ON THE RELATION OF CHRONIC INTERSTITIAL PANCREATITIS TO THE ISLANDS OF LANGERHANS AND TO DIABETES MELLITUS.

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PLATES XXVII AND XXVIII.

INTRODUCTION.

In the pancreas are found certain structures whose nature is still obscure, the architecture of the organ being much more complex than that of the salivary glands which it closely resembles. Within the acini, and apparently in their lumina, are the so-called centro-acinar cells whose origin and function are as yet unexplained. P. Langerhans, in the first important contribution to our knowledge of the histology of the pancreas, described groups of cells situated between the acini and differing markedly from those of the ordinary glandular type. These groups, usually round, are composed of small, irregularly polygonal cells with a round nucleus and homogeneous refractive cell body. Numerous observers have since described these structures, which are usually designated "islands of Langerhans."

In injected specimens Kühne and Lea found glomeruli composed of wide tortuous anastomosing capillaries between which lie the cells which Langerhans described. The ducts of the gland are not continued into these bodies.

Various opinions are held concerning the nature of these cell groups. Some observers have thought that they are follicles of lymphatic tissue scattered through the organ. Many believe that they have the same origin as the secreting elements of the gland and, formed during embryological life, persist thereafter and probably subserve some special function. Lewaschew subjected the pancreas to prolonged stimulation by overfeeding or by the repeated administration of pilocarpin, and thought that he was able to transform small groups of acini into typical interacinar islets, thus increasing their number at the expense of the secreting tissue. His experiments have not been confirmed.

It is not surprising that little is known concerning the function of structures whose nature is so little understood. Several writers (Laguesse, Schäfer, Diamare) have suggested that they furnish an internal secretion which influences carbohydrate metabolism. The only evidence in support of this suggestion is contained in the short preliminary notice of Ssobolew, which has appeared since the completion of the present study. He states that after feeding animals on carbohydrates the cells of the islands become more granular.

After ligating the duct of Wirsung in dogs the islands of Langerhans, he finds, are not implicated in the sclerotic process which ensues. He thinks that this fact explains the absence of glycosuria after ligation of the duct. In human cases I had observed similar resistance of the islands to the inflammation consequent upon obstruction of the duct. In the pancreas of two diabetics, Ssobolew was unable to discover islands of Langerhans.

2 Arch. f. mikros. Anat., 1886, xxvi, p. 452.
From a histological study of these structures in man and in lower animals, in injected specimens, and in glands stimulated by the administration of pilocarpin, I have reached the following conclusions:

1. The islands of Langerhans are composed of cells having the same origin as those of the glandular acini but forming structures which are independent of the secreting apparatus and in intimate relation with the vascular system.

2. In the splenic end of the cat's pancreas, they have a definite position within the lobule, each of which contains one of these structures.

3. In the human pancreas, they are more numerous in the splenic extremity or tail than elsewhere. Similar variation in their number is observed in cats and dogs.

4. Prolonged stimulation of the gland does not, as claimed by Lewaschew, transform groups of acini into islands of Langerhans.

Embedded as are these bodies in the substance of the organ, they cannot readily be subjected to experimental conditions which do not equally affect the secreting structures. It is particularly desirable, therefore, to observe what changes they undergo under pathological conditions and, if possible, to bring such alterations into correlation with concomitant pathological phenomena. From such a study, heretofore little pursued, we may hope for suggestions of the function or anatomical relationship of these obscure structures.

Acute rapidly destructive lesions of the pancreas, for example hemorrhagic pancreatitis, affect the various elements of the gland almost simultaneously, and complete disintegration of greater or less extent results. When the organ is attacked by the less active irritants which produce chronic inflammation, the different histological constituents are given greater opportunity to exhibit differences in their ability to withstand the destructive process. The islands of Langerhans do not always show alterations corresponding to those which occur in the tissues of the acini about them, often persisting, though the adjacent parenchyma is destroyed. Moreover, while in some varieties of chronic inflammation they are but little implicated in the sclerotic process, in others they may be markedly affected. It becomes of interest, therefore, to study the relation of these bodies to the various forms of chronic pancreatitis that are distinguishable.

*Bulletin of the Johns Hopkins Hospital, 1900, xi, p. 205.
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The histological details of chronic pancreatitis have been, however, little studied and slight attention has been given to the classification of the various types. For the purpose of the present study it is desirable to adopt a classification, although it is based upon the somewhat limited material available.

That form of chronic inflammation which occurs during fetal life and is associated with other manifestations of congenital syphilis presents histological features which distinguish it from the chronic pancreatitis of adult life. It is a disease of the developing organ and may appropriately be first considered.

CONGENITAL SYPHILITIC PANCREATITIS.

Birch-Hirschfeld first drew attention to the frequency with which the pancreas is affected by congenital syphilis, and described the lesion so accurately that nothing had been added to our knowledge of it until the appearance of the recent article of Schlesinger, who has made a systematic study of the condition.

Birch-Hirschfeld found the pancreas affected in 13 of 23 cases of congenital lues, but subsequent observers have found the lesion much less frequently and, indeed, Birch-Hirschfeld, studying a second group of cases, found changes in the organ only 29 times in 124 syphilitic new-born. Schlesinger in six instances found the enlarged firm organ the seat of a diffuse interstitial pancreatitis characterized by proliferation of interlobular and interacinar tissue penetrating at times between the cells of the acini. This inflammatory new growth is followed, he thinks, by atrophy of the parenchymatous elements, which, though they do not exhibit appearances of degeneration, atrophy and disappear. The growth of interstitial tissue, he finds, has its origin about the blood-vessels, and the arteries are the seat of a syphilitic periarteritis, the adventitia being infiltrated with lymphoid cells. As the lesion progresses the capillary network about the acini disappears. Schlesinger has observed that the islands of Langerhans are neither invaded by the new growth of interstitial

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5 Arch. d. Hilkunde, 1875, xvi, p. 174.
9 Virchow’s Archiv, 1898, cliv, p. 501.
tissue nor implicated in the atrophy which affects the cells of the acini.

The histological details which I have observed in two instances of congenital syphilis of the pancreas will be recorded. The relation of the islands of Langerhans to the inflammatory process is of interest.

Case I.—Infant lived three hours. Length of body 40 cm.

Anatomical diagnosis.—Congenital syphilis; interstitial pneumonia; interstitial pancreatitis; splenic tumor; chronic perisplenitis.

Microscopic examination of pancreas.—The interstitial tissue is greatly increased at the expense of the parenchyma. The lobules, composed of a few acini scattered irregularly in dense cellular stroma, form groups separated by looser cellular tissue in which are situated the small veins and arteries. The smallest ducts, beset with acini along their course, terminate in a group of acini which, though much less numerous than those ordinarily forming a lobule, are of normal size and are composed of cells showing no evidence of degeneration. The interstitial tissue, particularly that between the groups of lobules and hence about the smaller vessels, is very rich in cells, which often form foci of dense cellular infiltration. Cells of lymphoid and of epithelioid type are numerous, but in even greater number, particularly about the blood-vessels, are round, oval or polygonal cells with eccentrically situated nucleus. They have the characteristics of the plasma cells of Unna. Cells with eosinophilic granules are also abundant and are of two types: (a) Mononuclear cells whose protoplasm is closely packed with large conspicuous eosinophilic granulations; (b) small cells whose nucleus is usually bilobed or trilobed; eosinophilic granulations of smaller size scattered throughout the cell body are most abundant about the nucleus.

