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Lipid Distribution in Rat Liver After Partial Hepatectomy.

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(Introduced by H. E. Jordan.)
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It is commonly observed that the liver remnant becomes fatty during the first 24 hours following partial hepatectomy.[1, 2] Following this period, gross examination indicates a disappearance of the fatty liver. The present communication is a study of the lipid constituents of the livers of rats following partial hepatectomy.

Inbred male rats, 60 to 70 days of age, of Wistar stock were used as experimental animals. Between 65 and 70% of the total liver was removed according to the procedure of Higgins and Anderson.[3] These animals were fed a stock diet (Bal Ra) and were allowed food up to the time they were killed.

Analyses for total fatty acids, phospholipids, free and total cholesterol and iodine numbers were begun immediately after the liver was removed under ether anesthesia. During the first few days after partial hepatectomy, the entire liver remnant was used for analysis. After appreciable hypertrophy had begun, wedges were removed from different portions of the liver for analysis. Total fatty acids were determined after saponification.[4] Cholesterol determinations were carried out according to the method of Schoenheimer and Sperry.[4, 5] The phospholipid fatty acids, obtained after saponification, were determined by the oxidation procedure of Bloor.[6] The iodine numbers of total and phospholipid fatty acids were done according to the procedure outlined by Yasuda.[7] Total solids were obtained after heating tissue for 48 hours at 105°C.

Total Fatty Acids. On the first day after partial hepatectomy the fatty acid concentration of the wet tissue increases from the mean control value of 3.5 to 8.4%. There is a marked decrease in con-

1 Brues, A. M., Drury, D. R., and Brues, M. C., *Arch. Path.*, 1936, **22**, 658.

2 MacKay, E. M., and Carne, H. O., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 131.

3 Higgins, G. M., and Anderson, R. M., *Arch. Path.*, 1931, **12**, 186.

4 Hortenstine, J. C., Chanutin, A., and Ludewig, S., *J. Biol. Chem.*, 1938, **125**, 455.

5 Schoenheimer, R., and Sperry, W. M., *J. Biol. Chem.*, 1934, **106**, 745.

6 Bloor, W. R., *J. Biol. Chem.*, 1929, **82**, 273.

7 Yasuda. M., *J. Biol. Chem.*, 1931-32, **94**, 401.

TABLE I.
Average Liver Lipid Values of Partially Hepatectomized Rats.
Results are calculated on a dry fat-free weight basis in g per 100 g.

Days after operation	Neutral fat	Phospholipid	Total Cholesterol	Free Cholesterol	Esterified Cholesterol	Total Lipid	Phospholipid to neutral fat ratio
Controls	4.9	11.5	1.09	0.86	0.23	17.5	66:28
1	23.6 (380)*	17.5 (52)	1.68 (54)	1.10 (28)	0.58 (152)	42.8 (145)	41:55
2	15.8 (223)	14.3 (24)	1.60 (47)	1.15 (34)	0.45 (52)	31.7 (81)	45:50
3	7.2 (47)	13.1 (14)	1.31 (20)	1.09 (27)	0.22 (—4)	21.7 (24)	57:33
4	7.3 (49)	12.4 (8)	1.22 (12)	1.10 (28)	0.12 (—48)	20.9 (16)	59:35
7	5.5 (12)	12.3 (7)	1.13 (4)	0.97 (13)	0.16 (—30)	18.9 (8)	65:29

± Calculated on basis of total lipids.
* Values in parentheses represent percentage changes.

centration which approaches the control values on the third day. The mean iodine numbers of the fatty acids vary between 119 and 126 during the 7-day experimental period and statistical analysis shows no significant difference between any of the values obtained on different days.

Neutral Fat. The concentration of neutral fat in the dry fat-free liver is calculated from the available data (Table I). The greatest percentage increase of all the lipid constituents is recorded for the neutral fat during the first and second days after operation. On the seventh day the concentration approaches the control value.

Phospholipids. The phospholipid concentration in the dry fat-free liver (Table I) increases after operation but decreases slowly and does not reach the control level on the seventh day. There is a progressive increase in the iodine number from 125 to 159 during the experimental period.

Cholesterol. The concentration of free cholesterol in the dry fat-free liver (Table I) is increased slightly and remains elevated during the experimental period. The esterified cholesterol increases markedly during the first day and decreases below the control value on the third, fourth and seventh days.

Phospholipid-neutral Fat Ratio. Theis[8] has noted that the phospholipid-neutral fat ratio of the normal liver remains constant but changes markedly in the degenerating organ. These results have been confirmed, since the greatest deviation of this ratio from the normal occurs during the first 24 hours after operation. This change in ratio appears to be due to the proportionately large increase in the neutral fat concentration. After this time this ratio gradually increases and returns to the normal value on the seventh day.

Total Solids. The total solids of the dry fat-free liver decrease from the mean control value of 25.4% to 20.0 and 19.9%, respectively, on the first and second day after operation. There is a gradual increase on the third, fourth and seventh days to 21.0, 22.4, and 24.5%, respectively.

Brues and coworkers[1] have shown that there is no mitotic activity in the liver remnant during the first 24 hours after partial hepatectomy. During this period the liver increases in size between 50 and 60%. Much of this increase in weight must be due to the increased lipid deposition since the water and glycogen[9] content decreases at this time. It is thus evident that cellular inactivity under these experimental conditions is accompanied by a marked deposition

8 Theis, E. R., *J. Biol. Chem.*, 1929, **82**, 327.

9 Stone, C. S., *Arch. Surg.*, 1935, **31**, 662.

of lipids, particularly neutral fats. At the end of the first 48 hours, mitotic activity increases markedly and the liver remnant more than doubles its weight.[1] At this time the lipid concentration decreases appreciably but the water and glycogen are still low. Hence the increase in liver weight is probably due to new cells still containing appreciable amounts of lipid and a decreased water content. Further liver hypertrophy is associated with increased water and decreased lipid contents.

The capacity of the liver to increase in size after partial hepatectomy can be compared with sarcomatous[10] and embryonic tissue.[11] The degree of unsaturation of phospholipid fatty acids of tumor tissue in the rat was found to be low by Haven.[12] In the regenerating liver the iodine number of the phospholipid fatty acids was found to be higher than normal. The amount of phospholipid in tumors of various types has been shown to be large by a number of workers[13] but the increase in the regenerating liver is small and not appreciable. Thus it can be seen that two rapidly growing tissues such as the liver and tumors show definite differences in their phospholipid content.

Summary. During the first 24 hours after partial hepatectomy, the liver remnant becomes fatty due particularly to the deposition of large amounts of neutral fat and to increases in the phospholipid and cholesterol fractions. On the second and third days there is an appreciably sharp decrease in the concentration of all the lipid constituents. After 7 days the lipid values are all slightly above the respective control values excepting the combined cholesterol which is decreased.

The iodine numbers of the total fatty acids remain constant but those of the phospholipids increase progressively during the experimental period.

Liver injury produced by partial hepatectomy results in a marked disturbance in lipid metabolism. Regeneration of this tissue is accompanied by a return to normal values.

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10 Carrel, A., and Ebeling, A. H., *J. Exp. Med.*, 1928, **48**, 105.

11 Murray, H. A., *J. Gen. Physiol.*, 1926, **9**, 29.

12 Haven, F., *J. Biol. Chem.*, 1935, **109**, XLII.

13 Haven, F., *J. Biol. Chem.*, 1937, **118**, III.