ON HYPERTROPHY AND REGENERATION OF THE ISLANDS OF LANGERHANS.*

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PLATES 48 AND 49.

At the present time, there are two crucial problems in connection with the islands of Langerhans which must be solved before the "island theory" can be firmly established. The first, a morphological one, concerns the origin of the islands and the relationship existing between them and the glandular acini; the second, a physiological one, has to do with the connection between the islands and carbohydrate metabolism. It is of certain phases of the former problem that I propose to treat in this paper.

DEVELOPMENT OF THE ISLANDS OF LANGERHANS IN THE FETAL PANCREAS.

Before taking up the subject of hypertrophy and regeneration of the islands, it will not be amiss to review briefly the mode of development of the islands in the fetal pancreas. In this field of research on the islands, the results have been fairly harmonious. Laguesse (1), studying the histogenesis of the islands in sheep embryos, has shown that the islands are of epithelial origin, and develop in common with the acini from the primary tubules. Pearce (2), Küster (3), and Weichselbaum and Kyrle (4) have all studied the development of islands in the human embryo, and have reached almost identical conclusions. The results of their investigations are well summarized in the closing paragraphs of Küster's paper:

1. The islands of Langerhans appear in early embryonic life as anatomically differentiated structures in the pancreas.
2. The earliest anlage is found in offshoots from the ducts.

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(3) The anlage is marked by three characteristics:

(a) The nuclei are centrally located.
(b) The cells arrange themselves in bands or rows.
(c) The cells are in close contact with capillaries.

The Islands of Langerhans in Congenital Syphilis of the Pancreas.

In congenital syphilis of the pancreas, the normal development of the gland is retarded so that the various structures bear more or less resemblance to those observed in fetal life. Opie (5), Pearce, and more recently Karakascheff (6), have studied the islands in syphilitic pancreatitis and have noted that the islands, instead of being independent of other structures, are in many instances connected with the ducts or acini by slender cords or tubules of cells.

I have had the opportunity of studying sections from three cases of congenital syphilis of the pancreas.

Case 1.—(Dr. Opie’s case.) Infant, 40 cm. in length; lived three hours. 

Anatomical diagnosis.—Congenital syphilis, interstitial pneumonia, splenic tumor, chronic perisplenitis. Pancreas.—Microscopically, the interstitial tissue is greatly increased. The lobules are small and widely separated. The islands are imbedded in the stroma, but have not been invaded by the fibrous tissue. Some of them are in direct connection with the ducts by means of slender tubules lined with flattened epithelial cells (figure 1).

Case 2.—(Dr. Opie’s case.) Infant, 50 cm. in length; lived four hours.

Anatomical diagnosis.—Congenital syphilis, pemphigus neonatorum, interstitial pneumonia, interstitial hepatitis and pancreatitis, splenic tumor. Pancreas.—Microscopically, the interstitial tissue is greatly increased. The lobules contain fewer acini than normally. The islands are numerous and surrounded by dense bands of fibrous tissue. Some of the islands are in continuity with ducts, as in case 1.

Case 3.—(Presbyterian Hospital, autopsy No. 8,090.) Infant, male, 18 months old. 

Anatomical diagnosis.—Congenital syphilis, interstitial hepatitis, nephritis, pancreatitis, acute broncho-pneumonia. Pancreas.—Microscopically, there is a well marked increase of the interstitial tissue. The lobules are uneven in size, but the acini appear normal. The islands are numerous and well preserved. A few of them are found to be connected with ducts by short, slender tubules lined with flattened epithelial cells.

In the protocols of these cases, it will be observed that two of them were new-born, while the third was an infant eighteen months old. In all three cases, there is a well marked interstitial pan-
Hypertrophy of Islands of Langerhans.

creatitis, with more or less replacement of the parenchyma by fibrous tissue. The islands of Langerhans, however, are well preserved and quite numerous. Some of the islands are independent of the surrounding tissue, while others are in direct continuity with the ducts or acini. Occasionally one encounters a small duct from which islands and acini can be seen budding side by side. The connecting link between the island and the duct is a slender cord or tubule composed of a single or double row of low cuboidal epithelial cells (figure 1).

A careful study of the sections from these cases will convince one that Pearce and Opie are correct in considering the changes described as the result of interference with normal growth. The islands of Langerhans, instead of separating from the ducts, as they do under normal conditions, often remain in continuity with the tubular structures from which they have originated. The histological picture is that of a fetal pancreas, the seat of chronic interstitial inflammation.

HYPERTROPHY AND REGENERATION OF THE ISLANDS OF LANGERHANS.

