A STUDY OF THE PATHOLOGICAL ANATOMY OF THE PANCREAS IN NINETY CASES OF DIABETES MELLITUS.[1]

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PLATES V–VII.

Study of anatomical changes in diabetes mellitus has been limited in large part to lesions which occur in the pancreas. In 1889 were published the well-known experiments of von Mering and Minkowski (1), in which they showed that the removal of the pancreas in dogs produced typical diabetes. The diabetes of depancreatized dogs has suggested that the pancreas furnishes an internal secretion which controls carbohydrate metabolism. Since the other organs of internal secretion are ductless glands, the islands of Langerhans, the only parenchymatous tissue in the pancreas not in communication with the ducts, were associated with pancreatic internal secretion (Laguesse (2), Schäfer (3)) at a time when evidence of this association was wanting.

Opie (4), in 1900, described definite pathological changes in the islands of Langerhans in diabetes. These changes consisted most frequently in increase of fibrous tissue within and about the islands. In other cases of diabetes Opie found hyaline degeneration of the islands of Langerhans occasionally in a pancreas otherwise entirely normal. Opie reaches the conclusion that where diabetes is caused by a lesion of the pancreas, the lesion is of such a character as to injure or destroy the islands of Langerhans. These studies have been followed by a large number of articles upon the same subject, and some observers have supported, while others have opposed his views. In addition to the lesions described by Opie, other changes in the islands of Langerhans have been noted in association with

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diabetes mellitus. Schmidt (5) found acute inflammation limited to the interacinar islands in a child ten years old. Ssobolew (6) and others have reported absence of the islands of Langerhans, or great diminution in their number. Hypertrophy of these islands, associated with a peculiar adenoma-like arrangement of their cells, has been described by Reitmann (7), Herxheimer (8), MacCallum (9) and others.

Sauerbeck (10) in 1902 collected from various sources one hundred and seventy-six cases of diabetes in which the condition of the islands had been noted. He found that lesions in the islands of Langerhans had been observed in sixty-two per cent of the cases.

The present work was undertaken at the suggestion of Dr. Opie, with the hope that the study of a large number of cases by a single observer might furnish accurate information concerning the condition of the pancreas and of the islands of Langerhans in diabetes mellitus. So far as I know, only two of the following cases have been previously reported.

Gross Pathology of the Pancreas in Diabetes.—Of my cases, the pancreas has been described as small or atrophic in only twenty-five per cent. With the exception of this diminution in size, the pancreas exhibited very few notable macroscopic changes. The weight has been given in thirty-six cases, and ranges from thirty to one hundred and eighty-five grammes. The average weight was ninety-four grammes. This is scarcely less than the weight of the normal pancreas, which averages, according to Vierordt, ninety-seven grammes. The consistency of the gland in a good many cases was increased. The lobulation was indistinct in some instances and in fifteen an infiltration of fat tissue was visible with the naked eye. Neither cancer, cysts nor calculi of the pancreas were encountered. There were no cases of pancreatic apoplexy.

In considering the histological pathology of the pancreas in diabetes, it will be convenient to divide the subject into three parts: (1) Changes in the interstitial tissue. (2) Changes in the glandular acini. (3) Changes in the islands of Langerhans.

Changes in the Interstitial Tissue.—Opie (4) has shown that the interstitial changes which follow obstruction of the duct differ from

those observed in connection with diabetes. In the former, sclerosis is chiefly interlobular, and while the lobules may be invaded to a greater or less extent by the newly formed tisssue, the progress of the lesion is apparently inward from the periphery of the lobule. In the pancreatitis of diabetes, the reverse is true. The new growth originates between the acini, and interlobular sclerosis, if present at all, is a later phase of the process.

Of the ninety cases which I have studied, sixty-four, or seventy-one percent., show a definite chronic interacinar pancreatitis. In twenty-one, or twenty-four per cent., the sclerosis is marked. The distribution of this new growth is generally uneven, some lobules being more involved than others. In a number of cases this "focal" sclerosis is conspicuous. Where the induration is advanced, many of the lobules have been largely replaced by fibrous tissue, while the glandular acini which still survive are compressed and distorted, and may give evidence of atrophy. Although the newly formed fibrous tissue is often most conspicuous about the vessels and ducts, I have not been able to establish any constant relationship. In many cases, especially where the lesion is mild, the sclerosis seems more advanced in the neighborhood of the islands of Langerhans.

The relation of age to chronic interacinar inflammation is important. The lesion has been entirely absent in all of the four cases under twenty years of age. Between the ages of twenty and thirty, only twenty-five per cent. of cases show interacinar new growth. After thirty, interacinar sclerosis is the rule, being present in ninety per cent. of all cases.

Typical chronic inflammation of the interlobular variety has been observed in only four cases.

A well marked interacinar invasion was present in all four cases (Cases XXI, XXII, LII and LXII). A slight and very irregularly distributed interlobular fibrosis is seen in some severer instances of chronic intracinar inflammation, but here the process appears to be a local extension of the changes between the acini. Of the four cases just mentioned, one was associated with a duodenal ulcer, one with persistent vomiting, and another with diphtheritic colitis. In the fourth, no history was obtained. The associated intestinal lesion suggests ascending infection of the pancreatic duct.

The newly formed connective tissue which is seen in both types

of chronic interstitial pancreatitis is generally of a dense fibrous character and rather poor in spindle cells. In a number of my cases, however, the new growth is of a looser texture and quite cellular, resembling the stroma of an infant's pancreas. An extensive infiltration of lymphoid, eosinophile and plasma cells has been observed very frequently with both types of chronic interstitial pancreatitis. Of the sixty-four cases with interacinar pancreatitis, thirty have shown an abundant cellular infiltration. Lymphoid cells constitute the greater part of this infiltration, but eosinophile cells and plasma cells are also plentiful. The presence of a considerable number of cellular elements in the stroma would seem to indicate that the inflammatory process was still in the active stage. A marked infiltration of lymphoid cells was present in each of the four cases of chronic interlobular pancreatitis. Polymorphonuclear leucocytes were found in the stroma in greater or less numbers in eight cases, always associated with infiltration of lymphoid cells.

Considerable infiltration of the pancreatic stroma by adipose tissue was found in twenty-six of my cases. Three of these showed a very marked invasion, the lobules as well as many of the acini being widely separated by fatty tissue. In these three cases, the parenchyma appeared much reduced in amount and the sections gave the impression that many acini had been replaced by adipose tissue. The islands of Langerhans were very scarce in one case (Case XXXVI). In the other two (Cases L and LXXVIII) a considerable number of interacinar islands were found. One of these cases of pancreatic lipomatosis was associated with obesity.

Arteriosclerosis, it is well known, accompanies a large percentage of cases of diabetes. Of my cases, eighty per cent. showed a thickening of the wall of the pancreatic vessels and in half of these cases the vessels were also hyaline. The small arterioles seem to show this change first, and in many instances, the lumen of the smaller vessel has been almost entirely obliterated by hyperplasia of the medial coat. Hyaline changes were, moreover, more commonly observed in the small than in the large vessels.

The incidence of arteriosclerosis in diabetes increases rapidly with age. In my series, it was present in only forty per cent. of the cases between twenty and thirty years of age, increased to seventy-

seven per cent. in cases between thirty and forty, and was present in all but two cases occurring after the fortieth year.

Changes in the Secreting Parenchyma.—Clinically and experimentally, cases are constantly encountered which give no evidence of a disturbance in carbohydrate metabolism, although they show at autopsy extensive destruction of the glandular acini. According to my observations, the most common change of the acini with diabetes is the compression and atrophy, seen in association with the severer types of chronic interacinar pancreatitis. An acinus which has undergone this change is smaller than the normal; its constituent cells are pressed together and individual cells are ill defined; in some acini a number of the cells have already been destroyed, so that only a part of the original acinus remains. Many acini have been completely obliterated and their place is taken by connective tissue. In striking contrast to the atrophied acini and occasionally associated with them in the same section are acini which are larger than the normal, rich in centro-acinar cells; they suggest a compensatory hypertrophy.

The brightly staining eosinophile acini, first described by Opie, have been observed in nine of my cases. Such an acinus or group of acini, takes a bright pink stain in preparations stained with hæmatoxylin and eosin and is sharply defined from the surrounding alveoli.

Changes in the Islands of Langerhans.—In the ninety cases which I have studied, seventy-nine, or eighty-eight per cent., have shown definite anatomical changes in the islands. By far the commonest lesion is fibrosis, which has been observed in seventy-six cases. In forty it has been moderate; in thirty-six advanced. In the former cases the islands are surrounded by capsules of fibrous tissue which are thicker than the normal, almost invisible sheaths. The fibrillary coating of the insular capillaries is also definitely increased in thickness, converting the vessels into coarse septa which extend in from the capsule and anastomose at the center of the interacinar island. The cells forming the columns show little or no change in number or appearance.

The following are the cases which show *moderate* sclerosis of the islands. Cases V, X, XV, XIX, XXIV, XXV, XXXIII, XXXIV, XXXV, XXXVI,

XXXVIII, XXXIX, XL, XLI, XLII, XLIV, XLVII, XLIX, L, LI, LII, LV, LVI, LIX, LX, LXIII, LXIV, LXVIII, LXIX, LXX, LXXV, LXXVI, LXXVII, LXXVIII, LXXXII, LXXXIII, LXXXVI, LXXXVII, LXXXVIII, XC.

