# MITOTIC ACTIVITY IN THE LIVER OF SEXUALLY MATURE MICE AT VARIOUS AGES

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Reparative regeneration of the liver takes place mainly by mitotic cell division. The mechanisms of the physiological regeneration of the liver and of its growth have not yet been explained. The results of experimental studies [9, 13, 15, 19, 20] of the postnatal growth of the mammalian liver show that the high level of mitotic activity of its cells falls rapidly between 30 and 40 days after birth. It remains uncertain, however, how long mitotic activity remains in the liver and how high its level stands when the animal attains sexual maturity. The answers to these questions are important to the understanding of the mechanisms of regeneration and growth of the liver. Data in the literature are mainly concerned with the mitotic activity of the liver in rats; the liver of mice has not been investigated so thoroughly from this aspect.

We have studied the level of mitotic activity in the liver of sexually mature mice of different ages, and also the dynamics of the changes in size of the liver cells during growth of the organ.

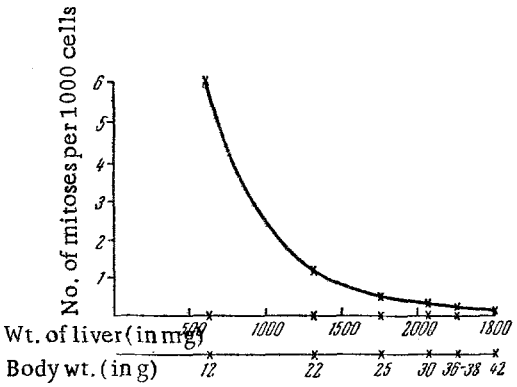
Mean Body Weight, Weight of Liver, Mitotic Activity, and Dimensions of Cells in Mice of Different Age Groups

| No. of animals | Body weight | Weight of liver | Relative weight of liver (in %) | Mitotic index (in %) | No. of animals in which mitoses were found | Area of liver cell (in $mm^2$) (×350) |
|---|---|---|---|---|---|---|
| 20 | 12 | 610 | 4.8 | 6.0 | 20 | 26.0 |
| 10 | 22 | 1300 | 5.8 | 1.2 | 10 | Not measured |
| 20 | 25 | 1750 | 6.4 | 0.5 | 15 | 29.1 |
| 20 | 30 | 2050 | 6.3 | 0.4 | 14 | 27.2 |
| 18 | 36-38 | 2249 | 6.1 | 0.2 | 11 | 33.5 |
| 18 | 39 | 2218 | 5.6 | 0.01 | 1 | 34.2 |
| 18 | 42 | 1800 | 4.7 | 0.02 | 2 | 31.6 |

* See results given in a previous paper [2].

## EXPERIMENTAL METHOD

Experiments were carried out on male and female mongrel albino mice of the following body weight: 12, 25, 30, 36, 37, 38, and 42 g. Each group consisted of 18-20 animals. The animals were sacrificed at 6 A.M., when the level of mitotic activity reaches its maximum [2]. The animals were sacrificed and the weight of the whole body and of the liver was determined. Paraffin-wax sections of the liver were cut to a thickness of 7 $\mu$ and stained with hematoxylin-eosin. The number of mitoses per 6000-7000 cells was counted. To measure the size of the liver cells, sections were cut in 10 mice from each age group by a special method [16], after which 150-200 cells from each animal was drawn with the aid of a drawing apparatus with a magnification of 350 times, and the area occupied by each liver cell was determined. The outlines of the individual cells were drawn on graph paper, cut out, and weighed on torsion scales. The weight of 1 $cm^2$ of paper was found, and hence the area of each individual cell was calculated.



Age changes in mitotic activity of liver cells in mice.

## EXPERIMENTAL RESULTS

It will be clear from the table that the body weight and weight of the liver of the albino mice continued to increase for a considerable time after the animals had attained sexual maturity (12-14 g). The mitotic activity of the liver cells fell with age. Both the number of mitoses in individual mice and the number of animals in which mitoses were found fell. The mitotic index in the mice with a mean weight of 12 g was 6%, 25 g – 0.5%, 30 g – 0.4%, 36-38 g – 0.2%, 39 g – 0.01%, and 42 g – 0.02% (see the figure).

The mitotic activity of the liver cells fell particularly during the period when the body weight of the mice rose from 12 to 22 g. The mitotic index at the end of this period was only one-sixth its value at the beginning.

It is interesting to note that in animals with a body weight of between 25 and 36 g, the mitotic index showed no significant changes, especially when the body weight rose from 25 to 30 g. This was a very important finding, for it provided evidence of the relative standardization of proliferative processes in the organ.

A sharp decrease in mitotic activity was observed in older mice with a body weight of 38-42 g. At this age both the absolute and relative weights of the liver fell. Not only the mitotic index, but also the dimensions of the cells showed a reduction, evidently associated with signs of senile atrophy of the organ.

