EXPERIMENTAL BIOLOGY

MITOTIC ACTIVITY OF THE RAT LIVER SUBJECTED TO VARIOUS SURGICAL INTERFERENCES

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V. F. Sidorova

Laboratory of Growth and Development (Head—Prof. L. D. Liozner),
Institute of Experimental Biology (Director—Prof. I. N. Maiskii), AMN SSSR, Moscow
(Presented by Active Member AMN SSSR N. A. Kraevskii)
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The great regenerative potentialities of the mammalian liver has been beyond question for a long time [6]. At the same time the regularities accompanying the process of regeneration of the organ have been inadequately studied. What has been stated in particular has pertained to the problem of the method of regeneration of the liver tissue.

One of the essential aspects for solving the problem of the method of liver regeneration is an elucidation of the number of dividing liver cells and the character of their distribution in the injured organ.

In the present work we determined the level of mitotic activity of liver cells and their localization in injured and uninjured lobes of the liver with excision of various quantities of hepatic tissue.

METHOD

The experiments were carried out on 55 white male rats weighing 110-155 g. In 5 animals we determined the weight of the liver, which averaged 7300 mg. The remaining 50 rats comprised five groups (10 animals in each) for carrying out the next five series of experiments (see figure).

In the I series the distal section of the left lateral lobe of the liver, weighing 200 mg, which comprised 2.7% of the weight of the entire organ, was removed. In the II series we removed from the left lateral and the central lobes of the liver their distal sections, which in total weighed 1380 mg (19% of the weight of the entire organ). In the III series we completely removed the left lateral lobe weighing 1650 mg (23%). In the IV-V series we completely removed the left lateral and central lobe of the liver, the weight of which was 4650 mg (64% of the organ weight).

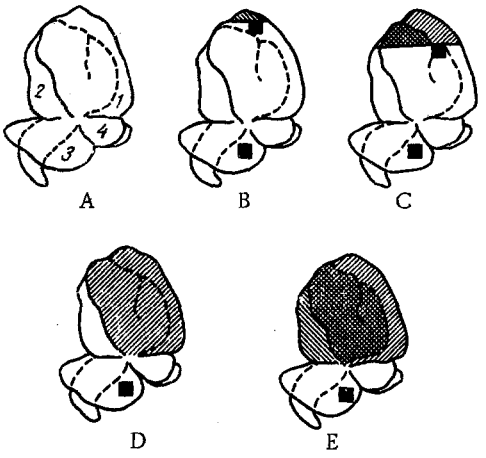
All animals were operated on and killed during the morning hours (from 4:30 to 7:00 A.M.). The rats of the I-IV series were killed 25 h after the operation and the animals of the V series 48 h afterwards. The hours and time of sacrifice were selected on the basis of the data in the literature, the bulk of which indicates that mitotic activity of liver cells during regeneration of the organ reaches a maximal level during the morning at the beginning of the second day postoperation [5, 8-11, 14]. Since certain researchers [12, 16] indicate that the maximal number of mitoses during regeneration of the liver after removal of $^2/_3$ of its mass drops by the end of the second day, we killed tha animals of the V series 48 h after partial hepatectomy. The regenerating liver was fixed in 10% formalin. The count of the number of mitoses and the investigation of their distribution were carried out in the I and II series of experiments in the injured left lobe close to the wound surface and in the uninjured right lobe, and in the III-IV series of experiments only in the right uninjured lobe (see figure).

The mitotic index was determined on 1000 cells with a count of the number of mitoses per 6000 cells for each experimental animal.

Mitotic Activity in the Rat Liver Upon Excision of Various Quantities of Tissue

Series	Time after operation (in hours)	Character of operation and quantity of excised liver tissue (in %)	Section of liver in which mitoses were counted	Number of mitoses in individual animals (per 6000 cells)										Average	Average mitotic index (in ‰)
				I	II	III	IV	V	VI	VII	VIII	IX	X		
I	25	Removal of distal section of left lateral lobe (2.7)	In left lobe close to wound surface	0	2	4	3	1	2	1	2	2	1	1,8	0,30
			In right lobe	0	1	4	6	0	1	4	2	0	1	1,9	0,33
II	25	Removal of distal sections from left lateral and central lobes (19)	In left lobe close to wound surface	4	7	11	17	13	18	39	10	217	11	34,7	5,8
			In right lobe	6	5	19	24	14	18	39	10	196	12	34,1	5,7
III	25	Total excision of left lateral lobe (23)	In right lobe	61	42	63	3	52	162	139	5	—	—	66	11
IV	25	Total excision of left lateral and central lobes (64)	In right lobe	443	214	99	96	685	486	40	54	618	23	276	46
V	48	Total excision of left lateral and central lobes (64)	In right lobe	229	75	65	115	98	170	126	86	194	144	130	21