In the second group of cases the lesions are of a similar nature, but more advanced. The islands of Langerhans are imbedded in dense fibrous tissue which separates them widely from the surrounding alveoli. The intrainsular sclerosis still follows the path of the insular capillaries, the walls of which are several times thicker than the normal (Fig. 1). Sections through the center of the body may show an extensive patch of dense fibrous material, rich in spindle cells and sending out broad septa towards the periphery (Fig. 2). The cells of the islands are often reduced in number, and appear small and compressed. Occasionally an island of Langerhans is found which has been almost completely converted into fibrous tissue (Cases IV, IX, XXVI and LXXX).

The following are the cases which show *advanced* sclerosis of the islands. Cases I, III, IV, VI, VIII, IX, XI, XII, XIV, XVI, XVII, XVIII, XX, XXI, XXII, XXVI, XXVIII, XXIX, XXXII, XXXVII, XLIII, XLV, XLVIII, LII, LIII, LVIII, LXI, LXII, LXV, LXVII, LXXII, LXXIX, LXXX, LXXXI, LXXXIV, LXXXV.

Insular sclerosis of the mild type is usually associated with a moderate chronic interacinar pancreatitis, but this relation is not present in all cases. In four of my cases where there was no evidence of a chronic interstitial inflammation, a definite increase of connective tissue was found in the interacinar islands (Cases V, XXXV, XXXVIII and LVI). In these four cases the age varied from twenty-six to seventy years. Advanced sclerosis of the islands of Langerhans was always associated with considerable interacinar sclerosis, and the insular lesion was always most severe in those areas where the induration was most marked.

The relationship between sclerosis of the islands of Langerhans and arteriosclerosis is of interest. Fibrous changes in the islands are, with few exceptions, associated with a sclerosis of the smaller pancreatic arterioles. Of my cases of insular sclerosis, all but five showed thickening of the vessel walls; in these five cases, no arterial sclerosis was recognizable. Sclerosis of the island of Langerhans in its early stages, is probably a part of more or less generalized arteriosclerosis. It doubtless affects the capillaries of the islands of

Langerhans or their afferent vessels and in this respect resembles the beginning fibrous changes in the glomeruli of the kidney. When the process is advanced, chronic interacinar inflammation is always present and the entire interstitial framework of the island becomes involved in the new growth. The insular capillaries, however, still bear the brunt of the attack.

The average duration of diabetes mellitus in forty-six cases with sclerosis of the islands of Langerhans was three years and eleven months.

Hyaline degeneration of the islands of Langerhans is the lesion which has occurred next in frequency to sclerosis, being present in twenty-seven cases (thirty per cent.). In most instances, it has been associated with sclerosis of the pancreatic vessels and of the islands of Langerhans. There were indeed only two exceptions to this rule (Cases LXXI and LXXIV). In Case LXXI the islands were so completely destroyed that their histological structure was entirely lost (Fig. 4). In six cases with hyaline changes in the interacinar islands there was no increase in the interacinar connective tissue (Cases LXXI, XL, XLIX, LXXXVI, LIV and LXIV. As a rule the majority of the islands of Langerhans were affected, but in a few cases only an occasional island showed the change. The hyaline material is first deposited along the capillaries of the island, separating the latter from the cells. As the process advances, it extends outward. Many of the cells are replaced by the hyaline substance, and those which still survive are often compressed and atrophic. Eventually, the entire area of the island may be occupied by homogeneous hyaline material. The nuclei of the endothelial cells appear to persist longest, but finally these too are destroyed.

I have found hyaline degeneration of the islands of Langerhans in only two of the cases under thirty years of age (Cases XXXIX and LXXIV). It appears to be most common after the fifth decade. In my cases I have found that this lesion was, with the exception of case XXXIX, always associated with diabetes of more than one year's duration. The average duration of the diabetes in sixteen cases with hyaline islands was three years and six months.

In nine cases I have observed a well-marked infiltration of leucocytes about the islands of Langerhans. A more or less general

infiltration of the same character sometimes accompanied this lesion, but the cells were more numerous and concentrated in the vicinity of the interacinar islands. The cells were generally arranged in the form of a halo about the island of Langerhans just outside of the capsule, though in some cases the island itself was invaded (Fig. 3). The average duration of the diabetes in the six cases of this group where the duration was definitely stated was only eleven months.

Hypertrophy of the Islands of Langerhans.—Laguesse (2) found that the islands of Langerhans in the normal pancreas of man varied from one hundred to four hundred microns in diameter. Islands of Langerhans exceeding four hundred microns were very rare. Lydia Dewitt (11) measured these bodies in the human pancreas, and found that they averaged .0153 c.mm. in volume. In her measurements the diameter never reached 400 microns. The pancreas in thirty-eight per cent. of my cases showed islands of Langerhans which equalled or exceeded 400 microns in diameter. Round or ovoid islands were selected and the long diameter was measured.

In Case XXVI, an island of Langerhans was found which measured sixteen hundred micromillimeters—a diameter about eight times that of normal (Fig. 5). In the cases where giant islands were found, the average size of the interacinar islands was increased. Hyaline degeneration of the islands was associated with about a third of the cases with hypertrophy (see Fig. 5) and it was observed that hypertrophied islands as a rule were free from hyaline material, or contained it in only small amounts.

Reitmann (7), Herxheimer (8), MacCallum (9) and others have described a peculiar form of hypertrophy of the interacinar islands, which they have encountered in the pancreas of some cases of diabetes. The cells displayed instead of their usual arrangement in irregular cords or masses, a definite columnar arrangement (Figs. 6 and 7), and were often grouped together in circular cords about capillaries. In seven of our cases, a similar lesion has been observed. The islands of Langerhans are considerably larger than the normal, some of them reaching a diameter of seven or eight hundred microns. Their contour is quite irregular; loops and cords of columnar epithelial cells push their way out between the adjacent acini, and, but for differences in staining reaction, might possibly be mis-

taken for normal glandular structure. In one of our cases (Case XXIX) the picture is truly remarkable. The islands are very numerous, and exceedingly large and irregular in outline; their general appearance is somewhat suggestive of a neoplasm. The pancreas was normal, however, in its gross appearance and all the islands shared in the hyperplasia. In six of these cases, hypertrophy of the islands of Langerhans was associated with increase of fibrous tissue about the insular capillaries.

Number of Islands of Langerhans.—The number of islands of Langerhans in the normal pancreas varies considerably. According to Laguesse (2), the average is somewhat less than one island to each square millimeter; Sauerbeck's estimation is one island per square millimeter, and Dewitt's one and five-tenths to the square millimeter. In a number of my cases, the number of interacinar islands has been large but this apparent increase in number may have been due in many cases to increase in size of the islands, as the two phenomena were usually observed together.

Diminution in the number of islands of Langerhans was a much commoner finding. While there was no instance in my series of a pancreas entirely devoid of islands of Langerhans there were a number of specimens in which they were exceedingly few.

Several writers have found an absence or scarcity of islands in diabetes. Ssobolew (6) reported fifteen cases in which the islands were either absent altogether or were much diminished in number. Two factors probably contribute to explain this diminution. First, there is a group of cases in which the pancreas may show little or no change, and where the condition is perhaps due to a congenital defect. Opie reports the case of a child, fourteen years old, with hereditary diabetes, in which the number of islands showed a well-marked diminution. In a second group of cases, the scarcity of islands of Langerhans is associated with chronic interacinar pancreatitis of severe type. Here the islands are probably destroyed and their places occupied by fibrous tissue.

In twenty of my cases the islands of Langerhans showed a marked diminution in number, recognizable by inspection of sections. These nineteen cases may be classified as follows: (1) scarcity of islands in a normal pancreas (5 cases); (2) scarcity of islands in association with chronic interacinar pancreatitis (15 cases).

Cases in Which the Pancreas was Normal.—Eleven of my cases showed no discoverable anatomical lesion in the pancreas. The pancreas in two cases of this group (Cases VII and LVII) was described as small, but in all other respects the gross appearance agreed with the microscopic in suggesting no pathological changes. In five cases (Cases VII, XIII, LVII, XLVI and LXX) diminution in the number of interacinar islands was marked. The islands were of small size in five cases. The age in all but one of these cases was under thirty-five years.

Relationship of Diabetes to Organs other than the Pancreas.—I have already discussed the relation of pancreatic lesions occurring with diabetes to general or pancreatic arteriosclerosis.

Cirrhosis of the liver was present in seven of my cases. The pancreas from all of these cases showed well-marked chronic interacinar inflammation, which in two instances was far advanced. One etiological factor is probably active in both organs. The same statement is perhaps applicable to chronic nephritis, which was present in twenty-five cases, and was in all instances associated with more or less advanced chronic inflammation of the pancreas.

Two cases of cirrhosis of the liver were accompanied by *hæmochromatosis* (Cases XLII and LIX). This remarkable disturbance of iron metabolism was first described by von Recklinghausen (12), and is characterized by a deposition of a brown iron-containing pigment in the various tissues and organs of the body. Hæmochromatosis with diabetes or "Bronzed diabetes" is well recognized. Von Recklinghausen found cirrhosis of the liver a constant feature of the disease, and more recently a number of writers have noted the occurrence of chronic interstitial pancreatitis.