In a previous paper, I (7) have emphasized the fact that hypertrophy of the islands may occur in one or the other of two forms. In the first, or simple hypertrophy, the island may show no abnormality except an increase in size, the arrangement of the cells in irregular cords being still preserved. In the second or columnar type of hypertrophy, the islands assume certain abnormal characteristics, the most striking of which is a change in the shape of the cells from a polyhedral to a high cylindrical form, with centrally placed nuclei.

Regeneration or new formation of the islands from the ducts was first described by Weichselbaum (8) in 1908. In 19 out of 151 cases of diabetes, he noted small buds composed of high cylindrical cells, which were growing out from the ducts, and which in serial sections he could demonstrate as connecting links between the ducts and rudimentary islands. These rudimentary islands were also composed of high columnar cells. As the newly formed
islands grew larger, they became separated in some instances from the ducts; but a duct could usually be found in the neighborhood of such islands. Weichselbaum thought this mode of regeneration of islands corresponded to that of their embryonic development as described by Pearce, Küster, and Karakaschff.

In the same year that Weichselbaum reported these observations, his pupil, Kyrle (9), described similar regenerative processes in partially depancreatized dogs and guinea pigs. In the neighborhood of the scars, he found many mitotic figures in the cells lining the pancreatic ducts and small buds which differentiated into new acini or new islands. He observed many giant islands but considered the regenerative processes more important from a compensatory standpoint than the hypertrophy of already existing islands.

The researches of Weichselbaum and Kyrle have explained, therefore, in a very satisfactory way the occurrence of two types of island hypertrophy. Simple hypertrophy is merely an enlargement of a pre-existing island. Columnar hypertrophy, on the other hand, is seen in connection with islands newly formed from the ducts.

During a previous study of the islands of Langerhans in diabetes, I (7) became interested in the subject of hypertrophy of the islands; and having since encountered the condition in a number of cases where there was no evidence of diabetes, it seemed worth while to review all the material at hand and, if possible, to contribute more knowledge to the subject. Such a study now appears the more desirable since Herxheimer (10), in his recent investigations on the islands after ligation of the pancreatic duct, has been unable to find any islands budding from ducts as described by Weichselbaum and Kyrle.

The cases in which I have encountered columnar hypertrophy and regeneration of the islands of Langerhans may be divided into the following groups: (1) diabetes mellitus; (2) chronic pancreatitis; (3) carcinoma of the pancreas; (4) cases in which the pancreas is for the most part normal.

In some cases, the hypertrophy has been more marked than the regenerative changes; in others, the reverse has been true. The
Hypertrophy is of two types: (1) Simple hypertrophy, in which there is more or less increase of size in preexisting islands. Such islands preserve their normal round or oval contour and their characteristic architecture. I have never seen islands of this type exceed a diameter of 0.6 of a millimeter. (2) The so-called columnar hypertrophy. This type is much more common. Here the structure of the island is changed, the cells being of a high cylindrical form and arranged in rows like columnar epithelium. In shape, the cells bear considerable resemblance to those lining the larger ducts. The cytoplasm takes the same bright stain with eosin and appears homogeneous. The nuclei, however, unlike those in the cells of the ducts are centrally located. They are large and vesicular and contain several chromatin granules. The cells are arranged side by side in curving and anastomosing bands or rows, sometimes singly, sometimes several rows together. The intimate relation of cells to capillaries is analogous to that seen in the normal island. The cords of cells twist themselves into various shapes, sometimes forming loops that simulate acini; but the absence of zymogen granules and the presence in many instances of a capillary in the lumen of such structures show their real nature. One of the striking traits of these columnar islands is their irregular contour, which is produced by the outgrowth of loops and processes of columnar cells into the surrounding tissue.

Hypertrophied islands of the columnar type may reach dimensions many times greater than those of normal islands. I (7) have recently reported one such island that measured 4 by 3.5 millimeters, and a number of others as large or larger have been reported. Diameters of 0.5 to 1.0 millimeter are not unusual in these cases.

Columnar islands are usually found in the neighborhood of ducts. In serial sections, a direct connection with the duct can often be demonstrated, in which case the island may be either sessile, or connected with the duct epithelium by a slender cord of cylindrical cells (figures 2 and 3).

Regeneration or new formation of islands I have usually found associated with columnar hypertrophy, for the obvious reason that they represent different stages of one and the same process. A
small bud or knob of cylindrical cells grows out from the duct, and, as the cells multiply, assumes the form of a small island of the columnar-cell type. The process corresponds closely to that described in connection with the development of the islands in the fetal pancreas. The newly formed islands exhibit a capacity for growth much greater than that of preexisting islands. One may, therefore, encounter all sizes of columnar islands from that of a bud consisting of only a few cells to that of one of the giant islands already referred to. Moreover, these large islands may send out an offshoot of cylindrical cells several hundred micromillimeters in length, at the end of which another columnar island will develop. Working as I have with autopsy material, I have naturally seen very few mitotic figures in either the ducts or the newly forming islands; but that they occur in large numbers in freshly fixed tissue, as described by Weichselbaum and Kyrle, I do not doubt. The islands develop from the small or moderate sized ducts. I have seen large islands connected with very small ducts and small islands connected with fairly large ones.

