THE PATHOLOGY OF DIABETES, WITH SPECIAL REFERENCE TO PANCREATIC REGENERATION*

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But little opportunity has been afforded for the pathological study of cases of diabetes treated by insulin and for determination of what effects, if any, this treatment has had upon the lesions. Twenty-six autopsied cases of diabetes, the disease process varying in duration from two months to thirty years, form the basis of this report. These cases were under the care of Dr. E. P. Joslin, and the histories and clinical findings are unusually complete, with only one or two exceptions. Of these twenty-six cases, seventeen were treated with insulin over periods ranging from ten hours to thirteen months.

In order to present briefly the salient facts in the pathology of these cases, they have been combined in Table 1. Although statements as to the exact time of onset of diabetes are somewhat uncertain, it has seemed best to arrange the cases in order of increasing duration. One case, where the patient had been under observation twenty-six days, but had undoubtedly been suffering from diabetes much longer, has been placed at the end of the table.

Pancreas. Though the weight or estimated size of the pancreas is given in most cases, it is of little value in estimating the amount of pancreatic substance owing to the great variation in the connective tissue and fat, chiefly interlobular, present in the organ. Thus of two pancreases, both of which contained but little pancreatic tissue, one weighed 30 gms. and one 240 gms. This variation is not altogether dependent on the weight of the individual from which the organ came, as both women weighed over 200 pounds.

No attempt has been made to count the number of islands, owing to the inaccuracy of any feasible method. However, in six cases the islands appeared to be distinctly less numerous than in normal pancreases. No one distinctive lesion of the islands has been encountered in this series, as is to be expected in light of the work of Allen,[1]

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TABLE 1

Number	Age	Duration of disease	Pancreas			Heart			Liver glycogen	Kidney		Aorta	Cause of death
			Wt. gms.	Islands	Acinar sclerosis	Wt.	Coronary arteries	Myocardium		Glycogen	Vascular disease		
4289	29.5	1 m. 27 d.	30	Lymphocytes	o	365	o	o	o	o	o	?	Septicemia
3592	64	6 m.+	116	H++	+	433	o	o	+	+	+	+	Multiple abscesses
2559	55	7 m.	?	H+++	o	?	S++	o	+	+	o	+++	Duodenal ulcer
3240	15.3	8 m.	Small	Few o	o	?	o	o	o	o	o	o	Coma
2720	19.2	11 m.	Small	Lymphocytes	o	?	o	o	+	+	o	o	Perinephric abscess
2446	36.9	1 yr. 1 m.	50	o	o	280	o	o	+	+	o	+++	Coma and pneumonia
1870	15	1 yr. 7 m.	Small	Lymphocytes	o	?	o	o	+	+	o	o	Coma
1907	24	1 yr. 10 m.+	Small	H++	++	?	o	o	?	+	o	o	Inanition
3210	65	1 yr. 10 m.+	Small	H+ few	++	250	S+++	S++	o	o	++	+++	Angina pectoris
2463	32.4	2 yr. 8 m.	Small	o	++	?	o	Hydrops	+	+	o	++	Abscesses of liver
4142	47.6	3 yr. 3 m.	80	H+++	+	290	o	o	+	+	++	+	Perinephric abscess
2988	56.3	4 yr.	Normal	H++	++	325	o	S+	o	+	+++	+	Pericarditis
1305	16	5 yr. 6 m.	Small	S+	++	?	o	S+	o	?	?	+	Coma
2479	69	9 yr.	Normal	o	++	325	S++	S++	+	+	++	+++	Chronic myocarditis
3679	46	9 yr. 6 m.	Small	Few S+++	+++	320	o	Hydrops S+	+	+	+	++	Appendicitis
896	69.2	10 yr. 8 m.	Cancer	H++	Cancer	330	S+++	S+++	+	+	+	++	Cancer of pancreas
3798	64	11 yr.	180	Few S+	++	315	S+++	S++	o	o	++	++	Gangrene and septicemia
705	66	14 yr.	?	H++	++	520	S+++	S+++	+	+	++	+++	Angina pectoris
1419	53.3	14 yr. 7 m.	240	S+H++	+	360	o	o	+	+	++	++	Appendicitis
263	48.7	14 yr. 9 m.	70	Few H+++	+	340	S+	S+++	o	o	++	++	Cardio-renal
870	53.2	16 yr. 11 m.	Normal	H+++		350	S+++	Aneurysm S+++	o	+	++	+++	Coronary thrombosis
3176	58.5	17 yr. 4 m.	Normal	S+++	+	?	o	S+	+	+	+	+	Phthisis
127	62	25 yr.	40	Few o	++	335	S+++	++	+	+	+	++	Coronary thrombosis
3242	52	25 yr.	?	H+++	++	?	+	o	o	o	o	?	Septicemia
1924*	53.9	30 yr. 2 m.	?	H++	+++	?	?	?	+	+	o	?	Gangrene and septicemia
3468	61	26 d. +	?	S+	++	610	S+++	S+++	o	+	++	+++	Gangrene and septicemia