A conspicuous feature of the histological picture is the presence of compact round masses of cells embedded in the interstitial tissue, which is usually concentrically arranged immediately about them. By the character of the cells which, polygonal in shape, are stained bright pink with eosin and by their arrangement in columns between which are capillary vessels, these structures are identified as the islands of Langerhans. Though they are embedded in the stroma, which separates widely the neighboring acini, they are not invaded by the inflammatory change. At times it is demonstrable, most conveniently in serial sections, that these islands are in continuity with the ducts and acini of the gland (Plate XXVII, Fig. 1). At the periphery of the island one of the columns projects beyond the general circular outline and is continuous with
epithelial cells which, staining less brightly with eosin, are arranged about a lumen and are in turn continuous with adjacent acini. In many instances, however, an island traced through a series of sections is found completely isolated in the fibrous tissue.

Case II.—Infant lived four hours. Length of body 50 cm.

Anatomical diagnosis.—Congenital syphilis; pemphigus neonatorum; interstitial pneumonia; interstitial hepatitis and pancreatitis; splenic tumor.

Microscopic examination of the pancreas.—The interstitial tissue is greatly increased and the parenchyma is in very great part replaced by it, acini and groups of acini being widely separated. The new tissue is very cellular, but the cells are for the most part of the epithelial type and accumulations of round cells are not found. Plasma cells and cells with eosinophilic granulations are but rarely seen. The acini form small groups which may be regarded as primary lobules, though the acini composing them are much less numerous than those of a normal lobule. Islands of Langerhans are conspicuous as compact round masses of epithelial cells and are scattered abundantly throughout the organ. The fibrous tissue is often concentrically arranged about them and at times they lie completely isolated. Not infrequently, however, as in Case I, they are in continuity with the neighboring acinar tissue; a double row of cells is found to be continuous on the one hand with a cell column of the island, on the other with a small duct.

The preceding cases apparently represent different stages of the syphilitic lesion. In Case I proliferating fixed tissue cells are very abundant, while cells, in part at least of vascular origin, namely, plasma cells and eosinophiles, are numerous and the condition may be interpreted as the active stage of a chronic inflammatory process. In Case II, though interstitial tissue is more abundant and the persistent parenchymatous elements are more scattered, cells of the lymphoid type are few in number, while plasma cells and eosinophiles are almost absent. The process here is more advanced and is no longer active.

A conspicuous feature in both cases is the presence of numerous islands of Langerhans surrounded by newly formed stroma, but uninvaded by it. In many instances the islands are found to be in continuity with the secreting structures of the gland (Plate XXVII, Fig. 1.) A cell column of the island is continuous with a small
duct-like structure, which is in turn continuous with glandular acini. The lumen of the duct does not penetrate into the island.

Birch-Hirschfeld, finding the pancreas of syphilitic fetuses rarely affected unless they had survived the full period of uterine development, came to the conclusion that the condition has its onset during the last months of fetal life. Schlesinger, however, cites the cases of Müller and Mraczek, in which, at the 5th month of development, advanced lesion of the organ occurred, and from his own experience concludes that the pancreas may be affected as early or as late as other organs.

The pancreas arises as an outgrowth from the intestinal canal, and the development of its parenchyma takes place in a mass of mesoblastic stroma which is replaced as the growth of the gland proceeds. At an early period of development, for example at the 5th month of fetal life, the acini form small groups widely separated by embryonic connective tissue. In my two cases of syphilitic pancreatitis the parenchyma presents the appearance observed about the 5th month of development, with the exception that the islands of Langerhans, which are inconspicuous in the undeveloped organ, are marked features in the syphilitic pancreas. In neither of the syphilitic cases was it possible to observe degenerative changes in the cells. The acini form irregular groups containing much fewer members than ordinarily compose a fetal lobule, or, as in the developing organ, form dilatations upon the sides of the small ducts. It is conceivable, therefore, that the disease, like many syphilitic lesions, is one of the interstitial tissue and the changes in the parenchyma result not so much from a destruction of the parenchyma as from an interference with its growth. The similarity between the syphilitic and the undeveloped organ may be thus explained. The development of the individual cell, however, is not retarded and the islands of Langerhans are the result of an early cell-differentiation. In many instances the islands remain in continuity with the tubular structures from which they had their origin. Often, however, the connecting strand of cells is no longer discoverable, and the condition resembles that ordinarily observed in the organ at the end of fetal development.
Several types of chronic pancreatitis affecting the fully developed organ have been described, and with the experimental demonstration of a relation between the pancreas and carbohydrate metabolism numerous attempts have been made to distinguish a variety of the lesion constantly associated with diabetes mellitus. A classification of these various forms of chronic inflammation based upon etiological data, though desirable, would be, with our present knowledge, as unsatisfactory as a similar classification of the varieties of hepatic cirrhosis. From an experimental study Carnot \(^{11}\) reaches the conclusion that pancreatitis may result (a) from mechanical cause, for example, obstruction of the pancreatic ducts, from the action \((b)\) of toxic material or \((c)\) of microorganisms carried to the gland by the blood, or by the lymph or by way of the duct. Such a classification does not aid in the interpretation of lesions observed at autopsy, the etiological factors concerned being in the majority of instances obscure.

In many examples of chronic pancreatitis fibrous tissue between the lobules is increased; in others the interacinar tissue shows marked proliferation; occasionally individual cells are apparently separated by strands of fibrous tissue. Corresponding types of inflammation have been described as interlobular, periacinous, and monocellular.

It has been thought that the increase of interstitial tissue may have at times a constant relation to the blood-vessels or to the ducts, being in part at least a proliferation of the connective tissue about these structures. Lemoine and Lannois \(^{12}\) have described perivascular interstitial pancreatitis. From a study of four cases of chronic inflammation associated with diabetes they have thought that the new growth of fibrous tissue has its origin in the walls of the blood-vessels. They find about the vessels masses of sclerotic tissue sending processes between the acini and even separating the individual cells (sclérose unicellulaire). G. Hoppe-Seyler \(^{13}\) has described chronic


\(^{12}\) Arch. de méd. expér., 1891, iii, p. 33.

interstitial changes which he thinks are the result of arterial sclerosis. The parenchyma, he believes, undergoes degeneration as a consequence of disturbed nutrition, but no anatomical relation exists between the vessels and the new-formed tissue. Chronic pancreatitis in a case described by Rosenthal was accompanied by what he regards as alterations of the lymph-vessels, "lymphangitis proliferans," indicative, he thinks, of a probable syphilitic origin.

In the instances of chronic inflammation of the pancreas which have been available for my study, no constant relation has been discoverable between the new-formed tissue and the veins, arteries, lymph-vessels, or ducts, and there is no evidence that the process had its origin about these structures. Even where chronic pancreatitis follows obstruction of the ducts, sclerotic tissue is not more abundant about the ducts than elsewhere.

