be increased by measures depending on vasodilation.

The poorest results in the arteriosclerotic groups are those suffering from the diabetic type. In the series, however, 40 per cent show "good" results, including obliteration of rest pain, distinct lessening of claudication and the complete healing of indolent ulcers; 20 per cent show "fair" results, indicating almost, but not quite, relief of rest pain and healing of the lesions; and 40 per cent are "poor" results which is relief of symptoms immediately during the treatment but not between treatments. (37)

The diathermic treatment may be tried in the dia-
abetic arteriosclerotic cases, if thrombophlebitis, extensive gangrene, phlegmon, ulcer, and infection are not present. It is, therefore, limited in its usefulness to those early cases in which symptoms of intermittent claudication are present together with threatened trophic disorders and gangrene, without actual gangrene or ulceration.

A method of employing this type of treatment is to seat the patient on a chair with each foot in a basin of warm salt water. Each basin is connected with one of the poles of the diathermic apparatus. This can be done simply by putting an electric plate electrode with connective wire into the water. The current is then turned on and increased according to the sensation of the patient, usually to about 700 M. A. The duration of treatment is from 25 to 30 minutes. The frequency depends upon the reaction.

The patient will feel the development of the heat in the region of the ankle, where the effects of warmth can be demonstrated by the touch. Subjectively, there is in addition to the feeling of heat, a dull ache which should not be allowed to become marked. Pain is a sign for diminishing the strength of the current. (12)
Hot air treatment may be used on the extremities and must be very carefully applied, and should exclude the part affected by trophic disturbances or gangrene. The temperature should be gradually elevated, being no higher than 125 degrees to 150 degrees F. at the beginning of treatment, and raised no higher than 220 degrees. Seances of 15 to 45 minutes, 3 to 6 times a day have given good results; Great care must be exercised in the use of hot air to avoid burning the patient, since dire results may follow such additional insult to the already damaged part.

The application of heat by means of special lamps will find use where a hot air apparatus is not obtainable. So also an electric thermophore is a valuable aid to other methods of treatment, and should be wrapped around the thigh and leg over a flannel bandage, the temperature being controlled by a thermometer.

It has been found advisable to alternate the postural treatment with hot air application, so that varying amounts of each type will be received by the patient each day. The reactionary circulation induced by the heat is not sufficiently intensive or lasting to be of appreciable service when one or two short daily applications are given alone. (12)
Treatment by Diet

One very important factor in any consideration of arteriosclerosis in diabetes is the change that dietary treatment has undergone since the introduction of insulin. The foundation for clinically demonstrable arteriosclerosis is laid months or years before it becomes manifest. The sclerotic diabetics of today are reaping the harvest sown long before by inadequate treatment or neglect of the diabetic condition.

Joslin summarized the stages of treatment through which his patients have passed. The average daily diet was:

In 1915-1916: Carbohydrate 26 grams; Protein 60 grams; Fat 82 grams.

In 1916: Carbohydrate 43 grams; Protein 60 grams; Fat 82 grams.

In 1916-1917: Carbohydrate 43 grams; Protein 60 grams; Fat 90 grams.

In 1923: Carbohydrate 71 grams; Protein 58 grams; Fat 123 grams; with 13 units of insulin.

In 1927: Carbohydrate 96 grams; Protein 60 grams; Fat 13 grams; with 21 units of insulin.

In 1930: Carbohydrate 125 grams; Protein 63 grams; Fat 92 grams; with 23 units of insulin.

In 1937: Carbohydrate 160 grams; Protein 80 grams;
Fat 99 grams; with 18 units of protamine insulin.

In 1938: Adults; Carbohydrate 147 grams; Protein 69 grams; Fat 87 grams; with 38 units of protamine insulin.

In 1938: Children; Carbohydrate 199 grams; Protein 83 grams; Fat 96 grams; with variable amounts of protamine insulin.