The relation which these hypertrophied and newly formed islands bear to the acini is an important phase of the subject. Is it possible for new islands to develop from acini? Can new acini develop from columnar islands? Kyrle, in his experiments on animals, found that new acini as well as new islands could develop from the ducts, but he was never convinced that either one of them might develop from the other. There are undoubtedly columnar islands that are connected neither with the ducts nor with other islands; and there are columnar islands whose columns of cells are apparently continued into glandular acini. It is very hard to decide, however, whether this connection of islands with acini is real or apparent. My own observations have led me to favor the latter view. Newly forming islands, pushing their way in between acini, come into such intimate contact with acinar cells that in microscopic sections one might readily be deceived by the picture. If there is an anatomical connection between the two, I should be inclined to favor the view that new islands were being differentiated from acini, such a process being more in harmony with the fetal
development of the islands than a development of acini from islands.

HYPERTROPHY AND REGENERATION OF THE ISLANDS OF LANGERHANS IN DIABETES.

Since Opie's study of the islands of Langerhans in diabetes, considerable attention has been given to the degenerative and fibrous changes in the islands so frequently encountered in this disease. Comparatively little, however, has been written about hypertrophy and regeneration of the islands in diabetes. Since lesions of the islands are generally found in association with diabetes, it would be in connection with diabetes that one would expect to find regenerative hypertrophy of the islands most frequently; and such indeed is the case. Herxheimer (11) was one of the first to observe hypertrophy of the islands. He describes some very large islands which he encountered in two cases of diabetes. Hypertrophied islands in association with diabetes have also been observed by Reitmann (12), Ssobolew (13), MacCallum (14), Karakascheff (6), and me (7).

These investigators all noted the peculiar columnar arrangement of the island cells in such cases, but offered no explanation of it. Weichselbaum, in the study already referred to, found that the columnar islands were always in the neighborhood of ducts and in some instances directly connected with them.

I have studied the pancreas in one hundred cases of diabetes, with special reference to hypertrophy and regeneration of the islands. In thirty-four out of the hundred cases, I have found one or the other condition present; usually both. By referring to the table, it will be seen that the lesions occurred at all ages and that, although they were generally found in association with chronic interacinar pancreatitis, there were eight cases where there was no interstitial new growth and eleven others in which the fibrosis was inconsiderable.

Other lesions of the islands were associated with hypertrophy and regeneration in thirty-one out of the thirty-four cases. The lesions found were hyaline degeneration in eight cases, round cell infiltration in two, and sclerosis in twenty-eight cases. The three
### CASES OF DIABETES SHOWING HYPERTROPHY AND REGENERATION OF THE ISLANDS.

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age in years</th>
<th>Pancreas</th>
<th>Islands of Langerhans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1. Presbyterian Hospital</td>
<td>57</td>
<td>Well marked chronic interstitial pancreatitis.</td>
<td>Sclerosis and hyaline degeneration.</td>
</tr>
<tr>
<td>Case 2. Presbyterian Hospital</td>
<td>27</td>
<td>Normal.</td>
<td>Considerable hypertrophy, sometimes columnar.</td>
</tr>
<tr>
<td>Case 3. Presbyterian Hospital</td>
<td>35</td>
<td>Moderate grade of chronic interstitial pancreatitis.</td>
<td>Small and very scanty. A few small columnar-celled islands.</td>
</tr>
<tr>
<td>Case 4. Presbyterian Hospital</td>
<td>60</td>
<td>Well marked chronic interstitial pancreatitis.</td>
<td>Quite scanty. Moderate sclerosis.</td>
</tr>
<tr>
<td>Case 5. Presbyterian Hospital</td>
<td>52</td>
<td>Considerable chronic interstitial pancreatitis.</td>
<td>A few small columnar-celled islands.</td>
</tr>
<tr>
<td>Case 6. Presbyterian Hospital</td>
<td>75</td>
<td>Considerable chronic interstitial pancreatitis and fatty infiltration.</td>
<td>Scanty and show considerable sclerosis. A few small columnar-celled islands.</td>
</tr>
<tr>
<td>Case 7. Dr. James's case.</td>
<td>36</td>
<td>Advanced chronic interstitial pancreatitis.</td>
<td>Sclerosis and hyaline degeneration. Many hypertrophied islands of columnar type. Some apparently connected with ducts.</td>
</tr>
<tr>
<td>Case 8. Royal Victoria Hospital.</td>
<td>20</td>
<td>Simple atrophy of pancreas. Microscopically no increase of interstitial tissue.</td>
<td>Considerable sclerosis and hypertrophy of islands, a few of them of the columnar-cell type.</td>
</tr>
<tr>
<td>Case 10. Royal Victoria Hospital.</td>
<td>75</td>
<td>Well marked chronic interstitial pancreatitis.</td>
<td>Marked hypertrophy of columnar type and extensive new formation of islands from ducts and acini. Island capillaries sclerotic.</td>
</tr>
<tr>
<td>Case 11. Royal Victoria Hospital.</td>
<td>29</td>
<td>Considerable interstitial new growth, and infiltration of fat.</td>
<td>Considerable sclerosis and hypertrophy. One giant island of columnar type, 1,800 micromillimeters in diameter.</td>
</tr>
<tr>
<td>Case 12. Royal Victoria Hospital.</td>
<td>70</td>
<td>Well marked chronic interstitial pancreatitis.</td>
<td>Considerable sclerosis and hypertrophy. A few columnar-celled islands, one of them in direct connection with a duct.</td>
</tr>
<tr>
<td>Case 13. Royal Victoria Hospital.</td>
<td>38</td>
<td>Slight increase of interstitial tissue in places.</td>
<td>Marked hypertrophy and regeneration of islands from ducts and acini, almost entirely of the columnar type. Slight sclerosis. Moderate sclerosis. Infiltration of lymphoid cells about some islands. Marked hypertrophy (columnar) and regeneration from ducts.</td>
</tr>
</tbody>
</table>
Hypertrophy of Islands of Langerhans.