* Restricted autopsy H = Hyalin S = Sclerosis ? = No data o = No pathology

Opie,[2] and Cecil.[3] Thirteen of the pancreases showed varying degrees of hyalinization of the islands. Only one of the thirteen patients whose islands showed hyalin change was under forty-five years old. Five showed more or less sclerosis of the islands, in three there was some lymphocytic infiltration about scattered islands, and there was no demonstrable pathology in the islands of five. The islands of three showed the type of enlargement described by Cecil[3] as adenomatous. In the few instances in which we found changes in the islands suggesting hydropic degeneration, post-mortem change could not be ruled out. The most likely case, No. 1870, only fifteen years old, died in coma after diabetes of short duration and was autopsied within an hour. No hydropic degeneration was apparent.

Through the kindness of Dr. Mallory we have been able to examine a slide of a pancreas sent to him by Dr. Willard S. Hastings from a case of fulminating diabetes. In this section every island shows extreme hydropic degeneration.

One outstanding feature of the various pathological changes is the wide variation in the condition of the islands in the same pancreases, and even in the same section. In one case of fourteen years' duration, No. 263, every stage is present from apparently normal islands to masses of hyalin imbedded in the stroma. We have found no pancreas in this series, no matter how severe the disease process or how marked the changes in the islands, in which a greater or less number of apparently normal islands could not be found. Moreover, a large number of pancreases from cases of diabetes other than those included in this series each showed at least a few apparently normal islands. Owing to the type of fixation of some of the tissues, Bensley's neutral gentian stain for the granules of island cells could be used only in a few cases. Through the courtesy of Mr. W. Bowie of Toronto we have been able to use his modification of Bensley's stain for the island cell granules in a number of cases where otherwise specific granule stains would have been impossible.

As regards the acinar tissue of the pancreas, varying degrees of sclerosis are present in some cases, independent of pathology in the islands. It is worthy of note that the acinar sclerosis is not apparent in any case much under two years' duration, even though the islands may show considerable change. In one case, No. 3592, which shows slight acinar sclerosis, the duration as given is six months, but an

accurate history could not be obtained and the disease probably had lasted for a much longer time. In another case, No. 896, most of the pancreas was replaced by a carcinoma and practically no acinar tissue was present. Islands persisted in the midst of the tumor and were very numerous in the tail, which had not been invaded by the tumor.

So far as we can determine there is no difference between the pancreases of those cases given insulin and those under dietary treatment alone, although we have the impression that in No. 263, treated with insulin for 13 months, there are more apparently normal islands than would ordinarily be the case.

There is no distinctive lesion in the young, uncomplicated cases of diabetes, as might be expected if there were one definite causal agent giving rise to the disease. Hyalinization of the islands occurs usually in those persons beyond middle age.

