# REGENERATION OF THE PANCREAS DURING SYNGENEIC AND ALLOGENEIC PARABIOSIS

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In parabiotically joined CBA mice, regeneration of the pancreas was more intensive than in single mice. The increase was more marked still in the early periods of parabiotic union of CBA mice and (CBA × C57BL/6J) $F_1$ hybrids. However, after a certain time destructive and inflammatory changes developed and the animals died.

Investigations have shown that the pancreas possesses low powers of regeneration, and that its main mechanism of recovery is regeneration hypertrophy [4, 7-9].

The object of the present investigation was to discover ways of stimulating the regenerative powers of the pancreas.

## EXPERIMENTAL METHOD

Three series of experiments were carried out on mice joined by celomic parabiosis in strictly controlled genetic systems. At the moment of union, the splenic part of the pancreas (about 40% of the total tissue) was resected from one partner. At each time of observation 5-7 pairs of mice were used in the experimental and control series.

Series A consisted of parabiosis between syngeneic CBA mice in which the pancreas of one partner was resected. Series B consisted of parabiosis between CBA mice and (CBA × C57BL/6J) $F_1$ hybrids in which the pancreas of the CBA partner was resected. Series C consisted of the same parabiosis, but with resection of the pancreas from the $F_1$ hybrid. Under the conditions of syngeneic parabiosos (Series A) tissue incompatibility is known not to arise. In parabiosis between nonsyngeneic mice (series B and C), an immunological reaction developed between the partners as a result of their unilateral incompatibility.

The following controls were used: 1) single mice with resection of the pancreas, 2) parabiotic pairs of mice without resection of the pancreas, and 3) single mice of the same age without resection of the pancreas. Allowing for the diurnal rhythm of mitotic activity [3, 5], the animals were sacrificed during the morning after starvation for 24 h. Material was fixed in 10% formalin and Carnoy's and Bouin's fluids. Paraffin sections, 5 $\mu$ in thickness, were stained with hematoxylin-eosin and by Gomori's method. The degree of regeneration of the pancreas was estimated from its weight, morphology, mitotic activity (mitoses were counted in 20,000-25,000 acinar and 5000 islet cells), the area of the acini, and the change in number of binuclear cells.

## EXPERIMENTAL RESULTS

In the case of syngeneic parabiosis, the weight of the regenerated pancreas was considerably restored, whereas in the control single mice no such recovery was observed (Table 1). The increase in size of the resected gland was more marked still in the case of parabiosis between nonsyngeneic mice if the pancreas

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TABLE 1. Changes in Weight (in mg) of the Mouse Pancreas after Resection under Parabiotic Conditions (M ± m)

| Time after resection (in days) | Experiment | | | | | | | Control | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | syngeneic parabiosis (CBA ~ CBA) | | nonsyngeneic parabiosis (CBA ~ $F_1$ hybrid) | | | | | resection without parabiosis | | single mice without resection | |
| | A | | B | | C | | | CBA | $F_1$ | CBA | $F_1$ |
| | resection | intact | CBA resection | CBA resection | $F_1$ resection | CBA intact | | | | | |
| 3—5 | 70± 2,5 | 110± 1,9 | 73± 2,5 | 118± 2,9 | 71± 2,9 | 110± 2,7 | | 60± 2,9 | 63± 2,7 | 103± 2,4 | 93± 2,7 |
| 6—10 | 90± 2,8 | 115± 1,7 | 87± 2,7 | 125± 2,3 | 112± 2,8 | 116± 2,0 | | 74± 2,7 | 75± 2,5 | 104± 2,1 | 94± 2,1 |
| 11—16 | 100± 2,6 | 118± 1,7 | 94± 3,1 | 130± 2,7 | 124± 2,6 | 119± 2,7 | | 76± 2,7 | 78± 2,2 | 104± 1,6 | 94± 1,9 |
| 17—22 | 103± 2,6 | 118± 2,9 | — | — | — | — | | 79± 3,0 | 83± 2,9 | 106± 1,9 | 95± 1,8 |
| 23—30 | 106± 3,0 | 120± 2,9 | — | — | — | — | | 78± 3,2 | 80± 1,4 | 109± 2,1 | 98± 2,3 |

