# CIRRHOSIS OF THE LIVER CAUSED BY EXCESS DIETARY CYSTINE

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Recently there has been considerable interest in the metabolism of cystine, homocystine, and methionine, and in the biological relationship of these amino acids to choline (1–6). This paper reports certain pathological changes produced by excess dietary cystine in albino rats.

Blum (7), in 1904, found that in dogs the intravenous administration of 1 gm. of cystine per kilo of body weight was nephrotoxic. In 1925, Lignac (8) reported that subcutaneous injections of cystine suspensions caused severe injury to the renal tubules of mice. He was able to find cystine crystals in the kidneys, liver, and spleen. In the same year, during the course of studies on the toxic effect of amino acids, Newburgh and Marsh (9) found similar lesions in dogs after intravenous injections of large doses of cystine. Later, a number of workers (10–12) studied the effects of the oral administration of excess cystine. Here again, renal damage was found, consisting of severe injury and necrosis of the cortical tubules, associated with hemorrhage into the renal capsule and parenchyma. Recently, György and Goldblatt (13), have stressed the similarity of the renal lesions caused by excess cystine feeding and by choline deficiency in the diet.

Changes in the liver of rats fed cystine have also been described by Curtis and Newburgh (14), Sullivan, Hess, and Sebrell (15), and Lillie (16). On 10 to 20 per cent cystine intralobular hemorrhagic necrosis of the liver occurred with death in 2 to 13 days. Rats fed smaller quantities of cystine showed fat accumulation in the liver and a much longer life span. The rats fed 10 to 20 per cent cystine also had more advanced renal lesions. Control rats on the 4 per cent casein diet showed only moderate fatty infiltrations in the liver.

The hepatic lesion found in young albino rats fed a choline deficient diet, is characterized by a massive fatty infiltration (5, 13). No necrosis, hemorrhage, or cirrhosis has been reported, although du Vigneaud (17) found evidence of cellular damage other than the fatty infiltration.

## *Materials and Methods*

Male albino rats of the Sherman stock, weighing between 60 and 70 gm., were housed in cages with raised wire mesh floors. Fresh water was supplied every day and the

various diets offered *ad lib.* No attempt to measure food intake was made, but it was noted that the animals fed the 10 per cent cystine ate very little of their diets. All other groups consumed their food readily.

The basal diet consisted of casein (vitamin-free) 5, lard 20, sucrose 61, brewer's yeast (Mead, Johnson) 5, cod liver oil 5, and salt mixture (18) 4. One group of controls received 10 per cent instead of 5 per cent casein. Cystine, obtained from Eastman Kodak Company, was given in a concentration of 5 per cent or 10 per cent of the diet and replaced an equivalent amount of sucrose. The McCollum stock diet (19) was used as indicated throughout the experiments.

The animals were observed daily, and when ill, more frequently. Weights were recorded at least 3 times a week. Except for rats 4, 16, 34, 42, 44, and 45, which died during the night, autopsy was performed within an hour of death. On sacrifice, autopsy was done immediately. A final body weight was recorded, the liver was rapidly dissected out, blotted gently, and weighed. The liver weight was recorded as per cent of normal.[1] Tissues were preserved in both Zenker's and 10 per cent formalin solutions and sections were stained with hematoxylin and eosin, and in many instances with Sudan III to determine the presence of fat.

The fat content of the liver was determined by extraction with absolute ether in the Soxhlet apparatus for 24 hours, followed by evaporation of the ether and determination of the weight of the ether-soluble substances. Prior to this procedure, the sample of liver was placed in the freezing compartment of a refrigerator for 2 days, and then dried over calcium chloride in a high vacuum desiccator. Fat values are expressed as per cent of the fresh, wet liver substance.