Case XLII was obtained through the kindness of Dr. MacCallum of the Johns Hopkins Hospital. A man, thirty-seven years of age, gave a history of diabetes of nine months' duration. The urine contained 6.5 per cent. of glucose. Acetone and diacetic acid were also present. There were ascites and pigmentation of the skin. The patient died in coma. At autopsy, marked pigmentation was found in the liver, heart, pancreas, lymph glands and skin. The liver showed cirrhosis and the heart was hypertrophied. The pancreas was large and firm and weighed 150 grammes. On section it was brown, and mottled with fat. Microscopically, there is a very marked infiltration of fat tissue which appears to have replaced the glandular structures in many places. This invasion is not confined to the interlobular tissue but separates the acini as well.

There is also a definite new growth of connective tissue between the acini, which is rich in spindle cells and infiltrated with a moderate number of lymphoid and plasma cells. The interstitial tissue is the seat of an abundant deposition of light brown pigment which reacts positively to the chemical test for iron. Many of the acinar cells are loaded with this pigment. Some of the acini are considerably swollen, and their cells stain faintly. The walls of the blood vessels are not appreciably thickened.

The islands of Langerhans are very scarce, and considerably smaller than the normal, none of them measuring over 200 microns in diameter. The fibrous capsules about the islands are thickened, and infiltrated by pigment. Some of the island cells also contain pigment but the remainder take their usual stain.

Case LIX was obtained through the kindness of Dr. Wright of the Massachusetts General Hospital. A man forty-five years of age had had three per cent. of glucose in his urine, as well as acetone and diacetic acid. The patient died in coma, and at autopsy there were found cirrhosis of the liver and pigmentation of the liver and pancreas. The pancreas was dark brown in color and rather soft.

Microscopically, sections from the pancreas show a marked new growth of connective tissue between the acini. The lobules are widely separated by adipose tissue. The stroma is the seat of a universal deposition of iron pigment which stains blue with ferrocyanide of potassium and hydrochloric acid. Many of the acinar cells are also loaded with pigment. The walls of the blood-vessels are somewhat thickened. Dense collections of lymphoid and polymorphonuclear cells are found in the neighborhood of the larger ducts. The islands of Langerhans are fairly numerous and normal in size; many of them are surrounded by dense capsules of fibrous tissue, and the insular capillaries are thickened. A considerable number of insular cells are distended with pigment (Fig. 8), and give evidence of degeneration, the nuclei staining indistinctly.

The islands in these two cases show very similar lesions, namely, encapsulation by fibrous tissue and a deposition of iron pigment in the insular cells (Fig. 8). In the case first described there was a marked diminution in the number of the islands of Langerhans, probably partly due to the advanced lipomatosis.

The association of diabetes with certain diseases of the ductless glands has been frequently observed. Hansemann (17) collected from the literature of the subject fifteen cases of *exophthalmic goitre* which had been accompanied by diabetes but there had been no opportunity to study the pancreas. A number of other writers have more recently observed glycosuria in connection with Grave's disease.

I have been able to include in the present series one case of diabetes which was associated with exophthalmic goitre. The case was reported by Dr. Morris Manges in the Mt. Sinai Hospital Re-

ports, Vol. II. Dr. Libman was kind enough to supply me with a part of the pancreas.

The patient, a woman, forty years of age, gave a history of diabetes of six months' duration, her chief complaint being weakness, emaciation and thirst. The urine contained five per cent. of glucose. Acidosis was present. There were marked exophthalmos, tachycardia and neuralgic pains. The latter were relieved by thyroid extract. Death occurred from asthenia and cardiac failure. At autopsy the thyroid gland was enlarged and firm; microscopically there were glandular hyperplasia and chronic inflammation. The pancreas was atrophic and weighed 45 grams; on section it was pale and soft.

Microscopically the pancreas exhibits typical chronic interacinar pancreatitis of advanced grade. The acini are small, and separated by dense fibrous tissue, which in some places has almost completely replaced the parenchyma. The stroma shows rich infiltration by lymphoid and plasma cells, with a few polymorphonuclear leucocytes. The vessel walls are thickened and hyaline. Islands of Langerhans are fairly numerous but have small area. In places where the sclerosis is severe the interacinar islands are much involved, being buried in dense fibrous tissue and invaded by the same material. Many of them have been almost obliterated by the fibrous hyperplasia.

Adenoma of the thyroid gland has been noted in the anatomical diagnosis in two of my cases with diabetes (Cases XXIX and XXXIV). It is a significant fact in this connection that in both cases the adenoma-like hypertrophy of the islands of Langerhans, described above, is present. In Cases XXIX this hypertrophy affects nearly all the islands of Langerhans, which often attain great size In Case XXXIV the insular hypertrophy is also well marked. The pancreas in both of these cases shows a well-marked chronic interacinar inflammation with considerable increase of fibrous tissue in and about the islands of Langerhans.

Myxœdema was found associated with diabetes in one of my cases (Case VI).

The patient, a woman, seventy fours years of age, was first admitted to the Presbyterian Hospital on March 12, 1899, complaining of weakness, shortness of breath, despondency, and gradual loss of mental powers.

There was a general thickening of the subcutaneous tissue. The skin was dry and scaly, and the nails and hair were brittle. There was puffiness under the eyes, and the tongue was thickened. Speech was deliberate and lisping in character. Pulse tension was high. At this time there was no glucose in the urine. The patient was treated with thyroid extract and improved rapidly.

A year and a half later, the patient was admitted again to the hospital complaining of thirst, poluria, puritus vulvæ and eczema. Myxœdema was much improved. The urine contained four per cent. of glucose. The amount of sugar diminished under treatment. During the two years following, the

patient was in the hospital several times, and finally died in coma September 6, 1902.

At autopsy the thyroid weighed only eight and a half grams; microscopically there is very advanced atrophy of the parenchyma. The alveoli have been almost completely obliterated and their places are occupied by fibrous tissue, densely infiltrated in places by lymphoid cells.

The pancreas weighed 120 grams, and was of tough consistency. Microscopically, advanced chronic interacinar inflammation, and universal infiltration of adipose tissue can be recognized in spite of extensive post-mortem digestion. The islands can be identified and show considerable sclerosis.

The occurrence of glycosuria with *acromegaly* has been observed in a considerable proportion of cases of this disease. Hansemann (17) and others have described such cases in which a chronic interstitial pancreatitis was found. Through the kindness of Dr. Norris I have been able to study the pancreas from a case of acromegaly which was accompanied by diabetes.

The case was reported by Dr. Norris in the *Proceedings* of the New York Pathological Society, February, 1907.

The patient, a man, thirty-three years old, was admitted to Bellevue Hospital with the following symptoms: Progressive enlargement of jaw, nose, ears, hands and feet. Persistent frontal headaches, and attacks of vertigo. Gradually increasing loss of vision, ending in atrophy of both optic nerves and almost complete blindness. There were recurrent epileptiform attacks. Glycosuria had been present during twenty two months.

At autopsy, a large tumor was found, connected by a broad pedicle to the pituitary gland which was itself enlarged; microscopically, the tumor is composed of cuboidal or oval cells which are arranged in irregular alveoli. The stroma is very scanty. The alveoli are separated by capillaries, whose endothelial lining is apparently in direct contact with the alveolar cells. In some places the capillaries are dilated, giving the tumor a very vascular appearance.

The pancreas was large and firm, and weighed 170 grams. The lobulation was distinct and no macroscopic lesions were noted.

Microscopically, the pancreas is free from interstitial induration. There has been some post-mortem digestion in a few places, but otherwise the glandular acini are normal in appearance. The walls of the blood-vessels are slightly thickened. The islands of Langerhans are numerous, irregular in outline, and larger than the normal; many are otherwise normal. One island is found which measures six hundred micromillimeters in diameter. Some of the larger islands present a very unusual appearance. The insular cells are large, and often columnar in shape and arrangement. In many instances the cords of cells form partial or complete circles, whose lumina contain the insular capillaries. These capillaries show definite sclerosis. There is a marked deposit of hyaline material in a few of the islands of Langerhans.

The coexistence of this adenoma-like hypertrophy of the islands

of Langerhans with adenoma of the pituitary gland is especially significant if it be borne in mind that the same type of insular hypertrophy was observed in association with the two cases of adenoma of the thyroid gland; at present I can offer no satisfactory explanation of this association.

In another case (Case LXXXIII) *calcification of the pituary gland* is mentioned as one of the anatomical findings. A well marked chronic interstitial inflammation which affects chiefly the interacinar tissue is found in the pancreas. The islands of Langerhans are small and rather scanty. They show definite fibrous changes, manifested by a thickening of the capillary walls.

Other anatomical changes associated with diabetes are of considerable interest.

