EXPERIMENTAL BIOLOGY

REGENERATION OF THE KIDNEY FOLLOWING COMPENSATORY HYPERTROPHY

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Several workers [2, 3, 4] have demonstrated the ability of the mammalian kidney to undergo reparative regeneration. They have shown that regeneration is observed only after the total extirpation of one kidney and the partial removal of the other. Resection of a part of one kidney is not accompanied by regeneration; in response to injury a compensatory hypertrophy of the opposite kidney takes place.

In the experiment of simultaneous removal of one kidney and injury to the other, the response to trauma is of a complex character. As may be imagined, it is a combination of the results of compensatory hypertrophy and of regeneration. The kidney on which the operation is performed reacts in the first place to the removal of the opposite kidney, this reaction is compensatory in character; secondly, it reacts to the removal of its own tissue, this reaction is regenerative in character. On the basis of such an experiment it is, therefore, difficult to decide which changes can be regarded as compensatory and which as regenerative. Difficulty arises in particular in connection with the fact that restoration of the kidney after operation proceeds along the lines of regenerative hypertrophy, i.e., all the tissues of the kidney are involved in it, even those not directly concerned in the injury [1].

So that we could study the processes of regeneration in a purer form, we first removed one kidney from a rat and produced compensatory hypertrophy of the other, and we then performed resection of one third of the remaining kidney.

EXPERIMENTAL METHOD

For the experiment we used male white rats weighing 100-140 g. The animals were subdivided into 4 groups. From all the animals of the first 3 groups the left kidney was removed; the fourth group (5 rats) acted as controls and no form of procedure was carried out on these animals. In the experimental animals of the first group (8 rats) about one third of the right kidney was resected one month after the operation. The rats were killed 49 days after the second operation. The second group of experimental animals (8 rats) were killed 30 days after nephrectomy, at the same time as the second operation was performed on the rats of the first group. The third group of experimental animals (9 animals) were killed 89 days after nephrectomy.

The part of the kidney resected was from the convexity. The incision was made parallel to its long axis. The area removed was mainly composed of cortical substance. The killed animals were weighed, and the kidneys weighed and measured.

By means of a planimeter the cross-sectional area through the middle of the kidney and the areas occupied by cortex and medulla were measured. The area of the individual Malpighian bodies was also measured and the mean value for 50 bodies was derived. In addition to this, we measured the diameter of the convoluted

TABLE 1

Weight and Dimensions of the Kidneys of Experimental and Control Rats

Group of animals	Wt of kidney		Dimensions of kidney, in mm²			Area of section, in mm²	
	abs., in mg	relative, in %	length	width	thick-ness	total	of cortical substance
1st, 2nd and 3rd groups. Initial values	468	0.38	14.1	8.0	6.3	17.9	15.1
1st group. Removal of the left kidney, followed month later by resection of the right	1 211	0.55	19.3	9.6	8.9	32.0	27.8
2nd group. Removal of the left kidney; animals killed after 1 month	1 125	0.58	18.6	10.8	8.8	32.8	28.4
3rd group. Removal of the left kidney; animals killed after 3 months	1 422	0.62	18.2	12.3	8.8	35.7	31.1
Control	918	0.39	16.6	10.3	6.9	30.6	26.9

tubules and the collecting tubules, the height of the tubular cells, the distance between the nuclei and the size of the lumen of the tubules and Malpighian bodies. In the case of each of the indices enumerated, the mean value of 50 measurements was calculated. Statistical treatment of the results showed that with this number of measurements it was possible to obtain values that were reproducible.

EXPERIMENTAL RESULTS

In Table 1 are shown the results characterizing the change in the weight and dimensions of the kidneys in all the groups of animals.