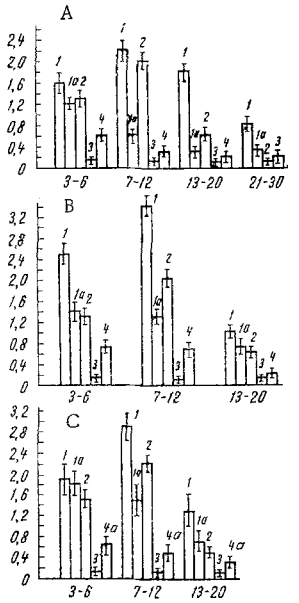


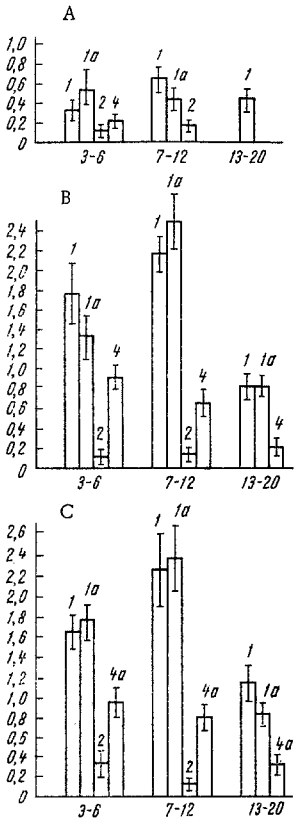

Fig. 1. Mitotic activity of pancreatic acinar cells in parabiotic mice after partial resection of the pancreas: A) syngeneic parabiosis; B) nonsyngeneic parabiosis, resection of the pancrease from the CBA partner; C) nonsyngeneic parabiosis, resection of the pancrease from the (CBA × C57BL/6J) $F_1$ hybrid partner. 1) Resected pancreas of the partner; 1a) intact pancreas of one partner after resection of the pancreas of the other partner; 2) resected pancreas from a single CBA mouse; 3) intact pancreas from a single $F_1$ mouse; 4) intact pancreas of CBA partner; 4a) intact pancreas of $F_1$ hybrid partner. Abscissa, days after operation; ordinate, number of mitoses (in %)

of the hybrid was resected. The resected pancreas of the CBA partner was not enlarged so considerably under these conditions. Meanwhile, destructive and inflammatory changes were found in the pancreas of the hybrids, just as Polyak et al. [6] observed in certain internal organs during parabiosis.

Consequently, the results show that parabiosis stimulates regeneration of the pancreas. In all series of experiments, the weight of the pancreas in the intact partner was greater than in the control, especially in series B, in which the hybrid remained intact.

The mitotic activity of the acinar cells of the residual part of the gland was greater in all series than in the control after resection of the pancreas from single mice, and reached its maximum on the 6th-7th day after the operation (Fig. 1). The mitotic index in the resected pancreas under nonsyngeneic parabiotic conditions was significantly higher than under syngeneic conditions ($P < 0.01$). In the intact partner the mitotic activity in the acinar cells was considerably increased, especially in the case of nonsyngeneic parabiosis. An increase in mitotic activity in certain organs of the intact parabiotic partner has been observed previously [1, 11, 14].

Unlike in the partner with the resected pancreas, in the intact partners mitotic activity reached a maximum on the 3rd-5th day, i.e.,



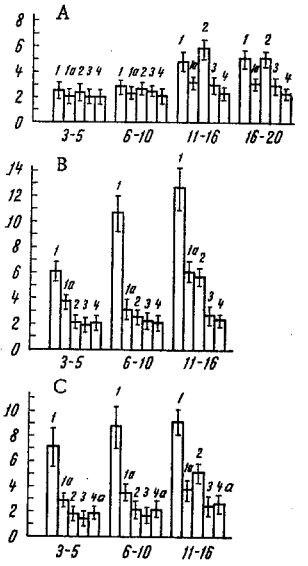




Fig. 2

Fig. 3

Fig. 2. Mitotic activity of pancreatic islet cells in parabiotic mouse partners after resection of the pancreas. Legend as in Fig. 1.

Fig. 3. Number of binuclear acinar cells in the pancreas of parabiotic mouse partners after resection of the organ. Abscissa, days after operation; ordinate, number of binuclear cells (in %).

soon after union. These results are in agreement with Alov's observations [2]. In syngeneic parabiosis mitotic activity in the intact partner was sharply reduced, whereas in nonsyngeneic parabiosis the decrease took place slowly. The reason was probably the gradually increasing destruction of the pancreas, leading to the appearance of products which, according to some authorities [10, 12, 13], stimulate growth processes.