In other words, the patients are steadily approaching a balanced normal diet. With each progressive step, some of the abnormal factors that may tend to produce arteriosclerosis are being reduced. (33)

Gray and Sansum have suggested the use of average diets containing 300 to 400 grams of carbohydrate or a ratio of 3:1 to 4:1 of carbohydrate over the fat.

Under this type of diet regime all the patients reported a sense of increased well being and physical fitness. The writers feel this type of diet will materially decrease the incidence of arteriosclerosis and the amount of insulin required will gradually be decreased to the improvement of the patient's condition, but no statistical proof is available as yet. (21)

Sansum has also used a diet in the treatment of high blood pressure that consists of alkaline-ash foods and one which is also low in protein and fat. This diet consists essentially of fruit, vegetables,
and milk. Milk and its products adequately replace meat, but patients miss the cereal products. Flour made up of lima beans have somewhat satisfactory replaced cereal flour in cereals and breads. On this type of diet the blood vessel complications of diabetes improve to the same degree as they apparently do in patients with high blood pressure not complicated with diabetes. In cases of gangrene of the toes with this type of treatment the leg is frequently saved by amputating one or more toes rather than having to resort to leg amputation. (73)

Coronary Disease

The signs and symptoms of coronary disease are no different in diabetes than in others. The usual cardiac drugs have proved to be of limited value in the treatment of coronary heart disease in this instance. Drugs with vasodilator action, such as nitroglycerin, have been used, but most patients place more reliance upon restriction of activity and periods of rest.

Insulin administration in the diabetic patient with coronary heart disease should be accurately gauged on the basis of frequent blood sugar and urine analysis. A marked loss in carbohydrate tolerance occurs in some cases of coronary thrombosis, particularly
if congestive failure is present. Insulin therapy is of distinct value in such cases. (66)

Insulin Therapy

Ordinarily in treating a diabetic he is kept sugar free and the blood sugar is kept in the normal or near normal range. In treating arteriosclerotic diabetics and especially is this exemplified by the patient with coronary disease, this theoretical ideal must be radically altered. These patients have become accustomed to and require a blood sugar at a higher level in order to function properly. If the heart with diseased coronary arteries is subjected to an artificial lowering of the blood sugar it may respond with angina or signs of myocardial weakness. Coronary thrombosis has been reported in a number of instances immediately following an insulin injection suggesting an etiological relationship. The blood sugar level should be maintained at that level at which the patient is able to function best. (69)

The adverse results of the insulin therapy are, a fall of blood pressure, the heart rate tends to increase, extra systoles of various origins are induced, and in some cases typical attacks of angina pectoris are always precipitated. The electrocardiograph shows changes which are to be interpreted as
indicative of the development of intraventricular heart block. Almost invariably during insulin administration the patients complain of a decreased sense of well-being. The usual complaints were weakness, prostration, dizziness, nervousness, palpitation, precordial pain and constriction.

In these patients the symptoms seem to grow worse as the diabetes improves. It seems probably that the high blood sugar levels usually found represent the optimum value as far as the patient's cardiovascular state is concerned. The deleterious effects of the therapeutic use of insulin does not seem to depend so much on the absolute sugar level attained as on the extent of the change from the accustomed to the new blood sugar level and on the length of time over which the insulin was administered. (81)

The angina attacks probably are due to the depletion of glycogen from the cardiac muscle in the hypoglycemic states causing a decrease in the contractability of the muscle involved. It is only the toxic dose of insulin which causes these symptoms of hypoglycemia. Since insulin is able to deposit glycogen in tissues, it can be considered as a possible therapeutic agent in angina pectoris provided the toxic effect of vascular spasm and depletion of tissue gly-
cogen is strictly avoided.

In the consideration of the use of insulin as a therapeutic agent, the following principles should be employed to protect the patient against even the mildest form of hypoglycemic reaction:

1. Diabetic Control. The caloric value of the diet should be equivalent to the total energy requirement of the body allowing for muscular activity. The amount of carbohydrate to be 3 grams per kilo of body weight, the protein 1 gram per kilo of body weight and fat to make up the rest of the caloric requirement.

