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## Cardiovascular changes complication diabetes mellitus

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UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE

Senior Thesis

1936

CARDIOVASCULAR CHANGES  
COMPLICATING DIABETES MELLITUS

Herbert D. Kuper

480781

## PREFACE

The clinical character of diabetes mellitus is changing. Improvements in diagnosis and the greater frequency of periodic examinations of supposedly healthy individuals have resulted in earlier diagnoses and, therefore, the discovery of milder cases. Better treatment has resulted in cases of longer duration. Most important of all, the discovery of insulin has revolutionized treatment and given to diabetic patients a longer and more active life. As the diabetic's protection against death from diabetes itself has improved, his need for protection against complications and for their surgical and medical treatment, should they arise, has become more apparent.

It has been well said that no disease is attended by more complications than has diabetes. Cardiovascular complications occur so frequently with this disease that they can hardly be considered complications but might better be treated as associated pathological changes occurring in conjunction with the disease process.

It is not the purpose of this thesis to bring to light the nature of all of these complications and the clinical characteristics which they manifest. All the

cardiovascular conditions cannot be fully described because of the voluminous nature of the subject. In this discourse it is hoped that the reader will gain a comprehensive knowledge of the incidence, etiology, pathology, treatment, and prevention of the more common cardiovascular complications of Diabetes Mellitus.

The various schools of thought, of which there are many, and the observations which support these various schools are considered where deemed to be of interest and importance.

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The serious importance of surgical disease and cardiovascular complications in diabetes mellitus is best shown by consideration of causes of death. Formerly patients died of coma. Between 1914 and 1922, among 1147 deaths reported by Dr. Joslin (2), coma was present in 585 cases or 51 per cent, and only 112 or 9.8 percent could be attributed to surgical diseases. Joslin (26) states that between April, 1919 and July, 1923, however, 11 out of 33 deaths occurring in the New England Deaconess Hospital or one-third were due to surgical diseases. In 1906 Naunyn reported 49 autopsies with 6 deaths from surgical and vascular diseases. Between 1920 and 1925 at the New England Deaconess Hospital, out of 26 autopsies the cause of death was a surgical disease in 14 cases and between January, 1925 and January, 1927, in 21 necropsies the cause of death was found to be surgical in 15 cases.

Joslin (1) also states that diabetic gangrene has been increasing as a menace to his patients and that the percentage of total mortality has risen from 2.3 per cent prior to 1914, to 5.1 per cent between that year and 1922, to 12.6 per cent from then until into 1926 and since that date has decreased slightly to 10.4 per cent. The mortality from diabetic coma as contrasted with gangrene has fallen in round numbers from 60 per cent to 5 per cent. Gangrene in his opinion deserves more intensive study and the investigation of the cause and type of arteriosclerosis which is responsible for it should help defer old age for us all. Joslin

further brings out other statistics. During 1933 at the Geo. F. Baker clinic of the New England Deaconess Hospital of 972 diabetic patients there were 32 deaths, 16 per cent of which were from gangrene. In Joslin 's private cases since 1926, it is interesting to note that in 1059 diabetic deaths, the average age has risen from 44 years to 61 years and the duration of the disease has risen to 10.4 years.

Lehnherr (3) is very definite in his statement that if arteriosclerosis among diabetic patients was important before the discovery of insulin it is more important now. The use of insulin has prolonged the life of the diabetic patient so that rapid diabetes is rare and he lives more in the arteriosclerotic zone. Eliason (4) quotes Joslin in the statement that surgery is entirely rewritten because diabetes is so often a surgical problem, more than one-fifth of all Boston diabetics dying of gangrene.

Joslin (5) in 1933 stated that every other diabetic now dies of arteriosclerosis and the percentage has been rising. He pointed out that in the Naunyn era from 1894-1914, 15 per cent of the cases of diabetes died of arteriosclerosis. In the Allen era, 1914-1922, 26 per cent of cases died from this cause. In the first part of the Banting era, 1922-1929, 42 per cent, and in the years 1929-1933, of 781 fatal cases, 50 per cent were due to arteriosclerosis. His explanation for this is that more escape coma, and that there is a greater length of life of diabetis.



Joslin has found that the localization of the pathology in the fatal cases has been as follows: Heart, 19.1 per cent, legs, 13.2 per cent, brain, 7.2 per cent, and kidney, 4.5 per cent.

Arteriosclerosis increases with the age at onset of the disease and also increases with the duration of the diabetes. Statistics supporting this have been compiled and it has been shown by Joslin that length of disease of less than five years leads to 30 per cent arteriosclerotic deaths, and in length of 15 to 19 years there is a 60 per cent death rate. Arteriosclerosis is beginning to make itself felt among the group dying under 40 and even 30 years of age. Shields Warren (27) states that in 300 diabetic autopsies there was no case with diabetes of five years duration which did not present arteriosclerosis.

Murphy and Moxon (6) found cardiorenal vascular disease in 273 of 827 cases studied. The diseases of the heart and kidney were for the most part produced by arteriosclerosis. Goskin, Strouse, Katz and Rukinfeld (7) state that arteriosclerosis accounts for a much larger percentage of deaths among diabetics than before the use of insulin, and the heart is affected more than the rest of the cardiovascular system. John (62) in 1928 reports, interestingly, that in a study of 2000 cases he had more deaths from coma than from any other cause. This is in disagreement with the findings of the greater majority of observers.

Lemann (9) gives incidence of gangrene as 5.3 per cent as compared with 3 per cent in Joslin's. However in Dr.

Lemann's series the statistics were taken from Charity Hospital, associated with Tulane University, where 21 per cent were negroes and the elements of poverty and ignorance are considered of significance and can't be compared with the private cases of Joslin. He points out that the negroes wear poor shoes, full of unevenness and holes and that their socks are of like condition. Their feet are neglected and in many cases, seldom washed.

Wilder (10) in necropsy findings of 81 diabetic cases found that gangrene caused death in 14 of the 81 cases and that arteriosclerosis of considerable degree occurred in nearly all cases when the age of the patient exceeded 40 years.

Not only should we be concerned with the death rate from the vascular complications of this disease but also with the general mortality trend of the diabetes itself. Joslin, Dublin and Marks (11) impart the information that with the mortality rate as it is now, 26 out of 1000 girl babies will die of diabetes mellitus, and 15 of every 1000 boy infants will have the same exitus. Joslin(47) states that 1,000,000 individuals in the U. S. either have or will have diabetes before they die. The death rate per 100,000 is now 22. The mortality is higher in this country than in other parts of the world. Most of the deaths come after middle life. The female and male death rates are about equal up to the age of 35 but the female rate increases until 65 when the female death rate from diabetes is twice that of the male. It is interesting to note that the negro

death rate is increasing in this disease faster than that of the whites and now is not much lower than that of the white race in the United States. Considering all ages, the male death rate has been on a slight decrease the last two decades but has increased somewhat the last few years.

In 1932, the diabetic death rate in Nebraska was the highest in 13 years. Conlin (12) in his report on 616 cases points out that one out of 3.2 patients had a surgical complication, and that 6.3 per cent of these cases developed gangrene.

We do not need to confine our deductions in regard to higher incidence of cardiovascular complications to causes of death. An extensive roentgenographic study of the legs and feet of 500 of Joslin's patients was made by Morrison and Bogan. (14) In this study, legs and feet were chosen instead of arms because the vessels of the legs show evidence of sclerosis earlier than arms. Calcification was not seen in the aortae even when the process was moderately advanced in the vessels of the legs, perhaps partly because of the fact that is more difficult to detect calcification in the aorta. Many details were considered and much care was exercised in study of the x-rays. It is the general opinion of the men supervising this study that arteriosclerosis in the vessels of the legs implies its existence in the heart.

In the normal person a vessel is rarely found in which calcium can be demonstrated by x-rays before the age of 40 years. In 36 per cent of 30 people 40 to 50 years

of age leading a normal life with no abnormal disease processes evident there was vessel calcification. In the same decade, 63 per cent of diabetic patients showed calcification. The incidence of calcified vessels increases with each decade of life, as one would expect, and it also increases in each decade of diabetes, according to Morrison and Bogan. Not only does the percentage of diabetic patients who have calcified vessels increase with age and duration of diabetes, but the extent of the calcification increases in the same manner. Results show, however, that the increase is not absolutely constant either according to the duration of the disease or with the age of the patient. Advanced calcification, was present in 68 patients all of whom were 40 years of age or more. In 22 per cent of these 68 patients with advanced calcification, pulsation was absent in one or both dorsalis pedis arteries.

48 of the 68 patients with advanced calcification of the vessels of the legs had evidence of vascular lesions elsewhere in the body. Clinical evidence of radial sclerosis was present in 39 patients. 12 patients had coronary disease and gangrene was present in 29 per cent of patients with marked calcification. 68 or 91 per cent of the patients had diabetes for 10 years. 62 or 91 per cent showed evidence of calcification--comparing favorably with Warren's autopsy findings. From this we may logically conclude that evidence of vascular calcification increases with the age of the patient and with the duration of the disease and is higher in

the diabetic than in the non-diabetic.

Starr (16, 17, 18 ) has approached the circulation problem through the use of the histamin skin reaction test. he has concluded that the majority of diabetics have abnormally low blood flow through their feet. This is based on observations on 100 patients.

