REGENERATIVE HYPERTROPHY OF THE PANCREAS IN GUINEA PIGS

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There is considerable experimental evidence that injury to the pancreas in mammals leads to the development of regenerative processes in the organ. After resection of part of the pancreas [3, 6, 8, 9] there is very slight regeneration of both the acinar and islet tissues. Experiments in which cells of the islets of Langerhans, the acinar tissue, and the ducts have been injured selectively [1, 2, 4, 5, 12] have shown that all the components of the glands may take part in the process of regeneration and that the degree of their participation depends on the experimental conditions.

Investigators have paid most attention to the histological processes taking place in regeneration of the pancreas, and the study of the reaction of the pancreas as a complete organ to its partial resection has been neglected. Cameron [11] resected the splenic portion of the pancreas in guinea pigs and investigated it microscopically 133-334 days after operation, as a result of which he reached certain very vague conclusions regarding the possible restoration of the weight of the pancreas and the area of the islet tissue, which he determined by a planimetric method on serial sections. Belli and co-workers [10], in experiments on rats, did not observe restoration of the weight of the organ after partial resection.

It remains uncertain, therefore, whether the weight of the organ is restored after resection, whether the pancreas regains its original shape, and how morphologically and functionally perfect is the regenerated organ. The object of the present research was to continue the study of this problem.

EXPERIMENTAL METHOD

Guinea pigs were used as experimental animals, for they have a compact pancreas, which enables a definite part of the organ to be removed and the possibility of its restoration to be elucidated.

In 18 guinea pigs (males) weighing 285-346 g, the splenic portion of the pancreas, accounting for approximately $^1/_3$ of the organ, was resected under ether anesthesia. The operation was conducted with sterile precautions. The animals were sacrificed 14 days, 4, and 10 months after operation, from 5 to 7 at a time. The pancreas was weighed, its length and volume measured, and fixed in Bouin's fluid and Carnoy's mixture. Serial sections 7 μ thick were stained with Heidenhain's azan, hematoxylin-eosin, and by van Gieson's and Brachet's methods. By means of a screw ocular micrometer two diameters of all the islets were measured in every 15th section, and the area of the islets was calculated from the formula for an ellipse. The measured islets were distributed into groups according to size in order to give some idea of whether hypertrophy of existing islets or formation of new ones had taken place. The total area of the islet tissue was also determined. The functional state of the regenerated pancreas was assessed by determination of the blood sugar by the Hagedorn-Jensen method. For control purposes we used the pancreas of 15 guinea pigs of corresponding weight and age.

EXPERIMENTAL RESULTS

It will be apparent from Table 1 that 14 days after operation the mean weight of the pancreas of the experimental animals was approximately $^2/_3$ of the weight of the organs in the control guinea pigs. The blood sugar of the experimental guinea pigs was within normal limits. No visible outgrowth of regenerating tissue was present on the surface of the wound.

Microscopic investigation showed that the structure of the greater part of the organ was normal. Near the wound surface there was a small area in which the structure of the acini was atypical. Mitoses and dedifferentiated

cells with translucent nuclei were present in the acinar cells. These cells often lay in small groups outside the acini, and were apparently newly forming islets. The total area of the islet tissue in the pancreases of the experimental animals was rather more than $^1/_3$ that of the controls. The RNA concentration in the acinar cells of the regenerated organs was much higher than that in the pancreases of the control guinea pigs, and the RNA content of the cells close to the wound surface in the experimental animals was the same as that of the cells of the head of the pancreas.