Heart. From this series, and from our experience with elderly diabetics in general, we feel that damage to the myocardium, chiefly through disease of the coronary arteries, is much more common in diabetics than in similar age groups from the general population. Of our seventeen patients over 40 years of age, three showed extensive healed infarcts in the wall of the left ventricle, one had an aneurysm of the wall of the left ventricle, five showed extreme sclerosis of myocardium (including two of the cases of infarct mentioned above), three showed moderate sclerosis (including the other case of infarct), four showed slight sclerosis and five showed none. The coronary arteries were correspondingly affected in these patients. In two cases there was occlusion of a main branch of the coronary artery, in one the left branch of the coronary artery was practically occluded, in seven there was marked coronary sclerosis, moderate sclerosis in two, slight in two, and no evidence of coronary disease in six. In two of the negative cases a single slide of the heart wall was the only tissue available.

Arteriosclerosis of the aorta generally ran fairly parallel with that of the coronary arteries, though in a few cases the aortic changes are either more or less marked than those in the coronaries. In one sixteen-year-old boy, No. 1305, who had very high blood fat, there were atheromatous plaques in the aorta and slight sclerosis of the myocardium.

We hope to make a detailed study of the heart and vessels in these and other diabetics, to be reported in a subsequent paper.

Liver. The only change characteristic of diabetes is the presence of glycogen within the nuclei of liver cells, and that is by no means pathognomonic of the condition. The liver cell nuclei show this deposit in fifteen of the cases.

The frequency of occurrence of gallstones in these cases is of interest, and is too great to be merely coincidence. Six cases, four of them males, totalling 30 per cent of those over thirty years old, showed gallstones at autopsy, and another case, also a male, had an obliterated gall bladder with numerous adhesions.

Kidneys. In the older cases there is a somewhat greater incidence of moderate chronic vascular nephritis than would be expected in a

TABLE 2

Insulin treated					Not insulin treated		
No.	Amount of insulin		Glycogen in liver	Glycogen in kidney	No.	Glycogen in liver	Glycogen in kidney
	Time	Units daily					
127	3 mos.	4–15	+	+	870	+	+
263	13 mos.	10–30	o	o	1870	+	+
705	6 days	2–6	+	+	1907	–	+
1305	11 weeks	2–16	o	–	1924	+	+
2446	1 day	100	+	+	2463	+	+
3176	8 days	15	+	+	2479	+	+
3240	10 hours	60	o	o	2559	+	+
3242	6 days	12–90	o	o	2720	+	+
3468	12 days	7–10	o	o	3210	o	o
3592	15 days	12–85	+	+			
3798	10 days	15–30	o	o			
4142	4 days	12–15	+	+			
3679	6 weeks	5–30	+	+			
2988	2 weeks	.....	o	+			
1419	1 day	50	+	+			
4289	22 days	5–75	o	o			
896	5 mos.	15–100	+	+			

similar age group of non-diabetics, 78 per cent as against 69 per cent in a series of 100 autopsies, done in this laboratory, of non-diabetic patients over forty-five years old. This corresponds well with the amount of vascular disease. In six cases we could find no evidence of glycogen in the epithelial cells of Henle's loops.

Glycogen. In Table 2 is shown the occurrence of glycogen in the nuclei of liver cells and in the epithelial cells of Henle's loops.

Forty per cent of the insulin-treated cases show no glycogen, while it is absent in only 11.1 per cent of the cases under dietary treatment. This last percentage is rendered unduly high by the small number in the series; it is quite remarkable to find no trace of glycogen in Henle's loops in diabetics who have not had insulin treatment.

Complications

Gangrene. Seven of these cases, summarized in Table 3, developed gangrene. There appears to be a definite relation between gangrene and obesity.

These eight cases average 44 per cent overweight, as against 26 per cent for the cases which did not develop gangrene.

