# REGENERATION OF THE ISLET TISSUE IN VARIOUS CONDITIONS OF DIET AND IN HYPO- OR HYPERTHYROIDISM

L. N. Kuleshova

Department of Histology and Embryology, Voronezh Medical Institute
(Presented by Active Member AMN SSSR A. V. Lebedinskii)
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Much research has been devoted to the study of the regeneration of the exo- and endocrine divisions of the pancreas in different experimental conditions [1-7]. Nevertheless, the problem of the intraglandular relationships between the acinose and islet cells in the course of the reparative regeneration of the pancreas has remained unsolved until recently. No unanimity exists regarding the ways and means of the formation of new islet tissue at the place of injury.

In the present report, which is not concerned with the methods of restoration of the exocrine epithelium, we present information concerning the sources of formation of the islet tissue of the regenerating pancreas under different conditions of diet and with marked variation in the concentration of thyroid hormone.

## EXPERIMENTAL METHOD

White rats were used as experimental animals. For 12 days before the experiment the rats were kept on an ordinary (mixed) diet or on a carbohydrate or protein diet. The greater part of the tail of the pancreas was removed from all the animals. In control experiments we studied the regeneration of the islets in animals receiving no form of medication. The experimental rats began to receive thyroidin or 6-methylthiouracil five days before partial pancreatectomy, and administration continued throughout the period of observation. The daily dose of thyroidin for each animal was 3 mg, and that of 6-methylthiouracil 5 mg. Material for investigation was taken 5 and 15 days after operation. The tissue was fixed in Zenker's or Bouin's fluid and embedded in paraffin wax. Sections were stained with hematoxylin and eosin, chrome-hematoxylin-fuchsin by Gomori's method, aldehyde-fuchsin and methyl green with pyronine. The number and size of the islets in the control and experimental groups were compared by measuring the diameter of the islets in the histological preparations and calculating the total area of islet tissue per unit area of the parenchyma of the gland as a whole. For this purpose in each experimental series of animals the outlines of the whole area of the histological section and also the outlines of the individual islets in 50 sections were traced on paper by means of the RA-4 drawing apparatus. In making the calculation the true magnification of the microscope was taken into consideration, and the areas were expressed in absolute figures.

## EXPERIMENTAL RESULTS

Measurement of the diameter of the islets and calculation of their area showed that the total mass of islet tissue in the areas of the pancreas left behind after partial pancreatectomy varied with the experimental conditions (see table)*

* The differences in the area of the islet tissue in the different series of experimental animals shown in the table were statistically significant. The differences between the series of animals kept on different diets were also significant.

Changes in the Islet Tissue in the Regenerating Pancreas and in the Residual Part of the Organ (15 Days after Operation) in Different Conditions of Diet and with Variations in the Concentration of Thyroid Hormone

| Group (diet) | Series | Mean diameter of islet (in $\mu$) | Relative area of islet tissue per 1 $mm^2$ of the glandular parenchyma of the organ |
|---|---|---|---|
| Mixed | Partial pancreatectomy (control). . . . . | 83.8 | 0.254 |
| | Partial pancreatectomy + thyroidin . . . . . | 93.6 | 0.275 |
| | Partial pancreatectomy + methylthiouracil . | 84.5 | 0.215 |
| Carbohydrate | Partial pancreatectomy (without medication) | 92.6 | 0.344 |
| | Partial pancreatectomy + thyroidin . . . . . | 125.4 | 0.477 |
| | Partial pancreatectomy + methylthiouracil . | 95.6 | 0.264 |
| Protein | Partial pancreatectomy (without medication) | 68.6 | 0.198 |
| | Partial pancreatectomy + thyroidin . . . . . | 82.3 | 0.210 |
| | Partial pancreatectomy + methylthiouracil . | 80.8 | 0.201 |

It will be seen from the figures in the table that in the animals of the "carbohydrate" group the dimensions and the total area of the islets increased considerably by comparison with the other two groups. This was most marked in the rats receiving thyroidin, in which the total area of the islets was almost twice that of the control animals 15 days after partial pancreatectomy. In animals on a protein diet very weak development of the islet tissue was observed.

