EFFECT OF INTERVAL BETWEEN SUCCESSIVE PARTIAL HEPATECTOMIES ON FORMATION OF THE HEPATIC LOBULES

I. N. Yashina

UDC 616.36-089.873-07:616.36-003.93+612.35:612.6.03

The areas of the hepatic lobules in the liver of rats were measured after three successive partial hepatectomies performed at intervals of 0.5 and 1 month. Hypertrophy of the hepatic lobules in the hepatectomized animals lagged behind hypertrophy of the whole liver, indicating the formation of new lobules. With shortening of the intervals between the operations, the role of hypertrophy of the hepatic lobules as a component of regeneration was increased.

Previous experiments on rats [4] have shown that after partial hepatectomy by the method of Higgins and Anderson the dimensions of the hepatic lobules 1 month after operation are increased compared with those in the intact liver on the average by 74%. After repeated partial hepatectomies, a further increase in size of the residual part of the liver took place. However, no further increase in the size of the hepatic lobules occurred. It was concluded from these facts that after the first operation regeneration of the liver took place primarily through hypertrophy of its structural units, while after repeated resections, as well as hypertrophy of the existing hepatic lobules, new lobules are formed, and this latter process is sharply intensified as the number of resections increases [4]. These findings are in good agreement with the results of investigation of ramification of blood vessels during regeneration of the liver after repeated partial hepatectomies [6]. At the same time, after repeated trauma, regeneration of organs is known to take place more intensively than after the primary injury [1, 2]. On the other hand, it is generally accepted at the present time that the rate and completeness of regeneration are determined by functional demands presented to the organ by the body as a whole [5].

On these grounds it may evidently be expected that the course of regeneration after repeated partial hepatectomies must depend on the stage after the preceeding operation that the succeeding resection is performed. This was the subject of the investigation described below.

EXPERIMENTAL METHOD

Experiments were carried out on 70 female albino rats weighing on the average 100 g at the beginning of the experiment. At the first operation on the rats the left lateral and central lobes of the liver, i.e., about 70% of the tissue, were removed. These hepatectomized animals were divided into two groups. The succeeding operations on rats of the first group were performed at intervals of 1 month, and in those of the second group at intervals of 0.5 month. At the second operation the upper part of the right lobe, about 32% of the tissue of the regenerating liver, was removed. At the third operation the lower part of the right lobe, or about 25% of the twice regenerating liver was removed. The rats were killed 1 month after the last operation. To determine the boundaries of the hepatic lobules the arterial system of the liver was injected with a mixture of ink and gelatin by Sidorova's method [3]. The liver was weighed. The length, width, and thickness of the inferior caudal lobe were measured and the area of the lobe determined. The outlines of the hepatic lobules were traced from tangential sections of the inferior caudal lobe with an Edinger's

Laboratory of Growth and Development, Institute of Medical Genetics, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. P. Avtsyn.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 70, No. 12, pp. 83-86, December, 1970. Original article submitted May 25, 1970.

TABLE 1. Dimensions of Inferior Caudal Lobe of Liver and of Hepatic Lobules Depending on the Number of Operations and Intervals between Them

Index studied	After 1st operation (n = 5)	After 2nd operation			After 3rd operation	
		1 month (n = 6)	½ month (n = 5)		1 month (n = 8)	½ month (n = 4)
Weight of regenerating liver (in g)	6	6,2	6,45		7,3	7,3
Mean area of inferior caudal lobe (in % of control)	293 (215—365)	480 (350—632)	475 (305—725)		545 (328—1 023)	427 (400—454)
Number of hepatic lobules measured	517	655	393		1 478	561
Mean area of hepatic lobule (in % of control)	174 (146—211)	201 (126—266)	291 (230—370)		172 (100—228)	215 (172—297)

Note. n denotes number of animals.

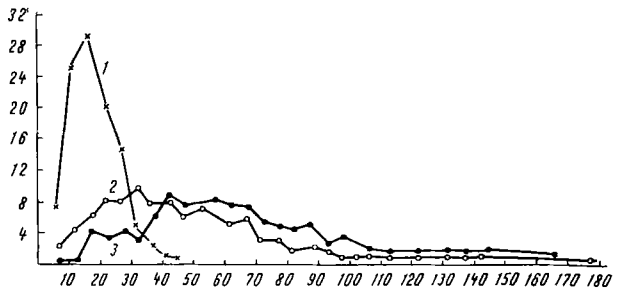

Fig. 1. Changes in size of hepatic lobules 1 month after second operation: 1) control; 2) intervals between operations 1 month; 3) intervals between operations 0.5 month. Abscissa, area of hepatic lobules (in conventional units); ordinate, number of lobules (in %).

drawing apparatus under a magnification of 27 times. The projections of the lobules drawn in this manner were cut out and weighed on torsion scales.