In the first line of Table 1 (initial values) details are given of the weight and dimensions of the left kidney which was removed at the beginning of the experiment. The figures in all the remaining lines relate to the right kidney, and this applies also to the control rats. The differences between the weight and dimensions of the right and left kidneys of the control animals were not statistically significant. As may be seen from Table 1, the kidneys undergoing compensatory hypertrophy (2nd and 3rd groups) grew more than either kidney of the control animals. Only one month after operation, the weight of the compensatorily hypertrophied kidney was greater than the weight of the kidney of the control animals, and at the end of the experiment the difference between then was even more significant. The weight of the kidney undergoing resection also increased noticeably; it exceeded the weight of the corresponding kidney in the control animals by 32%, and in respect to its relative weight, by as much as 41%. The weight of the protion of kidney removed amounted, on the average, to 452 mg. At the moment of resection the average weight of the kidney (as shown by the figures relating to the 2nd group of animals) was 1125 mg, so that it could be considered that the portion of the kidney remaining after resection weighed roughly 670 mg. At the end of the experiment the weight of the residual portion of the kidney was 1211 mg; it had thus almost doubled in size during the experiment. Whereas in the animals of the 3rd group the kidney had gained in weight over 297 mg after 2 months, in the 1st group the weight of the kidney had increased by 538 mg.

At the end of the experiment the kidney subjected to resection was longer than the kidney in the remaining groups of animals, and was the same thickness as the kidney of the animals of the experimental groups. Its width was only slightly less than that of the kidneys of the control animals. This difference was statistically significant ($p = 0.255$). Under these circumstances it must be remembered that the resection led to a considerable reduction in the width of the kidney by 4.5 mm, i.e., by almost half (the width of the kidney at the beginning of the experiment was 8 mm).

TABLE 2

Number of Malpighian Bodies and Their Area in the Kidneys of Experimental and Control Rats

Group of animals	Number of Malpighian bodies		Area of bodies, in μ^2		Maximum dimensions of cavity of body in μ	No. of nuclei in the outer layer of the capsule	Distance between nuclei, in μ
	abs.	relative, 1 mm^2 of cortical substance	of each one	total			
1st, 2nd and 3rd groups. Initial values	138	9.3	2 381	327 588	4.0	9.1	6.9
1st group. Removal of the left kidney, followed one month later by resection of the right	140	5.0	6 290	882 511	8.1	18.9	13.6
2nd group. Removal of the left kidney; animals killed after 1 month	143	5.1	4 566	653 539	5.4	11.2	10.7
3rd group. Removal of the left kidney; animals killed after 3 months	156	5.1	4 887	761 994	6.1	11.2	10.9
Control	157	5.9	3 678	575 856	4.0	10.9	8.3

The cross-sectional area through the middle of the resected kidney 2 months after operation was close to the original area at the time of resection, and was greater than the area of a section through the middle of the kidney of the control animals. These findings thus showed the considerable growth of the mass of the kidney after operation as the result of the regenerative processes taking place in it. Some idea of the nature of these processes may be gained from the figures in Table 2.

As may be seen from Table 2, during the experiment the number of Malpighian bodies in cross section was slightly increased in the animals not undergoing any form of procedure from 136-140 to 155-157. At the same time the mass of the cortical layer of the kidney grew at a greater rate, and the number of Malpighian bodies per unit area in this layer accordingly fell (from 9-9.8 to 5.9). The same relationships were also characteristic of the kidney which had undergone compensatory hypertrophy for 3 months; the number of bodies per mm^2 in this layer was even smaller, 5.1. In the resected kidney 2 months after operation the number of Malpighian bodies was slightly less than that in the kidney of the control animals, 140 compared with 157. If it is remembered, however, that a cross section of the resected portion of kidney contained on the average 100 Malpighian bodies, it is obvious that there was a considerable increase in their number during the experiment. In consequence of this, the number of bodies per mm^2 in the resected kidney became equal to that in the kidneys after compensatory hypertrophy. It is interesting that the dimensions of the renal corpuscles in the regenerating kidney were greater than in the kidneys of the remaining groups of animals. There was no overlapping of the ranges of the corresponding figures. The increase in the size of the Malpighian bodies was due to an enlargement of the cavity of the body and of the area taken up by its cells. The latter was dependent on an increase in the number of cells (the number of nuclei was 73% greater than in the controls) and also on their hypertrophy (the distance between the nuclei had increased to 64% greater than the control value). In the kidneys undergoing compensatory hypertrophy the differences in the size of the Malpighian bodies from that of the controls were less sharply expressed. It was particularly important to emphasize that in compensatory hypertrophy there was no increase in the number of cells in the capsule (the differences which occurred were not statistically significant, $p = 0.767$) and the increase in the size of the Malpighian body was thus mainly due to hypertrophy of the cells and to enlargement of the cavity.

