Degenerative Vascular Lesions and Diabetes Mellitus

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INTRODUCTION

THE CAUSES of death in diabetic patients have undergone a marked change since Naunyn published his classic description of the disease at the turn of the present century (1). He reported 49 patients with autopsies, of which 13 died in diabetic coma and 19 of tuberculosis. Only four died of arteriosclerotic disease. Moreover, the average duration of the disease, was only 2.6 years. Only two patients lived over 10 years with diabetes.

Of 527 diabetic autopsies performed between 1923 and 1938 reported by Warren in 21 per cent the duration was over ten years. In the present series, the patients lived an average per cent of 9.8 years, with 51 per cent exceeding ten years. This was longer than in previously reported series of diabetic autopsies (Warren), but still considerably below the life expectation of normal persons. Coma and tuberculosis were rare causes of death, but about two-thirds of the series succumbed to arteriosclerotic disease. In the future, new forms of treatment and the recognition of extrapancreatic factors in the disease may again change the predominating pathological findings and the present emphatic role of premature arteriosclerosis may be modified.

A study of diabetic autopsies in hospital patients includes the most gravely complicated cases and, therefore, gives a one-sided view of diabetes. Against this background should be considered the great number of mild, living cases, still outside the hospital. However, it is only by comparison of autopsied cases that the influence of changing types of treatment, duration of the disease and other factors, upon the course of the disease and its complications may be assessed.

This present series includes diabetic patients who came to postmortem examination at the New England Deaconess Hospital in the years 1940 through 1945. The group includes cases of unusual duration not only with onset in middle life, but also twelve patients whose diabetes began in childhood. The outstanding feature is the extraordinary degree of pathological change found in patients in whom diabetes of long duration had not been well controlled.

MATERIAL

Of the 110 patients, 59 females and 51 males, 79 had been followed clinically for at least six months

before death. Fifteen had been observed at intervals over 15 years, and one patient for over 29 years. Seventy-eight were listed as white Americans. Ten were Hebrews. The remainder included Italian, English, Danish, Irish, Greek, and Syrian persons. All autopsies were done under the direction of Dr. Shields Warren, Department of Pathology, New England Deaconess Hospital.

DURATION OF DIABETES

The diagnosis of diabetes was proved in each instance by the finding of hyperglycemia with glycosuria. When the duration of antecedent polyuria and polydipsia was known, the onset could in some cases be set back one or two years before glycosuria was first found. However, the onset of diabetes was often so insidious that the presumed date of onset must often have followed the actual date by many months or even years. In several cases, diabetes was found when the patient applied for insurance or developed a fatal disease. Among the 19 patients in this series with a record duration of under two years, two died of gangrene. Only one had had a urine examination within five years of the time the diagnosis was made. Fourteen could recall no previous examination. Seven had lost over thirty pounds in weight at least five years before the diagnosis was made. One feels certain that diabetes had been present more than two years in many of these persons. Similar presumed errors in the onset date must have occurred in patients with longer known durations. The date of onset was probably more ac-

TABLE I

DURATION OF LIFE IN 110 DIABETIC SUBJECTS EXPRESSED IN YEARS AND IN PERCENTAGE OF NON-DIABETIC LIFE EXPECTANCY FULFILLED

Age at Onset	Males			Females			Total		
	Number of Cases	Average Duration In Years	Average Life Expectancy Fulfilled Percent	Number of Cases	Average Duration In Years	Average Life Expectancy Fulfilled Percent	Number of Cases	Average Duration In Years	Average Life Expectancy Fulfilled Percent
10-19	5	11.0	20	5	13.4	23	10	12.2	22
20-29	1	6.0	13	1	4.0	9	2	5.0	11
30-39	2	4.9	15	5	14.2	38	7	11.7	33
40-49	13	11.5	45	9	12.5	45	22	11.9	45
50-59	14	9.9	44	23	11.0	54	37	10.6	50
60-69	10	11.0	82	13	6.4	30	23	8.4	53
70-79	6	2.8	35	1	3.3	58	7	3.3	39
80-89	—	—	—	2	1.8	38	2	1.8	38
	51	9.5	47	59	10.2	43	110	9.8	44

curate in the younger patients, whose disease usually begins in an explosive manner.

Table number 1 shows the average duration of life and life expectancy fulfilled for the various age groups. The males lived an average of 9.5 years, the females 10.2 years. The average for the whole group was 9.8 years. In nineteen, the known duration was under two years. Twenty-five lived with diabetes for 15 years or more and nine for over 20 years. The longest duration was a male, who developed diabetes at 47 years. He died at 82 of a myocardial infarct after 34.5 years of diabetes. The average duration of 651 patients in this clinic dying in the Charles H. Best era (January 1944 to May 1946) (2) was 14.1 years. This is 4.3 years longer than the duration of 9.8 years in this series. However, the former group included also patients dying at home. These 110 patients died in the hospital, many being emergencies.

The percentage of long duration cases autopsied at this hospital has increased. In the series of Warren (3) of 527 diabetics autopsied from 1923 to 1938, 12% were over 15 years duration. In our group, 23% were over 15 years.

As shown in Table number 1, the life expectancy fulfilled after diabetes had developed was only 44% for the group as a whole. These life expectancy figures are for the general population and based on Metropolitan Life Insurance Company statistics (4). Eight patients actually exceeded their expectancy. One patient developed diabetes at 60 years; he lived 24 years more, or 162% of his life expectancy. The fulfillment at the various age levels is more important. Thus, the ten patients in table number 1, with onset of diabetes in the second decade lived 12.2 years, longer than any other age group. However, they lived only 22% as long as they would have been expected to live if

they did not have diabetes. The longest duration for a childhood case was 20.9 years (case number 3761, table no. 2) who lived only 34% of her life expectancy. In contrast to the younger group, the patients with onset in the sixth and seventh decades did not live as long in actual years. However, they fulfilled a much greater proportion of their life expectancy, namely 50 and 53%. This is an indication of the greater severity of diabetes among the young. Hanssen (5) made a careful survey of diabetes in Bergen, Norway. He found a similar high mortality among the juvenile cases. In males under 30 years, the mortality was 8.8 times the expected number; in females 6.2 times. This was considerably higher than in the older age groups.