Rabinowitch (19) states that cardiovascular disease has replaced coma as one of the chief causes of death in diabetes. He points out this difference, coma was the result of uncontrolled diabetes; whereas cardiovascular disease apparently develops in spite of control. It develops whether the urine is or is not free from urine. It is not confined to elderly people. Only five years is usually necessary for its development, since with diabetes of 5 years duration arteriosclerosis has developed regardless of age. The frequent finding of calcification of arteries and other signs of arteriosclerosis in children is evidence of this fact.

The case of extensive arteriosclerosis and atherosclerosis in a young man of 27 reported by Cullinan and Graham (22) gives us definite proof of this tendency. Klotz and Manning (20) have reported fatty streaks in the intima of arteries in very young patients. Shepardson (23) has made a study of 50 patients under 40 years of age who have had the disease 5 years or more. The average age of this group was 23.4 years. The average length of the disease was 6.9 years. 36 per cent of these cases gave roentgenographic evidence of vascular sclerosis. Neither the severity of the disease nor the associated pathological changes could be considered as

factors in the causation of this change.

As to the direct of effect of diabetes upon the increases incidence of coronary disease we will consider that along with that subject later.

What is arteriosclerosis and what is the pathological change in the arteries which brings about the clinical manifestations that have been observed with such increased frequency in this disease of carbohydrate metabolism?

Clawson and Bell (67) say that arteriosclerosis is a collective term used to designate several anatomic forms of arterial disease that may or may not be related. Formerly syphilitic arteries and thrombo-angiitis obliterans were included. (a) Intimal atherosclerosis is the main type and is mainly found in the aorta, the carotids and the coronaries and may be found in any artery. It is characterized by proliferation of the connective tissue of the intima with edema, lipoid infiltration, necrosis and calcification of the newly formed tissue. It increases progressively with age, but some elderly persons show little. A juvenile form occurs which is usually associated with arteriosclerosis and hypertension. It is more severe in elderly persons with diabetes than in persons of the same age without diabetes. (b) Calcification of the media is a widespread condition (Monckeberg, Faber). It is found in the pelvic, gluteal and popliteal arteries of children. It tends to increase with age. It is more frequent and extensive in the arteries of the pelvis and lower extremities, but is also found in many other arteries.

Oskar Klotz (44) says that the term 'arteriosclerosis'

was introduced by Lobstein in 1831 and means 'hardening and thickening of the arteries.'

Many authorities insist that one cannot definitely say upon examination of a section of an involved artery whether or not it is due to diabetic condition. In other words, their contention is that the arterial lesions are so closely related with the findings in senile arteriosclerosis that they can make no distinction between them and conclude therefrom that no difference exists. Buerger (15) is of this opinion. Beard (29) says that the pathology is the same as in arteriosclerotic changes in the senile type with degeneration of the arterial walls with calcification and bone formation in the more advanced stages. He describes rigid pipestem arteries and places where there is atherosclerosis with dilatation of the vessels.

Ellason, Wright, and Murray (4) are impressed with the fact that gangrene in diabetes is analogous to senile or arteriosclerotic gangrene with the added local and general disturbances of metabolism that occur in diabetes.

McKittrick and Root (2) agree with Shields Warren and quote him in their book on diabetic surgery. They describe the work done by Drs. Warren and L. W. Smith in which they analyzed the records and pathological findings in the leg arteries of 33 diabetic legs amputated for gangrene or infection.

In the muscular arteries of the extremities the typical arteriosclerosis of the non-diabetic is characterized by changes in the media, as described by Monckeberg. There may

be slight thickening of the intima with some fat deposition, but the media shows swollen and necrotic muscle fibers, large deposits of calcium and even bone formation. Among diabetic patients a somewhat different picture is presented in the descriptions of specimens studies. In these 33 sections from anterior and posterior tibial, dorsalis pedis and popliteal arteries sections at various levels were obtained. In some instances the amputated legs were injected with barium sulphate through the popliteal artery in order to obtain roentgenograms of the circulation. The group consisted of 12 females and 21 males, ranging in age from 52 to 70 yrs. with diabetes varying in duration from a few weeks to 24 years. Treatment of the diabetes had been very slight in nearly all cases. In two instances insulin had been used for one year but in the remaining cases insulin had only been used for periods varying from two days to three months before operation. Two types of arterial lesion were found differing chiefly in degree of intimal as compared with medial involvement and exemplified in the following descriptions:

1. Endothelial proliferation and fatty deposition.-- the lumen is reduced to one-sixth normal size. Numerous endothelial leukocytes, some connective tissue ingrowth and moderate infiltration with endothelial leukocytes and lymphocytes. In the media there is a small focus of necrosis, infiltrated by lymphocytes, polymorphonuclears and



and endothelial leukocytes with occasional calcified granules and necrotic muscle fibers.

2. Medial calcification with intimal change-- there is marked calcification of the media with some bone formation. The lumen is reduced to one-eighth normal size. Marked thickening of the intima with large deposits of atheromatous material and toward the media, infiltration with endothelial leukocytes and lymphocytes.

Thrombo-angiitis obliterans was not found in this series. Medial sclerosis of the Monckeberg type was found in varying degrees in most cases, but the characteristic feature was a predominance of intimal changes. In the diabet, therefore, the pronounced intimal fatty change found in non-diabetics usually in the elastic arteries extends nearly to the muscular arteries of the extremities. This type may develop fairly rapidly as shown by its presence in cases of diabetes of but a few month's duration. That it may be present for long periods before the onset of gangrene is shown by the long duration of diabetes in certain cases, but especially by the existence of calcification and even bone formation within the intima. In cases with diabetes of long duration the best development of collateral circulation was found, but in some cases of short duration advanced intimal change and absence of compensatory collateral circulation obtained. The occurrence of gangrene seemed to depend upon the presence of infection before the development of adequate collateral circulation, or with collateral circulation inadec-

quate to combat virulent and extensive infection.

What clinical bearing have these pathological variations? The most valuable circulatory asset for a diabetic with sclerosis of the main arteries is a good collateral circulation. From these as well as from the group as a whole it appeared that the cases with long standing medial sclerosis had developed the best collateral circulation, whereas cases with relatively little medial sclerosis and marked intimal change had little collateral circulation. These conclusions seem justified: (1) Diabetes encourages the early extension into the the arteries of the trunk; (2) that a good collateral circulation is best developed when the medial type of sclerosis has been present for some time; (3) that as soon as diabetes is discovered in a person over 50 years of age it is advisable to attempt by means of exercises similar to those of Buerger or by other means to stimulate the development of collateral circulation.

McNealy (24) says, "We know that as the diabetic factor becomes more prominent, intimal changes in the muscular arteries become more prominent in comparison with medial changes. Fat deposition in the internal elastica becomes more and more prominent and medial sclerosis falls behind in the arteriosclerotic process."

Leary (36) says that examination of cases show atherosclerosis in early life, a thing which he considers a disease and not the inevitable consequence of age since it appears in the young and because of this may be highly selec-

tive in its localization. The characteristic lesion in youth is a fibrosis associated with the presence of lipoid cells, which do not accumulate in large aggregations because of the growth of fibrous tissue. The characteristic lesion in older age is the accumulation of large collections of lipoid cells with minimal connective tissue support as the result of poor nutrition, massive necrosis occurs giving rise to so-called atheromatous abscesses. The standard cause of death in the older group is thrombosis following sub-endothelial necrosis which extends to the endothelium. The process is primary in the intima, stresses favor the localization and morphologic lesions in the elastica and media occur secondarily. The disease is not inflammatory in origin.

In spite of the disagreement which seems to be prevalent, the more accurate observations would indicate that there is a fundamental difference in the diabetic type of vessel change and that of senile arteriosclerosis, and that the clinical manifestations seen are not simply due to a diabetes superimposed upon previous vessel change.

We now come to the question of what factors present in the disease process are conducive to this early vascular change. As in the question of pathology of this change we again find manifold opinions and the amount of research done in an attempt to answer this question cannot possibly be reviewed here. We are concerned, however, with knowing the various opinions which have been supported by the more worth-

while observations.

It goes without questioning that no chapter in the history of the study of disease has been filled with more conscientious effort and unrelenting persistence than has this one. The work in Joslin's clinic in conjunction with the New England Deaconess Hospital is a fit example of this, but that work does not eclipse the efforts made in many other clinics and by many other outstanding investigators, many of whom will be mentioned in this paper.

Joslin (37) mentions several of the factors which play a part in producing these arterial changes. Joslin (13) has found that there is a hereditary history in 37 per cent of cases of diabetes mellitus. The hereditary relationship which plays a part in the etiology of cardiovascular disease in the absence of diabetes is generally recognized. We can assume that this is an important factor.

Protein in the diet has been considered a factor also. Joslin does not entirely disagree with Clarkson, Newburgh, Marsh and Waller (38,39,40) who are profound exponents of the idea that it is the protein in the diet and not the fat or cholesterol content that plays a large part in the causation of atherosclerosis both in diabetes and in animal experiments. They mention (41) a group of patients who had liberal protein diets who were severely ill and worse in the hospital than at home. They report (38) an examination of the records of a group of patients treated with high fat diets and low protein content and observed that in the pa-

tients the lipoid content of the blood during the period of observation did not increase, and, of significance, they observed also that in the patients in whom hyperlipoidemia existed when they first came under observation, the total fat fell to approximately normal. This they present as argument that the assumption that diabetic hyperlipoidemia is dependent on the excessive ingestion is unwarranted. Blatherwick (42) observed the same situation in three cases.