Acidosis. In all except one of the ten cases which had severe acidosis, but not coma, the condition was brought on by an acute

Table 3

No.	Gangrene		Arteriosclerosis	Maximum weight above standard %	Age
	Location	Duration			
127 [1]	Left leg	20 days	Marked	55	62
1924	Right foot	4 days	———	66	54
2479	Left foot	14 weeks	Marked	40	69
3210	Left foot	2 weeks	Marked	11	65
3468	Right foot	10 days	Marked	46	61
3592	Right foot	15 days	Moderate	39	64
3798	Right foot	6 weeks	———	52	64

[1] Embolic in origin.

infection. That one exception was a young man of 24 whose diabetes was very severe. There is no apparent correlation between the condition and demonstrable pathology.

Coma. Of the six cases that died either in coma or within one month after recovery from coma, one omitted his insulin and had an infected hand, two broke diet, one developed pneumonia and another acute pericarditis, and one suffered from acute hyperthyroidism. Here again, as in acidosis, there is no characteristic pathological change. Four of the deaths occurred in those whose diabetes had lasted less than one year and seven months. None of these four

cases had demonstrable pancreatic pathology which could be clearly related to diabetes.

Out of 33 cases of coma reported by Joslin,[4] 17 occurred during the first year of the disease. That the first year of the disease is really the danger zone has long been apparent clinically [5] and generally explained as due to the patient's ignorance of means for its prevention or even to his ignorance of the existence of the disease. However, another factor must be considered; the regenerative power of the pancreas may be overwhelmed by the unknown toxic process at a time when the body metabolism is on a plane not yet adjusted to the disease. Especially in the young is this true for in them the metabolic requirements of growth add to the strain.

Obesity. There is a striking degree of obesity in most of these cases, particularly the older ones. The patients at their maximum averaged 32 per cent overweight, and if the five under 25 years of

TABLE 4

Obesity in Relation to Heart and Vascular Pathology

Case No.	Per Cent Overweight	Pathology
3468	46	+++
3210	11	+++
2479	40	++
896	46	+++
3798	52	+++
705	29	+++
263	35	+++
127	55	+++
870	16	+++

+++ = extreme coronary sclerosis {and / or} myocardial injury.

age are excluded, 37 per cent overweight. The weights given are for the most part those at onset of the disease. Unfortunately, the weight was not noted at autopsy in most cases. We feel, however, that the weight at death should be included in the autopsy data of all diabetic cases.

Duration. Several cases in this series were under observation for remarkably long periods. The lengths of time given are reckoned from the first definite diagnosis of the disease and so are minimal. The duration of the disease in seven is known for periods extending over fourteen to twenty-five years. One other, No. 1924, had been

refused life insurance repeatedly because of sugar in his urine thirty years before death. These clinically were relatively mild cases. In six of the eight cases the age at onset of the disease was under forty, and the average age at onset of all eight was thirty-six.

Of these eight cases, six showed a considerable degree of hyalinization of the islands of the pancreas, one showed marked sclerosis of the islands and extreme hyalin change of the arterioles of the pancreas, and the islands in another appeared normal, though seemingly decreased in number. In all the cases there was a greater or lesser degree of sclerosis of the acinar tissue.

The outstanding feature in all these cases is the presence of a few islands which show no demonstrable pathology, even though the majority may be seriously damaged.

Discussion

We have presented no direct evidence as to the etiology of diabetes, though obesity is very marked in some of these cases, especially in the older diabetics. The age at onset varies from ten to sixty years, and when above twenty years seems to have little effect on the duration of the disease so far as this series is concerned. The variation and inconstancy of the pancreatic lesions argue against an infectious origin for the disease, and the character of such lesions as may be present does not suggest the result of invasion by organisms. Indeed, one is tempted to wonder whether the changes in the islands may not be the result instead of the cause of diabetes. While it is true that in a few relatively early cases of diabetes we found lymphocytes about the islands, this can hardly be considered as evidence for an infectious origin of the lesion.

Whatever the cause may be, it seemingly acts over a long period of time, perhaps throughout the duration of the disease. The pathology which we find in the pancreas at autopsy rarely represents the initial damage to the organ, but rather the result of a long struggle between the regenerative activity of the pancreas and the degenerative changes caused by the diabetogenic factor. The pancreas is not a static organ like the brain or myocardium, unable to repair itself after injury.

