

JOURNAL
OF THE
Boston Society of Medical Sciences.

VOLUME IV. No. 10.

JUNE 12, 1900.

PATHOLOGICAL CHANGES AFFECTING THE ISLANDS OF
LANGERHANS OF THE PANCREAS.

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The pancreas is more complex in structure than the other acinar glands, which it closely resembles. Langerhans,¹ in an inaugural dissertation published in 1869, gave the first careful description of its histology and showed that it has not the relatively simple structure which it had previously been supposed to have. Scattered in the parenchyma he found groups of cells differing markedly from the columnar secreting cells which form the gland acini. These cell groups imbedded among the acini are usually round, and in tissue treated two or three days with Müller's fluid appear under low magnification as conspicuous points of bright yellow color. With high magnification they are found to be composed of small irregularly polygonal cells having a round nucleus and homogeneous refractive protoplasm. Of the nature of these cell groups Langerhans declares himself entirely ignorant.

¹Langerhans. Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse, Inaug. Diss., Berlin, 1869.

In injected specimens Kühne and Lea¹ found scattered through the pancreas glomerular structures composed of dilated and tortuous capillaries, and showed that these glomeruli correspond to the cell groups which Langerhans described. The islands are penetrated by numerous wide tortuous capillaries, which lie between the anastomosing columns of cells. These cells have no communication with the excretory ducts.

Various opinions are held concerning the nature of these bodies which are usually designated islands of Langerhans. Some observers have believed that they are independent of the secreting apparatus, but composed of cells of the same origin. Many have thought that they are follicle of lymphatic tissue scattered through the gland. Others have regarded them as modified acini, altered as the result of peculiar functional activity. Lewaschew² has claimed that he was able to increase their number at the expense of the acinar tissue by repeated over-stimulation of the gland with pilocarpin or by continued over-feeding.

It is by no means surprising that little is known concerning the function of structures whose nature is so little understood. Laguesse³ and Schäfer⁴ suggest that they furnish an internal secretion. The only experimental evidence which supports this hypothesis is contained in the short preliminary report of Ssobolew,⁵ which has appeared since the preparation of the present article. Imbedded in the substance of the organ, they cannot readily be subjected to experimental conditions which do not equally affect the secreting apparatus. 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. Before considering the pathological changes affecting them, it may be of interest briefly to mention several facts concerning their relation to the other structures of the gland.

¹ Kühne and Lea. *Untersuch. a. d. Physiolog. Institut. d. Univers. Heidelberg*, II., 448.

² Lewaschew. *Archiv. f. Mik. Anat.*, XXVI., 1886.

³ Laguesse. *Compt. rend. Soc. de Biol.*, p. 819, 1893.

⁴ Schäfer. *Lancet*, Aug. 10, 1895.

⁵ Ssobolew. *Centralb. f. allg. Path. u. path. Anat.*, XI., 202, 1900.

In the human pancreas lobules are not well defined. In the cat's pancreas, however, they are more sharply outlined by interstitial tissue. By ligating the ducts of the gland and thus producing an interstitial inflammation the demarcation becomes very distinct, every lobule being isolated by fibrous tissue. The islands of Langerhans are then found to be situated in the centre of the lobule and in the splenic end of the organ each lobule contains one of these structures. In the human pancreas this regular arrangement is not discoverable.

In the human organ the interacinar islets are more abundant in the tail or splenic end than in other parts. By counting their number in a given sectional area they are found equally numerous in the head and body, while in the tail they are three and one-half times as abundant as elsewhere.

Acute, rapidly destructive lesions of the pancreas, for example, hæmorrhagic pancreatitis, affect the various elements of the gland almost simultaneously. When the organ is attacked by the less active irritants which produce chronic inflammations the different histological elements of the tissue are given greater opportunity to exhibit differences in their ability to withstand the destructive process, and the islands of Langerhans do not always show alterations corresponding to those which occur in the secreting tissue about them. Moreover, while with some varieties of chronic inflammation they are little involved in the sclerotic process, with other varieties they may be markedly affected.

The histological details of chronic pancreatitis have been little studied and slight attention has been given to the classification of various types. For the purpose of the present study it has been necessary to adopt a provisional classification based upon a somewhat limited material.

That variety of chronic pancreatitis which occurs in foetal life and is associated with other manifestations of congenital syphilis presents histological features which distinguish it from the chronic inflammations of the fully developed organ. Birsch-Hirschfeld¹ first drew attention to the frequency with

¹ Birsch-Hirschfeld. Arch. d. Heilkunde, XVI., 174, 1875.

which the pancreas is affected by congenital syphilis and described the lesion so accurately that nothing has been added to our knowledge of it until the appearance of the recent article of Schlesinger,¹ who has made a systematic study of the condition.