Clarkson and Newburgh (39) point out that vascular disease caused by ingestion of cholesterol deffers in no way from that in animals fed a high protein diet, and corresponds to the descriptions found in textbooks dealing with disease of the human aortic intima. The process in their animals was never far enough advanced to present calcification but could be called atherosclerosis to designate a primary lesion of the intima. In the control group there was no primary intimal involvement. They are here, of course, presenting arguments against Joslin's ideas of causation of arteriosclerosis by high cholesterol intake which we shall describe later. They found atherosclerotic aortae in animals that had normal as well as high readings, and the animal that exhibited the most extreme hypercholesterolemia had a normal aorta. No definite relationship was present between amount of cholesterol fed and the time of feeding to the amount of cholesterol in the blood.

Joslin (37) thinks that persistent hyperglycemia may cause arterial change due to faulty metabolism along with

wear and tear, but feels that the patient kept sugar free is probably not hurt by the hyperglycemia proper.

As to the effect of acidosis on the development of arteriosclerosis and arterial changes, we can not present evidence which is of significance since acidosis of primary nature does not persist for long periods of time. The recent experiments on ketonurics where epilepsy is controlled by prolonged acidotic condition may bring to light some interesting observations.

Ophuls (43) and Klotz (44) mention the effect of infection. Klotz is of the opinion that no focus of infection is too small to be considered. Ophuls thinks that lipoids and atheromatous changes may not be the cause but absorption may aggravate a pathological process in the artery. He thinks that infectious diseases may injure the arterial walls in such a way that they tend to earlier and more rapid decay and in the manner lead to the development of arteriosclerosis. Moschcowitz (55) says that if infection is the cause of arteriosclerosis, why is it limited to one side of the circulation? Hepburn, Graham and Duncan (58) think that infection is probably the cause of this change\*-initial- the degenerative changes occurring later. In many cases of cardiovascular disease, they say, there often is improvement following removal of foci of infection. The susceptibility of the diabetic patient to infection and the detrimental effects of infection on the clinical course of diabetes mellitus, particularly in untreated diabetes, are only too well known. Is it not, they ask, probable that in

diabetes mellitus the premature vascular changes are the result of infection acting in the presence of the abnormal metabolism of the disease? If this be the case, one's efforts ought to be directed to prevention and eradication of infection as well as to the restoration of normal metabolism.

Anderson (34) admits he doesn't know the exact relationship between diabetes and early arteriosclerosis.

According to Joslin (37) alcoholism is seldom a problem in the diabetic and need not be considered.

Perhaps obesity is the commonest story in the diabetic. In 1000 cases Dr. Joslin found 85 per cent of those with onset after forty years to have been 5 to 70 per cent above standard weight. Indeed, the average maximum weight in 100 cases operated upon at the New England Deaconess Hosp. was 189 pounds (27-pg. 26). This obesity is not due to chance but to habits of life. Over-indulgence in food, not necessarily sweets, with relatively little exercise are commonly admitted. Conlin (12) reports an incidence of marked obesity in 60 per cent of 616 cases. Margolin (46) reports a similar incidence in the out-patient department of the University of Nebraska Coll. of Medicine.

It has been this constant observation that has led a great number of men to investigate the relation of fat metabolism to the causation of the previously described early vascular changes in diabetes.

Joslin is responsible for the statement (47) that "from an excess of fat diabetes begins and from an excess of fat diabetics die." At that time they observed that in 45 per

cent, increase in body fat preceded the onset of the disease. We must consider the significance of their statement by realizing that in this period, 60 per cent of Joslin's patients were dying of some which is essentially a fat metabolism phenomenon secondary to the carbohydrate disturbance.

Joslin has long been of the opinion that fat metabolism has something to do with the development of vascular disease in the diabetic. He has been supported in this opinion by such men as Bloor, Gray, Hunt, (Hazel) and Priscilla White along with many others. (48, 49, 50, 51, 52, 53 ).

The working basis for his opinions and the opinions of those supporting him may be found in the observations of Virchow and Aschoff. These observations can better be considered in the words of Aschoff (35). Chap. on Atherosclerosis.

"The expression 'atherosclerosis' was first coined by Marchand to indicate the peculiar changes observed, especially in elderly individuals, in the intima of the aorta and large vessels of the elastic type, which are so characteristic of the clinical picture generally termed arteriosclerosis. Marchand desired to emphasize by this expression that, in addition to the sclerotic changes, the so-called 'atheromatous' or fatty changes play a specific role. Since the fatty process, as we shall see, is of a unique nature and bears a definite relationship to the sclerotic process, particularly to calcification, the expression 'atherosclerosis' is thoroughly justifiable.

"We are indebted to Virchow for the first accurate histological description of the entire process. On the



occasion of the centennial celebration of his birth, I indicated that Virchow's original presentation, which has gradually been forgotten, today redeives the honor and recognition which it deserves.

"Virchow's interpretation of the atheromatous process was the first change consisted of a 'certain loosening of the connective tissue ground substance' of which the arterial intima is for the most part composed. This swelling of the ground substance, which Aschoff concludes must be attributed in a large measure to an increased imbibition of fluid elements from the passing blood stream, is recognized microscopically by the increased width and homogeneity of the connective tissue spaces.

"Sometimes these areas of swelling have a gelatinous appearance which may be recognized macroscopically, at times they are cartilaginous. Along with the thickening of the of the ground substance and its transformation, the connective tissue cells of the intima undergo changes. They enlarge in all dimensions, divide and form localized thickenings. In this manner the process assumes an active character such as we have assumed for inflammatory processes in general. In pointing out the marked vascularization of the outer coats of the aorta, in addition to the intimal thickening, Virchow believed that he had sufficiently demonstrated the irritative nature of the process. When the thickening of the intima has advanced to a certain degree, fatty metamorphosis generally puts in an appearance. Only under certain conditions do these progress to true atheromatosis; that is, when the fatty process begins in the depths

of the thickened intima and, becoming progressively softened, slowly extends to the surface. In other cases the fatty metamorphosis occurs directly in the most superficial layers. This Virchow termed *fettige usur*, which may occur without antecedent thickening of the intima. If we disregard this point for the present, then, according to Virchow, the entire atheromatous process represents a primary loosening of the intimal layer, due to the infiltration of blood plasma, which is accompanied or followed by a growth of intimal cells and a more marked vascularization of the media. This it is an active process, in which a fatty metamorphosis of the different layers may take place as well in an entirely passive manner.

"The *Primum movens* of the entire irritative process is therefore a loosening of the internal coat. In what manner do these changes arise? Virchow discussed two possibilities a humoral and a mechanical etiology. Virchow rejected the former, which may be called arthritic and which is conceived as a primary exudation of the arterial intima, and clearly and definitely accepted the mechanical etiology. One cannot find a better exponent than Virchow of the theory of the mechanical origin of atheromatosis. But it did not escape his keen perception that some dyscrasia must play a supplementary role.

" In the light of newer histological and chemical investigations concerning the nature of the atheromatous fatty process, as, for instance, those of Adami, Windaus and myself, all of which led to the similar conclusion that this fatty process depends purely on a deposition

of cholesterin esters, one may construct today, on the basis of Virchow's conception, an almost flawless picture of the atheromatous process in the aorta. I have called this conception of Virchow's the 'Imbibition theory,' and in the light of this theory, I should like to trace for you the development of the atheromatous process.

"In puberty and early adult life, in the earliest stages, approximately between the ages of sixteen and twenty, there appear on the posterior wall of the aorta, especially along the lines of tension between the origins of the intercostal arteries, very fine yellow streaks or spots, which are opaque and not at all, or at best only slightly, elevated. The younger they are the more do they appear to lie within the intima itself. Only gradually do they appear to lie within the intima itself. Only gradually do they rise above the surface. The longer the process lasts, the more distinct do these streaked flecks become, until finally the whole posterior wall of the aorta, even the area between and on either side of the intercostal arteries, is involved. The aorta, unchanged in its elastic properties, shows no other apparent abnormality.

"We have before us the picture presented by Virchow as an 'intimal fatty change', in contrast to actual atherosclerosis. Aschoff thinks that the so-called intima fatty change of youth is nothing else than the earliest beginning, or better still, a particular stage, of atheromatosis. This may be described as the atheromatosis of puberty. The essential microscopic picture is this: I must first recall to your minds that the intima of the aorta possesses an outer elastic

muscular longitudinal layer, and an elastic inner connective tissue layer which are separated from one another by what I have called an elastic stria terminalis. Outside the elastic muscular longitudinal layer lies the internal elastic lamella which divides the intima from the media.

"Where does the atheromatosis of puberty begin?