A study of the sections of the pancreas from animals of the different experimental groups and series confirmed the findings described above. The formation of islet tissue in the residual and the newly regenerating areas of the pancreas was observed in both control and experimental animals. The intensity of restoration of the intrasecretory portions of the gland at the site of the injury, and of the compensatory phenomena in the areas of the organ remaining after operation, followed a different course, however, in the various experimental conditions.

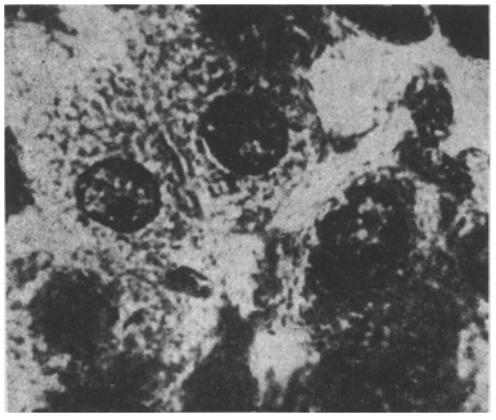

Fig. 1. Acinus containing three islet cells. Pancreas of a rat 5 days after operation. Carbohydrate diet. Magnification 1200 ×.

In the control animals kept on an ordinary mixed diet and receiving neither thyroidin nor methylthiouracil, the regeneration of islet tissue at the site of injury was effected by means of epithelial tubes and bands, which were formed as a result of the reorganization and proliferation of the cells of the acini and the cells of the small efferent ducts. These islets consisted of a small number of cells in direct association with the cells of the tubules or efferent ducts. In the residual portion of the gland the regeneration of islet tissue took place mainly by the conversion of acinose into islet cells. Mitoses were found very rarely in the islet cells. Among the acinose tissue individual cells were found with the typical granules and nuclei of islet cells. The structure of the acinose cells situated at the periphery of the islets was frequently modified; intermediate structures between the typical exocrine and islet cells were found. The cytoplasm of these cells in some cases was characteristic of the islets, and the nuclei still resembled those of the acinus cells. Cells were found with nuclei typical of islet cells, but with cytoplasm containing individual granules of zymogen. It must be pointed out that the appearance of new islet cells at the site of injury and in areas of the gland away from the defect always took place where there was an abundant blood supply.

A carbohydrate diet stimulated the formation of islet tissue; it stimulated in particular the process of formation of new islet cells in the part of the gland remaining after the operation. In animals on a nonprotein diet, in areas of the gland remote from the site of injury there were many small islets containing 2-5 cells. Islet cells, developing from acinus cells, were in close contact with the cells of the terminal portions of the gland or formed part of the acini themselves (Fig. 1). At the periphery of the islets (with a diameter from 51 to 87 $\mu$) transitional structures were observed (Fig. 2) far more often than in the animals kept on an ordinary mixed diet. As a result of this formation of islet cells from acinus tissue in the rats of the "carbohydrate" group the islets enlarged and increased in number.

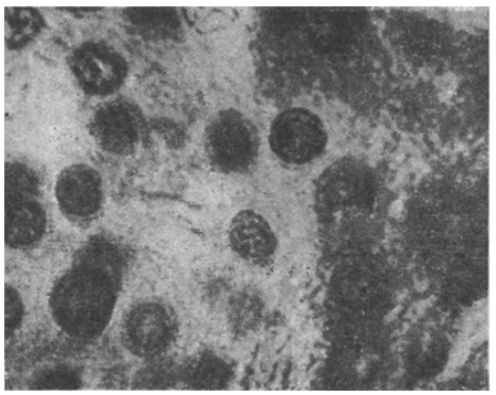

Fig. 2. Formation of new islet cells from adjacent acinus tissue. Pancreas of a rat 5 days after operation. Carbohydrate diet. Magnification 760 ×.

Keeping the white rats on a protein diet did not cause such an intensive formation of islet cells in the portion of the gland left after partial pancreatectomy. The conversion of acinus tissue into islet, and the development of new islet cells from the epithelial tubes and bands were more rarely found in animals on a protein diet than in rats kept on a mixed or carbohydrate diet. The feeble development of the islet tissue in the pancreas in rats receiving a diet with a high protein content and subjected to partial pancreatectomy was evidently caused by the lowered insulin requirement of the animal by comparison with that of animals of the "carbohydrate" group.