For some reason this static conception of the pancreas has become firmly established in spite of clinical and anatomical evidence to the contrary, probably because the diabetic patient cannot be cured and

frequently goes steadily downhill in spite of treatment. We believe that this unfavorable course of the disease is not due to failure of the pancreas to regenerate, but to continued injurious action on the organ by the causal agent, eventually overcoming the regenerative efforts. In a subsequent paper we are presenting the clinical evidence given by this same series of patients.

Perhaps one reason for the skepticism as to pancreatic regeneration in diabetes is the lack of the classical evidence of such activity — cells in mitosis and cells in abnormal situations and relations with one another.

We have found evidences of the power of the pancreas and of the island tissue in particular to regenerate after acute injury. Thus in a pancreas from a non-diabetic patient dying of lobar pneumonia (A15–16) we found numerous mitotic figures in the island cells, as high as seven mitoses in a single island (Fig. 1). Mitotic figures can occasionally be found in the island cells of cases dying of diphtheria and of lobar pneumonia. At times necrotic cells are found. This injury and subsequent repair not only indicate the regenerative power of the pancreas, but perhaps explain the transient glycosuria occasionally encountered in acute infections.

This same transient injury to the islands may explain the severe drop in sugar tolerance noted in diabetic patients during acute infections. The rapid reëstablishment of the former level of sugar tolerance following recovery from the acute process may well represent the result of the rapid regeneration of the island cells.

Bensley [6] states that in experimental animals after duct ligation occasionally a pancreas will be found which differs from the normal only by smaller size and increased fibrous interstitial tissue. This is interpreted as due to regeneration following accidental reëstablishment of the connection between duct and bowel. Bensley believes that under appropriate conditions the capacity of the pancreas for regeneration is 100 per cent.

Boyd and Robinson [7] have reported a case of a nine-year-old diabetic boy, accidentally killed after six months of insulin treatment, whose pancreas showed definite evidences of regeneration and whose insulin requirement had steadily fallen.

In one of our cases, No. 896, whose diabetes had lasted for fourteen years and who had been under insulin treatment for five months, receiving 15 to 100 units daily with gradual decrease of the

insulin requirement, there is evidence of regeneration of the islands. No acinar tissue is present. The bulk of the pancreas is occupied by a carcinoma, from which the patient died, but the tail is not invaded by the tumor. Here the islands are closely packed. Some show a moderate degree of hyalinization, but most are entirely free from hyalin or other degenerative changes. Columns of cells extend out from the islands into the surrounding stroma, and in places entire low power fields are made up of island tissue. There are more islands than could be accounted for by their concentration by contraction of the stroma of the pancreas following destruction of the acinar tissue.

In any disease as insidious in onset and as chronic as diabetes, with pathological changes largely restricted to one portion of a single organ, one cannot expect any striking evidences of either destruction or regeneration. It is not unnatural that the conception of the diabetic pancreas as an inert organ, passively submitting to gradual destruction, has become firmly established.

We may assume that the lesions in diabetes are not infectious but toxic in origin. Their course is extremely chronic, and consequently the attempts at regeneration are slow. Mitotic figures would hardly be expected under the circumstances.

Practically all toxic lesions of the same age in the same organ resemble one another, as in toxic myocarditis or central necrosis of the liver. But in the islands of the pancreas showing either hyalinization or sclerosis, practically every stage from masses of hyalin or dense connective tissue imbedded in the stroma to apparently normal islands can be found. It is difficult to conceive a toxic substance of very chronic action or a long-continued functional strain totally destroying one island and completely sparing the next. Much more logical is the assumption that we are dealing with a gradual destruction of islands, a formation of new islands to replace them, exposure of these to the toxic substance with consequent pathological change and still more islands formed to take their places. The apparently normal cells found represent those most recently formed. Eventually the destructive process wears down the regenerative powers of the organ and the end comes.