A peculiar fatty change in the above mentioned elastic stria terminalis in the deep layers of the intima is the first evidence of the disease process. This fatty change consists of a granular deposition of cholesterol 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 the simultaneous deposition of fat droplets. The rest of the intima, especially the inner elastic connective tissue layer, which lies over the stria terminalis, shows practically no changes, at most a slight loosening and swelling of the tissues. As the process continues the fatty deposits increase in the cement substance of the stria terminalis. At the same time there is a diffuse, finely granular layer of deposition and precipitation of finely nature between the elastic and connective tissue fibrillae of the overlying intimal layer, and finally, there occurs an accumulation of fat droplets in the intimal cells themselves. In this manner a real accumulation of fat takes place in the interstitial, as well as in the cellular, tissue. Characteristic of the entire process, however, is the predominating interstitial fatty change. With the increasing deposition of fat, the entire process extends to the surface

until it finally reaches the entothelium. Since, at the same time, there occurs a loosening of the surrounding tissues, which is caused, no doubt, by the presence of an increased amount of tissue fluids, and which is associated with a moderate multiplication of the intimal cells, the affected area tends to swell over the surface. The essential factors in this early picture of atheromatosis are, therefore, a swelling of the inner layers of the intima, with a diffuse minute granular deposition of fat beginning in the depths of the elastic stria terminalis and extending further and further toward the surface. No further changes take place in the atheroma of the ascending period of the vascular system. At most, the process may tend to retrogress and, as we know with certainty of infantile atheromatosis, may entirely disappear. These retrogressive processes have not as yet been followed microscopically with certainty.

" How can this peculiar phenomenon be explained? Why the deposition of fat. The chemical nature of the latter gives us the clue. The fat consists of cholesterol esters. Since this cannot arise from a transformation or decomposition of the elastin or collagen of the intima, it must be derived from an infiltrative process. The source just must be from the blood plasma itself. This nourishes, as is generally known, the inner layers of the vessel wall through a kind of imbibition stream. What more likely than the fact that under special circumstances the imbibition is abnormally increases, as well as in a certain sense slowed down, and thus gives rise to those changes which we call atheromatosis?

" This is intimately associated with physiochemical changes which at present are not entirely understood. However, the fact that the process begins just at the origin of the intercostal arteries indicates that definite mechanical factors, especially forces of a dragging and pulling nature, 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 these atheromatous spots may appear. This, it seems to me, is a sufficient concentration of lipoids, especially of cholesterolin content in the form of esters in the plasma.

"In atheromatosis of age, there is a truly severe disease, known as atherosclerosis. Here individual predisposition plays a large role. On one hand, we find at the most advanced ages aortas that are entirely smooth with only the signs of senile ectasis and senile sclerosis; while on the other hand, we observe even in the fourth and fifth decades the most advanced changes in the aorta. There are first signs of the disease in those areas of greatest stress and strain. In microscopic section of these areas we see the same imbibition process which is developing in, not a young and growing aorta, but in an aged and worn one. The more likely assumption here is that, no matter what noxious influences act on the intima of the aorta, the process of swelling and growth will be more marked in the presence of the great excess of connective tissue in the aorta of the

aged. Microscopic examination actually indicates that here, too, there are changes in the cement substance of the fibrillar and elastic elements. These fuse into a sort of hyalin substance, a process which is known as hyalin degeneration of the connective tissue. This process of swelling, in which the ground or intercellular substance becomes suffused or infiltrated with a sort of albuminous material, takes place especially in the deeper layers of the intima, and extends more and more to the surface. Because of the general tendency to overgrowth of the connective tissue of the intima in this descending period of the life of the vessel, the surrounding connective tissue reacts more intensely to the local lesion. This results in a reactive process in which the areas of swelling are covered by newly formed connective tissue. This, too, in time becomes affected by the swelling process. In this manner hyalin layer is added to hyalin layer, which leads to the formation of the patches so characteristic of early atherosclerosis."

Aschoff also points out the contributing factor of changed metabolism in diabetes or phthisis which is definitely related to formation of atherosclerosis. In this discussion Aschoff has intentionally limited himself to atherosclerosis of the aorta. The atherosclerosis of the arteries of the muscular type runs along somewhat different lines, for here the disease of the media, which in the aorta plays no important part, is very definite indeed unless we assume that in diabetes there is a special change in which the pathology characteristic of the elastic ar-

teries expresses itself in the muscular arteries.

The process of wear and tear of the vessel wall is in evidence, of course, not only in the intima but also in the media, and particularly in the media of the vessels of the muscular type.

Joslin (13) states that in 1914 diabetic coma caused the death of more than one-half of our diabetics and the relation of fat to its etiology seemed so close that the colored frontis-piece of lipemic blood in a diabetic monograph was appropriate. We have seen this cause of death change from a direct cause to what is probably now an indirect cause of death and because of this will follow this line of reasoning further.

Of the blood lipoids about 50 per cent exist as combined fatty acids, mainly oleic and palmitic; 30 per cent more or less, is in the form of cholesterol (and cholesterol esters) while the remaining 20 per cent is composed of lecithin and related bodies which are distinguished by their content of phosphorus. The lipoids represented by the cholesterol and lecithin groups constitute most of the "built in" fat of the body. Lipoids is a term used to cover any or all fatty substances: fatty acids, cholesterol and lecithin. Blood fat means those substances measured by Bloor's method for so-called "total fat", namely, fatty acids plus total cholesterol but not the lecithin.

Cholesterol is an animal body sterol and is one of the most complicated substances in the animal body. Chol-



erol is an animal sterol synthesized by the animal body, notably herbivora, but the principle human provision comes from ingestion of products of herbivora--eggs, milk and pork fats. Cholesterol is present in every cell. Starling (61) says, "In view of the great stability of this substance when exposed to the ordinary mechanisms of chemical change in the body, it seems probable that the part played by cholesterol is that of a framework or skeleton, in the interstices of which the more labile of the constituents of the protoplasm undergo the cycle of changes which make up the phenomena of life. It highly resists infection".

In 1916, Bloor (48) found the average cholesterol in the blood of diabetics to be far above normal and found an average value of 424 mg. in 100 cc. of blood.

Joslin (21) in 1927 reiterated that the fat in the blood of the diabetic tends to be above normal and is never reported in a series of cases as below normal. The percent of fat rises with the severity of the disease and varies particularly with the extent of acidosis and is especially related to the quantity of carbohydrate which is being oxidized rather than with the fat administered. Wells (54, pg. 460) says that in various diseases, exclusive of diabetes, the total lipin content has been found about normal, but the proportion of the different lipins varies somewhat. Earlier writers described incorrectly lipemia in many conditions but recent writers mention it chiefly as occurring in alcoholism, nephrosis and diabetes. By far the great-

est amounts of fat are observed in diabetes.

Cowie and Hoag (58) found the fat increases when eight diabetics were first examined but when their diabetes was more under control the fat fell just as it did under similar conditions in the series reported by Marsh and Waller (38). However, one should not overlook the fact that even under their well-designed treatment, the fat did not by any means always reach normal.

Not only is there an increased cholesterol value in the blood of the diabetic patient but there also is a greater deposition in the walls of the vessels. Lehnher (3) found in chemical analyses of 25 aortae, that the presence of arteriosclerosis in the aortae is associated with increased amounts of each lipid, changes in the lipid allocation, increased proportion of the total lipid as cholesterol, increased amounts of acid-soluble calcium and phosphorus, diminished calcium-phosphorus ratio and that the diabetic aortae show similar changes, but to an exaggerated degree. This difference was most marked in the group from 50 to 60 years of age in which the average value for each of the various lipids, the lipid allocations and the calcium content is actually greater than the corresponding values in the non-diabetic group 10 years older. With this criterion we may presume that the diabetic in middle life is prematurely aged. The duration of the diabetes had no definite relationship with the chemical findings in the aortae.

About 25 years ago Ignatowski (111) stimulated much interest in cholesterol feeding of herbivorous animals.

Since that time much work has been done on this problem. Anitschkov has summarized this work in his recent publication (1933).

What is the present status of artificial feeding of cholesterol to animals and the production of atheromatosis? What significance can be attached to such experimentation?

It is generally recognized that changes in the arteries resembling early atheromatous changes in human arteries can be produced in the herbivorous animals. Bischoff (59) mentions the ease with which arteriosclerotic changes can be produced in herbivorous animals by cholesterol feeding. He says that it remains a fact that arteriosclerosis has never been produced in experimental animals by cholesterol-free diets. The evidence at hand indicates that cholesterol might be the predisposing factor in all experiments in which arteriosclerosis has been produced. Evidence of hypercholesterolemia in humans suffering with hypertension and arteriosclerosis has been sought. Several have gotten positive results. Characteristic abnormalities in the blood lipids of patients suffering with these diseases were not found by Bloor and others. The negative evidence must be given preference since a variety of abnormalities in the blood in arteriosclerotics has been reported, none of which, however, is characteristic. Negative evidence by no means settles the question. Bloor believes that the deposition of cholesterol and its esters does not necessarily require a high blood cholesterol but depends on the ability of the blood to keep in solution a substance which is probably in a state of supersaturation.

Moschcowitz (55) discounts the work on herbivora and recounts that some results have been obtained in omnivora but this only in conjunction with hormonal changes brought on artificially in the laboratory. Moschcowitz has not observed a consistent rise in blood cholesterol in his experiments--this, however, may be explained on the basis of Bloor's theory before mentioned. He says that he has not observed the compensatory phenomena in herbivora as seen in human arteriosclerosis, such as hyperplasia of the elastica. He points out that the diffuseness of lipoid deposits in the laboratory is not characteristic of human arteriosclerosis. He points out that the lesions of experimental arteriosclerosis behave like the lipoid deposition of the arteries and mitral valves observed in infancy in that they disappear. Moschcowitz quotes Anitschkov as being convinced that cholesterinemia is not the entire story, for in his most recent studies he tries to show that the mechanical factor is important by using smaller doses of cholesterol combined with pressure. Moschcowitz criticizes the assumption of degree of arteriosclerosis by observing the greater arteries alone and points out the fact that capillary and venous sclerosis takes place also and should be observed. He offers the ideas of Allbutt (57) and agrees with Aschoff (35) that physiological stress may play a part in causation of arteriosclerosis.