One of the most striking facts elicited in this series is the severity of the vascular pathology found in the younger patients dying with diabetes of long duration. At autopsy, these patients showed severe premature arteriosclerosis with coronary occlusion, degenerative renal sclerosis, and even gangrene. Table number II in order of duration lists those 12 patients with onset of diabetes before thirty years of age. The first five all died within six years of the onset of the disease. They showed essentially no arteriosclerosis. The last seven lived for 14.2 to 20.9 years after onset. They all exhibited severe vascular degeneration.

In the first five patients, with durations of six years or less, no significant degenerative disease was found at postmortem examination. They died before 32 years of age of coma or infection and none showed significant coronary or renal arteriosclerosis. None had hypertension. These are the expected normal findings in non-diabetic persons of 30 years or less.

There is a marked contrast between these findings

TABLE II

Clinical and Pathological findings in twelve patients whose diabetes began under thirty years of age

Case Number	Sex	Age Onset Years	Age Death Years	Duration Years	History of Coma	Hypertension	Retinitis	Coronary Arteries	Nephritis	Principal Cause of Death
22,682	F	19	19	0.2	Yes	No	—	Normal	None	Coma
23,935	M	18	19	1.6	Yes	No	No	Normal	None	Coma
19,972	F	27	31	4.0	No	No	—	Normal	Pyelo-,Mild	Hepatitis
21,585	M	11	16	5.5	No	No	—	Normal	None	Sinusitis, TBC
16,099	M	22	28	6.0	No	No	No	Normal	None	Appendicitis
7,695	F	18	32	14.5	No	Yes	Diabetic	Occluded	Glomerulo-	Glomerulonephritis
9,500	M	13	27	14.7	Yes	Yes	Proliferans	Occluded	Pyelo-,Intercapillary	Pyelonephritis
9,111	F	11	26	15.0	Yes	Yes	—	Narrowed	Arteriolarsclerotic	Arteriolarsclerotic Nephritis
8,405	M	10	25	15.4	Yes	Yes	Proliferans	Narrowed	Intercapillary, Pyelo-,	Intercapillary Nephritis; After Sympathectomy
6,884	F	12	29	16.5	Yes	Yes	Diabetic	Sclerosis Present	Healed Pyelo-,	Hypoglycemia
6,346	M	12	30	17.7	Yes	Yes	Proliferans	Occluded	Intercapillary Pyelo-,	Intercapillary Nephritis After Sympathectomy
3,761	F	10	30	20.9	No	Yes	Proliferans	Narrowed	Arteriolarsclerotic	Arteriolarsclerotic Nephritis

and those present in the seven young patients all dying before 33 years of age with diabetes of 14.5 years or more duration. Three of the latter group had coronary occlusions; in three others the coronary arteries were significantly narrowed by atheromatous placques. All had serious kidney damage, and six of the seven died principally of renal disease. Intercapillary glomerulosclerosis accounted for two deaths. In these the typical ball shaped masses of hyaline material in the glomeruli were present. Pyelonephritis, nephrosclerosis, and chronic glomerulosclerosis accounted for four deaths. All seven patients had hypertension. Four had retinitis proliferans, a fifth had diabetic retinitis. Tolstoi (6) has suggested that diabetes might be another manifestation of a generalized vascular disease rather than a cause. If this were so, one would expect to find vascular disease in short duration juvenile cases. However, we found significant changes only in the cases of long duration.

In each of these seven long duration diabetic patients, the course of the disease had apparently been benign for the first five or ten years. It is true that coma had occurred in five of the seven and indeed repeatedly in cases number 9500, 6884 and 6346. In our experience, those juvenile patients who have had repeated attacks of coma show by far the highest incidence of visibly calcified vessels by X-ray and other stigmata of degenerative disease.

These autopsied patients are not characteristic of all juvenile diabetic subjects. It is true that in a considerable proportion of the twenty-year cases with onset in youth, arteriosclerosis albuminuria and retinitis are found (2). Dolger (7) stated that of 200 young patients with long duration of diabetes "not one escaped retinal hemorrhages, albuminuria, and/or hypertension in varying degree. Every diabetic would seem at present to be doomed to the inexorable development of vascular damage despite the benefit

TABLE III

Comparison of Patients with Diabetes under Five Years with those over Eleven Years

	0 to 5 years	11 years or more
	Duration of Diabetes	
Number of patients	32	53
Female	16	24
Sex — Male	16	29
Ave. Age at Death	60.6 yrs	61.6 yrs.
Ave. Age at onset	56.7 yrs.	46.0 yrs.
Onset under 30 yrs.	5 (16%)	7 (13%)
Insulin over 20 U.	14 (52%)	29 (56%)
Ave. Bld. Sugar 150 mgm % or over	13 (68%)	30 (68%)
Death primarily cardiovascular	17 (53%)	36 (68%)
Severe Coronary sclerosis	19 (61%)	40 (75%)
Degenerative renal lesions	15 (47%)	30 (57%)
Degenerative pancreatic islet lesions	21 (66%)	42 (81%)
Hypertension	16 (50%)	36 (68%)
Absent Dorsalis pedis pulsations	8 (25%)	24 (46%)

Percentages are adjusted for charts lacking necessary data

of insulin in prolonging life." However, in the group of 300 juvenile diabetics who have survived 20 years of diabetes studied by White (7a), 15 have been proved completely free of degenerative disease. These patients as of June 1947 have been examined especially in regard to blood pressure, renal function, capillary fragility and electrocardiogram, as well as intravenous pyelograms, X-rays of the legs and of the aorta for arteriosclerosis and finally by an ophthalmologist. These patients have demonstrated that even in youthful diabetics vascular and renal complications may be prevented for at least 20 years.

Since diabetes markedly accelerates degenerative processes, vascular complications are more common in long duration cases. This was shown above in Table II for the younger patients where degenerative disease occurred exclusively in the long duration patients. There was an appreciable increase with duration of diabetes in the incidence of complications when the group as a whole was considered. Table III shows the percentage of patients with various complications divided into those with a duration under five years and those with a duration of eleven years or more. The first, or short duration group, contained 32 patients; the eleven year or more group contained 53 patients. The two groups are similar in regard to sex distribution and age at death as well as severity of diabetes as measured by insulin dosage and average blood sugars. Both groups were found to have a striking number of complications. However, the longer duration patients showed a 10% to 27% greater incidence of cardiovascular deaths, degenerative renal and pancreatic lesions, hypertension, and absent dorsalis pedis pulsations. This cannot be explained on the basis of age at death, since the long duration cases lived only an average of 1.0 year longer than the short duration cases.