Two types of interstitial inflammation are, however, distinguishable. On the one hand, though the sclerosis is never accurately confined to one locality, it may be conspicuous between the lobules, the intralobular or interacinar tissue being little, if at all, increased. On the other hand the interlobular tissue may be only slightly altered, while fibrous tissue which replaces the parenchyma separates individual acini. In the first case the lobulation of the gland, which is normally obscure, becomes more conspicuous and wide bands of sclerotic tissue separate groups of lobules. The lobules are invaded in greater or less degree by the newly formed stroma and often entire lobules are in process of disintegration and replacement, but the progress of the lesion has been apparently inward from the periphery of the lobule. With the second type of chronic inflammation the lobulation of the gland is not accentuated, and the new fibrous tissue, primarily within the lobule, has a diffuse character, a network of irregular fibrous strands which vary much in thickness containing the glandular acini in its meshes.

The two types of chronic interstitial inflammation—(a) interlobular and (b) interacinar—characterized by the primary localization of the lesion, present other histological peculiarities. Of present interest is

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the different relation which they bear to the islands of Langerhans, and it is desirable to study separately the changes affecting these bodies in the two conditions. The cases which have been studied exhibit individual differences and in a few instances the histological details will be briefly described.

CHRONIC INTERLOBULAR PANCREATITIS.

The sclerosis of the gland which follows obstruction of the ducts belongs to the interlobular type. Its definite etiology, as well as certain histological features, serve to distinguish it from other varieties of chronic pancreatitis whose etiology is more obscure. I shall first consider chronic inflammation of the interlobular type not caused by duct-obstruction. Six examples of this form of inflammation have been studied. Chronic inflammation, the result of duct-obstruction, will be subsequently considered.

In two cases (III and IV) the increase of interstitial tissue is moderate in amount and is most marked between the lobules, defining them more clearly than usual. Accumulations of lymphoid cells, among which are plasma cells and eosinophiles, indicate that the inflammatory process is still active. The lumina of the acini are widely distended, the secreting cells are much flattened and often show marked alterations; the scant protoplasm may no longer present a basal zone which stains with nuclear dyes, e.g., methylene blue or hæmatoxylin, and the nucleus is often much swollen and irregular in shape and stains faintly. The islands of Langerhans are not the seat of similar changes; the cells composing them are normal in appearance, and though the acini are often separated by strands of sclerotic tissue, the islands are rarely, if ever, penetrated by this tissue.

In a third case (V) acute inflammation is associated with beginning proliferation of the interstitial tissue. The gland acini are distended and contain bacilli, morphologically of the colon type, and inflammatory products. The islands of Langerhans are apparently normal.

These three cases serve to direct attention to the fact that though the secreting acini have undergone marked degenerative changes, the islands of Langerhans may be unaltered. Anatomical peculiarities may explain the greater resistance of the interacinar structures to the
inflammatory process: (1) The vascular supply of the islands is richer than that of the adjacent acini. (2) Since the ducts do not penetrate them they are less exposed to the action of irritants which reach the gland by way of the duct.

In a fourth case of interlobular pancreatitis (Case VI) new fibrous tissue poor in cells outlines more conspicuously than is usual the gland lobules. The new-formed tissue penetrates the lobules and forms an intralobular network whose meshes are narrowest next the interlobular bands. Here the acini are atrophic in appearance. The islands of Langerhans surrounded by acini are, when the lobules are well defined, usually situated near their centre. The islands are therefore surrounded by the least changed acini and are themselves unaltered. Their very unusual abundance may be explained by the change in the parenchyma between them. The tissue being diminished in volume as a result of partial replacement by fibrous tissue, they are brought closer together and are more numerous in a given area.

Two cases (VII and VIII) represent advanced perilobular sclerosis. Wide bands of fibrous tissue, often containing lymphoid cells in great number, separate groups of lobules and send processes of new tissue into them. In places the glandular tissue is fairly well preserved, while elsewhere entire lobules are found in process of disintegration, the dilated and atrophied acini being separated by strands of fibrous tissue. The islands of Langerhans, scattered more abundantly than usual in the parenchyma and unaffected by the process, are surrounded by a delicate connective-tissue outline and are penetrated by delicate capillaries. Occasionally one finds an island surrounded by a few scattered acini, and though the neighboring secreting tissue has been almost entirely replaced by interstitial tissue, the island remains intact.

Chronic Pancreatitis Following Obstruction of the Ducts.

It has long been known that occlusion of the pancreatic ducts causes chronic interstitial inflammation of the gland. In human cases the usual causes of such obstruction are calculi or new growths, especially carcinoma, and numerous instances of pancreatitis follow-
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ing such lesions are recorded. A large number of experimenters have produced sclerosis in animals by ligating the ducts.

Arnozan and Vaillard have studied the progress of the lesion in rabbits. The ducts soon become dilated, their epithelium proliferates, and cells are desquamated into the lumen. At the end of twenty-four hours the protoplasm of the secreting cells becomes clearer and the nucleus stains more deeply with carmine. At the end of about four days the swollen nuclei may almost completely fill the cell. At the end of seven to nine days round cells are numerous and before the fourteenth day connective tissue in large part replaces the parenchyma. The authors think that sclerosis is caused by the ferment present in the retained secretion.

Carnot produced interstitial inflammation by injecting the ferment papain into the duct. He thinks that several factors are active in the production of the sclerosis which follows obstruction of the ducts. The retained secretion, he believes, has a toxic action upon the parenchymatous cells. Obstruction to the outflow of fluid favors extension of infection along the duct from the duodenum. The action of infection plays an important part when occlusion is caused by calculus formation, a process which he thinks is of bacterial origin. Carnot suggests, moreover, that alterations of the reflex nervous stimuli which reach the obstructed gland are etiological factors in producing atrophy of the parenchyma. Such stimuli are no longer capable of exciting normal functional activity and, he thinks, cease to exert their influence on the metabolism of the secreting cells. The atrophy of the parenchyma may be somewhat analogous to the muscular atrophy which follows section of motor nerves.

Since the cells forming the islands of Langerhans have no communication with the lumen of the ducts and, presumably, play no part in producing the pancreatic juice, the possible factors mentioned would, if active, affect primarily the acini and only secondarily, if at all, the interacinar islands.

In the cases which I have studied varying degrees of atrophy and sclerosis have followed partial or complete occlusion of the pancreatic

13 Arch. d. phys. norm. et path., 1884, 3. a., III., p. 287.
ducts. In two cases (IX and X) carcinoma of the gland was associated with chronic pancreatitis due to obstruction of the duct. In the first case (IX) retention cysts are numerous and changes are slight except in the immediate neighborhood of the largest of the cysts where dense fibrous stroma has replaced the glandular tissue. Dilated acini composed of flat atrophied cells are the only remnants of secreting tissue, while here and there are groups of epithelial cells, not differing from the islands of Langerhans present in the neighboring relatively normal parenchyma; they have withstood the sclerotic process. In the second case (X) the new growth has invaded the body of the pancreas and that part of the gland which is distal to the invading growth is alone sclerotic. Here the occurrence of an active chronic inflammatory process is shown by the presence of numerous lymphoid cells, plasma cells and eosinophiles in the interstitial tissue. Cell changes similar to those described by Arnozan and Vaillard are demonstrable. The most marked increase of fibrous tissue is between the lobules, but acini showing marked atrophic changes are often widely separated by new tissue. The structure of the islands of Langerhans is, however, unaltered.