Because selenium is known to cause cirrhosis (20), and because there is a possibility of selenium being present in the cystine used, analyses by the method of Horn (21) were carried out. 5 gm. of cystine gave a negative result to this reaction. The sensitivity of this test in this laboratory is such that 2 parts of selenium per million parts of the 10 per cent cystine diet and 1 part per million of the 5 per cent cystine diet would have been detected. The authors wish to express their thanks to Dr. M. I. Smith and Dr. B. B. Westfall of the National Institute of Health at Washington, D. C., who kindly examined a sample of cystine used in these experiments and found that no selenium was present. The significance of these results is discussed later.

## RESULTS

The essential findings with respect to diet, body weight, outcome, liver weight, liver fat, and histopathology are recorded in Table I. The histopathological findings were tabulated according to the schema appended to Table I, and were made by one of us while unaware of which diets the various animals had been fed.

*Effects of 10 Per Cent Cystine Fed to Albino Rats.*—A total of 26 rats were placed on the 10 per cent cystine diet.

*1. Course.*—All but two, Nos. 15 and 42, of the 26 rats receiving 10 per cent dietary cystine lost weight. As noted above, these animals ate poorly. At no time throughout

[1] Weight of liver × 100 ÷ 0.0431 × body weight (22).

the experiment was diarrhea, clinical jaundice, or gross hematuria noted. After 3 or 4 days of cystine feeding, the rats became quite lethargic and then cool to touch. Just before death, which was frequently very sudden, the respirations in many became extremely rapid. Those rats that survived the acute phase were sluggish and failed to grow, but the coats remained normal and there were no specific clinical findings.

Five rats were returned to the stock diet, four, Nos. 9, 11, 15, and 38, after 4 days, and one, No. 2, after 32 days of cystine feeding. Of these five, four, Nos. 2, 9, 11, and 38, became almost moribund. After 2 or 3 days on the stock diet all appeared normal and had gained weight.

In addition, two rats, Nos. 46 and 47, were given the stock diet on several days, scattered throughout the course of 2 and 4 weeks of 10 per cent cystine feeding. Although these rats did not gain weight, they appeared well and survived until sacrificed.

*2. Mortality.*—Of nineteen rats on the 10 per cent cystine diet, and that were not sacrificed or changed to the stock diet, nine or 47 per cent died on the 3rd or 4th day. Of sixteen rats (excluding those sacrificed) on continuous 10 per cent cystine feeding, only five or 31 per cent survived more than 9 days.

*3. Pathological Findings.*—The liver weight of the rat sacrificed after 1 day of 10 per cent cystine feeding was far above normal, but microscopically this liver and the liver of the animal sacrificed after 2 days showed no striking changes. The fat content of the livers was normal.

Six of the livers of seven rats which died or were sacrificed between the 3rd and 9th days, were enlarged. In the gross, all but one of the livers of the rats of this group were hemorrhagic. Microscopically, most striking and consistent feature of these livers was the hemorrhage and necrosis in the portal areas. The cytoplasm of the necrotic cells was deeply acidophilic and hyalinized, and the nuclei shrunken and pyknotic. Extravasated red blood cells were crowded about the necrotic cells (see Fig. 1, rat 40). In some instances, instead of hemorrhage about the necrotic cells, the sinusoids were engorged with blood. Many of the areas of necrosis were infiltrated by polymorphonuclear leucocytes. The liver cells of the central areas had fine and coarse vacuoles, many, but not all of which stained with Sudan III. Chemically, normal quantities of fat were observed in five of seven of the livers in this group. Two livers had slightly elevated fat concentrations of 5.3 and 7.9 per cent respectively. The lungs of many of these rats were very congested and several were frankly hemorrhagic. No lesions were found in the stomach, kidneys, suprarenal, spleen, and testes.