Gangrene is a common complication, and is generally attributed to two causes, arterio-sclerosis and lowered resistance in the tissue, resulting from the diabetes. Gangrene occurred in sixteen of my cases and was in all instances associated with arterio-sclerosis and well marked chronic interacinar pancreatitis. The youngest individual affected by gangrene was forty-three years of age. In eleven cases it was the lower, and in two, the upper extremity which was involved. There was one case of gangrene of the scrotum and one case in which the location of the gangrene was not mentioned.

Fat necrosis has been found to occur with various lesions of the pancreas, and accompanies the acute, more often than the chronic changes. Fat necrosis is mentioned in the anatomical diagnosis of four cases in the present series. I have been unable to find any common feature other than chronic intracinar induration present in these cases.

Cholelithiasis occurred in nine of my cases. Opie (13) has shown that where gall-stones are a causal factor in chronic pancreatitis, they produce sclerosis of the interlobular variety. The inflammatory process in these nine cases was definitely interacinar; it is probable, therefore, that the gall-stones were not related etiologically to the pancreatic lesions.

PATHOGENESIS OF DIABETES MELLITUS.

The islands of Langerhans are composed of columns of cells, with a rich vascular supply, but have no communication with the ducts. In this respect they resemble the parenchyma of the thyroid and adrenal glands. If the pancreas furnishes an internal secretion, it is possible that this function is performed by the islands of Langerhans. Attempts to study these islands experimentally are met by great difficulties. Marked sclerosis of the pancreas follows ligation of the pancreatic ducts in animals but the islands of Langerhans remain normal and no glycosuria occurs. A similar lesion unaccom-

panied by diabetes occurs as the result of occlusion of the pancreatic duct in man.

A number of observers believe that the islands of Langerhans are phases in the life history of the secreting alveoli, and are not independent structures. Dale (14) claims to have converted acini into islands of Langerhans by starvation and the injection of secretin. It is possible that Dale mistook for islands groups of acini exhausted by hypersecretion and similar to areas which, as previously mentioned, occur in diabetes and fail to exhibit the staining reaction of secreting acini. The peculiar structure and blood supply of the islands of Langerhans and the characteristic staining reactions which Lane (15) has demonstrated furnish strong evidence in favor of their independence.

In the present study of the pancreas from ninety cases of diabetes, the following pancreatic changes have been encountered:

1. Chronic Inflammation of the Pancreas.	
Interacinar pancreatitis; sclerosis of islands of Langerhans	39
Interlobular pancreatitis; sclerosis of islands of Langerhans	4
Interacinar pancreatitis; hyaline degeneration of islands of Langerhans	19
Interacinar pancreatitis with lipomatosis; sclerosis of islands of Langerhans	2
Interacinar pancreatitis, with lipomatosis; hyaline degeneration of islands of Langerhans	1
Interacinar pancreatitis, with siderosis of islands of Langerhans (hæmochromatosis)	2
2. Parenchyma normal; lesions of the islands of Langerhans.	
Sclerosis of the islands of Langerhans	4
Hyaline degeneration of the islands of Langerhans	7
Infiltration of leucocytes about islands of Langerhans	1
3. Pancreas normal	11
	90

Of the eleven cases of normal pancreas, five showed a marked diminution in the number of islands of Langerhans. In two other cases the pancreas was abnormally small.

In order to establish a causal relationship between lesions of the islands of Langerhans and pancreatic diabetes, the following premises must be proven:

1. Lesions of such a nature as to interfere with the performance of their function occur in the islands of Langerhans in diabetes.

2. These lesions are primary, and not secondary to diabetes.

1. The chief object of this study has been to determine the frequency of lesions of the islands of Langerhans in diabetes. Eighty-eight per cent. of my cases have shown definite changes in the islands. In thirty per cent. of cases, some or all of the islands of Langerhans exhibited hyaline degeneration with consequent partial destruction. Lesions of the islands of Langerhans have usually been associated with chronic interacinar pancreatitis and arteriosclerosis. In twelve cases insular changes have occurred in an otherwise normal pancreas.

Are the lesions of the islands of Langerhans sufficiently severe to produce loss of function?

In most instances, there can be little doubt that hyaline degeneration and sclerosis have an injurious effect. Even where there is only a moderate thickening of the insular capillaries, the change is doubtless sufficient to interfere with the proper nutrition of the cells.

2. Are the lesions of the islands of Langerhans secondary to diabetes? There is no evidence in support of this view. The variety of lesions of these structures associated with diabetes affords evidence that they are not the result of the same cause. As a rule sclerosis of islands of Langerhans is associated with chronic interacinar pancreatitis and diabetes with such destructive lesion of the pancreas is comparable to diabetes following partial removal of the gland in lower animals.

Is the cause of pancreatic diabetes to be found in lesions of the parenchyma, in lesions of the islands of Langerhans, or in both combined? Chronic interacinar pancreatitis alone does not answer the question, for both structures are implicated. On the other hand, with forms of chronic inflammation due, for example, to duct obstruction, where the parenchyma is destroyed and the islands of Langerhans remain intact, the absence of diabetes indicates that destruction of the glandular acini is not sufficient to produce the disease.

Most significant, however, are cases with partial or complete destruction of the islands of Langerhans and no changes in the parenchyma. Twelve cases in the present series have shown lesions of this character. In seven of these the interacinar islands were hyaline, in four they were sclerotic and in one they were infiltrated by polymorphonuclear and lymphoid cells. The selective character of these lesions is strong evidence in favor of the view that the islands stand in a causal relationship to diabetes.

The frequency of hypertrophy of the islands of Langerhans in diabetes is noteworthy. In thirty-eight per cent. of my cases islands of Langerhans measuring four hundred micromillimeters or more in diameter have been found (Fig. 5). Hypertrophy of the islands

has usually been associated with sclerosis or hyaline degeneration affecting the interacinar islands in the same gland, and is probably compensatory in character.

How may the occurrence of a normal pancreas with diabetes be explained? It is possible that diabetes in some of these cases is not of pancreatic origin. It is well known that temporary glycosuria can be caused by puncture of the fourth ventricle and by other injuries of the nervous system. Falta, Eppinger and Rudinger (16) in their studies of the relationship of the pancreas to the ductless glands reach the conclusion that the latter are almost equally instrumental with the pancreas in the production of diabetes. It is significant, however, that in the cases of this series in which diabetes has accompanied lesions of the ductless glands, for example, exophthalmic goitre and myxœdema, well-marked changes in the pancreas and in the islands of Langerhans have been found.

It has been said by Sauerbeck that the occurrence of normal pancreas associated with diabetes mellitus does not furnish evidence that lesions of the islands of Langerhans do not cause glycosuria, for it is equally unfavorable to the view which refers glycosuria to changes in the secreting parenchyma. Diminution in the number and size of the islands of Langerhans in an otherwise normal pancreas may play an important part in the production of diabetes, particularly in young individuals; and a deficiency of this kind is perhaps congenital.

CONCLUSIONS.

1. Anatomical lesions of the pancreas occur in more than seven-eighths of all cases of diabetes mellitus.

2. In diabetes associated with lesions of the pancreas, the islands of Langerhans constantly show pathological changes (sclerosis, hyaline degeneration, infiltration with leucocytes and hypertrophy).

3. In some cases of pancreatic diabetes (twelve of ninety cases) the lesion of the pancreas is limited to the islands of Langerhans.

4. In sixteen cases of diabetes associated with hyaline degeneration of the islands of Langerhans the average duration of the disease has been three and a half years; in forty-six cases with sclerosis of these bodies, three years and eleven months. In six cases of diabetes associated with an infiltration of leucocytes about the

islands of Langerhans the average duration has been eleven months.

5. Destructive lesions of the islands of Langerhans may be associated with compensatory hypertrophy of other interacinar islands.

6. Peculiar adenoma-like hypertrophy of the islands of Langerhans occurs in a small proportion of cases (seven of ninety) and may be associated with adenomata of the thyroid gland (two cases) and of the pituitary body (one case).

7. Diabetes mellitus occurring in association with hæmochromatosis (bronzed diabetes) is referable to pigmentation and destruction of the islands of Langerhans.

8. The pancreas is found to exhibit no pathological changes in twelve per cent. of cases. In approximately one-half of these cases it has been noted that the size of the gland or the number of islands is much less than normal.

9. Fifty per cent. of cases of diabetes mellitus occurring before the age of thirty years are associated with lesions of the pancreas; seventy-five per cent. of all cases of diabetes in which the pancreas is normal occur before the age of thirty years. Ninety-seven per cent. of cases of diabetes occurring after the age of thirty years are associated with lesions of the pancreas; and eighty-six per cent. occur in association with chronic interacinar pancreatitis accompanying arteriosclerosis.

10. Interacinar pancreatitis which occurs in seventy-three per cent. of all cases of diabetes is almost constantly associated with arteriosclerosis; gangrene of the extremities, which occurs with one-fourth of all cases of interacinar pancreatitis, is doubtless referable to the same cause.

11. Chronic interlobular pancreatitis, when associated with diabetes, is accompanied by sclerosis or hyaline degeneration of the islands of Langerhans.

12. Diabetes in association with myxœdema or with exophthalmic goiter may be referable to a lesion of the pancreas, namely, chronic interacinar inflammation with sclerosis of the islands of Langerhans; diabetes in association with acromegaly may be referable to a lesion of the islands of Langerhans, namely, sclerosis and hyaline degeneration with adenoma-like hypertrophy.