RESULTS



Character of operative interference in various series of experiments. A) Schematic depiction of the arrangement of the rat liver lobes in the norm: 1) left lateral; 2) central; 3) right; 4) caudal. Schemes of the operations in various series: B) In I; C) in II; D) in III; E) in IV. The part of the liver removed is hatched, the place where the mitoses were counted is designated by a black square.

During the histological investigation of the regenerating liver, in all series of experiments we noted a uniform distribution of the dividing liver cells throughout the entire organ regardless of the character of the inflicted damage. We elicited a direct dependence between the degree of mitotic activity of the liver cells and the quantity of tissue removed: the more massive the trauma, the greater the number of cells that divided (see table).

The size of the wound surface did not have a substantial effect on the distribution of dividing cells or on their number. As we see from the table, in the I series of experiments where a negligible quantity of tissue was removed (2.7%) and the wound surface was small, the mitotic activty of the liver cells was extremely low (0.3 ‰). For practical purposes it differed little from that in the normal liver of rats of the same age [2, 15]. This fact is in agreement with the data of one of the works [13] where it was demonstrated that excision of less than 8% of the liver does not greatly affect either the number of its nuclei labeled with radioactive thymidine or the number of mitoses.

The number and distribution of mitoses in this series of experiments was equal in the injured and intact lobes of the liver (respectively 0.30 and 0.33 ‰).

In the II series of experiments where the mass of the excised parenchyma of the organ was 19%, the number of dividing liver cells was appreciably greater; the mitotic index was 5.7‰ ($P = 0.001$). Although the area of the wound surface in these experiments was appreciably greater than in the I series, this did not affect the distribution of the mitoses. In the injured left lobe, close to the wound surface the mitotic index was 5.8‰, in the intact right lobe, 5.7‰. It is evident that not the character of the wound (the presence of a wound surface) but the mass of the excised parenchyma of the organ is determinative for the level of the mitotic activity of the liver during its regeneration. This becomes more evident upon analysis of the number of mitoses in the liver of the animals of the III series of experiments, where the quantity of excised tissue was close to that in the II series of experiments (23%), but the wound surface was practically absent. The mitotic index in this series of experiments was even somewhat higher than in the preceding (11 ‰). We did not obtain an actual difference in the number of mitoses between the II and III series of experiments ($P = 0.2$).

It is necessary to note the appreciable individual variations in the number of mitoses of individual animals in the II and III series of experiments, which substantially affected the investigation of the general characteristics of liver regeneration.

In the IV series of experiments the mass of excised parenchyma comprise more than half the mass of the entire organ (64%) and the mitotic activity of the liver cells was the highest (46 ‰).

Upon removal of an appreciable quantity of liver tissue (V series of experiments) the high mitotic activity was retained for 48 h postoperation (21 ‰). At the same time it is necessary to point out that by the end of the second day it dropped. This drop was statistically close to reliable ($P = 0.08$).

In conclusion it should be pointed out that the proliferative reaction arising during liver regeneration after its considerable surgical damage encompasses, as a rule, the entire organ regardless of the character of its injury. Mitotically dividing cells are observed in the entire injured organ without a noticeable tendency for them to localize near the wound surface.

These data are in accord with our previous data obtained when investigating the liver at later periods of regeneration, and also with most works of other authors [1, 7, 8, 11]. We need also indicate that when the liver is wounded by the formation of a small opening in one of its lobes by a hollow punch (when the removed mass of the

organ is very small) or some other insignificant injuries, the proliferative reaction can be restricted only to the portion of the organ directly surrounding the focus of damage. This was repeatedly observed by us [7] and other investigators [3, 4]. However, upon removal of an appreciable quantity of liver tissue the reaction to injury changes. Regenerative hypertrophy [6]—a characteristic method of regeneration of most internal organs of vertebrates-is observed.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.