Newburgh and Clarkson (39) found atherosclerotic aortae in animals that had normal as well as high readings, and the animal that exhibited the most extreme hypercholesterolemia had a normal aorta. No definite relationship was present

between amount of cholesterol fed and the time feeding to the amount of cholesterol in the blood. They attribute the elevation of blood cholesterol to a metabolic disturbance directly referable to the excess of protein in the diet and not to its cholesterol content.

Leary (36) points out that practically all of the chemical work and most of the experimental research and much of the morphologic studies have dealt with lesions of the aorta. From the standpoint of life, atherosclerosis of the aorta is of relatively minor importance. Moreover, the aorta is of highly complex structure histologically and is extremely rich in elastica.

Observations in rabbits in which medial sclerosis has been observed at first aroused a great deal of enthusiasm. Many have observed a high percentage of spontaneous medial sclerosis with calcification which resembles the peripheral arterial sclerosis described by Monckeberg. This type of change has been produced by the use of epinephrine and other drugs, but is not seen in the cholesterol experiments.

The common type of human arteriosclerosis is atherosclerosis which makes up 95 per cent of the sclerotic lesions (excepting syphilis) and is primarily in the intima, independent of the Monckeberg type.

Leary (36) thinks the fibrosis which is characteristic of human coronary lesions in the young is the characteristic lesion in cholesterol atherosclerosis in young rabbits. He concludes that the stages in the progression are distinguished with difficulty. He concludes from experiment that as far as

anyone knows no cholesterol is synthesized, in humans.

We see that the subject of the causation of arteriosclerosis is one in which there is much disagreement and much uncertainty. The ideas expressed by Allbutt (56) and others on hypertension as causing arteriosclerosis, must be considered. Even though the two go hand in hand, still the amount of sclerosis has no parallelism with the height of the pressure.

The problem of blood pressures in the diabetic is in itself a big chapter. The literature is divided in regard to the question of the blood pressure in the diabetic. Elliot (63) and Kahn (64) express the belief that the systolic blood pressure is not elevated in uncomplicated cases of diabetes. Kahn expressed the opinion that when hypertension is present in persons affected with this disease, the elevated blood pressure is suggestive of the presence of some other condition, which in itself is producing the hypertension. On the contrary many investigators believe that the blood pressure in diabetic persons tends to be elevated. Bell and Clawson (67) that 42.5 per cent of the patients in their series had a systolic blood pressure of 150 mm. of mercury or more, and they concluded that hypertension is 2.7 times as frequent in the diabetic as in non-diabetic persons over 50 years.

Kramer (68) in a study of 500 cases of d. m. found a systolic pressure of 150 mm. of mercury or more in 39 per cent. He concluded that the combination of hyperglycemia and hypertension occurs so frequently that it has ceased to

be looked upon as a coincidence. Other investigators have found a systolic blood pressure of 160 mm. or more in 25 per cent. Allbutt (57) states that arteriosclerosis of the low pressure kind is frequent in diabetes and runs in children often.

Major (66) made a statistical analysis of the blood pressure in a clinical series of cases of diabetes as compared with the blood pressure in a series of dispensary cases, with that in a series of hospital cases and finally, with that in a series of so-called normal persons. A necropsy series of diabetic cases was also studied, and the weights of the hearts and kidneys compared with the weight in the control series.

In elderly diabetic patients the systolic blood pressure according to the survey is slightly higher than that of patients seen in a dispensary series or in a hospital series, and is considerably higher than that in normal persons of the same age group. Although the mean systolic blood pressure in the diabetic series or hospital series, there is a greater tendency to a slight elevation of the systolic blood pressure in diabetic persons than those in the other series mentioned as shown by statistical study.

According to Sherrill (30) hypertensive heart disease is a latent manifestation in diabetes. It is uncommon to find it in the obese diabetic, but is a sequel to years of combined diabetes and obesity and occurs after the patient's nutrition has fallen to a low level. Since obesity is a

factor in producing heart disease in the non-diabetic, its presence would be expected to increase the incidence in diabetes. The solution of the problem of the relation of hypertension to diabetes is not an easy one. Hyperglycemia and impaired carbohydrate tolerance occurs commonly in hypertension. The view that hypertension produces arteriosclerosis is showed generally in which event sufficient visceral sclerosis involving the pancreas might be produced and involve the function of the Islands of Langerhans. The type of blood pressure occurring in diabetes mellitus is worthy of study. It is infrequent to observe the onset of diabetes with frank manifestations such as thirst, polyuria, and polyphagia in an early case of outspoken arterial hypertension. It is common to note its onset in hypertension of the senile type, that is, blood pressure with moderate systolic elevation. Sherrill thinks we can assume that the etiology of hypertension and diabetes may be the same factors of obesity, overeating, infection, prolonged worry etc.

Bogan and Morrison (14) quote Joslin as saying that the blood pressure in the diabetic is slightly below normal up to the 35th year and then is slightly above normal above 35 years.

What part this elevated blood pressure may play in the causation of the higher incidence and earlier development of the before-mentioned vascular changes is hard to determine, has not been determined and is a subject which requires more complete study than can be considered here.



The finding of high blood cholesterol in diabetic patients, especially those who are untreated or those who are poorly treated, and the fact that therapeutic tests prove that arteriosclerosis decreases following reduction of fat in the diet leads us to assume that excess cholesterol in the blood, whether it is due to abnormal ingestion or to a deranged metabolism, or total caloric intake including a protein factor, if not the direct cause is a contributing factor. In the words of S. Warren (19) "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 substance present."

Shepardson (23) says that in his studies the average cholesterol values are lower than heretofore and paralleling this reduction lower arteriosclerotic development. The definite lessening of the intensity of the damage resulting from prolonged exposure to diabetes consequent on the addition of insulin to diabetic therapy has resulted in a marked lowering of the average blood lipid content. The parallel reduction in the incidence of arteriosclerosis apparently necessitates the assumption that altered fat metabolism is a morbid factor in the development of vascular disease with diabetes mellitus.

In an earlier section of this paper the location of pathology following arterial damage and the proportion of incidence in these locations. In considering vascular pathology, we are not unmindful that the lymphatic system

is a part of the vascular makeup. The higher incidence of cataracts in the crystalline lens of the older diabetic is perhaps a lymphatic pathology in association with a deranged metabolism. Arcus senilis, likewise, is a not too well understood phenomenon involving the deposit of cholesterol and fatty granules. The diseased conditions involving changes in the veins and capillaries have been mentioned by Moschowitz.

We shall confine our discussion here to the two most common of the common localizations of vascular pathology, because it is here that we will be most often called upon to direct our prophylactic, diagnostic, therapeutic and prognostic attention. These two are the heart and the lower extremities.

There are innumerable reports all bearing out the abnormally high incidence of cardiac involvement directly associated with a diabetic process. This incidence is not confined to the older diabetic. Anderson (34) has reported a patient of 33 years dying of coronary disease with marked arteriosclerosis. Cullinan (22) reports an autopsy on a boy aged 27 dying of atheroma and coronary thrombosis. The heart had all chambers dilated, antemortem clots were in the appendix of the right auricle, and the left coronary artery showed much atheromatous degeneration. The aorta, especially the abdominal portion and main branches of the arch, pancreatic, splenic, femorals and their branches down to the dorsalis pedis all had marked atheromatous change. In searching the literature Cullinan in 1934 had found no account of a case in which there was such wide

spread arterial damage and death from coronary sclerosis at such an early age. McKittrick and Root (2, pg. 4) report atheromata in the aorta of a 16 year old boy.

Diabetes and angina pectoris have been recognized as clinical entities for many years, yet not until 1864 did Seegan comment on the occurrence of the two maladies in one patient. 19 years later, in 1883, Vergely emphasized the frequent association of these two diseases. He was so impressed with their coincidence that he published a paper emphasizing the importance of examining with caution the urine of all cases of angina. These early observations were soon confirmed in France by Dreyfous and Huchard, in Germany by Mayer, and in England by Ord.

Thereafter a large literature on this aspect of diabetes grew rapidly. Naunyn and Brunton, before the days of insulin, wrote at length on coronary disease in diabetes. More recently Warren and Root (70) of Joslin's clinic reported coronary sclerosis as a striking pathological finding in 65 per cent of 17 fatal cases over 40 years of age. Wilder (10) in 34 per cent of 49 fatal cases at the Mayo clinic and Strauss observed extensive cerebral and coronary sclerosis in 38 per cent of 54 fatal cases in his clinic in Berlin. Goskin, Strouse, and Katz (7) describe coronary sclerosis, thrombosis, infarction and myocardial degeneration as occurring in a high percentage in diabetics. Warren and Root (70) in a study of 17 patients over 40 years of age found on autopsy, three with extensive healed infarcts in the wall of the left ventricle. One had an aneurysm in the wall of the left ventricle, five showed

extensive sclerosis of the myocardium. Three showed marked to moderate sclerosis, and four slight sclerosis. In two occlusion of the main branch of the coronary artery, and in seven there was marked coronary sclerosis. In addition he found chronic vascular nephritis in 78 per cent as compared with 69 per cent in non-diabetics over 45 years.