The study of the state of the islet cells showed that parabiosis also stimulates regeneration of this part of the pancreas. The mitotic activity of the islet cells under parabiotic conditions without resection of the pancreas and on the 3rd-6th day of the experiment was higher than in the resected pancreas of the single mouse. Consequently, parabiotic union of the mice itself considerably stimulated proliferation of the islet cells. Resection of the pancreas, under these conditions, led to a more marked increase in mitotic activity both in the resected organ and in the pancreas of the intact partner. At the same time, nonsyngeneic parabiosis was observed to have a more marked stimulating effect on proliferative activity than syngeneic, in which mitotic activity was increased only during the first days of the experiment.

In all the series of experiments the area of the acini was increased in the residual part of the pancreas, but the dynamics of this increase differed. In syngeneic parabiosis, just as in the control, the area of the acini increased gradually until the 17th-20th day, after which it showed a tendency to decrease. In nonsyngeneic parabiosis, this process followed a more rapid course, and by the 6th-10th day the area of the acini was greater than in the syngeneic partners ($P < 0.2$ and $P < 0.01$). By the end of the period of observation, the area of the acini showed a smaller increase after resection of the pancreas in the CBA partner

in nonsyngeneic parabiosis, for it was indistinguishable from the control, whereas in syngeneic parabiosis, and in nonsyngeneic parabiosis when the pancreas in the hybrid partner was resected, the area of the acini was significantly greater than in the control ($P < 0.05$ and $P < 0.01$). In the intact partners some increase in area of the acini was observed both in the experimental and in the control series, although a significant increase in size of the acini compared with the control was observed only after resection of the pancreas in the hybrid partner ($P = 0.02$).

A significant increase in the number of binuclear cells in response to resection of the pancreas was discovered (Fig. 3) both in the experimental series and in the first control, while their number was also appreciably affected by the immunological conditions. In nonsyngeneic parabiosis, for instance, they were more numerous than in syngeneic ($P < 0.01$). Comparison of series B and C showed a larger number of binuclear cells in series B ($P < 0.01$), i.e., after resection of the pancreas in the CBA partner. The smaller increase in their number in the resected pancreas of the hybrid (series C) is evidently due to the parent's immunological reaction against the hybrid. The increase in number of binuclear cells in the intact partner was significant only in the case of nonsyngeneic parabiosis ($P < 0.01$).

Regeneration of the pancreas in syngeneic and nonsyngeneic parabiosis thus followed a different course. In the first case most of the indices studied were lower, although still higher than the control values. The weight of the pancreas was restored, which did not occur in the control. The reason for the high indices was probably the state of stress produced by parabiosis.

In nonsyngeneic parabiosis (series B and C) most of the indices studied were definitely higher in the resected organ than in series A and in the control. Allowing for the fact that this occurred in both series, it can be concluded that, as well as immunological factors, destructive processes in the pancreas leading to the appearance of protein products stimulating proliferative activity may also have been responsible for these results. This factor of destruction could also account for the higher mitotic index in the second control in the nonsyngeneic partners than in the syngeneic.

## LITERATURE CITED


1. I. A. Alov, Dokl. Akad. Nauk SSSR, 111, No. 1, 190 (1956).
2. I. A. Alov, Outlines of the Physiology of Mitotic Cell Division [in Russian], Moscow (1964), p. 236.
3. G. N. Voronin, in: Mechanisms of Nervous and Humoral Regulation of Physiological Processes [in Russian], Leningrad (1966), p. 26.
4. L. D. Liozner, A. G. Babaeva, and V. F. Sidorova, Byull. Éksperim. Biol. i Med., No. 10, 96 (1965).
5. I. V. Markelova, Tsitologiya, No. 3, 318 (1967).
6. A. I. Polyak, E. P. Zakharchenko, and E. S. Gulyantsev, in: Mechanisms of some Pathological Processes [in Russian], Rostov-on-Don (1967), p. 42.
7. S. S. Raitsina, L. M. Farutina, and V. M. Kashintseva, Arkh. Anat., No. 10, 43 (1965).
8. G. G. Samsonidze, Byull. Éksperim. Biol. i Med., No. 3, 81 (1969).
9. G. V. Segida, Byull. Éksperim. Biol. i Med., No. 11, 88 (1962).
10. G. D. Tumanishvili, Some Problems in Regulation of the Growth of Animal Tissues [in Russian], Tbilisi (1965).
11. N. L. Bucher, I. F. Scott, and I. C. Aub, Cancer Res., 11, 457 (1951).
12. A. Lahtiharju, Acta Path. Microbiol. Scand., Suppl. 150, 99 (1961).
13. A. Lahtiharju and H. Teir, Exp. Cell Res., 54, 205 (1964).
14. H. Wrba, H. Rabes, and G. Alber, Exp. Cell. Res., 46, 263 (1967).