In closing I wish to express my gratitude to Dr. Opie for much

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CASES OF DIABETES MELLITUS.

I. Pres. H., S. S., 72 yrs., M. Pan.—112 gms. Interacinar pancreatitis. I. of L.—Sclerotic hypertrophied. Arteries—Sclerotic, hyaline.

II. Pres. H., Mann., 10 yrs., M. Diab.—8 mos. Pan.—30 gms.; normal. I. of L.—Normal. Arteries—Normal.

III. Pres. H., L. S., 69 yrs., M. Pan.—120 gms. Interacinar pancreatitis, I. of L. — Sclerotic, hyaline, hypertrophied. Arteries — Sclerotic. Chronic nephritis.

IV. Pres. H., Dres., 71 yrs., F. Diab.—22 yrs. Pan.—100 gms. Interacinar pancreatitis. I. of L.—Very sclerotic, hypertrophied. Arteries — Sclerotic. Chronic nephritis.

V. Pres. H., Malm., 24 yrs., M. Diab.—2½ mos. Pan.—60 gms.; secreting parenchyma normal. I. of L.—Sclerotic, infiltrated with lymphoid cells, hypertrophied. Arteries—Normal.

VI. Pres. H., Pag., 74 yrs., F. Diab.—2 yrs. Pan.—120 gms. Interacinar pancreatitis. I. of L.—Very sclerotic. Arteries—Sclerotic, calcified. Myxœdema.

VII. Pres. H., Bon., 32 yrs., M. Diab.—3 yrs. Pan.—30 gms.; normal. I. of L.—Normal, very few in number. Arteries—Normal.

VIII. Pres. H., Bert., 51 yrs., M. Diab.—Several yrs. Pan.—120 gms. Interacinar pancreatitis. I. of L.—Sclerotic. Arteries—Sclerotic, hyaline. Gangrene of scrotum.

IX. Pres. H., Flie., 58 yrs., M. Marked interacinar pancreatitis. I. of L.—Sclerotic, hypertrophied. Arteries—Very sclerotic, hyaline. Cholelithiasis.

X. Pres. H., Dem., 51 yrs., M. Diab.—2 yrs. Pan.—60 gms. Interacinar pancreatitis. I. of L.—Sclerotic, infiltrated with lymphoid cells. Arteries—Sclerotic. Cholelithiasis.

XI. Pres. H., Brus., 60 yrs., F. Pan.—60 gms. Interacinar pancreatitis. I. of L.—Very sclerotic, hypertrophied. Arteries—Sclerotic, hyaline. Fat necrosis, cholelithiasis.

XII. Pres. H., Sno., 57 yrs., F. Diab.—1 yr. Pan.—90 gms. Interacinar pancreatitis. Polymorphonuclear leucocytes in stroma of pancreas. I. of L.—Sclerotic, hyaline, hypertrophied. Arteries—Sclerotic, hyaline. Chronic nephritis.

XIII. Pres. H., Sill., 27 yrs., M. Diab.—3 yrs. Pan.—60 gms.; normal. I. of L.—Small, otherwise normal; very few in number. Arteries—Normal.

XIV. Pres. H., Bot., 30 yrs., F. Pan.—45 gms. Interacinar pancreatitis. I. of L.—Very sclerotic, hyaline. Arteries—Sclerotic, hyaline.

XV. Pres. H., Lind., 35 yrs., M. Diab.—9 mos. Pan.—120 gms. Interacinar pancreatitis. Polymorphonuclear leucocytes in stroma of pancreas. I. of L.—Sclerotic, few in number. Arteries—Sclerotic.

XVI. Pres. H., Whel., 60 yrs., F. Pan.—100 gms. Interacinar pancreatitis. I. of L.—Very sclerotic, hypertrophied; adenoma-like hypertrophy. Arteries—Sclerotic. Chronic nephritis.

XVII. Pres. H., La T., 52 yrs., M. Diab.—15 mos. Pan.—185 gms. Interacinar pancreatitis. I. of L.—Very sclerotic; few in number. Arteries—Sclerotic, hyaline. Gangrene of foot.

XVIII. Pres. H., Odg., 75 yrs., F. Interacinar pancreatitis. I. of L.—Very sclerotic, hyaline. Arteries—Sclerotic. Chronic nephritis.

XIX. Pres. H., War., 27 yrs., M. Pan.—90 gms. Interacinar pancreatitis. I. of L.—Very small, sclerotic; few. Arteries—Sclerotic. Nephritis.

XX. Pres. H., Van W., 64 yrs., M. Pan.—60 gms. Interacinar pancreatitis. I. of L.—Very sclerotic; few in number. Arteries—Sclerotic, hyaline. Gangrene of foot. Chronic nephritis.

XXI. Case of Dr. James, 36 yrs., F. Diab.—About 1 yr. Interlobular pan-

creatitis. Polymorphonuclear leucocytes in stroma. I. of L.—Very sclerotic, hypertrophied. Arteries—Sclerotic. Persistent vomiting. Fat necrosis.

XXII. Pres. H., Mar. '90. Marked interlobular pancreatitis. Several miliary tubercles in stroma of pancreas. I. of L.—Very sclerotic; few in number. Arteries—sclerotic, hyaline.

XXIII. Royal V. H., 55—'97, 20 yrs., M. Diab.—"Acute course." Pan.—"Simple atrophy"; secreting parenchyma normal. I. of L.—Infiltrated with polymorphonuclear and lymphoid cells, hypertrophied. Insular cells show typical adenoma-like arrangement in a few instances. Arteries—Normal.

XXIV. Royal V. H., 73—'97, 31 yrs., M. Diab.—"Acute course." Pan.—40 gms.; "marked atrophy." Interacinar pancreatitis; infiltration of many polymorphonuclear leucocytes. I. of L.—Sclerotic, hypertrophied; cells columnar, with adenoma-like arrangement. Arteries—Sclerotic, hyaline. Fat necrosis.

XXV. Royal V. H., 32—'00, 65 yrs., M. Diab.—4 yrs. (at least). Pan.—150 gms. Interacinar pancreatitis. I. of L.—Sclerotic, hyaline, hypertrophied. Arteries—Sclerotic, hyaline. Gangrene of foot.

XXVI. Royal V. H., 95—'02, 75 yrs., M. Diab.—15 yrs. Pan.—175 gms. Interacinar pancreatitis. I. of L.—Very sclerotic, large. One very large island shows adenoma-like hypertrophy (Fig. 6). Arteries—Sclerotic, hyaline. Gangrene; cirrhosis of liver; chronic nephritis; atrophic adrenals.

XXVII. Royal V. H., 44—'03, 52 yrs., M. Diab.—15 yrs. Pan.—"Shrunken." Interacinar pancreatitis. I. of L.—Very sclerotic, hypertrophied. Arteries—Sclerotic hyaline. Chronic nephritis.

XXVIII. Royal V. H., 96—'03, 29 yrs., M. Diab.—18 mos. Pan.—150 gms. Interacinar pancreatitis. I. of L.—Very sclerotic, hypertrophied. Arteries—Sclerotic, hyaline. Cirrhosis of liver; chronic nephritis; obesity.

XXIX. Royal V. H., 79—'06, 70 yrs., M. Diab.—2 yrs. Interacinar pancreatitis. I. of L.—Very sclerotic, hypertrophied; cells columnar, with adenoma-like arrangement. Arteries—Sclerotic. Fat necrosis; adenoma of thyroid.

XXX. Royal V. H., 130—'06, 21 yrs., F. Diab.—1 yr. Pan.—Normal. I. of L.—Normal. Arteries—Normal. Chronic nephritis.

XXXI. Royal V. H., 15—'07, 15 yrs., M. Diab.—Discovered on day of death. Pan.—Normal. I. of L.—Normal. Arteries—Normal. Œdema of lungs, persistent thymus, lymphatic hyperplasia. 1.5 per cent. glucose in urine.

XXXII. Royal V. H., 102—'07, 54 yrs., F. Pan.—"Atrophied." Interacinar pancreatitis. I. of L.—Sclerotic, hyaline. Arteries—Sclerotic, hyaline. Cirrhosis of liver.

XXXIII. Royal V. H., 144—'07, 56 yrs., M. Diab.—7 yrs. Pan.—60 gms. Interacinar pancreatitis. I. of L.—Sclerotic, hyaline. Arteries—Sclerotic, hyaline.

XXXIV. Royal V. H., 14—'08, 38 yrs., F. Diab.—3 yrs. Pan.—"Atrophy." Interacinar pancreatitis. I. of L.—Sclerotic, infiltrated with lymphoid cells; adenoma-like hypertrophy. Arteries—Sclerotic. Adenoma of thyroid.

XXXV. Mont. Gen. H., '07—89, 28 yrs., M. Diab.—7 wks. Pan.—45 gms.; secreting parenchyma normal. I. of L.—Sclerotic, hypertrophied. Arteries—Some of them surrounded by leucocytes. Marked loss of weight.

XXXVI. Mont. Gen. H., '07—64, 58 yrs., M. Lipomatosis; interacinar pancreatitis. I. of L.—Sclerotic, hypertrophied; few. Arteries—Sclerotic. Chronic nephritis; obesity (great gain in weight).

