

REGENERATION OF THE LIVER
IN MICE OF DIFFERENT LINESL. D. Liozner, A. G. Babaeva, V. F. Sidorova,
and G. V. Kharlova

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The rate of regeneration of the liver after partial hepatectomy differs in mice of different lines. Proliferative activity in noninbred mice and also in mice of lines CC57Br and CBA begins to increase more rapidly (42 h after the operation) than in mice of lines C3H and C57Bl (48 h after operation). Delay in regeneration of the liver is also apparent in later observations. In C57Bl mice 7 days after the operation the weight of the liver was restored up to 68% of the control value, whereas in noninbred animals the weight of the organ was completely restored (101%). These differences in the regenerative power of the liver cannot be linked with the high or low incidence of spontaneous carcinoma in the lines.

The mammalian liver has good powers of regeneration and restoration of its initial mass [5]. Meanwhile, many years of experimental investigation in this field using animals sufficiently homogeneous with respect to certain characteristics (age, weight, and so on) have shown that considerable individual variations in the rate of regeneration, the level of mitotic activity, and so on exist [1-3, 5]. To reduce as far as possible the range of variations in such experiments, genetically homogeneous animals and, in particular, pure-line mice are used. However, since lines of mice are selected mainly in accordance with features (color, tendency to form tumors, etc.) which are unconnected with the power of regeneration, it has not yet been ascertained to what extent these lines are suitable for the experimental study of regeneration or whether their regenerative power differs from that of noninbred mice.

In the investigation described below the rate of regeneration of the liver was studied in mice of various lines.

EXPERIMENTAL METHOD

Male mice of lines C3H and CBA (with a high incidence of cancer), C57Bl, and CC57Br (with a low incidence of cancer) [4] and also noninbred mice were used in the experiment. Hepatectomy with the removal of two-thirds of the liver was performed on some animals of each group by the method of Higgins and Anderson, while the rest of the mice (9-15 in each group) served as the control and remained intact until the end of the experiment. The experimental and control animals were always sacrificed between 8 and 9.30 AM when mitotic activity is maximal, so that it was necessary to vary the time of the operation to some extent. Altogether four series of experiments, differing from each other in the length of the period of observation, were performed.

In Series I mice of lines C3H, C57Bl, CC57Br, and CBA and noninbred mice weighing 19-24 g were sacrificed 42 h after the operation.

In Series II mice of lines C3H and C57Bl and noninbred mice weighing 17-24 g were killed 40 and 44 h after the operation, and 4 h before sacrifice they were given an injection of demecolcine in order to determine whether the maximum of mitotic activity in the resected liver had been missed.

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TABLE 1. Statistics Relating to Regeneration of the Liver (weight and mitotic activity) in Mice of Different Lines

Time after operation	Noninbred mice		Mice of							
			C3H		C57Bl		CC57Br		CBA	
	wt. (in % of con- trol)	MI (in ‰)	wt. (in % of con- trol)	MI (in ‰)	wt. (in % of con- trol)	MI (in ‰)	wt. (in % of con- trol)	MI (in ‰)	wt. (in % of con- trol)	MI (in ‰)
42h	65	21 (13)	52	1,1 (10)	49	3,4 (8)	57	19,0 (12)	61	17,7 (15)
48h	60	31,3 (13)	44	31,6 (14)	50	24,9 (4)	—	—	—	—
7days	101	4,2 (20)	77,7	0,7 (12)	68,5	1,5 (11)	—	—	—	—

Note: Number of hepatectomized animals in which mitotic activity was determined is given in parenthesis. Results for mice sacrificed 40-44 h after the operation are not given in this table, for the conditions of this series of experiments differed from those of the rest.

In Series III noninbred mice and mice of lines C57Bl and C3H, weighing 19-25 g, were sacrificed 48 h after partial hepatectomy.

In Series IV three groups of noninbred mice and mice of lines C57Bl and C3H weighing 19-25 g were sacrificed 7 days after the operation.

After sacrifice all the animals were weighed. The liver was fixed in Carnoy's fluid and then weighed again in the fixed state.

