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MOVEMENT OF HEPATOCYTES ALONG THE HEPATIC TRABECULA DURING PHYSIOLOGICAL REGENERATION

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The distribution of mitoses among hepatocytes and of dying cells along the hepatic trabecula was determined in rats. The relative rate of movement of the hepatocytes along the trabecula was calculated from these distributions. The direction and velocity of movement of the hepatocytes along the hepatic trabecula were obtained by recording the shift of the peak of labeled cells one month after giving the rats six injections of thymidine-^{3}H.

KEY WORDS: *hepatic trabecula*; *movement of hepatocytes*; *physiological regeneration*.

The direction and velocity of movement of cells from zones of mitosis into zones of their death can be calculated from the distribution of mitoses and dying cells in the hepatic trabecula. If the length of the trabecula is stable, the number of dividing cells must be equal to the number of dying cells, and the velocity of movement of the cells from the zone of mitosis into the zone of death will depend on the mutual position of these zones. The velocity of movement of the cells will be greatest if special zones of dividing and dying hepatocytes are present along the length of the trabecula, but if these zones coincide, movement of the cells will fluctuate within the limits of the diameter of one cell.

The object of this investigation was to determine the distribution of mitoses and dying cells, and the direction and velocity of movement of the hepatocytes along the hepatic trabecula.

EXPERIMENTAL METHOD

Experiments were carried out on 12 male rats weighing 160-170 g. The plane along which the hepatocytes could move along the trabecula was determined from the arrangement of the metaphase plates relative to the axis of the trabecula, by means of an occular goniometer. These measurements were made on the liver of hepatectomized rats and the remaining investigations were performed on the liver of intact animals.

Complete karyolysis was used as the criterion of death of the hepatocytes [1, 2]. The distribution of mitoses and dying hepatocytes along the line (averaged for the number of

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TABLE 1. Distribution of Dividing and Dying Cells along Hepatic Trabecula, Velocity of Their Movements, and Duration of Stay of Hepatocytes in Each Position of the Trabecula

	No. of cells in trabecula (j)															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Distribution of mitoses	3	18	35	64	58	14	38	10	10	4	1	—	—	—	—	—
Distribution of dying cells	—	—	12	7	12	18	61	25	6	1	6	31	19	25	19	13
Difference: mitoses — death	3	18	23	57	46	−4	−23	−15	4	3	−5	−31	−19	−25	−19	−13
Cumulative total: mitosis — death	3	21	44	101	147	143	120	105	109	112	107	76	57	32	13	0
Velocity of movement	1.3	8.1	1.9	4.5	6.64	6.4	5.4	4.7	4.9	5.0	4.6	3.4	2.58	1.4	5.87	0
Position/days	10^{-3}	10^{-3}	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-2}	10^{-3}	
Duration of stay, days	738	123	50.3	22	15	15.5	18.5	21	20.3	19.8	20	29	38.8	69	170	∞

Note. Velocity and duration of stay of hepatocytes calculated for mean period of cell cycle (T = 138 days). Periods of cell cycle calculated on basis of values of mean diurnal mitotic index (MI = 0.3 °/₀₀) and density of distribution of mitoses, determined experimentally for each position of the trabecula.

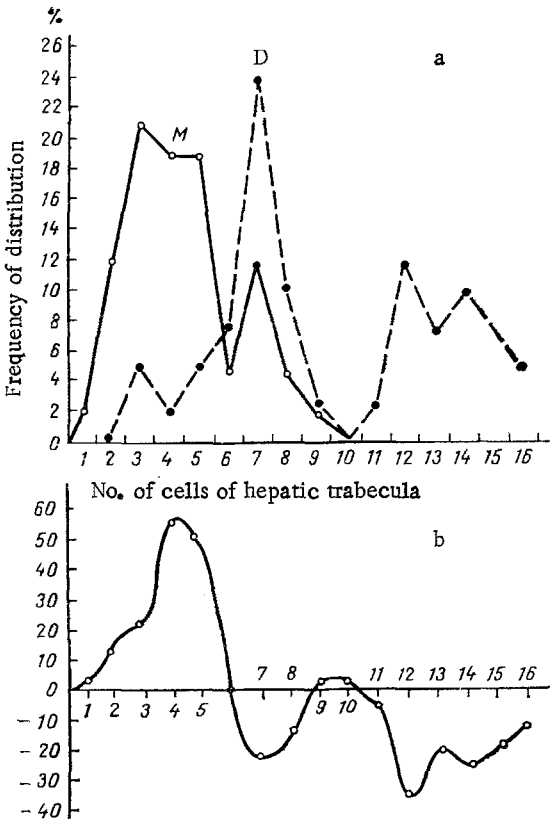

Fig. 1. Distribution of mitoses and dying hepatocytes (a) and of difference between numbers of dividing and dying cells (b) along hepatic trabecula of a rat. M) mitoses; D) dying hepatocytes. Abscissa, cell positions in hepatic trabecula in direction from triad to central vein; ordinate: a) number of mitoses and dying hepatocytes (in % of total number of cells), b) difference between number of mitoses and of dying hepatocytes.