XXXVII. Mont. Gen. H., '07—48, 66 yrs., F. Diab.—2½ yrs. Interacinar pancreatitis. I. of L.—Sclerotic, hyaline, hypertrophied. Arteries—Sclerotic, hyaline. Gangrene of feet; chronic nephritis.

XXXVIII. Mont. Gen. H., '08—86, 26 yrs., M. Diab.—8 wks. Pan.—"Small." No sclerosis; infiltration of lymphoid cells. I. of L.—Sclerotic, infiltrated with leucocytes, hypertrophied. Arteries—Sclerotic. Chronic nephritis.

XXXIX. Mont. Gen. H., '08—9, 26 yrs., M. Diab.—6 mos. Interacinar pancreatitis. I. of L.—Very small, sclerotic, hyaline. Arteries—Sclerotic. Chronic nephritis.

XL. Johns Hop. H., 2152, 70 yrs., M. Diab.—7 yrs. Pan.—101 gms. Normal. I. of L.—Sclerotic, hyaline. Arteries—Sclerotic, hyaline. Chronic nephritis.

XLI. Johns Hop. H., 2670. Pan.—38 gms.; normal. I. of L.—Small, otherwise normal; few in number. Arteries—Normal.

XLII. Johns Hop. H., 2782, 37 yrs., M. Diab.—9 mos. "Acute course." Pan.—150 gms. Interacinar pancreatitis; lipomatosis; siderosis. I. of L.—Small, sclerotic, infiltrated with iron pigment; few in number. Arteries—Normal. Hæmochromatosis; cirrhosis of liver.

XLIII. Johns Hop. H., 2929, 43 yrs., F. Pan.—"Areas of atrophy." Interacinar pancreatitis. I. of L.—Sclerotic, hyaline. Arteries—Sclerotic, hyaline. Gangrene of leg.

XLIV. Johns. Hop. H., 2954, 57 yrs., M. Diab.—8 yrs. Pan.—40 gms. Interacinar pancreatitis. I. of L.—Sclerotic. Arteries—Sclerotic. Cystic thyroid; gangrene of foot; chronic nephritis.

XLV. Mt. Sinai H., Hein., 58 yrs., M. Diab.—10 yrs. Interacinar pancreatitis. I. of L.—Very sclerotic. Arteries—Sclerotic, hyaline. Chronic nephritis.

XLVI. Mt. Sinai H., Isr., 44 yrs., F. Pan.—185 gms.; normal. I. of L.—Normal; very few in number. Arteries—Normal.

XLVII. Mt. Sinai H., Kop., 32 yrs., F. Interacinar pancreatitis; polymorphonuclear leucocytes in stroma. I. of L.—Sclerotic. Arteries—Sclerotic, hyaline.

XLVIII. Mt. Sinai H., Hirs., 44 yrs., F. Diab.—6 mos. Pan.—45 gms. Interacinar pancreatitis. I. of L.—Very sclerotic. Arteries—Sclerotic, hyaline. Exophthalmic goitre.

XLIX. Mt. Sinai H., Kauf., 56 yrs., M. Pan.—"Small"; secreting parenchyma normal. I. of L.—Sclerotic, hyaline. Arteries—Sclerotic, hyaline.

L. Mt. Sinai H., Ster., 75 yrs., M. Diab.—10 yrs., at least. Pan.—100 gms. Interacinar pancreatitis; lipomatosis. I. of L.—Sclerotic, hypertrophied. Arteries—Sclerotic, hyaline. Death from hemorrhage into gastro-intestinal tract. (No break in mucosa found.)

LI. Mt. Sinai H., Fat., 50 yrs., M. Diab.—Several years. Interacinar pancreatitis. I. of L.—Sclerotic. Arteries—Sclerotic, hyaline.

LII. Mass. Gen. H., 823, 45 yrs., F. Diab.—6 mos. Pan.—"Much diminished in size." Marked interlobular pancreatitis. I. of L.—Very sclerotic; few in number. Arteries—Sclerotic. Diphtheritic colitis; chronic nephritis.

LIII. Mass. Gen. H., 831, 58 yrs., F. Diab.—2 yrs. Interacinar pancreatitis. I. of L.—Very sclerotic, hyaline. Arteries—Sclerotic, hyaline. Cholelithiasis.

LIV. Mass. Gen. H., 833, 66 yrs., M. Diab.—9 yrs. Pan.—No sclerosis; rich infiltration of lymphoid cells. I. of L.—Hyaline, hypertrophied. Arteries—Sclerotic.

LV. Mass. Gen. H., 839, 53 yrs., F. Diab.—9 mos. Interacinar pancreatitis (slight). I. of L.—Sclerotic. Arteries—Sclerotic.

LVI. Mass. Gen. H., 1050, 70 yrs., F. Pan.—Secreting parenchyma normal. I. of L.—Sclerotic. Arteries—Sclerotic, hyaline. Senile kidney and liver.

LVII. Mass. Gen. H., 1094, 20 yrs., M. Diab.—3 wks. Pan.—"Small"; normal. I. of L.—Normal, but small, and few in number. Arteries—Normal.

LVIII. Mass. Gen. H., 1202, 60 yrs., M. Diab.—4 wks. Pan.—"Rather small." Marked interacinar pancreatitis; polymorphonuclear leucocytes in stroma of pancreas. I. of L.—Very sclerotic; few in number. Arteries—Sclerotic, hyaline. Gangrene of foot.

LIX. Mass. Gen. H., 1358, 45 yrs., M. Interacinar pancreatitis; siderosis. I. of L.—Sclerotic, infiltrated with iron pigment. Arteries—Sclerotic. Hæmochromatosis; cirrhosis of liver.

LX. Mass. Gen. H., 1493, 48 yrs., F. Pan.—"Rather small." Interacinar pancreatitis. I. of L.—Sclerotic, hyaline. Arteries—Sclerotic. Gangrene of arm, syphilitic (?) hepatitis.

LXI. Mass. Gen. H., 1595, 56 yrs., F. Diab.—15 yrs. Interacinar pancreatitis. I. of L.—Very sclerotic. Arteries—Sclerotic, hyaline.

LXII. Mass. Gen. H., 1643, 59 yrs., M. Pan.—"Rather small." Interlobular pancreatitis. I. of L.—Sclerotic, infiltrated with lymphoid cells; some larger than usual. Arteries—Sclerotic. Duodenal ulcer.

LXIII. Mass. Gen. H., 1770, 39 yrs., F. Diab.—Several yrs. Interacinar pancreatitis. I. of L.—Sclerotic, small. Very few in number. Arteries—Sclerotic. Gangrene of foot.

LXIV. Mass. Gen. H., 1855, 60 yrs., M. Diab.—1 yr. (at least). Pan.—Secreting parenchyma normal. I. of L.—Sclerotic, hyaline. Arteries—Sclerotic. Chronic cholecystitis.

LXV. Mass. Gen. H., 1890, 60 yrs., F. Diab.—Symptoms for 4 or 5 mos. Pan.—"Quite small." Interacinar pancreatitis. I. of L.—Sclerotic, infiltrated with lymphoid cells. Arteries—Sclerotic. Cholelithiasis.

LXVI. Mass. Gen. H., 1891, 30 yrs., M. Diab.—2 yrs. Interacinar pancreatitis; suppurative inflammation about ducts of pancreas. I. of L.—Sclerotic, infiltrated with lymphoid cells; few in number. Arteries—Normal.

LXVII. Mass. Gen. H., 1909, 68 yrs., F. Diab.—5-6 yrs. Interacinar pancreatitis. I. of L.—Sclerotic, hyaline, hypertrophied. Arteries—Sclerotic, hyaline. Gangrene of foot, fat necrosis.

LXVIII. Mass. Gen. H., 1917, 52 yrs., M. Diab.—1 yr. Interacinar pancreatitis. I. of L.—Sclerotic, hyaline, hypertrophied. Arteries—Sclerotic. Gangrene of toe.

LXIX. Mass. Gen. H., 2047, 31 yrs., M. Diab.—5 yrs. Interacinar pancreatitis. I. of L.—Sclerotic; very few in number. Arteries—Sclerotic.

LXX. Bost. City H., '08—73, 27 yrs., M. Normal. I. of L.—Normal; small and very few in number. Arteries—Sclerotic. Very severe diabetes.

LXXI. Bost. City H., '02—164, 43 yrs., M. Diab.—2 yrs. Pan.—Secreting parenchyma normal. I. of L.—Hyaline, hypertrophied. Arteries—Normal.

LXXII. Bost. City H., '07—82, 59 yrs., F. Diab.—6 yrs. Interacinar pancreatitis. I. of L.—Very sclerotic, hyaline, hypertrophied. Arteries—Sclerotic. Cholelithiasis; chronic cholecystitis.

LXXIII. Bost. City H., '99—20, 9 yrs., F. Diab.—8 mos. Pan.—Normal. I. of L.—Normal, and large. Arteries—Normal.

LXXIV. Long Isl. H., 4186, 12 yrs., M. Diab.—1 yr. Pan.—Secreting parenchyma normal. I. of L.—Many hyaline. Arteries—Normal.