In two examples which I have had the opportunity of studying the organ is the seat of an advanced diffuse chronic inflammation. Both interlobular and interacinar tissue, are greatly increased at the expense of the parenchyma. In one case lymphoid cells, plasma cells of Unna, and eosinophiles are very numerous in the interstitial tissue, indicating apparently that the lesion is in process of development; in the other case cells are less numerous and are of an epitheloid or fibroblast type. In both instances gland acini which are relatively few in number form small groups widely separated by the new tissue, so that the parenchyma has the appearance seen at an early period of foetal development. A conspicuous feature is the presence of very numerous compact round masses of cells imbedded in the interstitial tissue. By the character of the cells, which are polygonal in shape and are stained bright pink with eosin, and by their arrangement in columns between which are capillary vessels, one recognizes these structures to be islands of Langerhans. Though they are imbedded in the stroma which separates widely neighboring acini they are not invaded by the inflammatory new growth. At times it is demonstrable most readily with serial sections that these islands are in continuity with the ducts and acini of the gland. 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.

It seems not improbable that the disease, like many syphilitic lesions elsewhere, is one of the interstitial tissue. Changes in the parenchyma result not so much from destruction of acini already formed as from interference with their development. The islands of Langerhans, on the contrary, provided

¹Schlesinger. Virch. Arch., CLIV., 501, 1898.

with a rich vascular network, continue to develop, but remain in continuity with the acini with which they have a common origin.

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 the disease diabetes mellitus.

Among the examples of chronic inflammation available for study, no constant anatomical relation has been discoverable between the new-found tissue and the veins, arteries, lymph vessels or ducts, and there is no evidence that the process had its origin about these structures. Even when chronic pancreatitis follows duct obstruction 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 sclerotic process is never accurately confined to one locality, it may be conspicuous between the lobules while the interstitial tissue within the lobules and between the acini is less markedly increased. On the other hand the interlobular tissue may be only slightly altered, the fibrous tissue which replaces the parenchyma lying between individual acini. In the first case the lobulation of the gland, which is normally obscure, becomes conspicuous and wide bands of sclerotic tissue may separate groups of lobules. The lobules are invaded in greater or less degree by the new-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. 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 fibrous strands which vary much in thickness, containing in its meshes the gland acini.

These two types of chronic pancreatitis, which may be designated (*a*) interlobular, and (*b*) interacinar, characterized by the localization of the lesion, present other histo-

logical peculiarities. Of present interest are the changes undergone by the islands of Langerhans.

Where the pancreas is the seat of chronic inflammation of the interlobular type the acini often show marked alteration and may undergo complete disintegration, almost entire lobules being replaced by new interstitial tissue. The lumina of the acini become widely distended and occasionally contain polynuclear leucocytes; the secreting cells are much flattened and often show degenerative changes. The scant protoplasm stains poorly, while the nucleus is much swollen and distorted and stains faintly. The islands of Langerhans, however, are not the seat of similar changes; the cells composing them are normal in appearance and, though the acini be widely separated by fibrous strands, are rarely if ever penetrated by the sclerotic process. Occasionally one finds an island surrounded by fibrous tissue containing a few scattered atrophic acini, and though the secreting tissue about has been almost entirely replaced by interstitial tissue, the island remains intact.

Persistence of the islands of Langerhans is most readily observed where chronic interstitial inflammation has followed obstruction of the pancreatic ducts. Extreme sclerosis follows occlusion by calculi, and wide areas of parenchyma are almost completely replaced by fibrous tissue. The lesion is of interlobular type. Here one frequently finds dense sclerotic tissue containing scattered atrophied acini. Islands of Langerhans penetrated by delicate capillaries are, however, thickly studded in the new formed tissue and are little, if at all, altered. Not infrequently bands of scar-like tissue contain numerous islands, while other parenchymatous elements have entirely disappeared. The islands, though persisting long unchanged, finally undergo alterations; they are compressed by the dense contracting stroma and are invaded by it.

Anatomical peculiarities may explain the greater resistance of the interacinar structures to the inflammatory process: (1) The vascular supply is richer than that of the adjacent acini. (2) The islands are very frequently situated, as they

are in the cat's pancreas, near the centre of the lobule, and are therefore protected from the lesion which affects primarily the peripheral portion. The acini next the interlobular bands of sclerotic tissue are often most altered, while those about the islands are least changed. (3) Since the ducts do not penetrate them, they are less exposed to the action of irritants which reach the gland by way of the ducts. Microorganisms penetrating the gland along the ducts would not enter the islands of Langerhans.

The interacinar cell groups we have found resist the sclerotic process which follows the damming back of secretion upon the gland. This fact is not surprising when we consider that since the duct lumen is not continued into them it is hardly conceivable that they are concerned in the production of the pancreatic juice. They are therefore not exposed to its injurious action when its outflow is obstructed.