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<thead>
<tr>
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<th>Age in years</th>
<th>Pancreas</th>
<th>Islands of Langerhans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 17. Mass. General Hospital</td>
<td>45</td>
<td>Advanced sclerosis of pancreas.</td>
<td>Islands small, scarce, sclerotic. A few of them are columnar in type.</td>
</tr>
<tr>
<td>Case 25. Boston City Hospital</td>
<td>27</td>
<td>Normal.</td>
<td>Small and scarce but free from sclerosis. A few small columnar islands, apparently connected with acini.</td>
</tr>
<tr>
<td>Case 26. Boston City Hospital</td>
<td>59</td>
<td>Moderate grade of chronic interstitial pancreatitis.</td>
<td>Sclerosis and hypertrophy. Some show hyaline changes. A few columnar islands, one connected with a duct.</td>
</tr>
<tr>
<td>Case 27. Pennsylvania Hospital</td>
<td>51</td>
<td>Well marked chronic interstitial pancreatitis.</td>
<td>Scarce; moderately sclerotic. Some of the islands of the columnar type. One of them connected with a duct; one with acinus (?).</td>
</tr>
<tr>
<td>Case 28. New York City Hospital</td>
<td>50</td>
<td>Marked fatty infiltration.</td>
<td>Numerous; sclerotic, hyaline, hypertrophied. A few large columnar islands.</td>
</tr>
<tr>
<td>Case 29. Bellevue Hospital</td>
<td>33</td>
<td>Normal.</td>
<td>Sclerotic, some hyaline, marked hypertrophy of the columnar type. Considerable sclerosis and hyaline degeneration. A good many hypertrophied islands of the columnar type, one connected with duct.</td>
</tr>
<tr>
<td>Case 30. Bellevue Hospital</td>
<td>73</td>
<td>Moderate grade of chronic interstitial pancreatitis.</td>
<td>Scarce; sclerotic and hyaline. Many hypertrophied columnar islands about ducts.</td>
</tr>
<tr>
<td>Case 31. Mt. Sinai Hospital</td>
<td>73</td>
<td>Moderate grade of chronic interstitial pancreatitis.</td>
<td>Marked hyaline degeneration of nearly all islands. A few large columnar islands about ducts, one in direct connection.</td>
</tr>
<tr>
<td>Case 32. Presbyterian Hospital</td>
<td>52</td>
<td>Mild chronic interstitial pancreatitis.</td>
<td></td>
</tr>
</tbody>
</table>
cases in which no other changes were found occurred in young people; and in all three instances the islands were noted as small and scanty.

In twelve of the thirty-four cases, columnar islands were present, but no hypertrophied forms were encountered. Larger forms would doubtless have been found in some of the cases if more sections had been accessible. On the other hand, I have seen several specimens in which a simple hypertrophy of the islands existed, but where the columnar islands were lacking; that is, the preexisting islands had increased in size, but there had been no new formation of island tissue.