Six of the rats were on the diet containing 10 per cent cystine for 14 to 27 days. Of these, five had cirrhosis of the liver varying in severity. This lesion was characterized by periportal fibrosis, bile duct proliferation, and distortion of the lobular architecture by interlacing bands of fibrous connective tissue. Many thin walled, engorged veins and capillaries were present in the areas of scarring. This is illustrated by Fig. 2, rat 25. In several of these livers, necrosis, hemorrhage, and leucocytic infiltration occurred about the scarred areas. These latter features were not nearly as severe as they were in the rats on the diet for the shorter 3 to 4 day period. However, hypertrophy and vacuolization of the liver cells were much more striking in the rats on the longer period of cystine feeding. The liver fat content of the three rats of this group examined was between 13.1 and 19.1 per cent. The testes of several of these rats showed decreased spermatogenesis. No changes were observed in the other organs.

Five rats were on the 10 per cent cystine diet and then changed to the stock diet.

TABLE I

| Rat No. | Type of diet | Time on diet | Body weight | | Outcome | Liver weight, per cent normal* | Liver fat content† | Histopathology | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Start | End | | | | Hemorrhage | Necrosis | Cirrhosis | Bile duct proliferation | Vacuolization | Cell hypertrophy | Mitoses per L.P.F. | Leucocytic infiltration | |
| | | *days* | *gm.* | *gm.* | | *per cent* | *per cent* | | | | | | | | | |
| 36 | 10 % cystine | 1 | 64 | 59 | S‡ | 168 | 3.9 | | | | | ± | + | | | |
| 39 | " " " | 2 | 64 | 59 | S | 99 | 2.5 | | | | | | | | | |
| 32 | " " " | 3 | 66 | 52 | S | 127 | 2.5 | | ± | | ± | ++ | +++ | | | |
| 8 | " " " | 3 | 66 | 58 | D‡ | 159 | 3.1 | +++ | +++ | | | + | | | ± | |
| 29 | " " " | 3 | 62 | 59 | D | 125 | 4.1 | ± | ± | | | + | | | ± | |
| 16 | " " " | 3 | 65 | ? | D | — | — | +++ | + | | | + | | | | |
| 34 | " " " | 3 | 65 | ? | D | — | — | — | — | — | — | — | — | — | — | Postmortem autolysis |
| 31 | " " " | 4 | 62 | 53 | D | 140 | 3.8 | +++ | ++ | | | | | | ± | Hyaline bodies |
| 37 | " " " | 4 | 63 | 53 | D | 126 | 4.2 | +++ | +++ | | | | | | + | |
| 40 | " " " | 4 | 67 | 57 | D | 158 | 5.3 | ++ | + | | | ++ | | | ± | Fat stain ++ |
| 44 | " " " | 4 | 63 | 57 | D | — | — | ++++ | — | — | — | — | — | — | — | No section. In the gross |
| 45 | " " " | 4 | 61 | 58 | D | — | — | +++ | +++ | | | ± | | | | |
| 26 | " " " | 6 | 66 | 57 | S | 140 | 7.9 | | | | | +++ | +++ | 1/5 | | Fat stain ++ |
| 33 | " " " | 9 | 62 | 48 | D | 106 | 2.5 | ± | ± | | | | + | | ± | Fat stain neg. |
| 42 | " " " | 9 | 61 | 62 | D | — | — | ++ | + | | | ++++ | | | ± | Fat stain ++++ |
| 46 | " " " | 14§ | 70 | 62 | S | — | — | ++ | + | + | + | ++ | ++ | | ± | |
| 35 | " " " | 17 | 66 | 48 | S | 128 | 19.1 | | | | ± | +++ | +++ | 3/5 | | Fat stain +++ |
| 43 | " " " | 19 | 67 | 55 | S | 179 | 13.9 | FT | | ++ | ++ | +++ | +++ | | | |
| 25 | " " " | 22 | 67 | 55 | D | — | — | FT | ± | +++ | +++ | +++ | +++ | | | Fat stain ++ |
| 4 | " " " | 27 | 62 | 45 | D | — | — | | ± | ± | ± | | + | | + | Fat stain neg. |
| 47 | " " " | 27§ | 72 | 69 | S | 125 | 13.1 | | ± | +++ | +++ | +++ | +++ | | | Fat stain +++ |
| 9 | " " " | 4 | 62 | 59 | M | | | | | | | | | | | |
| | Stock | 5 | 59 | 86 | S | 104 | 2.0 | | | | | ++ | ++ | | | Fat stain ++ |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 38 | 10 % cystine | 4 | 59 | 49 | M | | | | | | | | | | | |
| | Stock | 10 | 49 | 87 | S | 126 | 3.2 | | | ++ | ++ | ++ | +++ | 10/3 | | Hemosiderin |
| 15 | 10 % cystine | 4 | 65 | 65 | | | | | | | | | | | | |
| | Stock | 12 | 65 | 120 | S | 127 | 3.0 | | + | | | + | ++ | 4/7 | | |
| 11 | 10 % cystine | 4 | 61 | 55 | M | | | | | | | | | | | |
| | Stock | 29 | 55 | 198 | S | 132 | 3.6 | | | | | +++ | +++ | 3/11 | | Congested |
| 2 | 10 % cystine | 32 | 62 | 55 | M | | | | | | | | | | | |
| | Stock | 8 | 55 | 98 | S | 148 | 3.3 | | | | | ++ | ++++ | 20/4 | | |
| 24 | 5 % cystine | 3 | 58 | 60 | S | 170 | 4.8 | | | | | ++++ | ++++ | 2/6 | | Fat + (hydropic) |
| 30 | " " " | 5 | 62 | 60 | S | 118 | 17.3 | | | | | ++++ | ++++ | 2/7 | | |

