RELATIONSHIP BETWEEN REGENERATION OF THE ADRENAL CORTEX AND CHARACTER OF THE OPERATION

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UDC 616.45-089.168-092.9-07:616.453-003.9+616.153-003.9-02:616.45-089

Half of one adrenal and the whole of the other were removed in rats. Regeneration of the remaining fragment was studied. The course of regeneration varied depending on whether the residual fragment was demedullated or not. However, after one month no significant differences were found in the weight of the regenerated fragments or their functional activity.

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It has been shown experimentally that after trauma a defect in the parenchyma of the adrenal cortex is often replaced by scar tissue, and that regeneration of the cortex by epimorphosis does not take place [5, 6, 8]. Observations of this kind may be explained by differences in the experimental technique, because slight injuries were inflicted on one gland while the other remained intact [1]. Meanwhile, it is well known that the cortex regenerates rapidly after enucleation of the adrenal [7, 9], demonstrating the high regenerative ability of the gland.

In the present investigation the course of regeneration in the adrenal cortex was studied after partial adrenalectomy depending on whether the central portion of the gland was removed or remained intact.

EXPERIMENTAL METHOD

Experiments were carried out on female Wistar rats weighing 175 ± 7.7 g. The animals were divided into three groups. The rats of group 1 (12) underwent a mock operation, the rats of group 2 (18) underwent left-sided adrenalectomy and resection of half of the right adrenal, while those of group 3 (24 rats) underwent left-sided adrenalectomy and resection of half the right adrenal with demedullation of the residual fragment of the gland. The operation was performed under Nembutal anesthesia (0.4 mg/100 g body weight intraperitoneally). The glands removed during operation were used as controls. In the postoperative period the animals received a mixed diet. They were sacrificed by decapitation after 3, 5, 10, 15, and 30 days, between 11 and 12 A.M. Material was fixed in neutral formalin or Carnoy's mixture. Histological preparations were stained with hematoxylin-eosin, Sudan black, Schiff's reagent for keto-groups, and by the Feulgen and Brachet reaction.

EXPERIMENTAL RESULTS

Changes in the glandular parenchyma of the adrenals in the early periods of observation were similar in the animals of both experimental groups. Considerable thickening of the capsule of the gland was observed, with loosening of the fibers as a result of edema, the development of localized areas of necrosis, thrombosis of small blood vessels, and infiltration by neutrophils, lymphocytes, and macrophages. Proliferation of the connective-tissue elements of the capsule was a characteristic feature and was particularly marked near the site of resection, on account of the formation of granulation in the resected areas. Cortical cells next to the wound surface showed fatty degeneration. Areas of necrosis of cortical tissue were also observed there, and in the case of demedullation they extended as far as the zona glomerulosa. By the 5th day the necrotic masses were completely surrounded by granulation tissue, while in the zone of

Department of Pathomorphology, Institute of Medical Radiology, Academy of Medical Sciences of the USSR, Obninsk (Presented by Active Member of the Academy of Medical Sciences of the USSR G. A. Zedgenidze). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 65, No. 4, pp. 103-107, April, 1968. Original article submitted September 5, 1966.

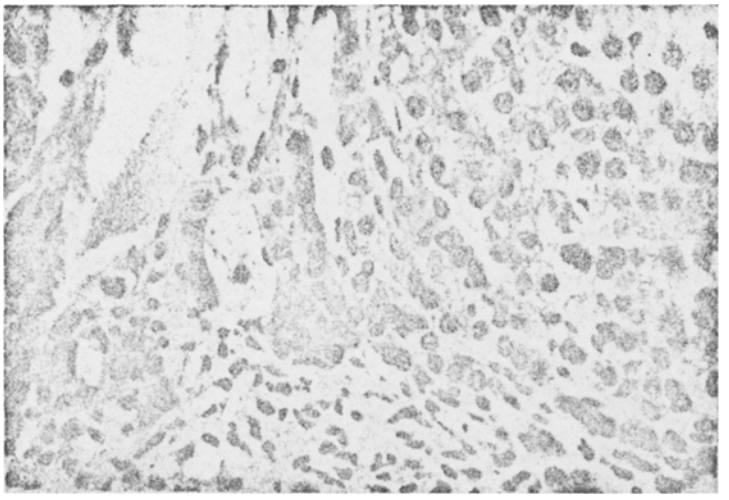

Fig. 1. Invasion of scar tissue along the course of the sinusoidal spaces by undifferentiated epithelial cells. Hematoxylin-eosin, 40 × 8.

resection, a delicate scar had begun to form. Organization of the necrotic masses was complete after 10-15 days. By the same time deposition of calcium salts in the masses was observed in all cases. The granulation tissue surrounding the areas of calcification formed granulomas, containing large numbers of foreign-body giant cells.

After 5 days the parenchyma of the gland was in direct contact with the newly formed scar. Later, after the 10th day, slit-like spaces appeared between the scar and the cortical tissue, becoming of large size after 2-3 weeks. Bands of cortical cells from the parenchyma intruded into these "sinusoids" and gradually filled them. Meanwhile, new spaces were formed along the inner border of the scar. The scar tissue thereby became considerably thinner and was shifted externally, so that the surface of the gland at the point of resection became spherical in shape. The decrease in the quantity of connective-tissue was particularly marked in the adrenals with demedullation of the residual fragment, in which thin bands of fibrous tissue were found after 20 days only along the course of the sinusoidal vessels and around the deposits of lime.