TABLE 1. Changes in the Weight, Length, and Volume of the Pancreas and in the Blood Sugar of Animals at Various Intervals after Partial Resection of the Organ (mean values)

Criteria	Time of experiments					
	14 days		4 months		10 months	
	control	expt.	control	expt.	control	expt.
Body weight (in g)	385	338.6	575.6	555.8	701.2	754
Absolute weight of pancreas (in g)	1.27	0.817	1.958	2.086	1.788	1.28
Relative weight of pancreas (in %)	0.329	0.241	0.34	0.375	0.254	0.168
Volume of pancreas (in cm^3)	1.24	0.75	2.01	2.09	1.94	1.28
Length of pancreas (in cm)	12.17	5.7	11.8	6.96	15.14	8.62
Blood sugar (in mg%)	100.2	107	102.5	116	126.4	253.4

Four months after operation, the mean weight of the pancreas of the experimental animals was slightly greater than the mean weight of the organs of the control guinea pigs. Meanwhile hardly any proliferation of regenerating tissue was taking place from the wound surface, and the length of the regenerating organs was almost the same as the length of the stump remaining after partial resection. Consequently, the increase in the weight of the organ took place as a result of the increased thickness of its uninjured part. The blood sugar of the experimental animal 4 months after operation was within normal limits.

Microscopic examination of the regenerating organs at the site of the wound surface revealed some degree of proliferation of the connective tissue and ducts, and the presence of a few atypical acini. A transverse section of this evidently newly formed part of the organ occupied one field of vision of the microscope (eyepiece 10, objective 8), and the thickness of the regenerating tissue was about 700 μ. Elsewhere the regenerating organs were almost indistinguishable in structure from the pancreas of the control animals. Consequently, regeneration from the wound surface constituted only an insignificant part of the process of regeneration as it affected the organ as a whole. Four months after the operation small groups of islet cells could be seen in the acinar tissue of the uninjured part of the regenerating pancreases (Fig. 1). Side by side with the formation of new islets, intensive hypertrophy of the islets remaining after the operation took place. The data in Table 2 show that the number of both very small and very large islets was much greater in the experimental animals than in the controls.

The total area of the islet tissue in the regenerating pancreases was slightly larger than the total area of the islet tissue of the pancreases of the control animals.

Four months after the operation the RNA concentration in the acinar cells of the regenerating pancreases, both near the woundsurface and in the region of the head of the organ, was higher than in the corresponding cells of the control animals.

Ten months after operation (see Table 1) both the absolute and the relative mean weights of the pancreases were lowered, not only by comparison with those in the control animals, but also by comparison with the mean weights of the regenerating organs of the guinea pigs sacrificed 4 months after operation. In no case was any appreciable regeneration to be seen on the wound surface. The length of the pancreases increased only very little during the experiment, and the splenic portion was totally absent in the experimental animals. All the experimental animals showed considerable hyperglycemia 10 months after operation. In two guinea pigs the blood sugar was 297 mg% and 423 mg%, with an average level of 253 mg%.

TABLE 2. Distribution of Islets of Langerhans According to Size (in groups)

Size of islets (product of 2 diameters of islets) in divisions of ocular micrometer	No. of islets in groups									
	control			after regeneration for						
				14 days			4 months		10 months	
	I	II	III	I	II	III	I	II	I	II
10^3—$16 \cdot 10^3$	303	270	318	61	82	84	305	308	102	95
$16 \cdot 10^3$—$32 \cdot 10^3$	639	459	508	144	174	250	532	534	390	48
$32 \cdot 10^3$—$48 \cdot 10^3$	363	353	360	106	133	134	393	356	268	29
$48 \cdot 10^3$—$64 \cdot 10^3$	200	191	219	62	56	64	315	206	153	102
$64 \cdot 10^3$—$80 \cdot 10^3$	110	104	106	44	44	55	205	119	124	108
$80 \cdot 10^3$—$96 \cdot 10^3$	104	75	92	29	40	33	151	163	69	82
$96 \cdot 10^3$—$112 \cdot 10^3$	63	55	50	18	20	18	91	75	60	43
$112 \cdot 10^3$—$128 \cdot 10^3$	45	42	52	15	20	17	71	46	41	50
$128 \cdot 10^3$—$160 \cdot 10^3$	56	50	48	18	26	15	86	70	54	62
$160 \cdot 10^3$—$192 \cdot 10^3$	25	24	20	16	16	12	37	45	49	55
$192 \cdot 10^3$—$224 \cdot 10^3$	12	15	10	6	3	5	18	20	36	22
$224 \cdot 10^3$—$256 \cdot 10^3$	3	5		2	2	4	8	6	29	25
$256 \cdot 10^3$—$288 \cdot 10^3$		1	4	2	4		17	15	25	18
$288 \cdot 10^3$—$320 \cdot 10^3$	3	2			2	2	27	24	29	32
$320 \cdot 10^3$—$352 \cdot 10^3$			2	3	1	1	31	22	45	50
$352 \cdot 10^3$—$384 \cdot 10^3$							26	21	32	45
$384 \cdot 10^3$—$592 \cdot 10^3$							7	5	19	12
$592 \cdot 10^3$—$800 \cdot 10^3$							2	3	5	10
$800 \cdot 10^3$—1 000 000							12	12	25	29
10^6—1 $992 \cdot 10^3$							1	3	9	6
Total area of islet tissue (in mm^2)	36,48	36,59	38,09	13,01	13,02	13,04	41,79	42,99	63,63	61,82