2. Insulin. Insulin should be started in small test doses which are gradually increased up to the point where sugar entirely disappeared from the urine or only appeared in traces.

3. Further Dietetic Measures. Since the duration of the insulin effect in its depression of the blood sugar is in direct proportion to the dose of insulin, a routine protective procedure of 15 grams of readily absorbable carbohydrate is given two hours after the dose of insulin to prevent insulin shock. With this procedure, hypoglycemic attacks become an extreme rarity.

By following this plan some patients have been entirely relieved of angina attacks, others have been
improved and none have been made worse. Insulin therapy should not be discarded in the diabetic with angina attacks when it can be used as a valuable therapeutic agent. (13)

The use of protamine insulin in the treatment of arteriosclerotic diabetic patients is full of dangers because of the increased danger of hypoglycemic reactions. If the cerebral vessels are markedly sclerotic there is danger of producing coma from depletion of glucose supply to the brain producing tonic and clonic spasms of muscles, and pathologic neurological signs. In cases of advanced coronary sclerosis, thrombosis and angina attacks are precipitated by hypoglycemia. The use of protamine insulin should be restricted to those who can be kept under rather constant supervision and control and proper cautions made to prevent hypoglycemia. (43)

Pancreatic Tissue Extract

Insulin free pancreatic extract has been used in cardiovascular arteriosclerosis manifested by angina pectoris or precordial pain and intermittent claudication in peripheral vascular diseases. Before treatment the average blood cholesterol level was 275 mg. per 100 cc. An average dose of 5 cc. was
used and within an hour following injection there was a lowering of plasma cholesterol of 40 mg. per 100 cc. and it did not return to the former level for about twenty-four hours. Some clinical improvement accompanied the lowered cholesterol level. The blood sugar level remained unaffected. For sustained effect and progressive drop in plasma cholesterol, patients require doses at frequent intervals. When treatment is interrupted or dosage is inadequate, the plasma cholesterol rises and there is an exacerbation of symptoms, precordial pain and intermittent claudication. This type of treatment is in the experimental stages and is not in wide use and final results after sustained use are not available. (71)

Treatment of Gangrene

It is important to differentiate between ulcers and infections of the lower extremities and gangrene of that region because the diagnosis of gangrene leads to amputation of many feet that could otherwise be saved. The majority of the patients with osteomyelitis and infection of the small parts may be discharged after comparatively minor operations. If there is limited gangrene without infection, prompt operation is not imperative but if there is present severe infection with loss of circulation
haste is imperative and a thigh amputation done early offers the only hope of a successful result. (14)

The indications for non-operative treatment of conditions due to deficient circulation are: (1) A superficial ulceration of gangrenous patch on the foot or lower leg with palpable pulsation in the dorsalis pedis artery, (2) a superficial lesion as above without palpable pulsation in the dorsalis pedis providing infection is slight, pain is not severe and the foot is warm and its color compares favorably with the other foot on elevation and depression, thus indicating the existence of an adequate collateral circulation; (3) a demarcated and apparently superficial area of gangrene near the tip of a toe with above conditions fulfilled, when time is no factor and when amputation of the toe might precipitate higher amputation; (4) failure to obtain first intention healing following any operation on a lower extremity provided spreading infection is absent; (49)

The object of local treatment of gangrene in diabetics is to prevent as far as possible, the development of secondary infection in the gangrenous area with its ultimate extension into the adjacent tissues. Cleanliness is of prime importance. Dressings should all be made preserving surgical asepsis. If there
are any purulent secretions wet mild antiseptic solutions, warm boric acid dressings, may be used. When the tissues appear relatively clean, a dry dressing or boric acid ointment may be applied. (70) Conservative treatment should also employ rest and warmth, with strict control of the diabetic condition through diet and insulin. Passive daily exercise as previously pointed out develop a remarkable compensatory collateral circulation which allows the healing and growth of granulation tissue in the lesion. (47)

Indications for amputation will depend upon whether conservative measures are successful or not, upon the general condition of the patient and on the severity of the symptoms. It will furthermore, be influenced by the rapidity with which the gangrene extends, and by the presence of a very extensive phlegmom that does not become arrested by conservative incision.