Blotner (72) autopsied 77 fatal cases of diabetes mellitus at the Peter Bent Brigham Hospital. 35, or 45 per cent showed well marked disease of the coronary vessels and 8 or 10 per cent died of coronary infarction. Blotner mentions to our interest that 15 of the 35 coronary cases in his group had a definite hypertension with systolic pressures above 180 and diastolic of 80 to 140. The coincidence of coronary sclerosis and hypertension in nearly one-half of the cases is simply further evidence of general vascular disease in diabetes. Coronary thrombosis occurred in 23 per cent of those with coronary disease. Blotner thinks that the fundamental lesion in coronary thrombosis is in no way a process peculiar to diabetes but one dependent upon vascular disease. The coronary vessels show arteriosclerosis with a diminution in the lumen of the vessels and occlusion or a part of one of the artery's course by secondary thrombosis. There seems to be a striking similarity between the process and that of diabetic gangrene.

Nathanson (73) in 1932 reported findings of coronary disease in 100 autopsied diabetics. He considered of clinical significance only those cases that had marked sclerosis of the lumen walls with definite narrowing and partial oblit-

eration of the lumen of one or more large branches. 41 per cent showed severe coronary disease as compared with 8 per cent in an even larger number of non-diabetics of the same age group. His findings of incidence of hypertensive hypertrophy indicates that hypertension is only slightly more frequent in the diabetic than in the non-diabetic. He found a higher incidence of coronary disease in cases with complicating gangrene. The essential lesion of diabetes according to Nathanson is coronary sclerosis.

A very complete report has been made by Sherrill (30) in 1933, in which he analyzed 425 cases autopsied. He observed 16 cases of angina pectoris, making up 3.8 per cent of the 425 cases. The average angina case came 9.1 years after the diabetes. The average age of his group with coronary occlusion and diabetes mellitus was 62.8 years, and the diabetes was known to have existed on an average 9.2 years. In a control group the death age without diabetes was 57.8 yrs.

He explains this older age in the diabetic by lower activity due to diet restriction. Autopsy, however, showed further development of coronary disease in the diabetic, Sherrill found hypertension and arteriosclerotic heart disease in 7.5 per cent of this series. Only one case of rheumatic heart disease was found in 350, which is unusually low but comparable to findings in other series. He found arteriosclerosis in 100 per cent of cases developing the disease after 30 or 40 years of age.

Danzer (74) mentions an interesting aspect of this problem. He says that the easy recognition of diabetes by rou-

tine laboratory methods has led to confusion in the evaluation and management of certain imminent medical disorders. The following are several of the conditions often misinterpreted or improperly handled because the diagnosis and treatment of coexisting diabetes has been overemphasized. Nephrosclerosis with cardiac insufficiency, arteriosclerotic congestive heart failure, uremia, coronary angina, apoplexy and pulmonary tbc.

Hepburn and Graham (58) mention that in the early days of insulin therapy it was observed that in cases of diabetes mellitus with cardiovascular disease the symptoms of the latter persisted and in some instances progressed causing death despite the successful treatment of the diabetes. In E. K. G. study of 123 cases of the disease these men found 56 of these showing E. K. G. findings of significance. All of these patients were controlled and sugar free. Analysis of the abnormal group indicates (1) that in cases of d. m. suffering from vascular disease with signs of cardiac failure at the beginning of diabetic treatment, the cardiac failure progresses despite the control of the disease; (2) that in cases of d. m. without hypertension and showing no signs of cardiac failure at the beginning of treatment, the abnormal E. K. G. returns to normal in a fair percentage of cases following effective treatment for the disease. (15 in 56 returned to normal).

The diagnosis of cardiac pathology need not be discussed here as there is nothing characteristic of the cardiac disease with diabetes in this respect that is not true in the non-diabetic. the increased incidence and the more

rapid development of this complication must ever be borne in mind in the handling of the diabetic patient. One should exhaust all means at his command in the way of history, physical examination, X-ray, E. K. G., and laboratory work. One should be careful not to attribute severe cardiac pathology to the general disease by disregarding significant symptoms.

The greater incidence of coronary sclerosis and cardiac complications is only partly because insulin is prolonging the lives of diabetics. Patients with this disease show much higher incidence of arterial disease as revealed in the younger diabetics. Thus, although insulin has to a great extent eliminated coma deaths, it is responsible for a number of cardiac deaths. Insulin shock is a real hazard to the heart, and is closely associated with hypoglycemia. Anginal symptoms of varying degrees follow the administration of insulin. This makes the use of insulin in arteriosclerotic diabetics doubtful, also the lowering of the blood sugar by diet restriction. Goskin, Strouse, Katz (7) report 7 patients with clinical evidence of coronary sclerosis or angina, and their blood sugar was kept at a low normal level. In every case following the giving of insulin, there was a fall in blood pressure, rapid heart, irregularity, paroxysmal tachycardia, and even typical angina attacks. The E. K. G. showed confirmatory changes, usually indicating intraventricular block. Subjectively, the patient noticed a decreased sense of well-being, weakness, palpitation, precordial pain, prostration, etc. In one case twenty five insulin units brought on an attack of auricular fibrillation with ventricular extra-

systoles. The disease myocardium requires sufficient carbohydrate nourishment.

Hepburn, Graham and Duncan (58) state that in many cases of cardiovascular disease there is improvement following the removal of foci of infection.

Sherrill (30) emphasized that in long standing cases of cardiac involvement hypoglycemia is very deleterious. One should not be too rigid in restriction of protein or carbohydrate. Rapid fluctuation in blood sugar is to be avoided. Hepburn, according to Sherrill, has shown that insulin increases the average consumption of the carbohydrate in the heart from .87 mg. per gram per hr. to 3.06 mg. per gm. per hr.

Visscher (88) in in vitro experiments has shown that insulin causes a more or less transitory increase of the power of the cardiac fibers, which appears as a decrease in the ventricular volume necessary to do a given amount of work. There is no direct stimulation by insulin of oxidative metabolism in the isolated heart.

Blotner (72) stresses the fact that hyperglycemia should not be reduced too quickly because the factors of acidosis and sudden reduction of sugar levels seem to play some part in coronary thrombosis. Joslin (21) gives these general principles: The sclerotic heart needs blood sugar high and sudden reduction may lead to sudden death. Be cautious with those with angina pectoris. The more outspoken the alterations in the vessels the more conservatively ought insulin to be given. Use the ophthalmoscope.



Angina pectoris in diabetes reacts more favorably in treatment than non-diabetics. He feels justified in speaking hopefully to a diabetic with high blood pressure, because the treatment of the diabetes will act favorably upon both diseases.

The further treatment of cardiac complications depends upon the condition of the patient in relation to the cardiac pathology and must be further treated along the lines indicated in the specific treatment of heart disease.

The pathology of the peripheral vascular changes has been discussed previously. The occurrence of vessel changes in the lower extremities has been mentioned. Mc Kittrick and Root (2, pg. 41) report 44 autopsied diabetic patients dying after operation or of a surgical disease in the New England Deaconess Hospital between Sept. 1920 and Jan. 1, 1928. Acute infections and arteriosclerosis of the vessels of the legs and the heart account for 30 deaths. Gangrene of a foot or toe occurred 16 times and in 11 instances, it was associated with marked coronary sclerosis.

This association of gangrene with diabetes was first mentioned by Marchal (de Calvi) in 1852. Since then numerous contributions have appeared in the literature. We shall here review the more recent and more significant discussions of the strikingly frequent association.

Gangrene as defined by Buerger signifies the macroscopically visible portions of the body, in a dying state. (15) Invisible liquefaction of tissue being known as molecular death or ulceration.

The work of Morrison and Bogan (14) which was done with great care on 500 patients gives us very concrete evidence

of the early calcification in the legs of diabetic patients. They state that not only does the percentage of diabetics who have calcified vessels increase with age and duration of the diabetes, but the extent of the calcification increases in the same manner. What is the result of this early calcification and why should we attach so much importance to it?

163 or 4.08 per cent of 4066 diabetic admissions to the New England Deaconess Hosp. between Jan 1, 1923 and Jan. 1, 1928, were the result of gangrene or infection of a lower extremity of sufficient severity to require operation. Lesions of the lower extremity are by far the most commonly seen and most often become of serious importance. Steel (77) says that the chronic diabetic is always face to face with the specter of gangrene.

According to Eliason (4) and others, diabetic gangrene sets in 10-12 years earlier than arteriosclerotic gangrene. Vogel (78) reports his experiments in the observation of cases of arteriosclerotic gangrene and diabetic gangrene during the period of 1912 to 1931 at the Surgical clinic, Uni. of Leipzig. He observed 314 cases of gangrene. We learn from him that the ratio of men to women was of incidence more than 2 : 1. From his observations he is able to confirm that diabetic gangrene manifests itself earlier than arteriosclerotic gangrene. This compilation does not show an age difference of 10-12 years, but only one of 6.4 years. Vogel feels that since he has observed a greater number of cases than most men that this figure is more truly indicative of the actual incidence. The total mortality of the 314 patients amounted to 58.2 per cent. The mortality of

the arteriosclerotic gangrene alone was 56.8 per cent. The mortality of diabetic gangrene was 60.7 per cent. When the cases of death from coma are deducted from the mortality figure of diabetic gangrene, a mortality rate of 48.7 per cent is obtained.