In the following cases advanced chronic interstitial pancreatitis has followed obstruction of the pancreatic ducts:

Case XI.—Summary of clinical history.—Female; aged 60 years. Illness began about one year before death with symptoms of obstruction of the common bile-duct. At operation performed by Dr. Halsted a carcinoma of the bile-papilla and diverticulum of Vater was found and removed. The biliary and pancreatic ducts were transplanted into the duodenum. Subsequently an anastomosis was made between the gall-bladder and duodenum.

Anatomical diagnosis.—Recurrent carcinoma of the duodenum; metastasis in liver; occlusion of pancreatic duct; chronic interstitial pancreatitis; biliary fistula.

Pancreas.—On the left lateral wall of the duodenum is a crater-like ulcer with raised edges abutting upon the head of the pancreas. The pancreatic duct is included in the carcinomatous tissue at the base of the ulcer. The duct is greatly dilated and the pancreas is small and sclerotic.

\[17\] This case is described by Dr. Halsted in the Bulletin of the Johns Hopkins Hospital, 1900, xi, p. 4.
Microscopic examination of pancreas.—The parenchyma of the head and body has been almost completely replaced by dense fibrous tissue which contains fat in considerable quantity. Small isolated masses of glandular tissue still persist and are subdivided by penetrating strands of fibrous tissue. The stroma is in great part very dense and poor in cells. Here and there, however, round cells of the lymphoid type form large accumulations and mingled with them plasma cells are very numerous. Cells with eosinophilic granulations are present in the periphery of such foci and in the dense fibrous bands as well. The small ducts are dilated. The glandular tissue is in part normal in appearance, the gland-cells being little affected by the sclerotic process. In other situations secreting tissue is undergoing disintegration and the connective tissue not infrequently marks out areas which correspond apparently to lobules, but contain only a few atrophied acini composed of flattened cells about a dilated lumen. Here the inflammatory process is active; the connective tissue separating the atrophic acini is very cellular and contains many lymphoid cells, plasma cells and eosinophiles.

Islands of Langerhans, more abundant in the tail and body than in the head, are present in the relatively normal glandular tissue and are unaltered (Plate XXVII, Fig. 2). One not infrequently sees an island situated in the centre of a lobule which is undergoing disintegration. Scattered atrophic acini are separated by interstitial tissue containing large numbers of proliferating or exuded cells, but the island is normal in appearance and is not invaded by the newly formed fibrous tissue which surrounds it and isolates the much changed acini.

About an unaltered island may be found only a few acini to indicate that it was formerly embedded in the parenchyma, while elsewhere in the dense fibrous bands are seen isolated structures whose cells do not differ in character or arrangement from those of the interacinar islets. Such islands though surrounded by sclerotic tissue are not invaded by it and their cells which are normal in appearance form columns separated by delicate capillary vessels.

These isolated islands, however, finally undergo degenerative changes. They are diminished in size and often distorted. The cells, particularly at the periphery, crowded together, become smaller, and their nucleus also smaller than usual is often irregular in shape and is stained very deeply. Further changes are followed with difficulty since the much altered groups of cells are hardly recognizable as islands. Small groups of epithelial cells separated by strands of connective tissue probably represent a late stage of atrophy and precede final disappearance and replacement by fibrous tissue.
CASE XII.—Summary of clinical history.—Male; aged 43 years. Diagnosis: Pulmonary tuberculosis. No symptoms of diabetes were noted.

Anatomical diagnosis.—Chronic pulmonary tuberculosis; gelatinous and caseous pneumonia; miliary tubercles; tuberculous pleurisy. Cirrhosis of the liver with fatty degeneration. Parenchymatous and fatty degeneration of the kidneys. Splenic tumor. Pancreatic calculi; interstitial pancreatitis; parapancreatic fat necrosis.

Pancreas.—The duct of Wirsung is much distended by numerous calculi. The small ducts are also dilated and filled with fine gritty material. The gland-tissue has in large part disappeared and is replaced by interstitial tissue containing much fat in which are small opaque white areas of necrosis. The concretions give the reactions of calcium carbonate.

Microscopic examination of pancreas.—The parenchyma has been in very great part replaced by dense sclerotic tissue in which are scattered foci of round cells. The ducts are widely dilated and contain clumps of calcareous material. In the head of the organ are small areas of glandular tissue subdivided by interlobular strands of fibrous tissue which occasionally send projections between the acini. Occasionally gland-lobules are found in process of disintegration, tubular atrophied acini with dilated lumen being separated by new-formed interstitial tissue. Scattered in the sclerotic tissue, most abundant in a section from the splenic end of the organ, are round and oval clumps of cells arranged in columns between which, though the tissue about is densely fibrous, one sees delicate capillaries, often distended with red blood-corpuscles. These bodies, which have the characteristic structure of islands of Langerhans, present no similarity to secreting tissue in process of destruction. Occasionally an island has the appearance of being compressed and distorted.

CASE XIII.—Summary of clinical history.—Male; aged 50 years. The patient gives a history of alcoholic excess. His illness began five months before its fatal termination with symptoms of pulmonary tuberculosis which gradually increased in intensity. On admission to the hospital two months after the onset of his illness the urine contained 5.2% of sugar. When given a diet very poor in carbohydrates (v. Noorden's standard diabetic diet) sugar disappeared from the urine and reappeared only when carbohydrates were added—90 grms. of white bread to the daily diet.

Anatomical diagnosis.—Pancreatic calculi; chronic interstitial pancreatitis. Chronic pulmonary tuberculosis with cavities. Chronic dif-
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fuse nephritis; large white kidneys. Anthracosis of lungs, spleen, and kidneys.

Pancreas.—The organ, which is intimately united to the adjacent structures, is much diminished in size and is tough and fibrous in consistence. The atrophy is most marked in its central part, which forms a narrow isthmus connecting the head and tail and consists of the duct and a small amount of fibrous tissue about it. The duct, slightly enlarged, contains viscid white fluid and a number of small, granular, gritty, yellow calculi, the largest being the size of a split pea. On section the tissue has a grayish-yellow color and small masses of parenchyma project prominently between thick bands of connective tissue. Minute opaque points suggest fat necroses.

Microscopic examination of the pancreas.—Sclerosis is far advanced and is most marked in the tail of the organ where glandular acini are almost entirely absent. The glandular tissue which persists occurs as compact masses rarely more than 2 or 3 mm. in diameter embedded in dense stroma. At the periphery of this relatively normal parenchyma are found lobules or portions of lobules in process of disintegration and replacement by the interstitial tissue. Here acini composed of low cells about a dilated lumen are scattered in the fibrous stroma. The fibrous tissue is in general poor in cells, but in many places, particularly about the large ducts, lymphoid and plasma cells are abundant.

In the masses of glandular tissue islands of Langerhans are present, and though of small size, are normal in appearance. Very numerous, particularly in the dense stroma of the body and tail, are masses of polygonal cells occupying conspicuous, sharply outlined, round or oval spaces in the sclerotic tissue. They do not differ from the islands of Langerhans found elsewhere. They are often situated almost side by side, separated by only a small amount of stroma, so that at times ten or twelve are seen in the field of the low power. Examination readily shows that they do not represent groups of acini in process of destruction. Very frequently in the fibrous tissue about these islands lymphoid cells and plasma cells are very numerous and it may be assumed that the inflammatory process is still active.

