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Site of Vitamin A Storage in the Liver.

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While it is generally accepted that the liver is the major depot for storage of Vitamin A in the body, the exact site of deposition of this substance has not been clearly defined. After administration of large doses of Vitamin A to animals, accumulation of a stainable lipoid in the Kupffer cells has been reported.[1, 2] However, others have seen little change in the Kupffer cells, and one report[3] describes lipoid deposition in the hepatic cells under these conditions. Popper's studies with the fluorescence microscope[4] suggest that Vitamin A is stored in both hepatic and Kupffer cells. In some cases of cirrhosis of the liver the Vitamin A stores are much depleted, and it has been pointed out[5] that this depletion is most marked in cases where active degeneration of liver cells is present, although histological evidence of Kupffer cell damage has not been noted. Lasch[6, 7] has provided the best evidence that the storage occurs in the Kupffer cells. He found decreased storage of administered Vitamin A in the livers of rabbit and guinea pigs after blockading the reticuloendothelial cells with a mixture of thorotrast, trypan red, trypan blue, and ferric oxide. He noted further that severe poisoning with phosphorus, which damaged the hepatic cells, caused no decrease in the ability of the liver to store this vitamin.

A study of 3 human cases which had passed through an episode of massive necrosis of the liver has yielded evidence that the hepatic parenchymal cells are not essential for Vitamin A storage. In each of these cases large amounts of liver substance had been converted to vascular connective tissue in which there were many small bile ducts but no demonstrable hepatic cells in histological sections. Each liver contained large, quite sharply demarcated nodules of normally arranged liver tissue with moderate enlargement of the hepatic cells

1 Domagk, G., and Dobeneck, P., *Virch. Arch.*, 1935, **290**, 385.
2 Strauss, K., *Beitr. z. path. Anat., u. z. allg. Path.*, 1934, **94**, 345.
3 v. Drigalski, W., and Laubmann, W., *Kl. Wchnschr.*, 1933, **12**, 1171.
4 Popper, H., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 133.
5 Cox, A., *Am. J. Path.*, 1939, **15**, 647.
6 Lasch, F., *Kl. Wchnschr.*, 1935, **14**, 1070.
7 Lasch, F., and Roller, D., *Kl. Wchnschr.*, 1936, **15**, 1636.

TABLE I.
Vitamin A Content of Liver.

	Interval following initial jaundice	Altered liver tissue	Intact liver tissue
Case 1 (7C-631)	3 weeks	+++	++
Case 2 (8C-527)	3 "	+++	++
Case 3 (9C-415)	6 mo.	++++	++

which showed no sign of injury. The appearance in each case indicated that the injurious agent had ceased acting before the patient died.

It was possible grossly to select portions of each liver which were made up largely of tissue free from hepatic cells, and to compare the Vitamin A content with that of nodules containing liver cells from the same liver. The Vitamin A determinations were made by using the Carr-Price antimony trichloride reaction on chloroform extracts of weighed samples of fresh liver dehydrated by grinding with anhydrous sodium sulphate. The blue color which developed was compared with permanent color standards which had been calibrated against a Vitamin A solution of known strength.

The quantity of Vitamin A recorded as +++ is estimated at about 250 international units per gram of liver, approximately the average amount in livers obtained at autopsy. ++ indicates half of this amount and ++++ refers to twice this value.

Although rough, these measurements show conclusively that in liver tissue from which the hepatic cells had been removed by previous massive injury (in one case the disease was related to cinchophen administration) the Vitamin A store was greater than in the portion containing hepatic cells, and therefore must have been stored elsewhere than in these cells. It is difficult to identify Kupffer cells in histological sections of the abnormal liver tissue because of the lack of any relationship to hepatic cell cords, and frequent absence of any other specific characteristics. However, in such regions there are scattered large spindle-shaped cells which contain fine fatty granules and particles of brown iron containing pigment. These are presumably Kupffer cells, and it is probable that the Vitamin A in the livers was stored in such cells. This conclusion implies that agents which produce massive liver necrosis may cause relatively little injury to Kupffer cells.

The greater concentration of Vitamin A in the abnormal regions than in the intact liver tissue may be due to concentration of Kupffer cells in the injured areas from which hepatic cells had been removed, and to hypertrophy and hyperplasia of the hepatic cells in the un-

damaged portions, thus separating the Kupffer cells and decreasing their number per unit weight of tissue.

The character of the injury in portal cirrhosis of the liver is quite different from that which has been described above, and it is possible that accompanying injury to the Kupffer cells results in the very low Vitamin A stores in this disease. However, the cause may be an insufficient supply of the vitamin, either because of impaired conversion of carotin in injured liver cells or inadequate intake of Vitamin A in patients with this disease.

Summary. In 3 cases of healed massive necrosis of the liver Vitamin A was more abundant in the parts of the liver from which hepatic cells had disappeared than in those where these cells had not been destroyed. Presumably it was stored in the Kupffer cells, which had been spared by the agent which produced the necrosis.

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Trypanocidal Action of 3-Nitrobenzoic Acid and Some Derivatives.

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Various sulfonamide derivatives prepared in this laboratory have been tested against *Trypanosome equiperdum* with negative results. 4-Nitrobenzoic acid which has a slight antibacterial action[1, 2] was found to have a trace of trypanocidal activity. Investigation of the isomers revealed that the meta derivative showed increased activity against trypanosomes, although without effect upon bacteria; 2-nitrobenzoic was inactive against both types of infection. A review of the literature revealed that Morgenroth found 3-hydroxybenzoic acid to possess some trypanocidal action.[3]

A more detailed study of 3-nitrobenzoic acid and some derivatives was undertaken. Mice were inoculated intraperitoneally with a quantity of trypanosomes that would cause death in 3 to 5 days. Therapy was usually begun on the second day after inoculation. The dosage

1 Mayer, R. L., and Oechslin, C., *Compt. rend. Soc. Biol.*, 1939, **130**, 211.

2 Rosenthal, S. M., and Bauer, H., *U. S. Pub. Health Rep.*, 1939, **54**, 1317.

3 Morgenroth, J., and Rosenthal, F., *Berlin. Klin. Wschnschr.*, 1912, **49**, 134.