Three types of uncomplicated gangrene are seen in the diabetic: (a) the arteriosclerotic, (b) the embolic, and what may be called (c) diabetic because of its distinctive features.

(a) The arteriosclerotic or senile gangrene is due to gradual occlusion of the larger vessels usually with superimposed attacks of thrombosis, the process of occlusion being more rapid than the establishment of collateral circulation with resultant atrophy, and if continued without trauma or infection, gradual mummification of the parts. This process may go on for months or years, and finally result in amputation because of pain, or, if allowed to proceed, to end in a dry, withering, gangrenous foot. Usually actual gangrene is precipitated, however, by some minor trauma. It is similar, apparently, to the senile gangrene of non-diabetic patients. As a rule, extensive collateral circulation is not present. Clinically, the diabetes is usually mild. Extensive general arteriosclerosis is present. Pain in the foot or leg is a prominent symptom and may be severe.

Frequently a past history of attacks of pain or numbness in the foot is obtained, indicating the thrombosis of one or more of the arteries by the time the patient comes for treatment. Fairly extensive gangrene involving one or more

toes with good pulsation in the popliteal artery, may be present, with but little evidence of collateral circulation; or there may be little actual gangrene. A foot blanched when elevated, mottled gray for some time when horizontal and dusky or reddish purple when dependent with or without one or small sluggish ulcerations, on the foot or lower leg. Marked hyperesthesia of the skin of the toes is frequently present.

(b) Embolic or thrombotic gangrene is sudden in onset, usually with severe pain or a sensation of burning caused by the sudden occlusion of a large vessel, due either to an embolus from some distant source (usually heart) or to a sudden development of an occluding thrombus on the wall of a vessel as a result of an acute infection, such as pneumonia. There is usually no previous history of circulatory disturbance in the leg and little of collateral circulation. Gangrene usually develops rapidly, its distribution depending largely on the vessel occluded. The prognosis is usually poor both in regard to limb and life. This type is probably more common in patients with diabetes than those without.

(c) Diabetic gangrene. This is the one type of gangrene, which, if any, is entitled to be called diabetic gangrene. It is not closely simulated clinically in non-diabetics except possibly in thrombo angiitis obliterans and is to a large degree preventable. There is usually a history indicating that some circulatory disturbance has been going on for months or maybe years, during which time an extensive collat-

eral circulation has been developed so that the patient may be nearly symptom-free and yet no pulsation can be felt in the dorsalis pedis artery and at times in the popliteal artery. The development of actual gangrene usually follows some very minor trauma, such as pressure from ill-fitting shoes or careless paring of a corn or callus. A small area of gangrenous slough may develop or infection set in. In the latter instance the swelling caused by the infection may shut off so much of the blood supply as to result in gangrene. On account of the deficient circulation, the infection is not localized so that, instead of an osteomyelitis or a localized collection of pus, the gangrene and infection spread. Red lines of infection extending along the lymphatics and veins are common. It is in these that septicemia is most likely to occur. The gangrene is rarely demarcated; Pain is usually but not always present, and it is rarely out of proportion to the acute process.

This type of gangrene may also occur in cases with pulsation in the dorsalis pedis artery. When neglected, local infection, such as an osteomyelitis of the phalanx, has extended to the foot and resulting swelling and thrombosis of smaller vessels resulting in necrosis of the neighboring soft parts.

This classification is adopted by Mc Kittrick and Root (2, pg. 105) and is also that of Labbe (81).

Buerger (15, pg. 481) adds that in appearance of the foot or leg there may be visualized at first an intense blanching with waxy cadaveric or ivory tint to the skin, or if the part be engorged with blood by virtue of intense venous stasis, a

cyánotic, livid hue will predominate. Later the color and appearance of the part will change as the condition of dry or moist or mixed gangrene is developed.

McNealy (24) thinks that arteriosclerotic gangrene in the diabetic is essentially similar to arteriosclerotic gangrene in the non-diabetic and is handled in much the same way. It occurs in the old age group. The diabetes itself, he thinks, is probably due to arteriosclerosis in the pancreas and is usually mild and fairly easily controlled. The difference he thinks is that once the diabetes is started, it hastens the arteriosclerosis. This acceleration is brought on by the fatty deposition in the intima and the medial sclerosis falls behind in the sclerotic picture.

As to etiology, Mc Nittrick and Root (2, pg. 110) dismiss the subject with the statement that except for cases which are embolic in origin, arteriosclerosis of a rather distinctive character is the background of all diabetic gangrene. Could one know how to prevent arteriosclerosis there would be little else to say or do about gangrene.

As to the treatment of gangrene, it, obviously, is impossible to review the literature in the limited space allotted here. Mason (61) states that the possibility of avoiding surgical interference of a radical nature in the gangrene patient is greater than formerly. In a series of 24 cases 36 per cent were treated without surgical interference in the Royal Victoria Hospital in Montreal.

Treatment by rest and warmth with strict control of the diabetes through insulin and diet. Patience and per-

sistence are essential. Moist dressings are to be avoided in all cases. Daily passive elevation and lowering of the extremity and in some cases voluntary exercise. Mason insists that compensatory circulation can develop with time even when the larger vessels of the leg and foot show marked calcification.

Steel (77) would have us realize that before the introduction of insulin the mortality of diabetic gangrene approached 100 per cent. With proper insulin and dietetic control the present death rate is about that of other types of wet gangrene. Adequate collateral circulation, he says, can be accomplished by rest, heat, cardiac stimulants, and the use of vasodilator drugs and position. His patients are confined to bed with the lower half of the body in a continuous hot air electric light bath at a temperature of 105 degrees to 110 F. The feet are soaked twice daily in warm saline solution for 15 minutes at a temp. of 120 degrees F. The skin is sprayed with mineral oil. Buerger's postural exercises are used three times daily. Digitalis and nitroglycerine are given to full physiologic desired effect. The effects of intravenous sodium citrate as a vasodilator are often of value. A change in the skin color of the face, from a waxy pallor to a healthy pink, following several weeks of treatment is indicative of success following the conservative treatment. The visible effect on the skin of the feet is less marked but may be sufficient to save a threatened member or limit an existing gangrene. Avoid local antiseptics and all

mildly traumatizing types of physical therapy, i. e. high degrees of heat, intermittent therapeutic lamp treatment, diathermy, suction apparatus and massage. When the gangrene has developed and systemic toxemia is slight, make an effort to save the leg. If infection is the predominating cause, incise the area freely in such a way that there is dependent drainage and no retention pockets. If the pulsating artery is present in the foot the leg can be saved in about 25 per cent of the cases. It can be saved in about 10 per cent of the cases with advanced arteriosclerosis without foot pulse.

The indications for non-operative treatment are (1) a superficial ulceration or gangrenous patch on the foot or lower leg with palpable pulsation in the dorsalis pedis artery; (2) a superficial lesion without palpable pulsation 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. The objects of this non-operative treatment are to remove existing infection, to remove gangrenous slough and to try to stimulate circulation and growth of new epithelium.



In infection rest in bed with foot level to afford best circulation to fit the need. Many solutions are used and McKittrick and Root favor Dakin's solution applied in the standard and accepted method. Hexylresorcinol, Dichloramine-T and other solutions are used. Proper and well-regulated use of ultra violet rays is of benefit.

Removal of the gangrenous slough may be accomplished by moist dressings during the day, changing to lanolin or boric ointment during the night. Gentle traction used when definite deparation occurs.

Stimulation of circulation may be done by the methods of Buerger (15, pg. 436). This is useless in the presence of extensive gangrene and should not be used in the presence of unlocalized or recent infection. These exercises aid in increasing local circulation. Active exercise is efficacious when all gross infection has quieted down and healing has started. Other agents such as typhoid vaccine administration, diathermy, vibrators etc. are of questionable value.

The indications for operation : (a) Gangrene of one or more toes; (b) severe pain, with or without a small area of local gangrene which has not yielded to conservative treatment; (c) deep or extensive infection which endangers life because of the patient's poor general condition; (d) a severe diabetic crisis demanding relief from the burden of sepsis; (e) economic exhaustion.

We cannot possibly consider the manifold operations done on the patient with a gangrenous process. Interesting are the results of operation.

Levin and Dealy (80) say, "The cases of gangrene are a serious problem. Of ~~44~~ gangrene patients 45 per cent died. Of all the thigh amputations, only one in every two survived, the mortality being 50 per cent. Such a mortality is certainly a challenging one and can be reduced...only by adherence to the following points: (1) an earlier resort to surgery in cases demanding operation. (2) No surgery at all unless it be radical surgery. Preliminary toe amputations or other minor procedures mean secondary amputations at a higher level with a progressively diminishing chance of survival. (3) Close observation in the cases of dry gangrene, ..... (4) prompt, radical amputation through the thigh in cases of the moist type or with infection, avoiding drainage wherever possible. (5) the scrupulous avoidance of a tourniquet for gangrene of any type. (6) Impartial selection of the anesthetic to be used.