Hemochromatosis, often known as bronzed diabetes, gives us an excellent opportunity to test this assumption. In this disease we are dealing with a known injurious agent, hemofuscin. This is a break-

down product derived from hemoglobin and is deposited in various cells of the body, where it very slowly changes to hemosiderin. Eventually the accumulated pigment causes necrosis of the cell containing it. The liver is the first site of deposit, but as its cells become filled, the pigment overflows, one might say, to other organs. The pancreas is one of these.

In those cases of hemochromatosis where the pancreas has become seriously involved before death, diabetes occurs. If the pathology referable to the pigment cirrhosis of other organs be disregarded, this diabetes differs in no whit from diabetes mellitus, except that the course is more rapid.

Here then we have an ideal means of studying diabetes, with a known etiology and a fairly rapid course.

We have had the opportunity of studying several cases of bronzed diabetes in this laboratory. We find the same variation in involvement of the islands as we have mentioned in our cases of diabetes mellitus, ranging from the remains of islands represented by clusters of pigment-loaded endothelial leucocytes and fibroblasts in the stroma to islands without pigment and apparently normal. The conclusion is inevitable that new islands are being formed to take the place of those destroyed by the pigment deposits. In further substantiation of this evidence, occasional mitotic figures (in Case A 17–8) can be found in the cells of the younger, pigment-free islands (Figs. 2, 3).

The pigment is not restricted to the island cells, but affects the acinar tissue as well. The same evidence of regeneration is offered by the acinar cells as by those of the islands.

The well-established evidence of destruction and regeneration of parenchymal cells in the liver offers a striking parallel to the changes in the pancreas in hemochromatosis. Just as in the liver the parenchymal cells show every stage from newly-formed pigment-free cells through those containing hemofuscin and those containing hemosiderin to necrotic cells, the same steps can be traced in the acinar and island cells of the pancreas.

If we substitute diabetes mellitus for hemochromatosis, hyalin formation in the islands for pigment deposit in the island cells, the analogy is complete.

There is no reason to doubt that the increased fibrous tissue noted in the pancreas in some cases of diabetes mellitus accumulates in the

same way as the fibrous tissue in cirrhosis of the liver. The parenchymal cells, sometimes of the islands, sometimes of the acinar tissue, or of both, are killed and disappear. Their stroma remains behind. The parenchymal cells regenerate and new stroma forms to support them. In this way the fibrous tissue gradually increases in amount. The increased fibrous tissue noted in the pancreas in some cases of diabetes is therefore not due to a simple proliferation of the interacinar and interlobular connective tissue. Probably in most cases there has been damage to and regeneration of the acinar tissue as well as the islands. There is some clinical evidence of disturbed external secretion of the pancreas in diabetic patients.[8]

In our series fibrosis of the pancreas is not found in those cases whose diabetes had existed less than two years. However, some of the cases of fairly long duration do not show any great increase in fibrous tissue.

Aside from the pathology of the pancreas, the changes in the blood vessels and myocardium are of interest. The frequency of severe myocardial damage and of sclerosis of the coronary arteries and the aorta is much greater than would be expected for similar age groups of non-diabetics. Of course our series is too small from which to draw any definite conclusions, but it does indicate an abnormal prevalence of vascular disease among diabetic patients. This may well be related to the abnormal fat metabolism and the striking tendency toward obesity.

In one sixteen-year-old boy (No. 1305) there were found at autopsy atheromatous plaques on the aorta. He had a high blood fat, and it seems quite possible that this is related to the arteriosclerosis. In addition, large numbers of lipoid-filled cells are present in the spleen. A similar case, a man of 22, reported by Smith,[9] showed slight atheromatous plaques in the aorta.

The frequency of chronic vascular nephritis in our series is also somewhat higher than is encountered in non-diabetic patients, reënforcing the other evidences of vascular disease.