EXPERIMENTAL RESULTS

The results are shown in Table 1. The weight of the intact liver was 4.6-6.7 g. The weight of the liver was completely restored 1 month after the operations, regardless of their number. The area of the inferior caudal lobe 1 month after the first operation was increased by 193% compared with the control, the area of the hepatic lobule being increased by 74%.

After the second operation there was a further increase in size of the residual liver, and this increase was evidently independent of the interval between operations. At the same time, the change in size of the hepatic lobules depended on the interval between the operations. In rats in which the interval between hepatectomies was 1 month the area of the hepatic lobule was increased on the average by 100% compared with the control, and it was virtually indistinguishable from the area of the lobule in rats undergoing only one hepatectomy. After a second resection 0.5 months after the first, the area of the hepatic lobule was increased by 291% over the control. Consequently, with shortening of the interval between operations the area of the hepatic lobule was increased by about 1.5 times ($P = 0.02$). This was associated with a decrease in the number of small lobules and an increase in the number of large (Fig. 1). After the third operation the size of the inferior caudal lobe likewise was independent of the frequency of the operations. In rats undergoing operations at intervals of 1 month the area of the inferior caudal lobe was increased by 445% over the control. If the interval between operations was 0.5 month, the area of the inferior caudal lobe was increased by 327% compared with the control. The difference between these figures is not statistically significant and can be explained by the fact that the area of the inferior caudal lobe in one rat of group 1 was 1023%. The area of the hepatic lobule in the rats of group 1 was increased on the average by 72% over the control. In the rats of group 2 the mean area of the hepatic lobule was increased by 115%.

In animals undergoing hepatectomy at intervals of 0.5 month, hypertrophy of the hepatic lobules was more marked than in rats hepatectomized at an interval of 1 month. The difference in size of the hepatic lobules of the animals of these two groups was about 35% ($P = 0.050$). The increase in mean size of the hepatic lobules associated with a shortening of the intervals between operations was accompanied by a decrease in the number of small lobules (Fig. 2).

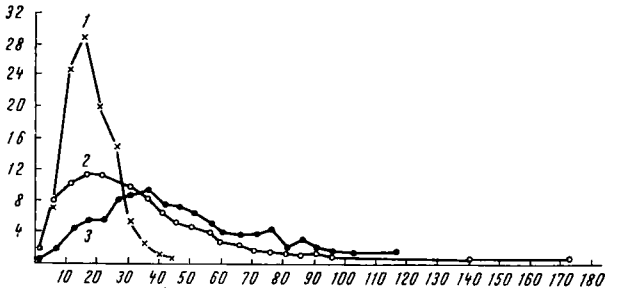

Fig. 2. Changes in size of hepatic lobules 1 month after third operation. Legend as in Fig. 1.

In all the hepatectomized animals the increase in size of the structural units lagged behind the increase in size of the residual liver as a whole. In some rats this lag was present after the first operation. It was increased after the second operation and was observed in all the animals, and after the third resection it was increased still more. The discrepancy between the increase in size of the liver as a whole and hypertrophy of the hepatic lobules may be confirmation of the fact that in the regenerating liver not only are existing hepatic lobules hypertrophied, but new ones also are formed. With a shortening of the intervals between operations, however, the role of hypertrophy of the hepatic lobules in regeneration was to some extent increased. Judging from the facts described above, the behavior of the hepatic lobules during repeated resections of the liver is dependent on the stage after the preceeding operation that the succeeding hepatectomy is performed. If it is done at a time when the regeneration induced by the preceding operation is not yet complete, the role of hypertrophy of the structural units in regeneration after the succeeding partial hepatectomy is increased. This may be because, with a shortening of the interval between operations, the functional deficiency is more marked, and this functional deficiency determines the shift in the balance of regeneration toward hypertrophy of the structural units. It is well known that at the cytological level regeneration hypertrophy of the liver is associated with two processes: with cell division and with cell hypertrophy. It is postulated that two processes also take place at the level of structural units: hypertrophy of hepatic lobules and their formation de novo. The relative importance of these two processes is determined by many factors. In particular, it depends on the degree of functional stress arising in the liver at the time of operation.

LITERATURE CITED

1. M. A. Vorontsova and L. D. Liozner, Physiological Regeneration [in Russian], Moscow (1955).
2. M. A. Vorontsova and L. D. Liozner, Asexual Reproduction and Regeneration [in Russian], Moscow (1957).
3. V. F. Sidorova, Byull. Éksperim. Biol. i Med., No. 8, 99 (1959).
4. I. N. Yashina, Byull. Éksperim. Biol. i Med., No. 10, 95 (1970).
5. R. Goss, Science, 153, 1615 (1966).
6. G. Simpson and E. Finckh, J. Path. Bact., 86, 361 (1963).