Insulin has enabled persons with diabetes to live long enough to develop degenerative complications. Thus the mortality has become greater in those with long durations of the disease. This is shown in Table 40 of the 8th Edition of the Treatment of Diabetes Mellitus (2). The mortality for all patients attending this clinic in the first five years of the disease in the 1944 to 1946 period was only 15%. It increased to over 20% in each five year group of over 10 years duration. This represents a reversal of the experience before insulin. Hanssen (5) found a similar rise in mortality with duration of the disease. However, he noted that the mortality rate in the younger patients actually decreased with duration. His mortality rates were low in juvenile diabetic subjects of over 10 years duration. He did not encounter such patients developing degenerative diseases. Likewise Lisa and Hart (8) found no evidence of significant arteriosclerosis in eight juvenile diabetics. However, none of their eight patients had had diabetes over 10 years. It is notable that some pediatric textbooks do not emphasize the severe vascular disease that appears in diabetic children, as described by Eisele (9) and Rosenbusch (10).

CAUSES OF DEATH

The autopsy protocols were examined and correlated with the clinical records. A principal, rather than a precipitating, cause of death was assigned to each case. For example, patients dying with a coronary occlusion after an amputation for gangrene were classed as gangrene deaths. In numerous autopsies, a striking number of severe lesions were found. On pathological grounds alone, these patients could have died from several causes.

In Table IV, the pathological data of the 110 autopsies are summarized. The first column lists the occurrence of the principal causes of death. Conditions present as a complication, but not as a principal cause of death are listed in the second column. For example,

TABLE IV

Summary of Pathological Findings in Diabetic Patients

	Principal Cause of Death	Also Present
1.. Diabetes		
Hypoglycemia	1	2
Coma	4	1
Total	5	
2. Vascular Degenerative Disease		
Myocardial infarct	29	43
Myocardial failure	9	39
Cerebral hemorrhage or thrombosis	5	3
Mesenteric infarct	2	0
Gangrene of extremity	10	3
Nephritis (excluding pyelonephritis)		
Intercapillary	2	3
Arteriolarsclerotic	6	29
Glomerular	1	2
Pulmonary embolus	1	9
Arteriosclerosis, all degrees	0	108
Total	65	
3. Infections		
Pyelonephritis, chronic	3	18
Lobar pneumonia	2	1
Abscesses, lungs	2	0
Cholecystitis, acute	2	3
Appendicitis, acute	2	0
Septicemia, pyemia	3	6
Tuberculosis		
Sinuses	1	0
Elsewhere	0	3
Duodenal ulcer perforated	1	3
Hepatitis, acute	1	2
Carbuncle	3	1
Syphilis	0	2
Rheumatic valvular heart disease	0	4
Total	20	
4. Carcinoma		
Total	16	8
5. Miscellaneous		
Hemochromatosis	2	1
Fracture, left femur	1	0
Periarteritis nodosa	1	0
Cirrhosis	0	12
Pathological changes in pancreatic islets	0	87
Total	4	
Total Deaths	110	

8 patients died of cardiac failure; in 39 others failure was present at time of death, but was not the principal cause of death.

Of the 110 patients, five died of disease directly attributable to diabetes itself (coma 4, hypoglycemia 1). Another group of 20 patients died of disease not related to diabetes mellitus (cancer 16 and miscellaneous 4). Of the remaining 85 patients (65 dying with vascular degenerative disease and 20 with infections) diabetes was undoubtedly a critical factor. Thus in 90 subjects or 82% of this series, diabetes was either directly or indirectly responsible for death. Before the advent of insulin, 67% of the patients of this clinic (2) died within the first five years of their disease, principally of diabetic coma. Now that acidosis can be prevented, only 16% of the patients die within the first five years of their disease. However, having passed the Scylla of coma by means of insulin diabetic persons eventually flounder upon the Charybdis of premature degenerative disease.

Because diabetes alone usually does not cause death, the word "diabetes" is often omitted from death certificates. Physicians are interested in the precipitating cause of death; this often is a disease which has been greatly aggravated or accelerated by the diabetes. However, if the diabetes seems not to be an immediate factor at the time of death, it may not even be entered on the death certificate. In this series there were nineteen patients who took no insulin before their final illness. Some had had diabetes as long as 16 years. The omission of this type of patient from mortality figures is very common and tends to minimize the importance and prevalence of diabetes. Joslin and Lombard (11) found the word "diabetes" omitted from death certificates of about one-third of 744 diabetic persons. Lundberg, quoted by Hanssen (12), stated that "It is probable that the time will come when it will be quite impossible to employ mortality figures for estimating the frequency of diabetes in the population."

DIABETIC COMA

From 1914 to 1922 coma accounted for 42% of the diabetic deaths in the experience of this clinic (2). With the advent of insulin, the coma death rate fell precipitously. Now only 3% of the deaths are associated with coma. The rare complications of diabetes are not curable; coma is, and such deaths are usually avoidable. In this series four patients died following diabetic acidosis. Three of these deaths perhaps could have been avoided if early and adequate treatment had been given. The fourth died with a coronary occlusion after apparent recovery from acidosis. A summary of these cases follows:

Case number 5233. A 67 year old female with diabetes of 22 years duration was transferred from another hospital after unconsciousness of 12 hours and anuria of several hours. Respirations were shallow, 30 minutes. Blood pressure was systolic 40 mm. Hg.; diastolic 0 mm. Hg. Blood sugar was 687 mgm%., blood carbon dioxide 10 mil. mol. per liter. She was given 400 units of insulin in 2 hours and intravenous normal saline solution. Anuria persisted and she died nine hours after admission. At autopsy, a

small focus of bronchopneumonia; petechial hemorrhages in brain, epicardium and pleurae; generalized arteriosclerosis; considerable glycogen in the cytoplasm of the hepatic cells were found. This patient is unusual because of the long duration of diabetes. She had not been seen for 18 years before final admission. No history was elicited from the family of previous serious difficulties with her diabetes.