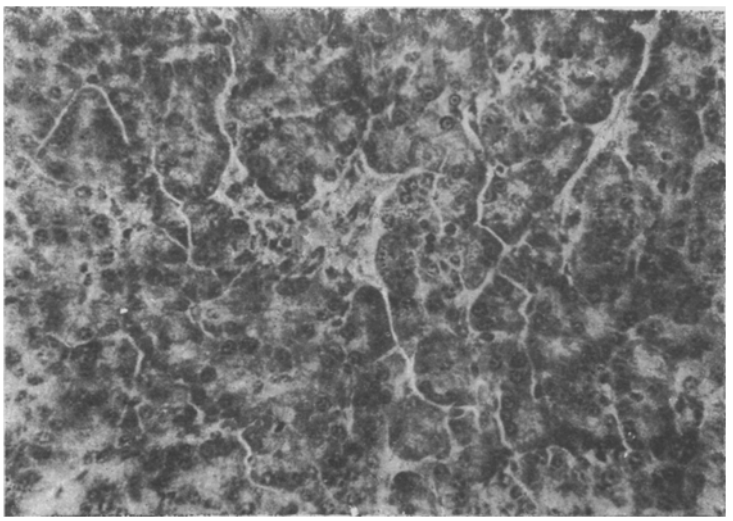

Fig. 1. Dedifferentiation of the acinar epithelium of the pancreas and formation of islets of Langerhans 4 months after partial resection of the organ. Stained by Heidenhain's azan method. Magnification 280.

Microscopic investigation revealed that the structure of the organ in the region of the former wound was atypical. The regenerated part of the organ appeared even smaller than in the guinea pigs sacrificed 4 months after the operation (Fig. 2). The uninjured portion of the pancreas contained many grossly hypertrophied islets of Langerhans (see Table 2). They were much larger in area than the largest islets of Langerhans in the control animals (Fig. 3). The presence of so many large islets led to a considerable increase in the total area of the islet tissue, which was much larger than the total area of the islet tissue in both the regenerated organs of the animals

sacrificed 4 months after the operation and the pancreases of the control guinea pigs. Notwithstanding the obvious hypertrophy of the islet tissue, there was apparent decompensation of the pancreatic function, as revealed by the presence of a marked hyperglycemia. This suggestion was confirmed by the results of a histochemical investigation: the RNA concentration was the same in the cells of all parts of the organ, but it was much lower than in the parenchyma of the pancreases of the control animals.