There was no apparent relation between the severity of the lesions in the islands and the extent of hypertrophy and regeneration of islands. For example, in case 32, practically every preexisting island in the section had been converted into hyaline material and only a few newly formed columnar islands had appeared. On the other hand, in case 9, there was only a slight sclerosis of the normal islands, and a remarkable hypertrophy and regeneration of the columnar type of island was observed.

**Hypertrophy and regeneration of the islands of Langerhans in chronic pancreatitis.**

Weichselbaum (4) has observed regeneration of the islands of Langerhans in some cases of chronic interstitial pancreatitis, where there was no diabetes. I have examined sections from thirty-three cases of chronic pancreatitis of the interlobular type. In ten cases the changes were moderate; in eighteen they were well marked; and in five cases there was advanced sclerosis with extensive destruction of parenchyma.
Hypertrophy of Islands of Langerhans.

The cases were associated with the following conditions:

- Cirrhosis of liver ......................... 13 cases.
- Gall stones ................................ 9 cases.
- Cardiac and renal disease ............... 6 cases.
- Chronic cholecystitis ..................... 1 case.
- Ulcer of stomach .......................... 1 case.
- Jaundice .................................. 1 case.
- Fatty liver ................................. 1 case.
- Septic peritonitis .......................... 1 case.

In these thirty-three cases, the islands were in many instances bunched together and surrounded by dense fibrous tissue, but in other respects they appeared normal. In only three cases was there any evidence of a regeneration of the islands. Two of these cases were among the group associated with cirrhosis of the liver; the other case was that of septic peritonitis. Each of the cases exemplified a different grade of cirrhosis.

A few small groups of columnar cells, arranged in the characteristic manner, occurred here and there in the sections, but the hypertrophied forms were absent. The process was so inconsiderable that I have omitted protocols of the cases.

The significant fact brought out by the study of this group is that extensive destruction of the pancreas may occur without there being any compensatory hypertrophy or regeneration of the islands. The islands are spared and no strain is placed upon the function of carbohydrate metabolism. The contrast between this group and the diabetic group is striking. In the latter, some of the most marked examples of regeneration and hypertrophy occurred in pancreases that showed little or no change.

Hypertrophy and regeneration of the islands of Langerhans in carcinoma of the pancreas.

In carcinoma of the pancreas, the new growth replaces in great part the secreting parenchyma, but the islands of Langerhans show a tendency to persist in the midst of cancerous tissue, just as they survive in advanced cirrhosis of the pancreas. That the islands, too, in some instances are finally destroyed is shown by the fact that in a certain number of cases of pancreatic carcinoma, sugar
is present in the urine, while in other cases an alimentary glycosuria is observed.

Pearce (15), in a study of carcinoma of the pancreas, noted a hypertrophy of the islands along the advancing edge of the tumor. Weichselbaum (8) has observed hypertrophy and regeneration of the islands in some cases of pancreatic carcinoma.

I have studied microscopical sections from seventeen cases of cancer of the pancreas, three of them primary, fourteen metastatic, in none of which is there any record of glycosuria. I have studied these cases with special reference to the islands of Langerhans. In six of them there was only a moderate invasion of the gland by the new growth; in the other remaining eleven cases there was extensive cancerous involvement, with considerable replacement of the parenchyma by the neoplasm. In those cases where the tumor had occluded the pancreatic duct, there was more or less interstitial pancreatitis. The islands, as a rule, appeared normal. In the advanced cases, they were often found bunched together in a fibrous stroma, as in cirrhosis of the pancreas, but still preserving their normal appearance. In several cases the islands had undergone more or less simple hypertrophy, some of them measuring 400 or 500 micromillimeters in diameter. In only one out of the seventeen cases was I able to find the characteristic columnar hypertrophy and regenerative changes which have been already described.

The patient, a woman, aged 64 years, was operated upon for gall stones. At operation, a small, very hard gall-bladder containing stones was removed. Microscopical sections through the thickened wall showed an adenocarcinoma. The patient died a few days later.

*Anatomical Diagnosis.*—Cholecystectomy; metastatic carcinoma of liver, pancreas, and retroperitoneal lymph glands; malignant stenosis of the pancreatic duct; chronic interstitial pancreatitis; fat necroses; general arterial sclerosis; jaundice.

The pancreas is enlarged and very hard. On section, the lobules are found separated by translucent tissue. There are several fat necroses in the tail of the pancreas. The pancreatic duct is greatly dilated. There are stenoses at several points.

Microscopical sections through the head of the pancreas show a marked increase of the interstitial tissue separating the lobules.
Hypertrophy of Islands of Langerhans.

The latter are compressed and atrophied. In a number of places there occur masses of large epithelial cells, in some places closely packed together, in others displaying a somewhat tubular arrangement. The islands of Langerhans are numerous and considerably larger than normally and many of them show typical columnar cell hypertrophy. The columnar islands are usually in the neighborhood of ducts.