Case number 23935. A 19 year old male with diabetes of 1.6 years duration broke his insulin syringe three days before admission. He was transferred from another hospital after unconsciousness of about 12 hours. During the preceding 24 hours he had received at least 500 grams of glucose. Temperature was 104° rectally, blood sugar 678 mgm%; and blood carbon dioxide 10.5 mil. mol. per liter. There was no acetone or diacetic acid in the urine. The blood contained a negligible amount of acetone bodies. After 220 units of insulin and intravenous salt solution, blood sugar fell to 220 mgm.% and blood carbon dioxide rose to 18 mil. mol. per liter. The patient died nine and one-half hours after admission without regaining consciousness. At autopsy, pulmonary congestion and edema, arteriosclerosis of aorta and liberal amounts of fat and glycogen in the liver were found.

This patient has been discussed in a case report by Root and Leech (13) as illustrating hyperglycemia stupor.

Case number 22682. A 19 year old female with diabetes of two months, never treated, was transferred from another hospital after a respiratory infection of four days and unconsciousness for most of 36 hours. On examination, blood pressure was 72 mm. Hg. systolic and 40 mm. Hg. diastolic; there was unconsciousness and severe pharyngitis. Blood sugar was 534 mgm.% and carbon dioxide 5 mil. mol. per liter. She was given 200 units of insulin and intravenous saline solution. Four hours after admission blood sugar was 165 mgm.%. She excreted only 20 cc. of urine and died six hours after admission.

Autopsy showed purulent sinusitis of the sphenoid and ethmoid, pulmonary congestion, early bronchopneumonia, atherosclerosis of aorta and glycogen in the hepatic cells.

This patient had a respiratory infection which induced coma in previously untreated diabetes.

Case number 5792. A 59 year old female with diabetes of 24 years duration complained of nausea, vomiting, and a "congestion" in the chest for two days before entry. Examination revealed a fully conscious patient with slight Kussmaul type breathing. Blood pressure was 100 mm. Hg. systolic and 60 mm. Hg. diastolic; blood sugar 512 mgm.% and blood carbon dioxide 9 mil. mol. per liter. Eighteen hours after admission, after 202 units of insulin and 2000 cc. of normal saline intravenously, blood sugar was 57 mgm.% and carbon dioxide 18 mil. mol. per liter. A later blood sugar was 244 mgm.%. She died 36 hours after admission in congestive heart failure.

At autopsy, coronary arteriosclerosis with a recent myocardial infarct, bilateral pleural effusion, islet cell adenoma of pancreas, and glycogen infiltration of liver were found.

This patient died in congestive heart failure following a recent myocardial infarct. She had chemically recovered from acidosis before death. Since acidosis and its treatment may have played a role in causing death this case is classed as due to acidosis.

HYPOGLYCEMIA

Most persons with diabetes fear insulin reactions more than the less dramatic, remote, degenerative complications, which are more apt to be death-dealing. Hypoglycemia is an ever-present challenge to their security. It often comes on with little warning, caus-

ing severe embarrassment. Although it may have severe deleterious effects, fortunately it is rarely fatal.

In this series, only one death was definitely caused by insulin hypoglycemia.

Case number 6884. A 29 year old female with diabetes of 16.5 years duration had a history of poor control with many attacks of acidosis and insulin reactions. She had been hospitalized for diabetic coma over ten times. While undergoing treatment in this hospital for peripheral neuritis, she developed a severe insulin reaction. It was suspected that she herself had taken 800 or 1600 units of insulin. She failed to regain consciousness and expired 31 days later, having been transferred to the Boston Psychopathic Hospital.

At autopsy, Dr. Paul Yakovlev (14) found "the meninges were thickened, opalescent, and congested . . . There were widespread degenerative, non-inflammatory, necrotizing lesions in almost every part of the brain. These consisted of degeneration and loss of nerve cells, marked increase in the nuclei of the microglia and protoplasmic glia . . . The silver impregnations showed presence of numerous argentaffine plaques exclusively in the cerebral cortex and striatum." Elsewhere healed pyelonephritis, coronary sclerosis, acute bronchitis, and hepatomegaly were found.

In a second case, hypoglycemia may have been an important factor.

Case number 25,539. A 63 year old female with diabetes of 7.0 years was admitted in an unconscious state. Blood sugar was 26 mgm.%. She regained consciousness five minutes after glucose was injected intravenously. She expired suddenly 20 hours later, shortly after a blood sugar (98 mgm.%) had been taken. At autopsy no cause of death was found. Unfortunately no head examination was permitted. In this case, the clinical diagnosis of cerebral hemorrhage has been accepted as correct.

The findings in death due to hypoglycemia have been described by Bowen and Beck (15), Root and Lawrence (16), et al. (17).

Hypoglycemia attacks are particulary common in sick diabetic subjects. The disease is apt to be out of control at this time and large doses of insulin used. Whether hypoglycemia is a factor in precipitating vascular occlusions in brain, heart or legs can not be answered from this material. Root and Styron (18) studied 205 insulin reactions in this clinic. No vascular accidents or attacks of angina pectoris were observed. Erstene and Altschule (19) found hypoglycemia was accompanied by increased cardiac work. Root concluded that hypoglycemia may have serious effects on already damaged heart in some instances. Harrison and Finks (20) described relative or actual hypoglycemia in non-diabetic subjects which precipitated attacks of angina pectoris, cardiac arrhythmias and hypertensive encephalopathy.

An autopsy is of extreme importance in all deaths believed due to an insulin reaction. This is illustrated in the case cited immediately above (number 27,539). Physicians and patients' families naturally tend to make this diagnosis in any illness involving unconsciousness in a person with diabetes. In the following two cases, simple hypoglycemia had been incriminated as the cause of death until the autopsies revealed other conditions.

Case number 25201. A 43 year old male with diabetes of six months duration died suddenly at home. A blood sugar

taken shortly after death was 52 mgm.%. At autopsy a recent coronary occlusion was found.

Case number 5570. A 79 year old male with diabetes of 15.3 years duration became unconscious at home. A blood sugar was 357 mgm.%. He was then given 140 units of insulin. On admission to this hospital the blood sugar was 37 mgm.%. At autopsy, a recent cerebral hemorrhage was found.