The chief difficulty arising during discussion of these results is that the liver of the mouse, like that of the rat, continues to grow practically throughout life. Yet it is not known how this process takes place. Some writers claim that from a very early age of the animals the postnatal growth of the liver is entirely determined by an increase in the size of the cells as a result of the polyploidization of their nuclei [8, 17]. This view, however, is not shared by other authors [18].

Because of this it cannot be confidently stated to what the mitoses found in the liver of the adult animals, the growth of the organ, and its physiological regeneration may be attributed, or whether more than one of these factors operates at the same time. Whereas a high level of mitotic activity in young mice (with a body weight of 12-22 g) may be evoked by a combination of the processes of growth of the organ and its physiological regeneration, it is perfectly feasible that in adult animals, with a body weight of more than 25 g, mitoses may be directed towards renewal of the organ, for its growth at this age is brought about mainly by an increase in the size of the cells, and very little change takes place in the level of mitotic activity (see the table). The difference between the dimensions of the cells in animals with body weights of 25-30 and 36 g is statistically signficiant ($P = 0.01$). At the same time it cannot be ruled out that some of the mitoses in the liver of adult animals of this age may also be directed towards growth of the organ.

The sharp decrease in the mitotic activity of the liver cells in the older animals (body weight over 38 g) may be explained both by the cessation of growth of the organ and by a lowering of the general level of physiological regeneration in these animals [6, 7, 11]. Evidence that some of the mitoses may be directed towards renewal of the organ is given by the fact that in hypophysectomized animals mitoses are found, although in much smaller numbers than in control animals [3]. If it is accepted, however, that physiological regeneration of the liver of adult animals takes place by mitosis alone, this suggests that development of this process is extremely slow, for the mitotic index in adult animals is very low (mean value 0.3%).

In a previous investigation [2], forming part of an investigation of the diurnal rhythm of mitosis in the liver of mice weighing 22 g, we observed a high number of mitoses during the morning, from which we concluded that the level of the processes of physiological regeneration of the liver is higher than is generally accepted. However, the present findings, obtained in older animals, and also the results obtained by workers investigating the liver by means of the method of labeling with isotopes [5, 10, 12, 14], demonstrate that the replacement of the cells in the liver of adult animals is a somewhat rare process. It appears that other mechanisms of renewal are characteristic of the liver. In particular, several authors consider [1, 4] that the processes of physiological regeneration in the liver take place mainly by the development of polyploid cells. It is clear that further experimental investigation of the mechanisms of physiological regeneration and growth of the liver is required.

## SUMMARY

Mitotic activity was studied in hepatic cells of albino mice, weighing 12, 22, 25, 30, 36, 38, 39, and 42 g. The animals were killed at 6 A.M. (18-20 at a time). From 6 to 7 thousand cells were counted in the liver of each animal. The average number of mitoses was: in mice weighing 12 g—6%, 22 g—1.2%, 25-30 g—0.4-0.5%, 36-38 g—0.2%, 39-42 g—0.01-0.02%. With increasing age not only the number of mitoses in individual mice, but also the number of animals in which mitoses occur, decreased.


## LITERATURE CITED


1. V. Ya. Brodskii and A. A. Kushch, Doklady Akad. Nauk SSSR, 147, 3, 713 (1962).
2. L. D. Liozner and V. F. Sidorova, Byull. éksper. biol., 12, 93 (1959).
3. L. D. Liozner, N. S. Artem'eva, A. G. Babaeva, et al., Byull. éksper. biol., 8, 77 (1962).
4. G. K. Khrushchov and V. Ya. Brodskii, Uspekhi sovr. biol., 52, 2(5), 181 (1961).
5. J. Edwards and R. Klein, Am. J. Path., 38, p. 437 (1961).
6. R. Fry, S. Lesher, and H. Kohn, Am. J. Phsyiol., 201, p. 213 (1961).
7. B. Hellman and C. Hellerström, Acta path. microbiol. scand., 51, p. 347 (1961).
8. H. Helweg-Larsen, Ibid., Suppl. 92 (1952).
9. B. Jackson, Anat. Rec., 134, p. 365 (1959).
10. C. P. Leblond and B. E. Walker, Physiol. Rev., 36, p. 255 (1956).
11. S. Lesher, R. Fry, and H. Kohn, Gerontologia (Basel), 5, p. 176 (1961).
12. R. A. MacDonald, Arch. intern. Med., 107, p. 335 (1961).
13. M. McKellar, Am. J. Anat., 85, p. 263 (1949).
14. B. Messier and C. P. Leblond, Ibid., 106, p. 247 (1960).
15. R. Peters, Z. Naturforsch., Bd. 17b, S. 164 (1962).
16. M. H. Ross and J. M. Flaharty, Stain Technol., 35, p. 354 (1960).
17. U. Siess and H. Stegmann, Arch. Path. Anat., Bd. 318, S. 534 (1950).
18. C. Stevens, R. Daoust, and C. Leblond, J. biol. Chem., 202, p. 177 (1953).
19. H. Teir and K. Ravanti, Exp. Cell. Res., 5, p. 500 (1953).
20. E. G. White, J. Anat., 73, p. 365 (1939).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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.**