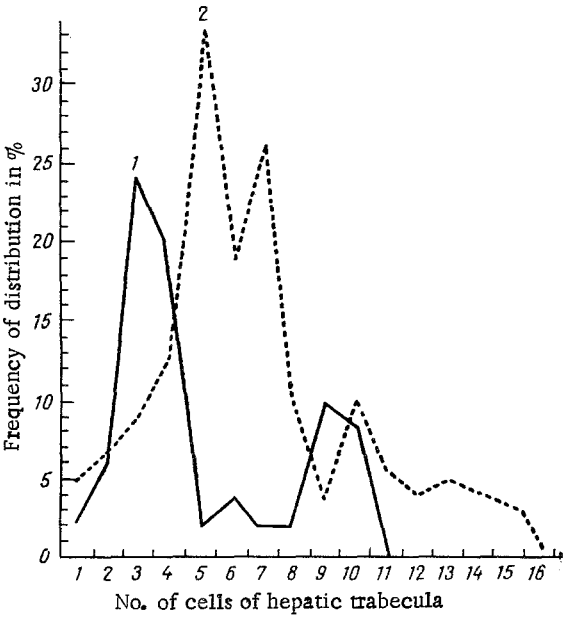

Fig. 2. Distribution of labeled hepatocytes along hepatic trabecula 1 h after injection of thymidine-^{3}H (1) and 1 month after last injection of thymidine-^{3}H (2). Abscissa, cell position in hepatic trabecula in direction from triad toward central vein; ordinate, percentage of labeled cells.

cells [4]) of the trabecula was established from the frequency with which they were found in histological preparations 11 μ thick stained with hematoxylin and eosin.

The direction and velocity of movement of the hepatocytes along the hepatic trabecula were determined by recording the shift of the peaks of labeled cells during comparison of two distributions; the first distribution was obtained 1 h after a single injection of thymidine-^{3}H into two rats in a dose of 0.5 μCi/g body weight, the second 1 month after six injections of thymidine-^{3}H into two rats, with the same dose each time, at intervals of 8 h.

The absolute velocity of movement of the hepatocytes in the trabecula was determined from the difference between the distributions of mitoses and of dying hepatocytes. The reciprocal of velocity represents the duration of stay of the hepatocytes in a particular position in the trabecula.

EXPERIMENTAL RESULTS

To determine the direction of movement of the hepatocytes in the hepatic trabecula the frequency with which the axis of the metaphase plate was oriented in a certain direction relative to the axis of the hepatic trabecula was calculated in a group of 206 mitoses. The following results were obtained: A perpendicular position (90°) was observed in 53% of all cases, an angle of 67° in 13% of cases, 45° in 14%, and 22° in 9% of observation; a parallel arrangement (0°) was found in 11% of cases. This indicates that if the hepatocytes moved, motion of the cells was mainly along the axis of the hepatic trabecula.

In group of 255 trabeculae containing cells with mitoses and of 73 trabeculae with anuclear cells, distributions of mitoses and of dying hepatocytes in the trabecula were obtained (Table 1).

It follows from Fig. 1a that mitoses predominated at the beginning of the trabecula as far as the sixth position, and elsewhere in the trabecula the majority of cells were dying. It will be clear from the distribution of the difference between dividing and dying cells that at the beginning of the trabecula the difference was positive, i.e., cell division predominated over death; conversely, in the remaining two-thirds of the trabecula the increase

in the number of dividing cells was counterbalanced by death of the hepatocytes (Fig. 1b).

It follows from the above remarks that the only direction of free movement of the cells was along the axis of the trabecula from left to right, i.e., from the triad toward the central vein.

The cumulative total of differences between mitoses and dying hepatocytes constitutes the number of cells arriving from the left from a given position (j) in the hepatic trabecula. If the number of cells obtained are divided by the mean period of the cells cycle for the trabecula, the calculated velocity of movement of the cells is obtained for that particular position of the cells in the trabecula. The velocities are given in the sixth row in Table 1. From the beginning of the trabecula the velocity of the movements of the hepatocytes increases until position 5 and thereafter it decreases gradually to zero in the last cell position in the trabecula. The velocity of movement of the hepatocytes along the trabecula was determined experimentally by recording the shift in the distribution of labeled cells (Fig. 2).

As Fig. 2 shows, 1 month after the beginning of injection of thymidine-^{3}H the maxima of the number of labeled cells were displaced along the trabecula toward the central vein through two or three positions; meanwhile both peaks become wider and split up. The widening of the peaks and their displacement were due to division of the labeled and unlabeled cells over a period of 1 month.

The minimum of the number of labeled cells moved from the fifth to the ninth position in the hepatic trabecula and the cells shifted to the right through 4 to 5 cell positions, i.e., twice as far as the cells moved in the zone of the maximum; this was due to the cumulative contribution of the dividing cells of the whole zone of reproduction (from the first to the fifth cells of the hepatic trabecula) to the velocity of movement of the hepatocytes and to the convergence of the trabeculae toward the center of the lobule.

The duration of stay of the hepatocytes in each position of the hepatic trabecula is shown in the seventh row of Table 1, except for the numbers for positions 1 and 16 in the hepatic trabecula. For position 1 this number does not stand for movement of the first cell into the second position but it is the mean period between divisions of the first cell. In position 16 infinity means the low probability of cell division and high probability of cell death in this position.

It was thus shown theoretically and experimentally that during physiological regeneration of the rat liver hepatocytes move from the zones of mitosis to the zone of death with unequal velocity, which increases from position 2 to position 5 of the hepatic trabecula and then decreases to zero in position 16 of the trabecula.

This and a previous investigation [4] give formal proof (in the form of the presence of zones of mitosis and zones of death of cells and movement of the cells from the zone of mitosis into the zone of death [3]) that the liver is a self-renewing organ.

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