ARTERIOSCLEROTIC HEART DISEASE

Arteriosclerotic heart disease was the most important single cause of death. Twenty-nine patients died of myocardial infarction. Nine others died primarily of congestive heart failure, due to arteriosclerotic heart disease. Thus 38 patients (36%) died of degenerative heart disease. The proportion of cardiac deaths among all patients attending this clinic has risen from 6% to 45% in the last 25 years largely at the expense of coma deaths. Robbins and Tucker (21) in 1944 found that coronary occlusion was 2.5 times as common a cause of death in their series of diabetic as in non-diabetic subjects.

The total incidence of coronary atherosclerosis in these patients is even more remarkable. Of 110 patients, examination of the coronary arteries was permitted in 106 instances. The arteriosclerotic lesions were classified after the method of Root, Bland, et. al. (22) as follows: Class I — no macroscopic lesion of the coronary arteries — 11 patients (10%); Class II — sclerosis without significant narrowing of the coronary arteries — 22 patients (21%); Class III — significant narrowing of coronary arteries without actual occlusion — 36 patients (34%); Class IV — occlusion of coronary artery — 36 patients (34%). In Table V these percentages are compared with those of Root, Bland, et. al.

TABLE V

Degree of Coronary Sclerosis in Diabetics and non-diabetics

	Class I	Class II	Class III	Class IV
106 cases diabetes (this series)	10%	21%	34%	34%
349 cases diabetes (Root, Bland et al.)	26%	23%	20%	32%
3400 cases not diabetes (Root, Bland et al.)	52%	27%	14%	6%

The two diabetic series show an incidence of 34% and 32% respectively with coronary occlusions (Class IV). This is over five times the occurrence of this lesion in the non-diabetic group (6%). Similarly only 10% of the present series had no macroscopic sclerosis of the coronary arteries (Class I), whereas Root, Bland, et. al, found over half (52%) of the non-diabetics with normal coronary arteries.

Lisa, Magiday et. al, (23) found coronary occlusions in 30% of 138 diabetic autopsies. This compared with an incidence of 22% in their adjusted non-diabetic control series. They concluded that arterio-

sclerosis appeared earlier in persons with diabetes. Hanssen (5) however reported only six of 108 deaths due to arteriosclerotic heart disease with 11 other patients showing some coronary sclerosis.

The figures above in Table V on coronary sclerosis give an indication of the prevalence of arteriosclerosis in this series. Thus 95 or 89% of 106 patients showed arteriosclerosis of the coronary arteries. In four not included in the 106 patients in Table V, only abdominal examination was permitted. All four showed marked sclerosis of the aorta. Of the remaining 11 patients without macroscopic sclerosis of the coronary arteries or aorta, all but two showed microscopic degeneration of the coronary arteries or atherosclerosis elsewhere. Therefore, of 110 patients, 108 showed some degree of arteriosclerosis. The two showing none were cases number 23,935 and 19,972 in Table II, both young persons dying within five years of the onset of diabetes.

However, atherosclerosis of minimal degrees may be of little clinical significance. Above it was shown that 72 patients either had coronary occlusions or marked narrowing of the arteries by atherosclerosis. Of the remaining 38 patients with little or no coronary sclerosis, 13 had either nephrosclerosis or absence of one or both dorsalis pedis pulsation. Thus 85 (77%) of 110 diabetic patients showed evidence of atherosclerosis of clinical importance.

The severe arteriosclerosis found in the seven young diabetics of long duration has been shown above in Table II. These seven patients were of an age at which degenerative vascular disease is very uncommon in non-diabetics. However, three (aged 28, 30 and 32 years) had coronary occlusions and three others showed severe coronary sclerosis without actual occlusions. The occurrence of coronary occlusions in young diabetics has been described by Warren (3) and Cullin an and Graham (24).

CEREBROVASCULAR ACCIDENTS

Five patients died principally of cerebrovascular accidents; this was an incidental finding in three others. It is of interest that all eight were suspected initially to be hypoglycemic coma. In only one, however, was there a definite relationship. This was case number 27,-539 discussed under hypoglycemia. Jordan and Watters (25) in 1933 reviewed 70 cases of cerebrovascular accidents in this clinic. They concluded that such accidents did not differ from similar occurrences in non-diabetic subjects.

PULMONARY EMBOLUS

White (26) wrote that pulmonary embolism is variously recorded as being found in 8 to 12 per cent of routine autopsies. Therefore the incidence of 10 (9%) in this series is not remarkable. Of the ten patients with pulmonary emboli, in only one was this the principal cause of death, but it was the immediate and precipitating cause in five others. Four deaths followed surgical operations. In five of the ten subjects, venous or right auricular thrombi were identified.

PERIPHERAL VASCULAR DISEASE

The high incidence of arteriosclerosis obliterans in diabetes mellitus as well as its high frequency among long duration cases, and its apparent postponement by early insulin therapy were illustrated in this material.

Of 110 patients, 45 (41%) showed absence of pulsations of one or both dorsalis pedis arteries. Thus over two-fifths of the patients had evidence presumably of significant peripheral vascular disease; gangrene probably could have occurred in any of them within a few years if they had not died of other causes. Dry and Hines (27) found peripheral arterial insufficiency eleven times as common in diabetics as among non-diabetic patients and that it tended to occur at an earlier age.

The absence of dorsalis pedis pulsations was noted more frequently among the long duration patients. Thus only eight (25%) of the 32 persons with a duration of diabetes of five years or less showed absent pulsations; whereas twelve (48%) of those 25 persons with diabetes 15 years or longer had no dorsalis pedis pulsations. In Naide's (28) series of 100 patients with a duration of ten years or more, 30% had one or more absent pulsations.

Peripheral vascular disease was more common among those who had delayed the use of insulin. Of 45 patients with absent dorsalis pedis pulsations, 40 required insulin for proper control of their diabetes. They did not begin taking insulin until an average of 4.7 years after onset of their disease. Of the 65 patients with normal dorsalis pedis pulsations, 60 required insulin. They began insulin much earlier, at an average of 1.7 years after onset of diabetes. This was three years earlier than those with absent pulsations. This finding suggests that early use of insulin is instrumental in avoiding peripheral vascular complications. In Joslin, Root, et. al, (2) a similar finding is recorded. Two hundred and thirty patients who underwent amputations in the years 1939-1942 took no insulin for an average of 6.9 years after the onset of the diabetes.