The persistent islands are finally involved in the general sclerosis. An increase of fibrous tissue occurs along their capillaries which become coarse strands subdividing the body into small masses of atrophied cells. One finds broad bands of dense fibrous tissue containing no epithelial elements or only an occasional compressed group of cells similar to those forming the islands.
In the preceding cases (XI, XII and XIII) advanced chronic pancreatitis has followed obstruction of the ducts. The organ is densely sclerotic, glandular tissue having been replaced in very large part by fibrous stroma. Small masses of relatively well-preserved parenchyma, little if at all invaded, are embedded in fibrous tissue which contains almost no epithelial elements. Areas are seen where disintegration of the glandular substance is in active progress and here lymphoid cells are present in large numbers. A striking feature of the process is the abundance of the plasma cells of Unna, among which are cells with eosinophilic granulations.

The scattered acini show atrophic changes similar to those previously described. The islands of Langerhans which occur in this altered glandular tissue are unchanged and, even though the neighboring acini are widely separated by inflammatory new growth, are uninjured (Plate XXVII, Fig. 2). The secreting tissue about them finally disappears and they remain completely isolated in the stroma, not infrequently the only vestiges of parenchymatous tissue in wide sclerotic bands. In a section from such an area, isolated islands may be very numerous, and since the sclerotic tissue occupies less space than the acini which it has replaced, they appear to be much more abundant than in the normal glandular parenchyma.

As it is improbable that the vessels supplying the islands with blood remain unchanged in the indurated stroma, it can hardly be doubted that the nutrition of the cells suffers. The tissue growing older apparently contracts and compresses them; their cells become smaller, the nuclei are small, irregular, and stain deeply. They finally disappear, being replaced by fibrous tissue, which may contain an occasional isolated group of much atrophied cells or may be completely devoid of such structures.

The islands of Langerhans resist the sclerotic process which follows the damming back of secretion upon the gland, and finally suffer only when the acini are almost entirely destroyed and replaced by dense scar-like tissue. This is what we might expect when we consider that since the lumen of the duct is not continued into the islands it is hardly conceivable that they are concerned in the production of the
pancreatic juice, so that they are not exposed to its injurious action when the outflow is obstructed. The changes which the isolated islands undergo are, it appears, due to compression by the contracting scar-like tissue in which they are embedded and to alterations of their blood-vessels. Doubtless the rich vascular system of the parenchyma is in large part obliterated when the acini are replaced by interstitial tissue and, consequently, the network of vessels within the island, which freely anastomose with the adjacent capillaries, is, as the process advances, less freely supplied with blood.

**CHRONIC INTERACINAR PANCREATITIS.**

The type of pancreatitis, which may be conveniently designated "interacinar," is characterized by the presence of new-formed tissue within the lobules. The lesion is diffuse but somewhat irregular in distribution; at one point there may be a general thickening of the connective-tissue network supporting the acini, while elsewhere occur compact bands or small masses of stroma. Though the interlobular tissue is not unaffected by the inflammatory change, its proliferation is not a constant feature of the histological picture. The lobulation of the gland is not accentuated as with the interlobular type, but, on the contrary, is obscured, since masses and strands of new tissue within the lobules make inconspicuous the interlobular boundaries. This type is much less common than the perilobular form, and I have been able to study it in only three cases. One of these was associated with the condition of general pigmentation to which von Recklinghausen gave the name hæmochromatosis, and, differing slightly from the other two, it will be considered separately.

**CASE XIV.—Summary of clinical history.**—The patient gives no history of alcoholic excess. The present illness began twenty months before death with polyuria. Much body weight has been lost. A year and a half before death the spleen was palpable and hæmatemesis occurred at intervals. At this time the urine contained 3.5 to 3.8% of sugar. The patient was readmitted to the hospital four days before

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his death with ascites and dilated superficial abdominal veins. The urine contained 2.5% of sugar.


Pancreas.—The organ is small and firm in consistence.

Microscopic examination of the pancreas.—The interstitial tissue is greatly increased and is richly infiltrated with fat. Almost every acinus is in greater or less degree surrounded by fibrous tissue, but the lobulation of the parenchyma is not more distinct than usual. Details of structure are somewhat obscured by partial post-mortem change, but the distribution of fibrous tissue is clearly demonstrable particularly in sections stained with phosphomolybdic-acid haematoxylin (Ribbert's method). The connective tissue forms a network in whose meshes lie the acini; the coarseness of the fibrous strands and the size of the meshes which they form vary much and correspond to the greater or less alteration of the contained acini. In many places the glandular tissue of a limited area is almost completely replaced, being represented only by widely separated atrophic acini. The new growth of tissue, which is often conspicuous about the ducts and blood-vessels, bears no constant relation to these structures.

Islands of Langerhans are very abundant and are sharply outlined in sections stained with phosphomolybdic-acid haematoxylin, since fibrous tissue, concentrically arranged, forms coarse capsules, separating them from adjacent acini. There is, moreover, a proliferation of the connective tissue within them. Along the capillaries somewhat irregular, spindle-shaped, or elongated nuclei are more numerous than usual, and there is an increased amount of fibrillated material which gives the staining reactions of white fibres. The cells of the islands are often very small and their nuclei, diminished in size, stain deeply. They are closely packed together to form wide irregular columns. Not infrequently the interacinar fibrous tissue is much more abundant in the immediate neighborhood of the islands than elsewhere and here forms a close network of coarse strands with small meshes containing atrophied acini.

Case XV.—Summary of clinical history.—Male; aged 47 years. The patient has used alcohol in excess. His health has been good until six months before death. On several occasions he has vomited blood. For three months the appetite has been poor, but thirst has been excessive;
polyuria has been present. The body weight has been fairly well re-
tained. The patient was in the hospital five days preceding his death,
during which time the urine contained 0.6 to 2.46% of sugar; acetone was
present. He was dull, drowsy and at times delirious.

Anatomical diagnosis.—Chronic interstitial pancreatitis. Cirrhosis of
the liver. Chronic passive congestion of the spleen. Ascites. Para-

Pancreas.—Weight, 108 grms. The organ is firm, particularly at its
splenic end. Here the lobulation is obscured, the texture of the gland-
tissue is compact, and on careful examination of the cut surface minute
opaque points are seen. In the fat within and about the organ are small
opaque yellowish-white areas.

Microscopic examination of the pancreas.—Throughout the organ there
is an abundant diffuse new growth of interstitial tissue which bears no
constant relation to the blood-vessels or ducts or to the interlobular tis-
sue but is between the individual acini. This new tissue is poor in cells
and those which it contains have elongated spindle-shaped nuclei. It
consists in great part of white fibres loosely packed together. In the
meshes of the irregular network which it forms lie acini or small groups
of acini which are often atrophic in appearance. Acini of large size con-
taining many centro-acinar cells are seen.