The second type of chronic pancreatitis, which may be conveniently designated interacinar, is characterized by the presence of new formed interstitial tissue within the lobules. The lesion is diffuse but somewhat irregular in distribution: in one locality there may be a general thickening of the fibrous tissue network supporting the acini, while elsewhere occur compact bands or small masses of stroma. The interlobular boundaries are not accentuated as with the interlobular type. I have observed this lesion in only three instances, of which in two it was accompanied by diabetes mellitus. The third case¹ was associated with the condition of general pigmentation described by von Recklinghausen under the name "hæmochromatosis." Here an iron-containing pigment derived from the hæmoglobin of the blood is deposited in the parenchymatous cells of the pancreas and of other organs. The cells undergo degenerative changes, are destroyed and replaced by fibrous tissue.

While with the interlobular type of chronic interstitial inflammation the islands of Langerhans are unaffected by the sclerotic process or show changes only when the lesion has reached a very advanced stage, with the interacinar variety,

¹ Case so reported in the *Jour. of Exper. Med.*, IV., 279, 1899.

on the contrary, the new formed tissue between the acini invades them. They are almost constantly surrounded by fibrous tissue, forming a capsule separating them from neighboring acini. About the capillaries within the islands there is a proliferation of interstitial tissue forming coarse strands between the columns of cells. When the process is advanced the cells are diminished in size; the nuclei are small and stain deeply.

In the study of lesions of the pancreas great interest centres in their relation to the disease diabetes mellitus. Before discussing the possible relationship to this disease of alterations affecting the island of Langerhans I will mention a very remarkable lesion of the organ, occurring in a girl seventeen years of age who for two years before her death had suffered with diabetes. Throughout the gland, but most abundant in the splenic end, one finds conspicuous hyaline areas, the largest of which, almost a millimeter in diameter, are visible to the naked eye. These areas are composed in large part of structureless hyaline material deposited between the capillary vessels, and the parenchyma cells which form narrow compressed rows between adjacent columns of hyaline. The lesion partially destroys a considerable portion of the parenchyma isolating it from the vascular system. The present interest of the condition lies in 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 as such. That intact islands are no longer discoverable is particularly surprising when we find a considerable proportion of the parenchyma very slightly changed.

Experimental investigations inaugurated by Mehring and Minkowski,¹ and abundant clinical observation, have demonstrated that removal or destruction of the pancreas is followed by disturbance of carbohydrate metabolism. Chronic interstitial pancreatitis is frequently accompanied by diabetes mellitus. On the other hand, chronic inflammation of the pancreas may be unaccompanied by the disease. For the purpose of

¹ Mehring and Minkowski. Arch. f. exp. Path. u. Phar., XXVI., 371, 1890.

the present study it is pertinent to inquire what histological changes are associated with the occurrence of diabetes.

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 a readily demonstrable influence on metabolism. When this influence is withdrawn the disease diabetes mellitus has been shown to ensue. Is the disease dependent upon changes occurring in the islands of Langerhans?

It is well known that diabetes is not always associated with a lesion of the pancreas, but may apparently be dependent upon other factors with which we are not familiar. I have had the opportunity to examine the organ from eleven cases of diabetes, and in four instances such marked change was present that one could not doubt the relationship of the general disease to the lesion.

The limited number of cases of pancreatic diabetes available for study make far reaching conclusions impossible, nevertheless several facts may be noted:

With the type of chronic pancreatitis which I have designated interlobular the islands of Langerhans are involved in the sclerotic process only when the lesion has reached a very advanced grade. In one of eleven instances the lesion was associated with diabetes. In this case the sclerosis which followed obstruction of the duct by calculi was far advanced, and the islands imbedded in dense sclerotic tissue often exhibited alteration. The glycosuria present was of a mild type and disappeared when the individual was placed upon a diet poor in carbohydrates.

The second type of pancreatitis, designated interacinar, is characterized by a diffuse inflammatory change involving the islands of Langerhans. In two of three instances diabetes was present. In the third case the lesion was accompanied by the condition of general pigmentation known as hæmochromatosis. It has been shown that individuals affected

with this disease die with diabetes accompanying chronic pancreatitis. The condition is the bronzed diabetes of French writers, so called on account of the dark pigmentation of the skin. In the present instance typhoid fever caused death before the lesion of the pancreas had reached a sufficient grade of intensity to cause glycosuria.

A fourth case of diabetes was associated with the remarkable hyaline change previously mentioned. Hyaline deposit between parenchyma cells and capillary vessels had so completely altered the islands of Langerhans that they were no longer recognizable as such.

In the four cases of diabetes referable to lesions of the pancreas changes were demonstrable in the interacinar cell islets.