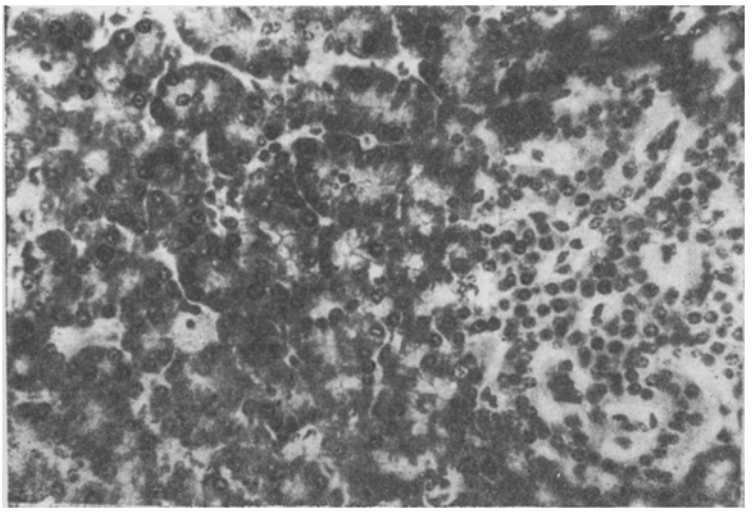

Fig. 2. Proliferation of connective tissue and atypical acini in the region of the wound surface 10 months after operation. Stained with hematoxylin-eosin. Magnification 120.

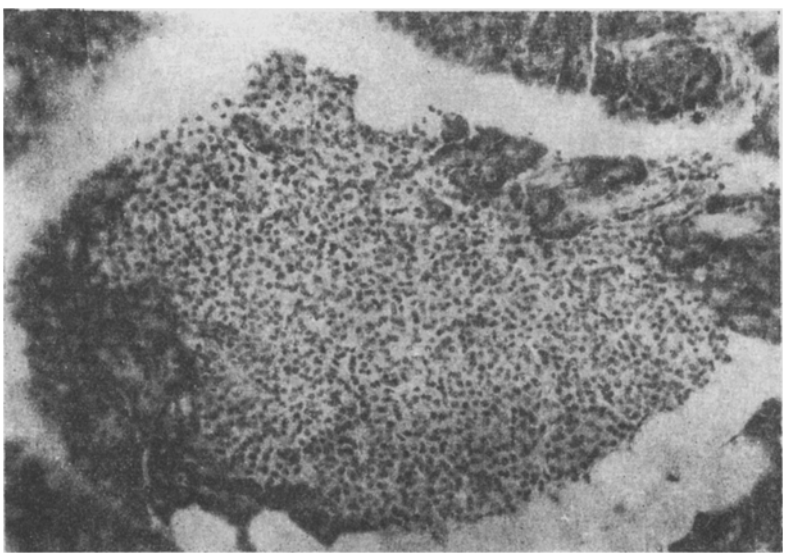

Fig. 3. Hypertrophied islet, occupying nearly the whole of a lobule. Ten months after partial resection of the pancreas. Stained by van Gieson's method. Magnification 120.

It may be concluded from these findings that regeneration of the pancreas after resection of a considerable part of the organ takes place mainly as a result of regenerative hypertrophy. This process is characterized by failure of restoration of the initial shape of the organ associated with full restoration of its weight, as a result of the proliferative processes occurring in its uninjured part and ultimately responsible for maintaining the normal insulin-producing function of the organ. Ten months after operation, however, decompensation has occurred, as revealed

by a decrease in the weight of the organ and the presence of hyperglycemia. A similar finding has been described in respect of the liver of rats, undergoing regenerative hypertrophy, followed by atrophic changes one year after operation [7]. These results, indicating that regenerative hypertrophy of the pancreas is the principal form of the reaction to resection, are not in disagreement with the results obtained by other workers, for there are no reports in the literature of regeneration taking place by the outgrowing of regenerating tissues to a significant extent from the wound surface.

SUMMARY

Four months after the removal of the splenic portion of the pancreas in guinea pigs the weight of the organ is restored at the expense of the increased mass of its uninjured portion. The length of the gland and its initial shape are not restored, i.e., regeneration is effected by the way of regenerative hypertrophy. Following the regenerative hypertrophy, 4 months after the operation, the area of the insular tissue in the pancreas was found to be restored; this occurred both at the expense of the island hypertrophy and of their neoformation. The blood sugar level of such animals is within the normal level. Ten months after the operation the weight of the gland diminishes and the RNA concentration in the acinous cells drops (as compared to control). Marked hyperglycemia is noted, notwithstanding the considerable insular hypertrophy.

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