As a rule small groups of tiny cortical cells with round, hyperchromic nuclei were seen to appear at the border with the scar (Fig. 1). The cytoplasm of these cells was basophilic and their nucleic acid content was much higher than that of the adjacent hypertrophied cells. These "dedifferentiated" cells usually lay along the course of the sinusoidal vessels, penetrating as bands into the connective-tissue layers between them. In the late stages, collections of cortical cells of different sizes were found among the scar tissue, forming distinctive "adenomatous" nodules (Fig. 2).

Considerable changes in the adrenal cortex were also present in parts of the residual fragment remote from the site of resection. Characteristically they showed a compensation reaction in the form of changes in the relationships between the zones of the adrenal cortex, hypertrophy and hyperplasia of the cortical cells, and the formation of pseudoglandular structures and areas of hemorrhagic infiltration, interpreted as morphological signs of adrenocortical insufficiency. After 3 days the zona fasciculata became basophilic and gave an intensive reaction by Brachet's method, while lipids remained as only a few droplets in solitary cells. After 15-20 days lipids reappeared in small quantities, together with ketosteroids, mainly in the zona glomerulosa and the outer part of the zona fasciculata. No differentiation of the cells into zones could be seen in the glands of the animals of group 3 during the first two weeks. Subcapsular parts of the cortex were highly edematous, and contained columns of hypertrophied, juicy cells between which could be seen delicate fibrous structures and a few connective-tissue cells. After about two weeks, marked sclerosis developed in these areas. After one month the zona glomerulosa was completely formed, but was much narrower than in the control glands. The accumulation of lipid material and keto-groups took place more slowly in these animals than in the animals whose glands were not demedullated, although after one month no significant differences could be seen between the rats of the two experimental groups.

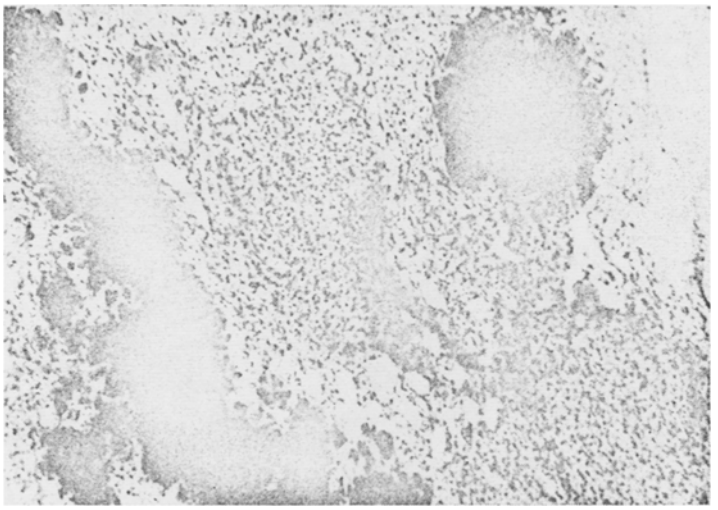

Fig. 2. Adenomatous proliferation of cortical tissue in the region of the newly formed scar. Deposits of lime with collections of foreign-body giant cells can be seen. Hematoxylin-eosin, 10 × 8.

Marked hypertrophy of the cells both of the zona glomerulosa and of the zona fasciculata developed by the 3rd day after resection, the degree of hypertrophy being the same in both zones, varying with the time. Meanwhile considerable proliferation of cortical cells was observed. In the animals with demedullation of the residual fragment of the gland, the number of mitoses during the first days was 8-10 times greater than the number of mitoses in animals undergoing the mock operation. Mitoses were most numerous in the subcapsular regions of the gland, frequently in parts just next to the inner border of the capsule. Later the number of mitoses in the rats of this group progressively decreased and the location of their maximum moved into deeper parts of the cortex. In the animals undergoing partial adrenalectomy, the increase in number of mitoses was not so sharp, and the maximum occured after 10 days. Most mitoses in the rats of this group were located in the "transitional" zone and the outer parts of the zona fasciculata.

Besides diffuse hyperplasia, the formation of nodular collections of cortical cells, often multiple, in the adrenal capsule and scar tissue was often observed. Usually these "adenomas" were perivascular in distribution. In some cases in serial sections these nodules could be seen to connect directly with the main part of the parenchyma of the adrenal cortex prolapsing into the slit-like spaces in the capsule.

It is clear from the account given above that the intensity of repair taking place in the adrenal cortex was largely determined by the character of the operation. After demedullation of the residual fragment, because of necrosis of the central portions of the cortex after the operation less of the cortical parenchyma was preserved than after resection. However, toward the end of the experiment there was no significant difference either in the weight of the regenerated fragments or in their functional activity, judging from the results of histochemical tests. In every case regeneration of the adrenal cortex took place by proliferation of cells from different parts of the residual fragment, mainly from its outer portions, and also by penetration of relatively undifferentiated cells into the scar tissue which had formed. This last process was more characteristic in cases of demedullation of the residual fragment of the gland, when massive proliferation of undifferentiated gland cells could be seen along the course of the developing sinusoidal spaces, leading to restoration of the normal appearance of the cortex and to the formation of "adenomatous" foci of proliferating cortical tissue among the scar and to marked reduction in the amount of fibrous tissue. Resorption of connective tissue also took place in sclerotic areas of the zona glomerulosa, an indication of the intensity of the regenerative process [3].

Deposits of lime constantly observed in the necrotic masses were evidently associated with the hypercalcemia [10] developing in cases of adrenocortical insufficiency. A further factor contributing to this phenomenon was probably the addition of chalk as a mineral additive to the animals' diet.

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