LXXV. Penn. H., 785, 57 yrs., F. Diab.—2 yrs. Interacinar pancreatitis. I. of L.—Sclerotic, hypertrophied; few. Arteries—Sclerotic, hyaline. Goiter.

LXXVI. Penn. H., 938, 70 yrs., F. Diab.—4 yrs. Pan.—90 gms. Interacinar pancreatitis. I. of L.—Sclerotic, hyaline, hypertrophied. Arteries—Sclerotic. Cholelithiasis; chronic cholecystitis; chronic nephritis.

LXXVII. Penn. H., 608, 36 yrs., F. Pan.—90 gms. Interacinar pancreatitis. I. of L.—Sclerotic, hypertrophied. Arteries—Sclerotic. Cholelithiasis.

LXXVIII. N. Y. City H., Doy., 50 yrs., F. Diab.—9 mos. in hospital. Pan.—"Small." Interacinar pancreatitis; lipomatosis. I. of L.—Sclerotic, hyaline, hypertrophied. Arteries—Sclerotic, hyaline. Gangrene of foot; chronic nephritis.

LXXIX. N. Y. City H., Schro., 69 yrs., M. Interacinar pancreatitis. I. of L.—Sclerotic. Arteries—Sclerotic, hyaline. Chronic nephritis.

LXXX. N. Y. City H., Nst., 65 yrs., F. Pan.—100 gms. Interacinar pancreatitis. I. of L.—Small, sclerotic; very few in number. Arteries—Sclerotic. Cirrhosis of liver; chronic nephritis.

LXXXI. N. Y. City H., Fsh., 56 yrs., M. Marked interacinar pancreatitis. I. of L.—Very sclerotic. Arteries—Sclerotic. Atrophy of adrenals; gangrene of leg.

LXXXII. N. Y. City H., Mar., 47 yrs., M. Diab.—1 yr. Interacinar pancreatitis. I. of L.—Sclerotic. Arteries—Sclerotic, hyaline. Chronic nephritis.

LXXXIII. N. Y. City H., Con., 60 yrs., M. Diab.—3¾ yrs. Pan.—"Small." Interacinar pancreatitis. I. of L.—Small, sclerotic; very few in number. Arteries—Sclerotic, hyaline.

LXXXIV. N. Y. City H., Hen., 51 yrs., F. Interacinar pancreatitis. I. of L.—Very sclerotic, hyaline. Arteries—Sclerotic. Gangrene of hand; obesity.

LXXXV. Case of Dr. Stein's, 43, yrs., M. Diab.—4 yrs. Interacinar pancreatitis; in places, stroma of pancreas shows dense infiltration of polymorphonuclear leucocytes. I. of L.—Very sclerotic. Arteries—Sclerotic.

LXXXVI. Bellevue H., 1163, 33 yrs., M. Diab.—22 mos. Pan.—170 gms. Normal. I. of L.—Sclerotic, hyaline, hypertrophied; some show adenoma-like hypertrophy. Arteries—Sclerotic. Acromegaly; adenoma of pituitary body.

LXXXVII. Bellevue H., 1100, 73 yrs., M. Diab.—6 mos. Interacinar pancreatitis. I. of L.—Very sclerotic, hyaline. Arteries—Sclerotic, hyaline.

LXXXVIII. Mt. Sinai H., Nov., '08, 73 yrs., M. Pan.—180 gms. Interacinar pancreatitis. I. of L.—Sclerotic, hyaline. Arteries—Sclerotic, hyaline.

LXXXIX. Bost. City H., '05—172, 21 yrs., M. Pan.—Normal. I. of L.—Normal. Arteries—Normal.

XC. St. Luke's H. Interacinar pancreatitis. Stroma of pancreas densely infiltrated with polynuclear leucocytes. I. of L.—Sclerotic, infiltrated with leucocytes. Arteries—Normal.

EXPLANATION OF PLATES V–VII.

These photographs have been made by Dr. Edward Leaming at the Rockefeller Institute for Medical Research.

FIG. 1. Sclerosis of island of Langerhans; newly formed fibrous tissue about capillaries (Case XXXVIII).

FIG. 2. Sclerosis of island of Langerhans; central mass of new fibrous tissue (Case LXI).

FIG. 3. Island of Langerhans surrounded and infiltrated with lymphoid cells (Case XXXIV).

FIG. 4. Hyaline degeneration of islands of Langerhans; secreting parenchyma normal (Case LXXI).

FIG. 5. Hyaline degeneration together with simple hypertrophy of islands of Langerhans (Case XXXVII).

FIG. 6. Enormous adenomatous hypertrophy of an island of Langerhans (Case XXVI); the diameter is 1600 microns, magnification being the same as that of Figs. 4 and 5. The enlarged island is well preserved, though the surrounding tissue exhibits self-digestion.

FIG. 7. Adenoma-like hypertrophy of island of Langerhans (Case XXIX).

FIG. 8. Pigmentation of island of Langerhans with hæmochromatosis (Case LIX).

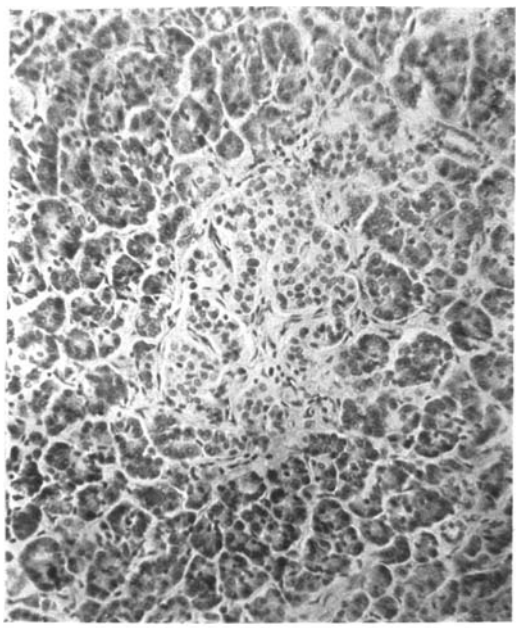

FIG. 1.

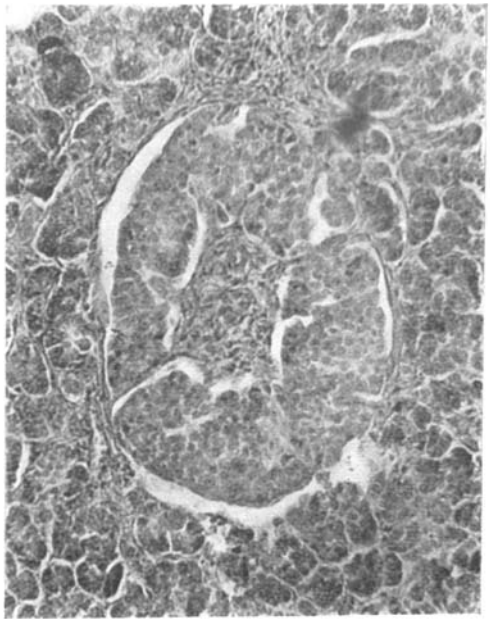

FIG. 2.

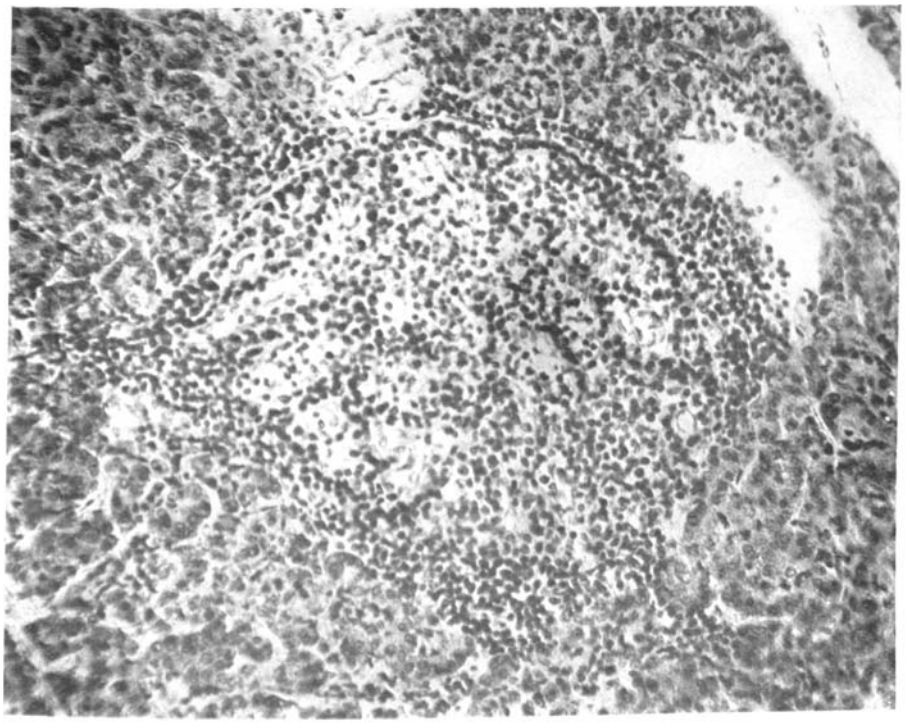

FIG. 3.