McKittrick, and Pratt (83) remind us that every case of diabetic gangrene is actually or potentially infected. Eisenbud (82) states that it is impossible to formulate a routine standard treatment for the management of the diabetic requiring surgical care, as the details of the procedure will vary with the individual metabolic state of the patient; as well as with the nature of the surgical condition for which the patient is to be treated. This serves to emphasize the fact that there is no place in medicine where the cooperation of the medical man and the surgeon is more important than in diabetic or arteriosclerotic gangrene.

There is no treatment of a disease which will parallel the effectiveness of prevention of that disease. How can the medical profession and the patient cooperate in preventing not only diabetes but also the cardiovascular complications which now cause over 50 per cent of the deaths in diabetic patients today?

Obviously, the diabetic patient has nothing to say about the race or the ancestors which he claims. Therefore he has little to say about a familial trend toward the disease itself, cardiovascular disease tendencies, or obesity trends. However, in our review of the causes of cardiovascular disease in diabetes, many factors have been mentioned many of which can be controlled by the patient himself to an appreciable extent.

Hygiene of the feet is essential in the older diabetic. Joslin (1) suggests a beauty parlor for diabetic feet. Daily baths are necessary. The prevention of trauma is important, since that is a very frequent history in gangrene. As to cleanliness, Lemann (9) quotes Joslin in the statement that if 90 per cent of diabetic patients could be persuaded to wash their feet carefully each night, 90 per cent of gangrene would disappear. Burning, imperfect fitting shoes, and epidermophytosis all play a big part in inciting gangrene.

If each diabetic patient could observe the effects of gangrene another patient would be won over to the group striving to prevent this specter which is face to face with the chronic diabetic.

Diabetic patients should be particularly careful about infections about minor cuts, pared corns and calluses and infections about the toe-nails. All possible foci of infection should be cleared up because of the possible relationship to the arteriosclerotic process.

Syphilis plays a part in the bringing on of gangrene according to Lemann (9) so this factor should be eliminated by the diabetic patient. It is well to bear in mind the fact that there is a predominance of diabetes in women from the age of 35 up and this likewise holds true in gangrene.

From the standpoint of the medical man his problem after the patient has presented himself at an early stage in his disease is to encourage that patient to control his physiological processes and to give definite instructions for the effecting of this control. Dr. F. M. Allen (92) says that the surest way to produce gangrene is to keep the patients alive but to only half treat them. Gangrene is not heaven-sent but is earth-born.

How are we going to control diabetes? What criteria are we going to use in determination of the true progress of our control measures?

The most obvious criterion is that of the urinalysis. We have seen, however, that arteriosclerosis develops even in the presence of a urine free from sugar. Blood sugar determinations are of great value as are sugar tolerance curves. Check on the quantitative intake and output of carbohydrate is exceedingly valuable.

Gray (50) has stressed the analysis of the blood fat as being very valuable both in diagnosis and in prognosis.

Rabinowitch (91) agrees that the lipid content of the blood is a better index of the course of the disease than the blood sugar level. With high cholesterol the slightest dietary deficiencies cause persistent hyperglycemias. There is a striking relationship of high blood cholesterol with gangrene. Increased cholesterol is not compatible with a favorable progress. The best behaved patients have the lowest cholesterol values. Bloor (98) says that in general the amount of blood lipins increases with the severity of the disease. He has found that a diet high in fat does not influence the fat in the blood unless over 80 per cent of the total calories are taken in this form.

Over nutrition is followed by an increase in blood cholesterol. Diabetic coma is associated with cholesterolemia in every instance. White (52)

Sansum, Blatherwick and Bowden (93) have proved by experiment that high blood fat alters the glucose tolerance.

How can high blood cholesterol readings be prevented? Control of obesity is important. Normal or only slightly above normal weight should be insisted upon. Insulin therapy has given an inroad to the reduction of cholesterol values. In 1916 (48) Bloor found the average cholesterol to be far above normal--424 mg. in 100 cc. In 1932 (98) he found the average about 212 mg. per 100 cc. This change has no doubt been brought about by insulin therapy.

In Rabinowitch's clinic (19) the observation has been made that with a high carbohydrate-low calorie diet, Xanthosis is rare and gangrene is disappearing. Since 1931

they have had 36 cases of gangrene but 25 had gangrene on entrance and 11 evidently developed it later. Without exception everyone of these failed to follow the treatment. Rabinowitch (98) makes another observation that in 500 cases of severe surgical complications he had only 16 failures with the high carbohydrate diet which gave all the cardiac patients sufficient sugar.

McNealy and Shapiro(24) advocate a high carbohydrate diet with insulin. It is preferable to the high fat diet without insulin because of the lipemia which encourages intimal atheromatosis, and they think this factor which not only hastens the vascular occlusion but also paralyzes the development of collateral circulation.

Richardson (99) in discussion of Newburgh and Marshs' high fat and low carbohydrate diet points out that some claim such a diet is not well absorbed or borne by the body. He, Richardson, says that acidosis cannot always be demonstrated but that the patient does not feel as well as he should. He mentions Allen's finding that fat has a definite influence on the amount of insulin necessary, which falls in line with Sansum's ideas.

Richardson at present feels that with insulin there is no bar on the amount of carbohydrate so the insulin dosage can be raised accordingly. He has given up to 200 units daily. From the practical standpoint the high carbohydrate diet is better in that the patient adheres to the diet better, feels better and by this diet a balanced ratio between fat and carbohydrate is brought about, and at the same

time the possibility of fat causing arteriosclerosis is prevented. Richardson found that with fat reduced, the carbohydrate in the diet can be greatly increased in many patients without showing sugar in the urine or having an increased blood sugar.

Newburgh (101) is inclined to support the high fat diet in that it affords more calories with perhaps less bulk of food necessary. This diet obviates the necessity for such high insulin dosage. He attributes the lipemia and subsequent tendency to arterial change to an abnormal metabolism due to the disease itself and not to the ingestion of high fat.

Joslin (13) admits that the last chapter in the treatment of diabetes mellitus is not complete. He recognizes the fact that lower cholesterol values are related to insulin, but not related to the duration of diabetes. He favors a tendency to decrease fat and increase the carbohydrate in the diet but does not go to the same extreme as does Richardson. He stresses the importance of avoiding overfeeding. This last idea is supported by observations in the Allen era from 1914-1922 where control of calories brought a marked lowering of death from coma.

As evidence of this unwritten chapter we have only to refer to the recent work of Best, Hershey and Huntsman (106,107,108) in which they show that lecithin aids in the transportation of fatty acids to the liver and are there de-saturated and become available for use. The choline in

lecithin prevented storage of fat in the liver of depancreatized dogs. We still do not know the exact mechanism of the use of liver in pernicious anemia, which is still an unwritten chapter. Perhaps the answer to the relationship of hypercholesterolemia may be solved by further study on the relation of thyroid gland and potassium iodide to the development of atherosclerotic changes in rabbits as suggested by Turner and Khayat (109,110).

#### Summary and conclusions:

In this thesis we have considered the more important aspects of cardiovascular changes complicating diabetes mellitus. From this study we can come to some very definite conclusions which are here enumerated:

1. Cardiovascular complications have replaced coma as the most important cause of death in Diabetes today. About 50 per cent of the deaths in this disease today are caused by these complications. Coma as a cause of death in this disease has fallen from 60 per cent in 1914 to 5 per cent in 1933.

2. The localization of the pathology in the fatal cases is as follows:- Heart, 19.1 per cent; legs, 13.2 per cent; brain, 7.2 per cent; and kidney, 4.5 per cent.

3. The general diabetic death rate is increasing in the U. S. and the world and is now 22 per 100,000. The rate in the U. S. is greater than in any other country.

4. Arteriosclerosis occurrence approaches 100 per cent in all cases with the onset of disease after 40 yrs. of age and demonstrable vascular changes occur in about



85 per cent of cases with disease of duration of five years or more.

5. Evidence points to the conclusion that there is a special type of vascular change occurring often in the diabetic and characterized by marked intimal atheromatosis and atherosclerosis in which collateral circulation development is retarded.

6. Heredity, obesity, foci of infection, persistent hyperglycemia, acidosis and syphilis play a part in the causation of cardiovascular pathology in diabetes mellitus. Diet abnormalities including excessive caloric intake, excessive fat in the form of cholesterol, protein, the deranged metabolism of the disease itself causing deficient intracellular metabolism in the walls of the blood vessels, play a large part in the etiology.

7. Endocrines play a part in this premature change ~~as~~ evidenced by animal experimentation.

8. High blood pressures in diabetics play, in all probability a very small part in the increased incidence of arteriosclerosis in diabetes. The blood pressure in the diabetic tends to be somewhat elevated.

9. Evidence would indicate that arteriosclerosis occurs from 6.5 to 10 years earlier in the diabetic than in the non-diabetic.

10. Most men agree that hypercholesterolemia in the blood of diabetics is an unfavorable indication but the cause of this association is still under question.

11. Animal experimentation has not satisfactorily explained the mechanism of the development of atherosclerosis.

12. The incidence of 41 per cent of coronary disease in patients above 50 years of age with diabetes as compared with incidence of 8 per cent in the non-diabetic group of the same age leads to special consideration of cardiac complications. This complication also requires special therapeutic consideration.

13. Gangrene is a very frequent and serious complication and is for the most part preventable by hygienic measures, prevention of trauma, and careful control of the disease by diet and insulin. Normal weight should also be insisted upon.

14. There is at present a trend toward the use of the high carbohydrate-low calorie diet in the treatment of diabetes mellitus.

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