*Hemorrhage.*—FT, very slight hemorrhage in scarred areas. ±, less than ¼ of liver hemorrhagic. +, ¼ of liver hemorrhagic. ++, ½ of liver hemorrhagic. +++, ¾ of liver hemorrhagic. ++++, liver completely hemorrhagic.

*Necrosis.*—FT, a few scattered necrotic cells. ±, definite portal necrosis but less than ¼ of liver involved. +, ¼ of liver cells necrotic. ++, ½ liver cells necrotic. +++, ¾ liver cells necrotic.

*Cirrhosis.*—±, definite scarring but less than ¼ portal areas involved. +, ¼ portal areas scarred. ++, ½ portal areas scarred. +++, ¾ portal areas scarred. ++++, all portal areas scarred.

*Bile Duct Proliferation.*—± to ++++ as under cirrhosis.

*Vacuolization and Cell Hypertrophy.*—± to ++++ attempts to weigh both the number of cells involved and also the degree of involvement of the cells.

*Mitoses.*—The first figure represents the number of mitoses seen in the number of low powered fields examined as stated by the second figure.

*Polymorphonuclear Leucocytic Infiltration.*—±, a few of the necrotic areas involved. +, most of the necrotic areas involved.

— = not examined.

Blank space = negative finding.

* Liver weight ÷ 0.0431 × body weight (22). The livers of five control rats of the same strain on stock diet varied between 98 and 114 per cent of normal.

† The fat content of the livers of five control rats of the same strain varied between 3.4 and 4.5 per cent.

‡ S = sacrificed. D = died. M = moribund.

§ Includes, scattered throughout the period of cystine feeding, several short periods of stock diet to prolong life.