HYPERTROPHY AND REGENERATION OF THE ISLANDS OF LANGERHANS IN CASES WHERE THE PANCREAS WAS FOR THE MOST PART NORMAL.

In diabetes, chronic pancreatitis, and carcinoma of the pancreas, the occurrence of hypertrophy and regeneration of the islands may be explained more or less satisfactorily. There remains, however, still another class of cases, a particularly interesting group, where, with none of these diseases present, the islands show definite hypertrophic and regenerative changes.

In the course of routine examinations of the pancreas from autopsies at the Presbyterian Hospital, I have encountered four such cases, and one other has been added through the kindness of Dr. Humphreys of the German Hospital, New York. The following are brief protocols of the cases.


Presbyterian Hospital, Autopsy No. 7,923. Anatomical Diagnosis.—Chronic interstitial nephritis; infantile right kidney; arterial sclerosis; hypertrophy of heart; fatty liver; calcified nodes in lungs; chronic fibrous pleuritis; myoma of uterus; chronic cervicitis; vaginal ulcers.

The pancreas is firm, and on section it appears normal. Microscopically, there is a moderate amount of adipose tissue between the lobules, but little if any increase of the interstitial tissue. Marked endarteritis. The islands are very numerous and larger than normally. A considerable number of them are composed of columnar cells. The columnar islands are generally found about the small ducts and some are found connected with the ducts. In some of the larger branches of the pancreatic duct, the epithelium is thrown up into papillomatous folds which appear almost to occlude the lumen of the duct. These folds consist of a delicate central stalk of fibrous tissue which is covered with a single layer of very tall columnar epithelial cells, larger than those lining a normal duct. Here and there are groups of dilated acini, whose cells are flattened and hyaline and whose lumina are filled with a pink-staining, structureless material.
Case 2.—F. M., male, aged 25 years. Student. Admitted for mastoiditis. Had undergone an operation for nephrectomy sometime previously (pyonephrosis). Mastoid cells found filled with pus. Patient died in uremic coma after operation.

Presbyterian Hospital, Autopsy No. 7,777. Anatomical Diagnosis.—Pyonephrosis and chronic interstitial nephritis of right kidney; absence of left kidney; chronic cystitis; chronic pulmonary tuberculosis; tuberculosis of peribronchial lymph glands; acute bronchopneumonia; edema of lungs and brain.

The pancreas is pale and firm; ducts and vessels are normal. Microscopically, the pancreas is free from sclerosis. A few dilated acini lined with flattened hyaline cells occur. The islands are numerous and in some cases considerably larger than normally. A moderate number of the islands are of the columnar-celled type and situated near the ducts. The rest of the islands are normal. The walls of the arteries are not thickened. The main duct appears normal. In some of the larger branches, however, the lining epithelium is thrown up into papillomatous folds, similar to those described in case 1. Many of the cells on those folds have taken on the goblet form.

Case 3.—J. D., female, aged 34 years. Moderately alcoholic. No evidence of lues. Marked obesity. Operated on for pus tube. Died twelve days after operation, after running a high continuous temperature.

Presbyterian Hospital, Autopsy No. 3,817. Anatomical Diagnosis.—Salpingectomy on right side; cloudy swelling of viscera; obesity; operation wound.

The pancreas weighs 180 grams. It is large, pale, and of firm consistence. Microscopically, the pancreas shows no increase of interstitial tissue, but there are small collections of lymphoid cells about some of the vessels and ducts. The main duct is entirely devoid of epithelium, being lined with cellular fibrous tissue. The islands are very numerous and show extreme hypertrophy of the columnar type. The picture resembles that seen in several of the diabetic cases.


Presbyterian Hospital, Autopsy No. 7,810. Anatomical Diagnosis.—Adenocarcinoma of colon; chronic interstitial nephritis; arterial sclerosis; hypertrophy of prostate.

The pancreas is firm and pale. The ducts are normal. Microscopically, the pancreas shows no increase in the stroma. The acini are normal. The islands are quite numerous and in some instances normal. The greater number, however, are composed of columnar cells and are larger than normally. Some of them are in direct connection with smaller ducts, while others are apparently connected with acini. One large island measures 4 mm. in diameter and is hyaline. There is infiltration of polymuclear leucocytes and lymphoid cells into the walls of the larger ducts, which also show hyaline changes. In some of the larger ducts, the epithelium is of the tall columnar type, folds of which project into the lumen.

Case 5.—A. B., male, aged 64 years. Admitted to the German Hospital, New York, in a moribund condition and markedly dyspneic. Clinical diagnosis.—asthma, emphysema, and myocarditis.

This case has been reported by me in the Journal of Experimental Medicine, 1911, xiii, 595.
Hypertrophy of Islands of Langerhans.