In the experience of this clinic (2), the percentage of gangrene deaths rose from 4.2% to 8.1% with the advent of insulin. Until recently most patients with gangrene died of infection. Now gangrene deaths have fallen to only 3.1% due to the value of chemotherapy and antibiotics in controlling infection. Most deaths due to gangrene now are precipitated by vascular accidents elsewhere in the body. In this series, of ten patients who died principally of gangrene, the immediate cause of death in all was arteriosclerosis elsewhere. Of these, five died in cardiac failure due to arteriosclerotic heart disease, three of coronary occlusions, and two of pulmonary emboli. Seven of these deaths occurred after amputation; in the other three amputation had been considered but had not been done because of the condition of the patient.

Three patients in addition to the ten above had gangrene at the time of death as a secondary finding.

These died respectively of carcinoma of the liver, gangrene of the mesentery, and following sympathectomy in a patient with pyelonephritis and intercapillary glomerulosclerosis. This last patient, Case 6346, Table II, was the youngest in whom gangrene occurred, being 30 years of age at death.

Allen, Barker, and Hines (29) state that "the factors which produce arteriosclerosis obliterans of the lower extremities are likely to lead to similar lesions in other parts of the body . . . Within a few years arterial lesions frequently appear in one of the vital organs." This is illustrated in this series by the eight patients who finally came to autopsy and who had had amputations for gangrene 6 months to 3.5 years previously. One died of infection but seven of the eight died of vascular accidents. Three of these also had further gangrene at death.

RENAL DISEASE

The kidney has become a particularly vulnerable site of fatal disease in diabetes mellitus. This has followed in the wake of degenerative vascular disease. Fifty-seven (52%) of 110 autopsy protocols recorded well-marked nephritis. In 26 patients, two or more forms of renal disease were present. In 12 chronic nephritis was the cause of death.

The commonest form of nephritis was arteriolar, occurring in 35 cases. This accompanied the high incidence of hypertension (59%). Six patients died in uremia due to this disease.

Persons with diabetes mellitus are peculiarly susceptible to pyelonephritis, at present perhaps the most important single infection (Sharkley and Root (29a); Bowen and Kutzman (29b)). Harrison and Bailey (30) reported bacilluria in 27 of 50 unselected diabetic subjects. Robbins and Tucker (21) reported that 21 of their 301 diabetic subjects died of pyelonephritis. This was 4.5 times as common a cause of death as in their adjusted control non-diabetic group.

In our series, 13 patients had active pyelonephritis at autopsy; in three of these, this was the principal cause of death. No instances of necrotizing pyelonephritis (31, 32) were present. In eight other patients healed pyelonephritis was present. This indicates that diabetics often can heal this lesion.

Intercapillary glomerulosclerosis has been widely reported since Kimmelstiel and Wilson (33) in 1936 first described "a striking hyaline thickening of the intercapillary connective tissue of the glomerulus." Horn and Smetana (34) and Goodoff (35) in large series found this lesion in advanced form only in diabetes mellitus. Laipply, Eitzen, and Dutra (36) considered this lesion as more specific of diabetes than hyalinization of the islets of Langerhans.

The autopsy protocols of 15 (14%) of 110 patients recorded the presence of well marked intercapillary glomerulosclerosis. Laipply, Eitzen and Dutra (36) found some degree of change in as high as 64% but a severe degree occurred in only 11% of their series. Of

15 subjects 12 were over 50 years of age at death. They were principally patients with diabetes of long duration. Only 2 of the 15 had had diabetes under 5 years. Goodoff (35) also found the incidence to increase with duration.

Because of the frequent association of intercapillary glomerulosclerosis with other forms of renal disease, it has been difficult to assess its relative importance. Of the 15 patients with this lesion, six had arteriolar nephrosclerosis, four pyelonephritis in addition to the intercapillary lesions. Horn and Smetana (34) and Laipply, Eitzen, et al. (36), called attention to the high incidence of nephrosclerosis in such patients.

A patient with severe intercapillary glomerulosclerosis may show a typical complete renal syndrome of nephrosis and later renal failure as described by Derow, Altschule, et al, (38) and by Newberger and Peters (39). However, such a typical course has proven to be the exception in our experience. It is true that 14 of the 15 subjects had hypertension and albuminuria. However, only three developed a nephrotic phase with hypoproteinemia and edema. In two of these three, the predominating renal lesion was pyelonephritis. Siegal and Allen (40) and Laipply, Eitzen et al. (36) also found the complete renal syndrome often absent. Bell (41) concluded that intercapillary glomerulosclerosis could not be diagnosed with certainty during life.

The seriousness of renal disease in young diabetic subjects is indicated by the fact that six of the seven juvenile long duration patients died of nephritis. The seventh patient had had a right nephrectomy three years before death for pyelonephritis. These patients all ran essentially similar clinical course whether the underlying predominating renal lesions were intercapillary glomerulosclerosis, pyelonephritis, nephrosclerosis or glomerulonephritis.

Rosenbusch (10) recently reported glomerulosclerosis as a late complication among 80 subjects whose diabetes began in childhood. Typically the patients showed albuminuria with benign nephrosis in the early stages and later malignant hypertension, retinitis and cataracts. Many of his patients at autopsy showed more than one form of nephritis.

Clinically many instances of chronic nephritis in young diabetics have been observed in this hospital in addition to the six listed in Table II. In these patients there has usually been a history of irregularity of diet. During the first few years of the disease diet has been carefully observed and the urine kept nearly sugar free. Then, however, these young patients, especially during adolescence, have given up careful diet and have no longer attempted to keep blood and urine tests normal. In most, recurrent diabetic acidosis has occurred. During the first few months of the renal disease, edema and albuminuria associated with a definite nephrotic syndrome may appear. However, the nephrotic phase often is absent. Invariably after a period of months or a year or two, the stage of nitrogen retention occurs. When this becomes established there usually appears retinitis and hypertension progressing to blindness, deficient peripheral vascular disease, angina pectoris, or coronary occlusion. The course is rapidly downward with death in a year or two.