So far as differences in pathological findings in those cases treated with insulin and those not treated with insulin are concerned, there is nothing startling. We have an impression that there are rather more normal appearing islands in the pancreases of insulin-treated cases than in those of cases under dietary treatment alone. Glycogen is much less frequently found in the liver cell nuclei and in the

cells of Henle's loops in insulin-treated cases, as might be expected with the improved utilization of carbohydrates.

Summary

1. The pathological findings in twenty-six cases of diabetes mellitus are presented. The duration of the disease in eight of these is known to be over fourteen years.

2. Thirteen cases show hyalinization of the islands of Langerhans. Only one of these cases was under forty-five years old. Five show varying degrees of sclerosis of the islands. In three more there is slight lymphocytic infiltration about scattered islands, and the islands in five appear normal, though decreased in number in two of these five.

3. Apparently normal islands are present in all pancreases examined, no matter how badly damaged the bulk of the islands may be. In two cases, insulin-treated over five months, there seem to be more islands of normal appearance than in cases under dietary treatment.

4. The character of the lesions in the islands of Langerhans suggests a toxic origin, and an injurious agent acting over a long period of time.

5. Occasionally in acute infections, such as lobar pneumonia and diphtheria, there is toxic injury of the island cells, and subsequent regeneration of the islands. This is probably the explanation of the transient glycosuria sometimes met with in the course of acute infections.

6. In hemochromatosis there is definite evidence of regeneration of both the acinar tissue and island tissue of the pancreas. The type of diabetes in hemochromatosis is the same as that in diabetes mellitus.

7. The increased fibrous tissue found in certain pancreases in diabetes is due to destruction of island or acinar cells or both, with persistence and condensation of their stroma. The parenchymal tissue regenerates and forms new stroma, with resulting increase in connective tissue.

8. The acinar tissue of the pancreas does not show evidence of increased fibrosis in cases of diabetes of short duration.

9. Insulin treatment decreases the frequency with which glycogen is found in liver cell nuclei and in the epithelium of Henle's loops.

10. The frequency of severe myocardial damage, due to coronary sclerosis, is high in diabetics over forty.

11. The patients developing gangrene averaged 44 per cent overweight, while the others averaged 26 per cent overweight.

12. The patients over twenty-five years of age in this series averaged 37 per cent overweight.

Conclusions

1. A new interpretation is offered of the pathology of the pancreas in diabetes mellitus.

2. The long-continued action of an injurious agent (or possibly excessive functional activity) causes a gradual destruction of island, and at times of acinar cells. New cells are formed to take the place of those destroyed, only to be exposed to the injurious influence with consequent pathological change. Their injury is followed by the production of still more new cells.

3. Eventually the destructive process wears down the regenerative powers of the pancreas, thus explaining the unfavorable course of the disease.

4. In pneumonia and other infectious diseases, the pancreas readily regenerates after acute injury.

5. The disturbed carbohydrate metabolism giving rise to abnormal fat or protein metabolites may be the cause of the high incidence of vascular disease in diabetic patients.

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DESCRIPTION OF PLATE LXVI

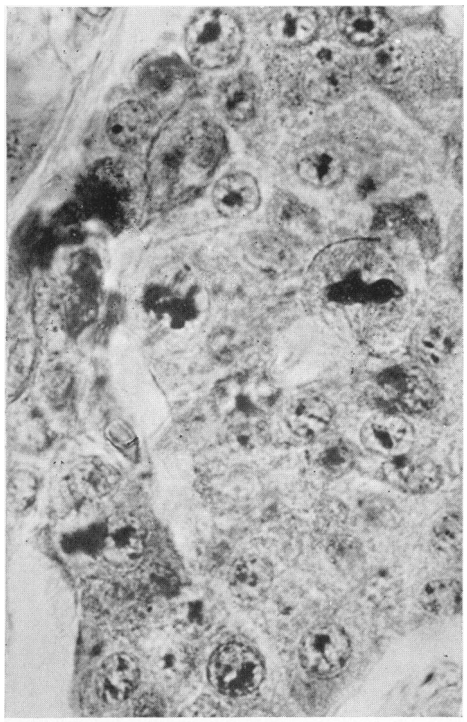
Fig. 1. Island of Langerhans from case dying of lobar pneumonia, showing three mitoses. x 1000.