There is no unanimity of opinion regarding just where and when to amputate in cases of this sort. In general when conservative treatment has failed, which includes methods of enhancing circulation, conservative incisions, dressings, and amputation of small extremities, when gangrene shows evidence of progression, when no line of demarcation forms, and the suppur-
ative process threatens the patient, then amputation above the knee preferably at the lower third or middle of the femur is to be performed. The results of amputation through the thigh are fairly good in arteriosclerotic gangrene. Any ablation below the knee is so dubious in its outcome as far as ultimate healing is concerned, that nothing but the high gives a good chance of non extension. (12)

There are some arguments against amputation above the knee. In all amputations the mortality rises in direct proportion to the nearness of the point of amputation to the trunk, and it is seldom possible to fit an artificial limb satisfactorily above the knee. A pressure bearing stump can be obtained with but little difficulty but leverage to manipulate the leg is lacking. This is a point which cannot be overlooked. Usefulness after amputation is almost as an important consideration as is merely saving life. (45) (70)

In deciding upon the type of operation to perform, it is very important that the patient be considered as a whole with special emphasis on the condition of the well foot. Given a choice, as far as circulation is concerned, between a lower leg, a Gritti-Stokes or a thigh amputation, the surgeon should
select the one best suited to the immediate as well as the subsequent needs of the patient. Several points of importance in this connection are:

1. A thigh amputation is the simplest and safest operation.

2. The most serviceable stump is that following a Gritti-Stokes amputation.

3. The most natural gait after any amputation is obtained after a lower leg amputation.

4. Amputation through the lower leg is a safe and sound procedure if the circulatory condition of the leg has been carefully studied and found to be satisfactory. (49)

Sodium Chloride Therapy

Sandstead has prescribed oral administration of sodium chloride to diabetics with neuritis, 3 of his 13 cases having severe arteriosclerosis. The patients received sodium chloride (14 to 42 grams daily) over interrupted periods of 20 days to 6 months. All obtained relief of neuritic pain and definite improvement in circulation as shown by color changes and temperature increases in the feet and by the histamine test. In one patient there was satisfactory healing of an indolent ischemic ulcer of the foot.
while under the salt therapy.

No explanation for the action of the sodium chloride in producing the circulatory changes observed seems to be present. Studies of blood chloride, calcium, and cholesterol showed no changes. Urinary chloride output increased only in proportion to the amount given. (72)

It has been discovered by McQuarrie that ingestion of high amounts of sodium chloride per day, 60 grams or more, caused an increase in the systolic blood pressure of some 30 to 40 degrees and a marked decrease in the amount of glucosuria of diabetics. Discontinuance of the added sodium chloride caused a reversal of the picture. Potassium chloride was found to have opposite effects to that of sodium chloride. No clinical application of this therapeutic means to reduce the incidence of arteriosclerotic hypertension has been made. (50)

Evaluation of Therapy

There are limits to what any type of therapy or combinations can do. When occlusion occurs, collateral circulation develops quickly for about a year and continues to do so at a slower rate for at least two or three years longer. After this first period
the circulation remains at a remarkably stationary level for an indefinite number of years, during which the collateral circulation is maintained. In patients with arteriosclerosis there follows a third period, in which the collateral circulation itself becomes involved in the arteriosclerotic process, and a progressive diminution of circulation results. In the first period, treatment may accelerate the development of the collateral circulation, but it will develop without it. It is obvious that one must know to what stage the disease process has developed in order to evaluate therapy properly. (77)
SUMMARY

Since the advent of insulin therapy of diabetes mellitus the lives of the affected individuals have been prolonged but an increasing incidence of arteriosclerosis has occurred in these patients. This condition predisposes the diabetic to a termination by one of the cardiovascular complications, coronary disease, apoplexy, or gangrene.