In the tail, islands of Langerhans are abundant and often of very large
size, corresponding apparently to the opaque points seen macroscopically.
They are surrounded by new fibrous tissue which often forms a thick
capsule and separates them widely from adjacent acini. They are,
moreover, invaded by the new tissue which often forms coarse ingrowths
along their capillaries (Plate XXVIII, Fig. 3). Elongated and spindle-
shaped nuclei are somewhat increased in number, but the perivascular
thickening is in great part produced by fibrillated interstitial material
which, like white fibres elsewhere, stains with phosphomolybdic-acid
haematoxylin and with acid fuchsin. All the islands are surrounded by
dense sclerotic tissue, but some are only slightly invaded by the pro-
cess. Where there is marked thickening about the capillary vessels,
the epithelial cells are diminished in size and are closely packed together;
the nuclei are small and stain deeply.

While with the interlobular type of chronic interstitial inflammation
the islands of Langerhans are unaffected by the sclerosis and show
changes only when the lesion has reached a very advanced stage, in the
cases just recorded a new growth of tissue within the lobules and
between the acini invades the interacinar cell-islands. They are almost constantly surrounded by fibrous tissue, which forms, as it were, a capsule separating them from adjacent acini, which are themselves abnormally separated from one another. About the capillaries there is a proliferation of interstitial tissue forming coarse strands between the columns of cells.

In certain instances of the interlobular type, proliferation of interstitial tissue occurs between the acini, but is confined to the periphery of the lobule (Case VI). The islands of Langerhans, situated in the midst of the secreting tissue, often near the centre of the more or less clearly defined lobule, are surrounded by the least changed acini. The condition present in the interacinar type of sclerosis is of different character. In the immediate neighborhood of the island may be found the greatest proliferation of fibrous stroma and the acini, separated from it and from one another by coarse strands of white fibrous tissue, are more atrophic than those at a greater distance. When the inflammatory process affects primarily the periphery of the lobule and progresses toward the centre, the islands are affected only when the lesion is very advanced. When the change occurs diffusely within the lobule all parts are equally affected and the islands suffer in common with the acini. Indeed, it often appears that the favorite seat of the lesion is the immediate neighborhood of the bodies.

**Chronic Pancreatitis Associated with Haemochromatosis.**

Chronic pancreatitis associated with the condition which von Recklinghausen described as haemochromatosis was found, in the only case available for examination, to belong to the interacinar type.

In this disease an iron-containing pigment derived from the haemoglobin of the blood is deposited in various cells of the body. The seat of most abundant pigmentation is the glandular organs, notably the liver, and hepatic cirrhosis is constantly associated with the condition. As the process advances chronic interstitial inflammation of the other organs ensues. The increasing accumulation of pigment acts injuriously upon the cells and finally causes their disintegration. Fibrous tissue replaces the destroyed cells and contains the pigment set free by their death. Pigment accumulation followed
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by cell-death and chronic inflammatory reaction is readily observable in the pancreas to be described.

Case XVI.—Male; aged 55 years.
Clinical diagnosis.—Typhoid fever. The skin showed a deep bronze-like pigmentation. Glycosuria was not present.
Anatomical diagnosis.—Typhoid fever; ulcers in the ileum; broncho-pneumonia. Hæmochromatosis; pigmentation of the liver, pancreas, heart, stomach, intestine, peritoneum, lymphatic glands, skin and testicles. Cirrhosis of the liver. Chronic interstitial pancreatitis.
Pancreas.—Weight 170 grms. The organ is firm in consistence. The cut surface has a uniform deep chocolate-brown color. Septa of fibrous and adipose tissue penetrate the gland.

Microscopic examination of the pancreas.—Interstitial tissue is much increased; in many places it defines the lobules, but as a rule it is diffusely distributed, occurring as irregular masses and strands separating small groups of acini or individual acini. A conspicuous feature is the presence of brown-yellow pigment giving the microchemical reactions of iron both in the gland-cells and in the interstitial tissue. The cells of the acini contain the pigment in varying amount; here and there are seen acini whose cells are distended with pigment-granules, their protoplasm being almost entirely replaced. Such cells often show evidence of degeneration; at times the nucleus has an irregular outline and stains very palely, while in many instances no nucleus is demonstrable. The fibrous tissue replacing the disintegrated cells contains free granules of pigment which are larger and more globular than those within the cells.

Islands of Langerhans are fairly abundant throughout the organ, but are most numerous in sections from the tail. They are constantly surrounded by a small area of fibrous tissue containing pigment in considerable quantity. Embedded in stroma they no longer possess a regular round or oval outline, but are irregular in shape and are penetrated by thickened fibrous strands which follow the capillary vessels. The cells, forming compact columns, contain numerous pigment-granules which when least abundant are situated in the portion of the cell most distant from the capillaries and hence tend to occupy the mid-line of the cell columns. The cells of the islands usually contain much more pigment than those of the adjacent acini. In preparations hardened in Flem-
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Ming's solution fat can be found in many of the secreting cells, but is constantly present in the cells of the interacinar islets.

The new-formed fibrous tissue is diffusely distributed and bears no constant relation to the lobules. The lesion affects primarily the parenchymatous cells and shows no special tendency to involve those in the periphery of the lobule. The stroma, irregularly thickened between the acini, is constantly increased in the immediate vicinity of the interacinar cell-groups.

The alterations of the islands of Langerhans associated with the deposition of an iron-containing pigment, haemosiderin, in the parenchymatous cells are as follows: (1) Pigment is abundant in the cells and tends to accumulate in that part which is most distant from the capillaries. (2) The cells undergo fatty degeneration. (3) The island is embedded in a capsule-like mass of fibrous tissue containing pigment granules. (4) Strands of similar tissue penetrate the island, following its capillaries.

HYALINE DEGENERATION OF THE PANCREAS.

In the study of lesions of the pancreas the greatest interest centres in their relation to the disease diabetes mellitus. Before discussing the possible relationship of changes affecting the islands of Langerhans to this disease, I shall describe a very remarkable lesion of the organ occurring in a girl, who, for two years before death, had suffered from diabetes. For the tissues from the case I am indebted to Dr. Flexner, who has kindly placed them at my disposal.

The pancreas is the seat of a lesion which obliterates the vascular supply of a considerable proportion of the parenchyma. Of special interest is the fact that the process, though not confined to the islands of Langerhans, has so completely altered them that in no part of the gland are they recognizable. That intact islands are not discoverable is surprising when we find a considerable proportion of the parenchyma very slightly changed.

CASE XVII.—Summary of clinical history.—Female; aged 17 years. As a child the patient has never been healthy and when 17 months old her parents state that she suffered with an abscess of the abdominal wall
near the liver. The onset of symptoms of the fatal illness occurred two years before death with extreme thirst and polyuria; sugar was found in the urine and has been constantly present in large amount until death. Record of the quantity has not been preserved. Upon diabetic diet the sugar diminished in amount but did not disappear. Marked loss of body-weight was not noted. Death occurred with coma which appeared suddenly and lasted hardly more than twenty-four hours.

Autopsy.—The only lesion noted was that affecting the pancreas. The entire organ was preserved for microscopic study.

Microscopic examination of the pancreas.—The organ is in large part self-digested and stained specimens have a blurred appearance, cell protoplasm and nuclei staining with almost equal intensity. In the tail, however, several areas where the tissue is well preserved give a clear histological picture of the lesions which are present. The interstitial tissue is increased only in localized areas. Throughout the organ, readily distinguishable even in the most digested portions of the gland, are very conspicuous, sharply defined, round, or oval, hyaline areas embedded in the parenchyma. They vary considerably in size. Where the parenchyma stains deeply with hematoxylin these bodies stand out conspicuously as almost completely unstained areas formed by a congeries of tortuous hyaline columns between which are compressed lines of cells apparently of parenchymatous origin.