German Hospital, Autopsy No. 367. Anatomical Diagnosis.—Acute broncho-pneumonia; acute and chronic bronchitis (asthma); emphysema; renal calculi; hydronephrosis; compensatory hypertrophy of right kidney; chronic interstitial nephritis; cardiac hypertrophy; arterial sclerosis.

The pancreas is fairly firm. On section, the middle portion of the duct is found to be markedly dilated, but there is no obstruction at its duodenal end. In the middle of the pancreas, near the duct are several small foci 5 to 10 mm. in diameter, which contain a greyish white, soft, coherent material. They do not look like cysts, but rather like masses of some tissue which is very soft; otherwise the lobulation of the pancreas is normal. Microscopically, sections through the soft white areas show them to be small tumors enclosed by fibrous capsules and composed of anastomosing epithelial processes which resemble the epithelium of ducts. These papillary processes are lined with high cylindrical cells some of which are goblet cells. Here and there in the tumor are small collections of mucoid material, evidently the secretion of the cells. The tumor has apparently been produced by the marked proliferation of the epithelium lining one of the ducts. The fibrous capsule of the tumor (wall of duct?) is infiltrated with lymphoid cells. Adjacent to one of the tumors there are several greatly dilated ducts. The parenchyma about the ducts shows a well marked interlobular sclerosis. Another section shows normal ducts and normal secreting parenchyma. The islands of Langerhans, however, are very numerous and many of them show considerable hypertrophy of the columnar type. The newly formed islands are usually in the neighborhood of ducts, and a direct continuation between island and duct can be demonstrated at one point. The larger arteries show advanced endarteritis.

We have then five cases of well marked regeneration of the islands of Langerhans in which there was no evidence of diabetes and no destruction of the pancreatic parenchyma by cirrhosis or cancer. There is, of course, no way of excluding an alimentary glycosuria or transient diabetes in any of them. Briefly they were: (1) cardio-renal disease, (2) pyonephrosis, (3) pyosalpinx, (4) carcinoma of colon, (5) cardio-renal disease.

Of the five cases, the two that occurred in young people were associated with infections, while of the other three, two were cardio-nephritics and one was a case of carcinoma of the colon. There is nothing in the cause of death in these cases to explain the regenerative changes in the islands. So far as we know, there is no connection between any of these diseases and carbohydrate metabolism. There is no associated lesion in another organ, common to all five cases, that would serve to explain the condition of the islands, nor does the gross appearance of the pancreas in this group
throw light on the question. Microscopically, however, a comparison of the pancreases is rather instructive.

<table>
<thead>
<tr>
<th>Case number</th>
<th>Condition of ducts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adenomatous proliferation of lining epithelium of ducts. Some of the acini are dilated and lined with flattened hyaline cells.</td>
</tr>
<tr>
<td>2</td>
<td>Adenomatous proliferation of lining epithelium. Some acini are dilated and lined with flattened hyaline cells.</td>
</tr>
<tr>
<td>3</td>
<td>Collections of lymphoid cells about some of the ducts. The main duct is entirely devoid of epithelium, being lined with cellular connective tissue.</td>
</tr>
<tr>
<td>4</td>
<td>Adenomatous proliferation of lining epithelium of large ducts. Coats of large ducts are hyaline and infiltrated with polynuclear leucocytes and lymphoid cells.</td>
</tr>
<tr>
<td>5</td>
<td>Marked adenomatous proliferation of epithelium lining large ducts, producing obstruction of the lumen and dilatation of distal portion of duct. Infiltration of lymphoid cells into walls of ducts.</td>
</tr>
</tbody>
</table>

Of the five cases, three showed definite chronic inflammatory changes in the ducts; in four cases there was a well marked adenomatous proliferation of the epithelium lining the large or medium sized ducts. One or both of these conditions was present in each of the five cases. This adenomatous hypertrophy of the duct epithelium is the same as that which has been described by Winternitz (16) in association with chronic pancreatitis. The epithelium is thrown up into papillary folds, the lumen being often completely filled with them. The cells are no longer cubical but are high cylindrical; they stain deeply with eosin and often assume the goblet form. The nuclei are usually vesicular.

Winternitz offers the suggestion that the new formation of duct epithelium might be an effort on the part of the pancreas to regenerate after chronic inflammatory processes, but he thinks it more probable that the change in the ducts and the fibrous overgrowth may both be due to a third process, often some form of duct obstruction. From a study of my own cases, I am convinced that the duct changes may be independent of chronic pancreatitis.
In only one of the three cases which I have reported was there any interstitial new growth, and in that the sclerosis was confined to the neighborhood of the dilated ducts and apparently secondary to the duct changes.