Mitotic activity of the cells was expressed in promille after the number of mitoses in 4,000 cells from each animal had been counted. The degree of restoration of weight of the regenerating liver in the partially hepatectomized animals was determined by calculating the ratio between the weight of the liver in the experimental and control animals. These values were expressed as percentages. The numerical results were subjected to statistical analysis by the Fisher-Student method.

EXPERIMENTAL RESULTS

During the experiment it was found that mice of different lines react differently to the operative trauma. This was shown both in the behavior of the animals after the operation and in their survival rate. Noninbred mice and animals of lines CC57Br, CBA, and C3H tolerated the operation of partial hepatectomy satisfactorily. Soon after the operation they reacquired their normal reactivity and their survival rate was high (70% or more, Table 1). Animals of lines C57Bl behaved differently: as a result of the operation they were greatly weakened and the mortality rate among them was unexpectedly high (only 20% or, more rarely, 40-50% survived).

The mice of different lines also differed from each other substantially in the degree of restoration of weight of the regenerating liver. For example, 42 h after the operation of removal of 65% of the liver tissue the weight of the regenerating liver, expressed as a ratio to the weight of the organ in the corresponding control, was 65% in noninbred mice, 61% in CBA mice, 57% in CC57Br, 52% in C3H, and 49% in C57Bl. In animals sacrificed 48 h after the operation these differences were confirmed: In the noninbred mice the liver regenerated more rapidly than in the pure-line animals; the percentage restoration of weight of the organ was as follows: in noninbred mice 60, in C3H mice 44, and in C57Bl 50. These differences in the rate of regeneration of the liver were very conspicuous 7 days after the operation: In noninbred mice the weight of the liver in the experimental series was comparable with that in the control (101%), while in C57Bl and C3H mice it was 68.5 and 77.7% of the control respectively (the mice of the other lines were not investigated at this time).

Histological examination showed that the differences in the rate of restoration of the liver mass in the hepatectomized mice of the various lines were due primarily to differences in the degree of proliferative activity of the liver cells. Comparison of the mitotic index of the regenerating liver in the mice of the various lines gave the following results 42 h after the operation: in noninbred mice 21‰, in CC57Br mice 19‰, CBA 17.7‰, C3H 1.1‰, and C57Bl 3.4‰.

Counting the mitoses in the liver of the mice in the experiments of Series II showed that the low level of proliferative activity of the hepatocytes in the C3H and C57Bl mice was due to delay in cell division in these animals after operation.

The mice of Series II received injections of demecolcine 4 h before sacrifice, i.e., 36 and 40 h after the operation. This enabled the changes in the proliferative activity in their liver to be determined between 36 and 44 h after partial hepatectomy. The number of dividing liver cells in the mice of these lines was much smaller than in noninbred animals (the mitotic index in C3H and C57Bl mice was 1.4% , and in noninbred mice 22%).

In the mice with a more slowly regenerating liver (lines C3H and C57Bl) the level of proliferative activity of the liver cells was approximately the same as in the noninbred (with a more rapidly regenerating liver) animals 48 h after the operation only. In noninbred mice the mitotic index at this time was 31.3% , in C3H mice 31.6% , and in C57Bl mice 24.9% . However, after 7 days the mitotic activity of the liver cells in the C57Bl mice fell again (1.5%), although the weight of the organ was still far from being completely restored (68.5%). In noninbred mice, on the other hand, the mitotic activity in the liver was still high (4.2%), despite complete restoration of the initial weight of the organ (101%).

It can be concluded from the results of this investigation that the rate and character of regeneration of the liver (the rate of increase in weight of the organ and the proliferative activity of the liver cells) may differ even in animals (mice) of the same species, as the result of genotypic differences.

However, these differences cannot be linked with the high or low level of incidence of spontaneous carcinoma in the line concerned. Mice belonging to the same group in accordance with this feature, e.g., C57Bl and CC57Br (low incidence of carcinoma) differed in their regeneration response. The rate of regeneration also differed in mice of lines C3H and CBA, both with a high incidence of carcinoma. This fact must be taken into account when appropriate experiments are planned.

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