Much clearer pictures are obtained in sections from the tail of the gland where self-digestion is least advanced. Here in preparations stained with hematoxylin and eosin these structures form sharply defined areas (Plate XXVIII, Fig. 4), taking a bright eosin stain in marked contrast to the general ground of glandular tissue which contains many nuclei staining deeply. Their structure is as follows: Coarse, tortuous, hyaline columns separate strands of tissue, containing nuclei and representing in part at least capillary endothelium, from compressed rows of epithelial cells, evidently atrophied parenchymatous cells. The hyaline material lies immediately outside the capillary wall, between capillary and parenchyma. Occasionally the lumen of the capillary is visible and may contain shadows of red corpuscles.

The hyaline material has at times an indistinctly striated appearance, the striation being parallel to the course of the capillaries. A zone near the capillary endothelium, but not in immediate contact with it, often contains a deposit of calcium salts and stains deeply with hematoxylin. The epithelial cells between the tortuous hyaline columns form compressed rows varying in width. The cell-bodies are diminished in size and at times are hardly recognizable. The cells are usually arranged in
columns giving no indication of acinar arrangement, but rarely within such an area or more frequently at its periphery is found a double row of cells about a well-marked lumen.

The hyaline material does not stain by Weigert's method for the staining of fibrin. Reactions for amyloid were not obtained with specimens hardened in alcohol. When sections are stained with phosphomolybdic-acid haematoxylin, the hyaline takes a peculiar bright-blue stain in marked contrast to the deep blue-black of the fibrous tissue.

In general the parenchyma in which the hyaline masses lie is not markedly changed. The cells are somewhat smaller than usual and in material hardened in Flemming's solution are found to contain numerous fat droplets. The interstitial tissue is not as a rule increased. In the tail the parenchyma, representing several groups of lobules, has been almost completely replaced by the hyaline structures described, between which is fibrous tissue containing only a few atrophied acini composed of low cubical cells about a distinct lumen. Islands of Langerhans of normal structure are not found. The blood-vessels outside the hyaline areas show no change.

Microscopic examination of other organs.—The liver is normal in appearance; there is no increase of interstitial tissue and the blood-vessels are normal. In a section of the kidney a small collection of lymphoid cells is present at one point. Otherwise no change is noted.

The very remarkable lesion just described has apparently obstructed the vascular supply of a very large proportion of the gland-parenchyma. New-formed hyaline material is deposited between the capillaries and the parenchyma-cells (Plate XXVIII, Fig. 4). This material has a homogeneous hyaline appearance and stains deeply with acid dyes. The tissue which was studied was hardened in 95 per cent alcohol and the absence of reactions for amyloid was not conclusive. That the lesion is not this form of degeneration is shown by the absence of similar change in other organs which, much more frequently than the pancreas, are the seat of amyloid degeneration. I have found in the literature no reference to a similar lesion of the gland.

In the tail of the pancreas areas of hyaline transformation are larger and more numerous than elsewhere, involving at least two-thirds of the sectional area. Though the remainder of the parenchyma is in a fair state of preservation, islands of Langerhans are
not found. This fact is especially remarkable when we remember that the interacinar islets are normally most abundant in this part of the organ. It is evident, therefore, that the lesion implicates these structures, but that it is not confined to them is shown by the extent and abundance of the affected areas. Often they correspond in size and shape to the islands, but they may be several times as large. The occurrence of epithelial cells arranged about a lumen, particularly at the periphery of the altered tissue, shows that acini as well as interacinar islets are affected. In the head and body of the gland, areas of hyaline transformation are less abundant and smaller, usually corresponding in size to islands of Langerhans. Unfortunately, self-digestion of these parts of the organ prevents the recognition of very early stages of the lesion and their relation to the various histological elements.

Of present importance is the fact that the islands of Langerhans are destroyed, or at least isolated from their vascular supply, while a considerable part of the secreting parenchyma is not markedly changed. The occurrence of diabetes mellitus under these conditions is of interest and will be now discussed.

DIABETES MELLITUS.

The great amount of experimental and clinical study which has been devoted to glycosuria and diabetes has brought forth few hypotheses which are not still disputed. That the pancreas has an important influence on carbohydrate metabolism is no longer denied, and it is generally accepted that complete destruction of the organ in animals causes diabetes. The following facts concern the present study:

(1) Extirpation of the pancreas in animals is followed by symptoms which are characteristic of diabetes mellitus in man. Extirpation of a very large proportion of the organ, less than an eighth or a twelfth remaining (Minkowski), is followed by diabetes of greater or less severity. That man is not an exception to this general rule is shown by a limited number of cases where, following operative removal of a portion of the organ, diabetes has ensued.

(2) Diabetes mellitus is in a considerable proportion of cases accom-
panied by diseases of the pancreas, chronic interstitial inflammation or, less frequently, acute inflammation. The frequent association of two relatively uncommon conditions is evidence that they bear some definite relation to one another.

(3) There is no evidence that pancreatitis is caused by the diabetic condition, and when diabetes accompanies changes in the gland which follow obstruction of the duct by calculi or are associated with malignant growth, conditions certainly not consequent upon diabetes, there can be no reasonable doubt, in view of experimental results, that diabetes is secondary and caused by the lesion of the pancreas. The same conclusion may be reached when chronic interstitial inflammation of the pancreas of obscure etiology is associated with diabetes.

It is well known that diabetes is not always associated with a demonstrable lesion of the pancreas. In the production of glycosuria many factors doubtless take part, and in the present immature knowledge of carbohydrate metabolism it is impossible to maintain that diabetes is always caused by disease of the pancreas. Nevertheless, the experimental and clinical evidence is sufficient to justify the assumption that when diabetes is associated with a destructive lesion of the pancreas, the latter is the cause of the first-named condition.

Chronic pancreatitis is not always or, indeed, in the majority of instances, accompanied by diabetes. Since experimental investigations have shown that in order to produce glycosuria it is necessary to remove a large proportion of the pancreas, we need not expect the condition unless a great part of the parenchyma has been destroyed or functionally impaired.

Various observers have attempted to define a type of pancreatitis peculiar to diabetes. G. Hoppe-Seyler and Fleiner have described cases of the disease in which chronic interstitial inflammation of the organ accompanied general arterial sclerosis. Both writers think that changes in the vessels are followed by nutritive disturbances which cause degeneration of the parenchyma and its replacement by fibrous tissue. The condition, Fleiner suggests, is analogous

101 "Berl. klin. Wochenschr., 1894, xxxi, pp. 5, 38."
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to the contracted kidney which is at times associated with general arterial sclerosis, and to changes in the liver, heart and brain following arterial disease. Lemoine and Lannois, as already noted, have studied pancreatitis in four cases of diabetes and have thought that the new growth of interstitial tissue has its seat of origin in the perivascular tissue whence fibrous processes extend between the parenchymatous structures. An important feature of the inflammatory change described by them is the penetration of fibrous strands into the acini, separating the cells and producing what they designate unicellular sclerosis.

