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Production and Apparent Prevention of a Dietary Liver Cirrhosis in Rats.

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Lillie, Daft and Sebrell,[1] among others in the past few years, have reported liver cirrhosis in animals given special diets. György and Goldblatt[2] reported liver injury as a regular complication in rats on a diet containing 10% casein and 22% fat. Necrosis or cirrhosis or both was observed from the 100th to 150th experimental days. They state "Addition of from 10 to 20 mg of choline daily reduced the incidence and severity of the liver injury but not to a great extent." In a later paper György, Poling, and Goldblatt[3] refer to this work and state "These changes can be prevented to a large extent by the addition of casein to the diet, but this is accomplished more effectively by the combined oral administration of cystine and choline." Blumberg and McCollum[4] reported that liver cirrhosis in rats on a diet containing 10% casein and 55 or 70% fat, occurring in 125 to 150 days on the lower fat intake and in 100 to 140 days on the higher, could be prevented by including 10 mg per gram of choline in the diet and could be slowed but not prevented by methionine at 25 mg per rat per day. Earle and Victor[5] reported liver cirrhosis in 14 to 27 days in rats given a diet containing 10% cystine. They also reported cirrhosis in one of a number of rats given a diet containing 5% cystine.

We wish to report at this time the consistent and fairly rapid production of liver cirrhosis in rats on a low protein, low fat diet with added cystine and the apparent prevention of the cirrhosis by choline, methionine and casein, singly or in combination.

Rats were placed at weaning or shortly thereafter on our diet No. 545. consisting of leached casein 4%, cystine 0.5%, cod liver oil 2%, Wesson Oil 3%, Osborne and Mendel salt mixture 4%, and

1 Lillie, R. D., Daft, F. S., and Sebrell, W. H., *Pub. Health Rep.*, 1941, **56**, 1255.

2 György, P., and Goldblatt, H., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 492.

3 György, P., Poling, E. C., and Goldblatt, H., PROC. SOC. EXP. BIOL. AND MED., 1941, **47**, 41.

4 Blumberg, H., and McCollum, E. V., *Science*, 1941, **93**, 598.

5 Earle, D. P., and Victor, J., *J. Exp. Med.*, 1941, **73**, 161.

cornstarch 86.5%. They were given approximately 20% alcohol in place of drinking water and daily supplements of 100 μg of thiamin, 50 of riboflavin, 20 of pyridoxine, 50 of calcium pantothenate and 1 mg of nicotinic acid. Of 20 rats examined to date, all died between the 46th and 111th experimental days (average 83) and all showed moderate to marked liver cirrhosis on gross and histological examination. In a preventive experiment, 40 litter mates were given 20 mg of choline daily in the supplement or 0.7% of methionine in the diet or the dietary casein was raised from 4% to 30% at the expense of the cornstarch. Combinations of these changes were also employed. None of the rats sacrificed at the end of 90 or 140 experimental days or dying during the experiment showed any evidence of liver cirrhosis. Most of them are alive and apparently healthy, some after an experimental period as long as 6 months. The experiment is being continued to make certain that this represents a true prevention rather than a slowing of the cirrhotic process.

Since rats given diet number 545 and water but no alcohol have died with an indistinguishable liver pathology, it appears that the diet is here the essential factor.

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Production of Cytoplasmic Inclusions in Liver Cells of Rats Injected with Certain Proteins.

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In connection with studies on the effect of intravenous injection of rats with hemolytic streptococcus extract toxin[1] * (toxic serum extracts of hemolytic streptococci), we discovered that under certain conditions large cytoplasmic bodies appear within the liver cells. On further study, we found that other proteins also caused the development of similar bodies. This preliminary paper deals with the methods used for the production of this lesion and its description and is based on a study of 850 rats.

In Table I are presented: first, the substances that cause the lesion

1 Weld, J. T., *J. Exp. Med.*, 1934, **59**, 83.

* In this work the streptococcus extract toxin is referred to as "streptococcus toxin."