A change in the concentration of thyroid hormone in the experimental animals kept on different diets was, in turn, reflected in the regeneration of the islet tissue of the pancreas. The process of formation of new islets in the regenerating portion of the gland was effected after administration of thyroidin, like in the control animals, by two methods: from the epithelial tubes and bands formed as a result of the reorganization and proliferation of the cells of the acini and of the intermediate divisions and of the cells of the efferent ducts, and in the residual part of the organ—mainly by means of the conversion of acinus tissue into islet tissue. In the animals subjected to the action of thyroidin, however, the total area of the endocrine part of the gland was slightly larger than in the controls. This increase in the total mass of islet tissue in the rats receiving thyroidin was associated with the intensive proliferation of epithelial structures in the region of the injury, as a result of which the formation of many small islets was observed. The conversion of acinus tissue into islet tissue was more obvious in the areas of the gland remote from the place of the defect. For this reason islets of large size were often encountered in the residual portion of the head of the pancreas.

A considerable increase in islet tissue took place in animals kept on a carbohydrate diet and receiving a small dose of thyroidin. In these conditions, at the periphery of the islets we observed in large numbers not only individual acinose cells undergoing conversion into islet cells, but also complete large acini of a modified structure (Fig. 3). Such acini contained cells at different stages of conversion of exocrine tissue into islet tissue. Under these circumstances the cells turning into islet cells had the characteristic cytoplasm of islet cells; the cells situated near the acini, however, still contained a homogeneous, basophilic zone of cytoplasm. The incretory activity of the islet cells in animals on a carbohydrate diet and receiving thyroidin was greatly intensified. This was shown by an increase in the number of $\alpha$-cells in the large islets and the large number of small islets containing only $\beta$-cells. The marked increase in function of the islet tissue could be explained by the increased insulin requirement of the animal, caused by the partial pancreatectomy, the stimulation of the endocrine tissue, the carbohydrate diet and the administration of thyroidin. It may be assumed that the excessive stimulation of the islet tissue (more prolonged maintenance of the animals on a protein-free diet than in our experiments and the use of large doses of thyroidin) would lead not to an increase in the regenerative power of the islets, but to their functional exhaustion.

A protein diet, coupled with administration of thyroidin, did not lead to the intensive formation of islets. In such conditions the total area of islet tissue 15 days after partial pancreatectomy was always much smaller than when the animals were kept on a carbohydrate diet.

The regeneration of the islet tissue in the animals of the different experimental groups when an inadequate concentration of thyroid hormone was present was effected mainly in the part of the gland remaining after the operation, for the proliferative processes at the site of injury were strongly depressed. In response to the administration of 6-methylthiouracil, islets were formed most frequently of all from the epithelium of the small efferent ducts, and only here and there were islet cells observed to be formed from acinus tissue.

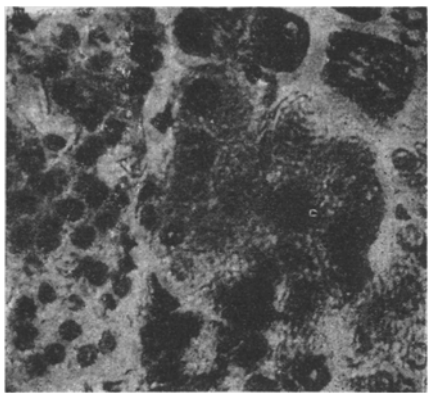

Fig. 3. Acinus of modified structure, situated near an islet. Pancreas of a white rat on a carbohydrate diet and receiving thyroidin, 5 days after operation. Magnification 360 ×.

When taken as a whole, our findings indicate that the source from which islet tissue is formed in the pancreas of rats may be both the reorganizing and proliferating epithelium of the acini and cells of the small efferent ducts, and also the acinose tissue itself of that organ. The process of the formation of new islet tissue varies with the character of the diet and the level of the basal metabolism, as determined by the concentration of thyroid hormone in the body.

## SUMMARY

A study was made of the sources of insular tissue formation in the pancreas of albino rats during its restoration in conditions of different diet and changes of the thyroid hormone concentration. The reconstructing and proliferating acinus epithelium, the cells of small efferent ducts and acinus tissue of the remaining parts of the organ proved to be the source of the insular tissue formation. The process of the new insular tissue formation was the most intense in conditions of carbohydrate nutrition and thyroidization.

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