Hansemann has attempted to define a variety of pancreatitis always associated with diabetes. The organ is diminished in size and is flattened from before back. Its interstitial tissue is in continuity with that of adjacent structures and consequently the removal of the organ is more difficult than usual. The microscope demonstrates an atrophy of the parenchymatous elements which are in part replaced by new fibrous tissue. He thinks that the lesion is similar to certain forms of granular atrophy of the kidneys.

Should there be, as Hansemann claims, a type of pancreatitis peculiar to diabetes, that is, a form of inflammation impairing the internal function of the gland, glycosuria would not ensue until the lesion had reached a certain grade of intensity, and in its earliest stage the lesion would not be accompanied by diabetes. On the other hand, when chronic interstitial pancreatitis, whatever the type may be, has destroyed a very large part of the parenchyma, one may expect diabetes; the specific type, should such exist, would be associated with the disease at an earlier stage.

For the purpose of the present study it is pertinent to inquire what histological changes are associated with the occurrence of diabetes. When a lesion of the pancreas is the cause of the disease, is the condition dependent upon changes in the acini or in the islands of Langerhans or in both? Total destruction of the acini is often accompanied by destruction or alteration of the interacinar structures, and rarely,

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if ever, are the islands the seat of marked lesion while the acini are unchanged.

The islands of Langerhans are composed of columns of cells having no communication with the ducts of the gland, but in intimate relation with a rich capillary network. An analogous condition is found in the thyroid gland and in the adrenal. The pancreas, as do these organs, exerts through the medium of the blood an important influence on metabolism, and it has been suggested by several observers that the islands of Langerhans may furnish an internal secretion to the blood. Whether the gland furnishes some substance which aids carbohydrate assimilation or destroys some noxious product hindering it, is immaterial to the present study. Where diabetes is the result of pancreatic disease, do the islands exhibit lesions?

I have examined microscopically the pancreas from eleven cases of diabetes, and in four instances such marked change was found that one could not doubt the relationship of the general disease to the lesion of the organ. The limited number of cases makes far reaching conclusions impossible. Nevertheless, several facts of considerable interest appear.

Where (Case XVII) the pancreas was found to be the seat of advanced hyaline degeneration, the islands of Langerhans were universally involved in the process so that structures recognizable as inter-acinar islets were not discoverable. It is probable that the lesion had its origin in these bodies, though with its advance it has passed their limits. On the other hand, a considerable proportion of the secreting tissue, though the seat of fatty degeneration, was in a fair state of preservation and there was no hyaline deposit about its blood-vessels. Where the histological picture was not obscured by self-digestion, which is itself evidence of functional activity, the gland-cells were relatively normal in appearance. In this case fatal diabetes followed a lesion which had in great part obliterated the islands of Langerhans, though a considerable proportion of the intervening parenchyma was relatively intact.

Of eleven instances of chronic inflammation, classified as interlobular pancreatitis, in only one case (XIII) was the lesion accom-
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panied by diabetes mellitus. Here glycosuria was of a mild type and disappeared when the individual was placed upon a diet from which carbohydrates were as far as possible eliminated. With this type of inflammation the islands of Langerhans are implicated only when the lesion has reached an advanced stage so that the organ may be markedly sclerotic while the interacinar structures are still unaltered.

Advanced parenchymatous degeneration and interstitial inflammation were found in three cases where obstruction of the ducts had been caused by calculi or by neoplasm (XI, XII and XIII). Diabetes of a mild type was present in one of these cases (XIII), and inflammatory atrophy of the gland was of an extreme grade. A very large proportion of the parenchyma had been replaced by fibrous tissue; the islands which persist are often embedded in dense sclerotic tissue containing no other epithelial elements and often show marked alterations. Compressed by the scar-like tissue, their cells are atrophied and thickened strands of stroma penetrate along their capillaries.

It is well known that obstruction of the pancreatic duct in human cases is accompanied by diabetes only when the consequent atrophy has caused great destruction of the gland. In animals it is extremely difficult, if indeed possible, to produce glycosuria by ligation of the ducts. These facts are explicable, should we assume that the islands of Langerhans, which resist the sclerosis, are the elements of the gland influencing carbohydrate metabolism.

In two of three cases, classified as interacinar pancreatitis, diabetes accompanied the lesion. Microscopic examination of the gland demonstrated less change than was observable in several instances of the interlobular type unattended by diabetes (Cases VII, XI and XII). Microscopic examination revealed the presence of advanced diffuse sclerosis. In accord with what one might expect from the diffuse interacinar character of the newly formed stroma, the islands of Langerhans are not spared but are surrounded and invaded by new tissue.

In one case of interacinar sclerosis (XVI) diabetes was not observed. The inflammation here accompanied the disease, hæmo-
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chromatosis. This condition has been shown by P. Marie, Anschütz, and Opie to cause chronic interstitial inflammation of the pancreas, which, having reached a certain grade of intensity, is in turn followed by diabetes, the diabetes with pigmentation, or diabète bronzé of French writers. The pancreas in the case recorded weighed 170 grms. and the chronic inflammatory changes were not very advanced. The individual affected with hæmochromatosis died of intercurrent typhoid fever, and it is probable that his pancreatitis had not reached a sufficient intensity to cause diabetes.

SUMMARY AND CONCLUSIONS.

(1) Congenital syphilitic pancreatitis retards the development of the glandular acini but does not affect the islands of Langerhans. Embedded in the stroma, but not invaded by it, the latter maintain their continuity with the small ducts and acini with which they have a common origin.

(2) Two types of chronic interstitial inflammation affecting the developed pancreas are distinguishable:

(a) Interlobular Pancreatitis.—In the interlobular variety the inflammatory process is localized chiefly at the periphery of the lobule and implicates the islands of Langerhans only when the sclerotic process has reached a very advanced grade. When pancreatitis has followed obstruction of the ducts, the islands long remain unaltered though embedded in dense scar-like tissue.

(b) Interacinar Pancreatitis.—In the interacinar type the process is diffuse, invading the lobules and separating individual acini. The inflammatory change invades the islands of Langerhans.

(3) A relationship has been observed between lesions of the islands of Langerhans and the occurrence of diabetes mellitus.

(a) In one of eleven cases of interlobular pancreatitis diabetes of mild intensity occurred. The sclerosis, which in this case followed obstruction of the ducts by calculi, was far advanced and affected the islands of Langerhans.
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(b) In two of three cases of interacinar pancreatitis, diabetes was present. The third case was associated with a condition, haemochromatosis, which at a later stage is associated with diabetes, the result of pancreatic lesion.

(c) In a fourth case of diabetes, hyaline deposit between the capillaries and the parenchymatous cells had so completely altered the islands of Langerhans that they were no longer recognizable.

DESCRIPTION OF PLATES XXVII AND XXVIII.

PLATE XXVII.

Fig. 1.—Congenital syphilitic pancreatitis (Case I). Showing a cell-column of an island of Langerhans in continuity with a small duct.

Fig. 2.—Chronic interstitial pancreatitis following duct-obstruction (Case XI). Showing islands unchanged though embedded in sclerotic tissue.

PLATE XXVIII.

Fig. 3.—Chronic interstitial pancreatitis of interacinar type (Case XV). Showing the invasion of an island by the inflammatory process.

Fig. 4.—Hyaline degeneration of the pancreas (Case XVII).