Fig. 2. Island of Langerhans from case dying of hemochromatosis, showing pigment-free island and two mitotic figures. x 1000.

Fig. 3. Island of Langerhans from case dying of hemochromatosis, showing one mitotic figure, and small amount of pigment. x 1000.

Fig. 4. Island of Langerhans from case dying of hemochromatosis, showing one mitotic figure.

Photomicrographs by Dr. F. B. Mallory.



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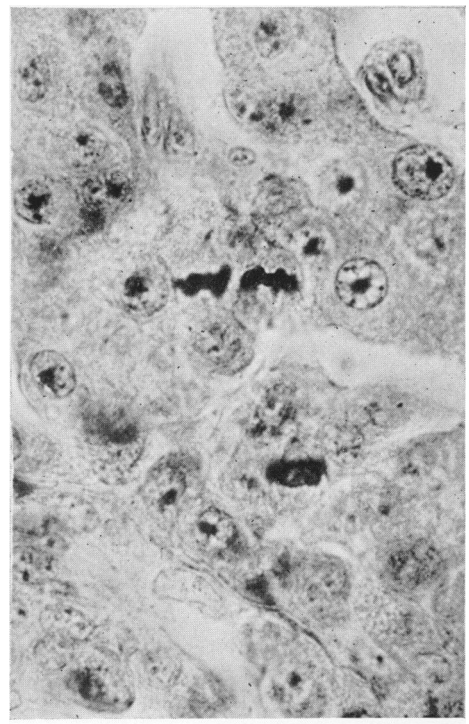

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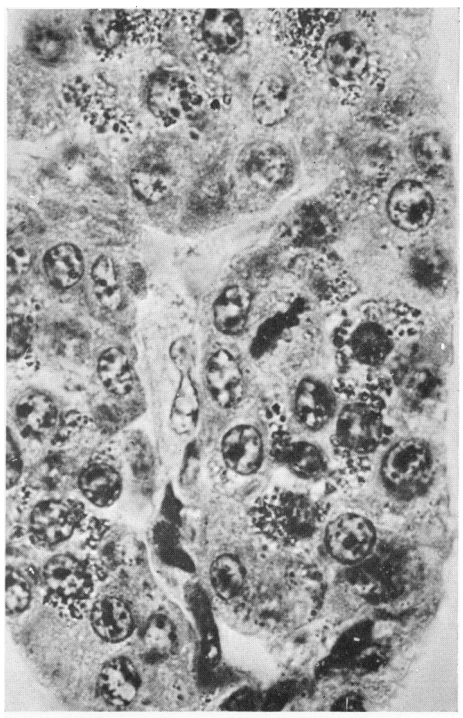

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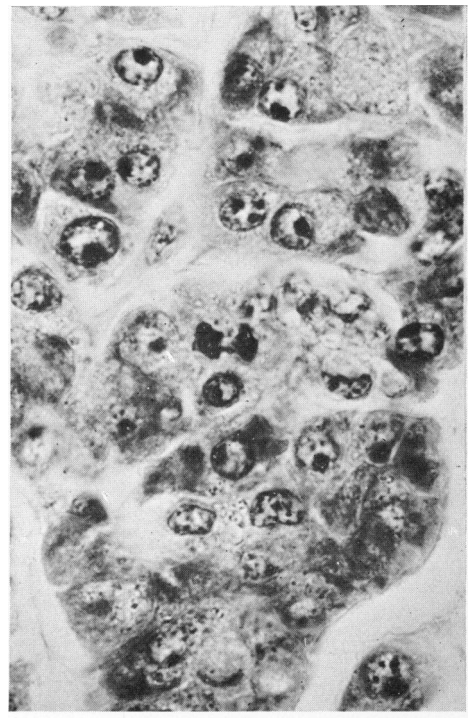

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