The difficulties involved in etiological diagnosis in the younger patients are illustrated by Case 9500, Table II, where a typical course justifying the diagnosis of intercapillary glomerulosis had been followed. After about ten years of diabetes he began to show albuminuria, then edema, and finally hypertension. His retinitis began with hemorrhages and later entered the proliferative stage. He had had coma on more than one occasion. The final death from coronary occlusion occurred after a period of some months during which nitrogen retention, edema and uremic symptoms had been present. The kidney lesions were chiefly those of pyelonephritis with however some typical areas of intercapillary glomerulosclerosis. Similarly Case 3761 (Table II) who died of arteriolarsclerotic nephritis without significant intercapillary changes exhibited a nephrotic syndrome and later uremia. On the other hand, only one of the two patients who did die of intercapillary glomerulosclerosis had clinical nephrosis.

PANCREATIC FINDINGS

Abnormalities of the pancreas were noted in 87 autopsies (79%). These changes consisted of hyalinization of the islets of Langerhans, diminished number of islets, or interstitial fibrosis. This is in addition to five cancers of the pancreas. In other large series of diabetic autopsies, changes in the pancreas have likewise been found in about 80%. Thus Warren at this hospital (2) found 76% in 527 autopsies; Dry and Tessmer (42) 85% of 201 cases; and Gibb and Logan (43) 77% of 142 cases.

Pancreatic changes were more frequent in the long duration and older cases. The above abnormalities were present in only 66% of those with a duration of five years or less; in those of longer duration, i. e. six years or more, 86% showed changes. In regard to age at death, among those 20 patients dying at 50 or less years of age, 65% showed pancreatic changes. Those subjects 51 years or more at death showed changes in 82% of the cases. The data showed no relationship between changes in the pancreas and the incidence of hypertension; kidney, heart, or peripheral vascular diseases; nor to poor control and prolonged hyperglycemia. Lukens and Dohan (44) have recently produced diabetes in cats by maintaining prolonged hyperglycemia.

HYPERTENSION

Sixty-five (59%) of 110 patients had blood pressure over 150 mm. Hg. systolic and 90 mm. diastolic which were used as the lower limits of normal (26). A high rate of hypertension among diabetic persons has been often recorded. Root and Sharkey (45) in 1936 reported hypertension in 54% of 175 diabetic deaths. Edeiken (46) found that 38% of 100 living persons with diabetes over 10 years had high blood

pressure. Hanssen (5) in Norway found a similar high percentage among persons over 50 years of age. However, he found that its occurrence in younger patients was rare. Our experience is in striking contrast to this, as is illustrated in Table II. Among those twelve persons whose diabetes began before 30 years of age none had hypertension where the duration was under 10 years. However, all seven of the long duration cases had well-marked high blood pressure, the oldest being only 32 years of age at death.

This frequency of hypertension (59%) accompanied in this series the high incidence of significant arteriosclerosis (68%) and arteriolarsclerotic nephritis (23%). Thirty-nine per cent of the hypertensive subjects showed coronary occlusions, while only 24% of the non-hypertensive group had coronary occlusions. Ten of 13 persons with gangrene as well as 30 of 45 persons with absent dorsalis pedis pulsations had hypertension.

TABLE VI

The Incidence of Hypertension in Relation to Duration of Diabetes

Duration in Years	Total Patients	Patients with Hypertension	Percentage With Hypertension
0 to 5	35	16	46%
6 to 10	24	15	63%
11 to 15	25	14	56%
16 and over	26	20	77%
	110 patients	65 patients	59%

A definitely higher incidence of hypertension was found among those persons who had diabetes the longest. Table VI shows that the incidence of high blood pressure was 46% in those dying after diabetes of five years or less. This is a high figure, but in those persons with diabetes of 15 years or more, the occurrence of hypertension was 77%.

INFECTION

Of 110 patients, twenty died primarily of infections. Five died with peritoneal infection and rupture of an abdominal viscus (appendix 2, gall bladder 2, duodenum 1). Two of these five died after surgical procedures. Carbuncles, non-tuberculous pulmonary infection, septicemia, and pyemia accounted for nine deaths. One cannot say that diabetes was responsible for these deaths. However, it probably was a severe aggravating factor in each case. The low resistance to infection and the decreased carbohydrate tolerance during infection is discussed by Joslin, Root, et. al,(2).

Acute hepatitis was the cause of death in a 31 year old woman Case 19,972, Table II, who died four months after a successfully terminated pregnancy. Two

other patients showed mild hepatitis at autopsy as an incidental finding. Vannjätt (47) considered a certain tendency toward hepatitis on the part of diabetic subjects to be probable. He and Droller (48) described epidemics of acute hepatitis occurring in diabetic clinics. Twelve patients showed mild cirrhosis.

Only one patient died of tuberculosis. This was a 16 year old boy (Case 21,585, Table II) with diabetes of 5.5 years duration who developed tuberculosis of the antrum. He died when the process spread to the central nervous system, causing an acute tuberculous meningitis. In five other patients small foci of tuberculosis were present in the lungs, ilium or kidney. None of these had been recognized during life. Persons with diabetes and pulmonary tuberculosis for the most part die in sanatoria and not in a general hospital. Therefore they would not be in a series such as this. At present 2.5% of all our patients die of tuberculosis (2). Richardson and Bowie (49) found nine cases among 100 living diabetic persons. Hanssen (5) reported 4.1% of the deaths in his series in Norway as due to tuberculosis. However, Vartiainen (50) in Finland found a very high incidence. Eighteen of 85 patients in the insulin era died of this disease. These statistics all represent a great improvement over Naunyn's mortality of 39% in 1906.

CANCER

Cancer was the cause of death in 16 patients. In 8 other persons small carcinomata were present as incidental findings. Five (21%) of the 24 carcinomata were pancreatic in origin. The unexplained high incidence of carcinoma of the pancreas has been noted previously but the relationship to diabetes is not understood. At this hospital in 1928 McKittrick and Root (51) reported 12 pancreatic among 37 cancers, while Marble (52) found 33 among 256. Elsewhere Dry and Tessmer (42) found 6 in 38 diabetic persons dying of cancer. However, Ellinger and Lansman (53) reported only 2 among 39 malignancies.