The changes taking place in the convoluted tubules of the cortical layer may be seen from the results given in Table 3.

TABLE 3

Dimensions of the Convoluted Tubules of Experimental and Control Rats

Group of animals	Diameter of tubule, in μ	Size of lumen, in μ	Area occupied by cells, in μ^2	No. of nuclei per transverse section	Distance between nuclei in μ	Height of cells, in μ
1st, 2nd and 3rd groups. Initial values	30.9	10.9	838.9	3.5	6.1	9.7
1st group. Removal of the left kidney followed one month later, by resection of the right	45.8	19.8	1 714.2	6.9	9.7	12.5
2nd group. Removal of the left kidney; animals killed after 1 month	38.1	15.1	1 224.5	4.5	8.4	11.6
3rd group. Removal of the left kidney; animals killed after 3 months	39.6	16.2	1 308.0	4.6	8.7	11.8
Control	33.8	11.3	1 013.4	4.3	7.5	10.7

These results show that the diameter of the tubules reached its largest size in the kidneys undergoing regeneration. This increase in diameter was statistically significant. The difference in the size of the tubules in the kidneys undergoing compensatory hypertrophy and regeneration was due not only to enlargement of their lumen but also to an increase in the area occupied by their cells (transgression absent). The number of cells (nuclei) per transverse section of a tubule was significantly greater (by 60%) in the kidneys undergoing regeneration than in the controls (transgression absent); this indicated that cell hyperplasia w as taking place during regeneration. In the kidneys undergoing compensatory hypertrophy there was no increase in the number of cells by comparison with the controls (the differences were not statistically significant). Hypertrophy of the cells of the convoluted tubules was observed in all the groups of experimental animals, but it was not very marked and did not exceed 30%. The differences in the degree of hypertrophy in the tubules of the kidneys undergoing compensatory hypertrophy and regeneration were very small, but they were nevertheless statistically significant.

We found the same relationships, i.e., the presence of hyperplasia during regeneration and its absence during compensatory hypertrophy, from measurements taken on the collecting tubules in both the cortical and medullary layers. These results are not given here.

Summing up, it may be concluded that the kidney in which compensatory processes had taken place for one month was capable of further growth as the result of continuing compensatory hypertrophy and of regeneration in response to removal of a portion of the organ. When regeneration was observed, it took place more quickly than compensatory hypertrophy, i.e., the increase in the weight of the kidney was more strongly expressed. It is thus possible to produce experimentally regeneration of the kidney differing in a number of signs from compensatory hypertrophy. In the conditions of our experiments regeneration took place against a background of compensatory hypertrophy.

From a comparison of the course of compensatory hypertrophy (after removal of one kidney) and regenerative hypertrophy (after resection of part of a kidney), it is possible to define the essential defferences between them. During regeneration the number of Malpighian bodies was increased; this was not observed during compensatory hypertrophy under the conditions of our experiments. The dimensions of the Malpighian bodies and tubules were greater in the kidney undergoing resection. It was particularly important that the dimensions of the Malpighian bodies and tubules of different type increased during regeneration mainly on account of hyperplasia of the cells, and partially on account of their hypertrophy, whereas in compensatory hypertrophy this increase was due mainly to cell hypertrophy. The processes of regeneration and of compensatory hypertrophy therefore possess distinctive features enabling them to be differentiated within certain limits.

SUMMARY

Left kidney was removed in sexually mature rats; in a month $^1/_3$ of the remaining kidney was resected. Comparative study of changes occurring in the regenerating kidney and those taking place in the kidneys undergoing compensatory hypertrophy (conducted for the period of 1 and 3 months) demonstrated that they are somewhat different. The regenerating kidney approaches the kidneys undergoing compensatory hypertrophy by its size and weight, but is much larger than the kidneys of control animals. Malpighian bodies and tubules are larger in size in regenerating kidney than in the kidneys of control animals and in the organs which underwent compensatory hypertrophy. This enlargement is mainly caused by the cellular hyperplasia. As to compensatory hypertrophy, cellular hypertrophy is the main process occurring.

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