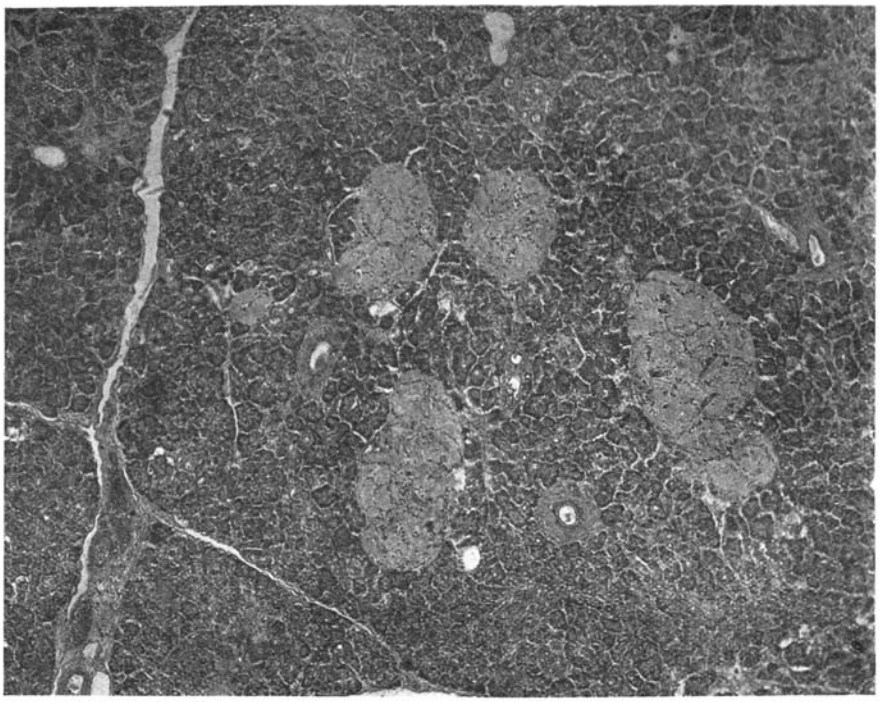

FIG. 4.

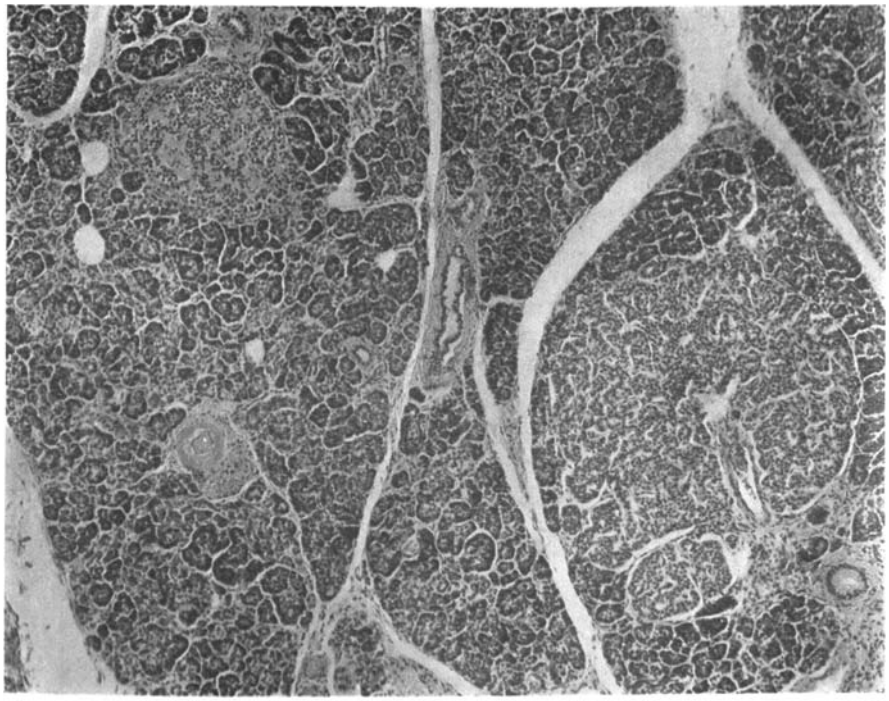

FIG. 5.

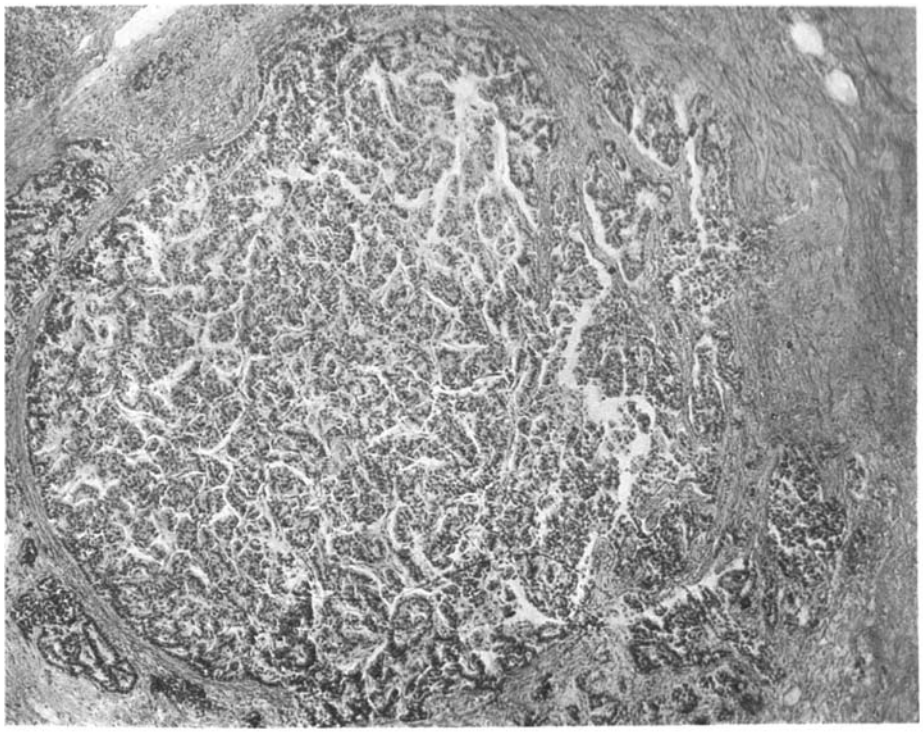

FIG. 6.

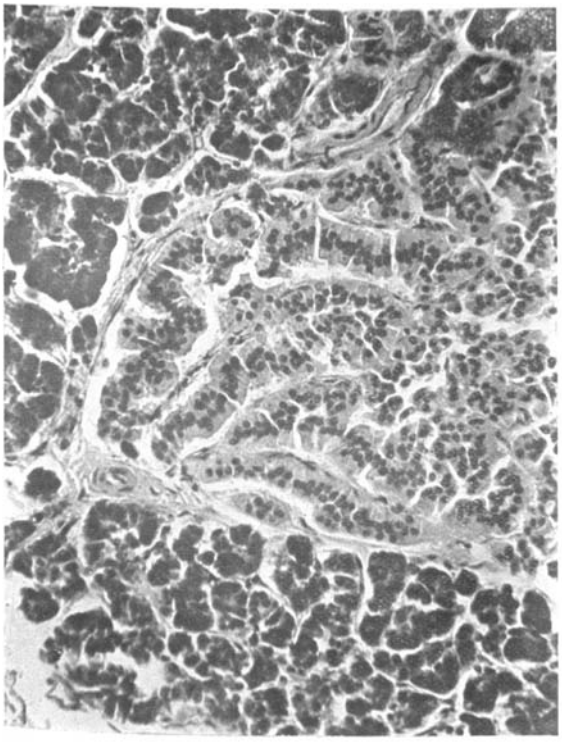

FIG. 7.

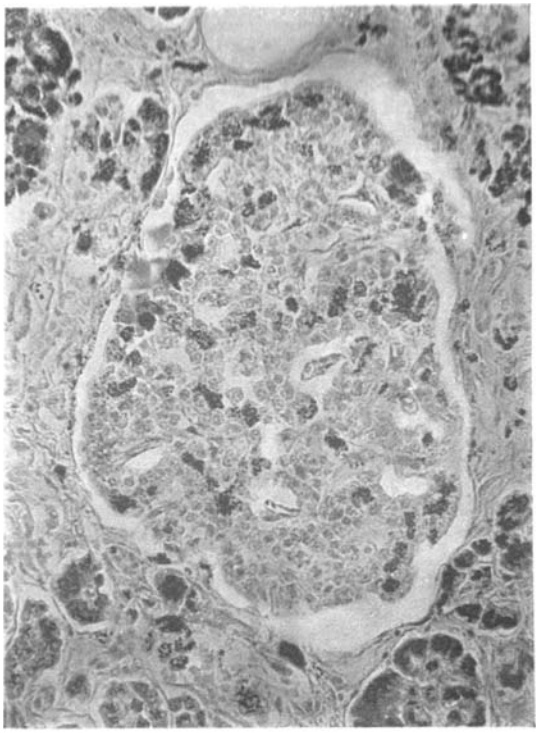

FIG. 8.