It is, of course, impossible to establish a causal relationship between either inflammatory or adenomatous changes in the ducts and the regeneration of islands which we have seen associated with them. Since the islands regenerate from the ducts, it would be natural to suspect some connection between adenomatous hypertrophy of the duct epithelium and regeneration or adenomatous hypertrophy of the islands. This suspicion is enhanced by the similarity which exists between the two processes. I agree with Winternitz, however, that both changes should probably be attributed to a third common factor. In all the cases of this group, the regenerative changes are much more marked than the hypertrophic changes. Indeed, the columnar islands are often quite small and duct connections are readily found. In the absence of any evidence of carbohydrate derangement, it is hard to look upon this process as a compensatory one. It would rather seem to be a reaction following a disturbance of some kind in the ducts. Obstruction of the ducts, as suggested by Winternitz, may be the etiological factor in some cases. In one of my cases (case 5), there was marked dilatation of the larger ducts. In the one case of carcinoma of the pancreas where columnar hypertrophy and regeneration of the islands were observed, there was obstruction and dilatation of the main duct. In this instance, however, the proliferation of the duct epithelium was not noted.

These studies have shown that regeneration of the islands of Langerhans may occur in various conditions, and that such regeneration takes place by means of a budding off of columnar cells from the ducts. I am not sure that there is ever a real connection between these newly forming islands and the adjacent acini, though in some cases, like case 4 in the last group, the association is so intimate that the possibility of a direct connection cannot be excluded. The fact that processes of columnar cells push out between the acini and that in many places they are in immediate contact with acini would explain the apparent continuations of the one into
Russell L. Cecil.

the other that are sometimes seen. The absence of regeneration of the islands in cases of advanced cirrhosis and carcinoma of the pancreas where the islands have been spared, and the occurrence, on the other hand, of regeneration and hypertrophy of the islands in many cases of diabetes where there has been little or no destruction of parenchyma, speak strongly for the functional independence of the islands and for their relation to carbohydrate metabolism.

The occurrence of hypertrophy and regeneration of the islands in cases where there is no evidence of diabetes may be explained in several ways. When associated with cirrhosis or carcinoma of the pancreas, we may look upon it as an effort on the part of nature to replace destroyed islands. In the five cases where regeneration of the islands has been associated with neither diabetes nor destruction of pancreatic tissue, an adequate explanation of their occurrence has not been offered. They have been associated, however, in every instance with abnormalities in the ducts; in three cases with chronic inflammatory changes; in four cases with adenomatous proliferation of the duct epithelium.

CONCLUSIONS.

1. Hypertrophy of the islands of Langerhans occurs in two forms: (1) the simple type which is nothing more than an increase in size of pre-existing islands; and (2) the columnar type, in which the islands are composed of anastomosing columns of cylindrical cells.

2. Regeneration of the islands of Langerhans takes place by means of a budding off of columnar cells from the ducts. The process is analogous to the development of the islands in the fetal pancreas.

3. Newly formed islands of Langerhans are composed of cylindrical cells similar in all respects to those constituting hypertrophied islands of the columnar type. The two structures are identical, the latter being a later phase of the former.

4. Newly formed islands of Langerhans are capable of a greater hypertrophy than pre-existing islands. Both types of insular hypertrophy are usually of a compensatory character, the columnar, or regenerative type, being the more important.
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Hypertrophy of Islands of Langerhans.

5. Hypertrophy and regeneration of the islands of Langerhans occur most frequently in diabetes mellitus (34 per cent. of 100 cases studied). These changes are usually associated with sclerosis or hyaline degeneration of other islands.

6. Hypertrophy and regeneration of the islands of Langerhans are occasionally observed in cirrhosis and carcinoma of the pancreas. In some of the most advanced cases, however, the islands have been spared and neither hypertrophy nor regeneration are present.

7. Regeneration of the islands of Langerhans has been noted in five cases in which there was no evidence of diabetes and where the pancreas was for the most part normal. In four of these cases, columnar hypertrophy of the islands was also observed. All five cases were associated with abnormalities of the larger ducts—obstruction, chronic inflammation, and adenomatous proliferation of the lining epithelium.

8. The occurrence of hypertrophy and regeneration of the islands of Langerhans affords considerable evidence in favor of their anatomic and functional independence.

BIBLIOGRAPHY.

EXPLANATION OF PLATES.

PLATE 48.

Fig. 1. Congenital syphilis. Case 1. The drawing shows an island of Langerhans surrounded by connective tissue, and directly continuous with a small duct.

Fig. 2. Diabetes. Case 33. In the centre, a medium sized columnar island is seen in connection with a small duct.

PLATE 49.

Fig. 3. Diabetes. Case 12. An hypertrophied island of the columnar type is directly connected with a small duct.