Cancer like infections may be considered as an "accident" in the lives of persons with diabetes, usually causing death before the onset of severe degenerative disease. Thirty-four of 75 persons who did not die of cancer or infection had coronary occlusions at autopsy; whereas only 2 of the 34 subjects dying of cancer or infection had coronary occlusions.

TREATMENT

The immediate goals in the treatment of diabetes are the attainment of normal body weight, freedom from acidosis, and absence of characteristic diabetic symptoms. However, the more important object is the prevention of severe vascular degeneration such as occurred in this series. During periods of hospital observation control of the diabetes was sought by the use of insulin and diets providing 150 to 200 and occasionally perhaps to 300 grams carbohydrate with 30 to 50 calories per kilogram of body weight. However, in this group the periods of close observation were brief and the great part of the patient's diabetic life

was spent away from medical observation and evidently in most cases without close supervision. The use of high carbohydrate diets began in 1926. Stolte (54) and many others have advocated a "free" diet particularly for children. Recently the opinion has been expressed often that the use of insulin without rigid dietary restriction is proper therapy. As yet no series of autopsies has appeared indicating that vascular complications are thereby lessened.

The opposing view has been that careful treatment by diet and insulin indicated by normal blood and urine tests would protect the patient against such complications as coma and premature degenerative diseases. (Joslin 2, Ricketts 55). The use of insulin even with slight dietary treatment will protect most patients during the first years. During this time patients may "adapt" to their disease as in Selye's experiments. Selye (56) has shown that an animal is able to adapt to various noxious stimuli for a considerable time without apparent ill effects. In Selye's experiments following the period of adaptation to noxious stimuli an exhaustion, phase appeared characterized by degenerative vascular disease. The vascular disease in diabetes may represent this exhaustion phase after a long exposure to the strain of the abnormal carbohydrate metabolism. We believe that efforts to keep the metabolism as nearly normal as possible by the use of insulin and diet may postpone the advent of degenerative disease. It has not been proven that there is any deficiency other than insulin in diabetes. Diabetic subjects die chiefly of vascular disease in legs, heart and kidneys. The importance of diabetes in causing these lesions is often minimized, but death comes much earlier on the average than in non-diabetic patients. This amounts to a few years in aged persons but to several decades in the young. Therefore, to evaluate diabetic therapy properly, no matter how brilliant the immediate results may be, one must wait 15, 20, or even more years in young patients. A further difficulty in assessing diabetic therapy is that it is often impossible to tell the actual degree of day to day control of sugar metabolism by insulin. Most patients when feeling well see a physician only occasionally. Furthermore, individual temperaments and intelligence vary widely.

CONCLUSION

1. The records of 110 diabetic patients examined post-mortem at the New England Deaconess Hospital between 1940 and Jan. 1, 1946 disclosed degenerative vascular complications involving principally the coronary arteries and kidneys as the chief cause of death. In this series are included 10 patients whose diabetes began under 20 years of age and two with onset between 22 and 27.

2. ;Although the average duration of life of 9.8 years in this series has increased almost fourfold as compared with the series of Naunyn, 1906, and has exceeded the duration of diabetes in other series of autopsied cases from this same hospital, nevertheless, few patients attained normal life expectancy and the average only fulfilled 44 per cent of the life expectancy for non-diabetic patients of the same age.

3. In five patients whose diabetes began between the ages of 11 years and 27 years, no significant arteriosclerosis was found in the coronary vessels or other arteries, when the duration of the diabetes varied from 0.2 years to 6.0 years. In contrast, seven cases with onset of diabetes between the age of 10 years and 18 years, with duration of diabetes varying from 14 years to 20.9 years, demonstrated marked narrowing or complete occlusion of coronary arteries in addition to arteriosclerotic lesions elsewhere including the kidneys and legs.

4. Diabetes of long duration produces in young patients vascular lesions of all three types. The early evidences may be in the retinal vessels or demonstrable as visible calcification by X-ray in the vessels of the legs. The development of renal failure in the seven youthful cases of long duration was characterized by early edema with an apparently benign nephrotic syndrome including increased blood values for cholesterol and hypoproteinemia. This apparently benign stage within a period of one or two years was followed by hypertension of a malignant type associated with eye ground changes and eventually nitrogen retention. This course has occurred with any of three different predominating renal lesions or with combinations, that is, arteriolar nephrosclerosis, intercapillary glomerulosclerosis, or pyelonephritis.

5. The striking feature of the histories of the young patients subsequently developing vascular disease and a renal failure was that during the first few years of the disease the diabetes was well controlled by careful dietary treatment and insulin. However, during the last eight or ten years of the disease usually diabetes was no longer under control owing to laxity in following diet, periods of acidosis, and intercurrent infection. In the etiology of vascular disease associated with diabetes, the first factor to be considered is the essential deficiency of a single hormone, insulin. A dietary or nutritional factor in some way related to the lack of balance between the supply of the specific hormone insulin and the normal utilization of a proper diet is clearly indicated. Diabetic coma, indicating the maximal degree of the uncontrolled diabetes, had been present in five of the seven youthful cases with severe arteriosclerosis.

6. Some degree of arteriosclerosis was present in 99 per cent and was of clinical significance in 77 per cent of the 110 patients. Severe coronary arteriosclerosis occurred in 68 per cent of the cases and peripheral vascular disease in 41 per cent. Degenerative changes in the Islands of Langerhans in the pancreas were present in 79 per cent and chronic renal disease was present in 52 per cent of the series as a whole.

7. The gradual development of vascular lesions in youthful diabetic patients needs study by various functional tests of renal, cardiac and vascular phenomena as well as by X-ray examinations. Youthful patients must be followed for 15 years or more if any con-

clusions are to be drawn as to the presence or absence of degenerative vascular lesions and particularly if conclusions are to be drawn with regard to the effect of different types of treatment. In the present series no cases are found in whom long periods of carefully controlled diabetes were associated with the develop‐ ment of premature vascular disease in young people. In middle aged and older patients in whom mild dia‐ betes had long been controlled by dietary treatment, severe vascular lesions seemed to be postponed. In young patients the postponement of premature vascular lesions seemed also to occur chiefly in those cases in whom the avoidance of diabetic coma and other types of uncontrolled diabetes has been possible over long periods of time.

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