Many associated etiological factors are connected with the process, obesity, hypertension, race, etc. but the underlying cause appears to be a faulty fat metabolism in the diabetic. There appears to be an altered cholesterol mechanism in these patients with an increase of this substance in the blood plasma and a deposition of it into the tissues of the peripheral arteries. The theory most widely accepted as to the manner of the deposition is the imbibition theory of Aschoff. The blood plasma carries an increased concentration of cholesterol and this substance infiltrates through the intima of the vessels causing a loosening of the ground substance and deposits on the stria terminalis causing the formation of atheromatous plaques which greatly increases the thickness of the intimal layer encroaching upon the lumen of the vessel and
ultimately occluding it. Once the cholesterol is present in the vessel wall a tissue response sets in which develops into sclerosis and associated calcification of the vessel wall. The process in the peripheral arteries differs from the arteriosclerosis of senescence in which the pathological process is situated in the medial layer of the vessel wall, and the lumen is not primarily affected. In the coronary arteries the pathological process is identical in both diabetic and senile arteriosclerosis.

The presence of this condition may be determined by palpation of the three peripheral arteries of the lower extremities, dorsalis pedis, posterior tibial, and popliteal. The absence of the pulsation of these vessels is indicative of their involvement by the obliterating process. Observation of the appearance of the extremity and the determination of a marked change in the temperature of the levels of the extremities also is indicative of vessel involvement. Roentgenological plates of the extremities and heart have some value in determining the diagnosis of arterial involvement by demonstrating calcium in the vessel walls. Symptoms are rather rare in this disease.
The prophylactic treatment of diabetic arteriosclerosis has been to modify the patient's diet so that he is now receiving a moderate average diet with normal carbohydrate and fat intake and controlling the diabetic symptoms with the use of adequate doses of regular and protamine insulin. No special limitations of food substances are insisted upon but avoidance of fats high in cholesterol value is practiced.

The treatment of sclerosis once present can not alter the lesions but will assist in the formation of collateral circulation in the extremities. One of the easiest and simplest methods is by the use of Buerger's exercises, alternating elevation and depression of the extremities to increase the circulation, supplemented by the use of local heat by some method. There are no drugs that have much value in this condition except insulin and it is used for its beneficial effect in the diabetes and not for the arteriosclerosis.

When some of the complications arise they are treated depending upon the seriousness of the condition. Extensive gangrene is cared for by amputation while a localized lesion may be treated conservatively. Coronary involvement is handled in the
usual manner, care being taken not to produce card-
ial shock by the production of hypoglycemia from an
over dose of insulin.

The aim of the management of the diabetic pat-
ient is to prevent premature arteriosclerosis and to
extend his life expectancy to that of an normal per-
son unaffected by diabetes mellitus.

Conclusions:

After a fairly extensive survey of the liter-
ature of the subject, the clinical and laboratory
findings and theoretical postulations of the var-ious authors have been considered and some definite
conclusions concerning diabetic arteriosclerosis may
be advanced with a definite degree of validity:

1. Arteriosclerosis appears in practically all
patients suffering from diabetes mellitus for more
than five years.

2. This type of arteriosclerosis has a predelect-
ion for the peripheral arteries of the extremities.

3. The typical pathological process consists of
atheromatous formation increasing the thickness of
the intimal layer of the vessel wall.

4. The principle underlying cause of the format-
ion is a faulty lipid mechanism associated with the
diabetes producing an plasma cholesterolemia.
5. The etiological factors of obesity and hypertension generally found in diabetes are not directly associated in the production.

6. The mortality of the disease is due to the occurrence of two main complications, coronary disease and gangrene caused by deficient circulation from obliteration of the lumen of the arteries.

7. An average diet, consisting of approximately 100 grams of carbohydrate, adequate protein, and a low fat intake, the sugar level controlled by insulin, is the most useful prophylatic factor available to decrease the incidence of arteriosclerosis.

8. Proper treatment of the complication of gangrene is by radical surgery, amputation of the extremity being performed above the lowest level of good circulation.
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