TABLE I—*Concluded*

| Rat No. | Type of diet | Time on diet | Body weight | | Outcome | Liver weight, per cent normal* | Liver fat content† | Histopathology | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Start | End | | | | Hemorrhage | Necrosis | Cirrhosis | Bile duct proliferation | Vacuolization | Cell hypertrophy | Mitoses per L.P.F. | Leucocytic infiltration | |
| | | *days* | *gm.* | *gm.* | | *per cent* | *per cent* | | | | | | | | | |
| 41 | 5 % cystine | 7 | 58 | 54 | S | 92 | — | | | | | +++ | | | | Fat stain +++ |
| 10 | " " " | 8 | 69 | 75 | S | 102 | 17.4 | | | | | +++ | + | 1/8 | | |
| 18 | " " " | 15 | 69 | 73 | S | 166 | 29.1 | ++ | ++ | | + | ++++ | +++ | | + | Fat stain ++++. Hyaline bodies. Pericholangiolitis. Icteric index 100 |
| 23 | " " " | 20 | 62 | 44 | M, S | 118 | 7.6 | | | | | ++ | +++ | | | Fat stain ++. Yellow pigment in mononuclear W.B.C. Icteric index 12. Hyaline bodies |
| 6 | " " " | 28 | 70 | 90 | S | 206 | 42.3 | | ++ | | | ++++ | ++++ | | | Fat stain ++++ |
| 21 | " " " | 40 | 69 | 121 | S | 120 | 7.6 | ± | ± | ++ | ++ | +++ | ++ | 2/4 | ± | Fat stain +++. Hyaline bodies |
| 14 | " " " | 43 | 70 | 140 | S | 140 | 15.6 | | ± | | | ++++ | ++++ | | | Hyaline bodies. Yellow pigment in mononuclear W.B.C. |
| 5 | " " " | 18 | 68 | 82 | | | | | | | | | | | | |
| | Stock | 12 | 82 | 104 | S | 118 | 3.8 | | FT | | | ++ | +++ | 3/6 | | |
| 19 | 5 % cystine | 18 | 61 | 70 | | | | | | | | | | | | |
| | Stock | 22 | 70 | 196 | S | 114 | 2.9 | | | | | ++ | +++ | | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 28 | 5 % casein | 3 | 61 | 61 | S | 145 | 5.5 | | | | ++++ | ++++ | 1/10 | | |
| 22 | " " " | 9 | 64 | 56 | S | 136 | 7.3 | | | | | ++ | | | |
| 20 | " " " | 29 | 69 | 73 | S | 135 | 8.2 | | | | ++++ | +++ | 2/10 | | |
| 17 | " " " | 40 | 65 | 61 | S | 114 | 12.3 | | | | ++ | ++++ | | | |
| 27 | " " " | 12 | 68 | 56 | | | | | | | | | | | |
| | Stock | 26 | 56 | 205 | S | 104 | 2.2 | | | | ++ | +++ | | | |
| 12 | 10 % casein | 6 | 58 | 59 | S | 118 | 4.2 | | | | +++ | +++ | | | |
| 13 | " " " | 10 | 70 | 67 | S | 114 | 6.5 | | | | +++ | +++ | | | |
| 1 | " " " | 25 | 68 | 125 | S | 125 | 13.3 | FT | | | ++++ | ++++ | 4/4 | Fat stain ++ | |
| 7 | " " " | 35 | 64 | 178 | S | 98 | 5.9 | | | | +++ | +++ | | | |
| 3 | " " " | 10 | 62 | 62 | | | | | | | | | | | |
| | Stock | 25 | 62 | 170 | S | 98 | 3.2 | | | | + | +++ | | | |

Four of these were on the cystine diet for 4 days and then sacrificed 5 days to 4 weeks after the stock diet feeding was begun. One was on the cystine diet for 32 days and then on the stock diet for 8 days. All showed hypertrophy and vacuolization of the liver cells, although the fat content was normal. Those on the stock diet longer than a week showed signs of liver cell regeneration, evidenced by large numbers of mitotic figures. Cirrhosis of the liver was present in one, No. 38. That hemorrhage had occurred in this liver was indicated by the presence of hemosiderin in the scar tissue. All other organs were normal, except for immature testes in rat 2.

*Effects of 5 Per Cent Cystine Fed to Albino Rats.*—Eleven animals were placed on a diet containing 5 per cent cystine.

*1. Course.*—During the 1st week there was a slight loss of weight, regained during the 2nd week. Thereafter, there was a slow but steady weight gain and all the animals appeared well, except for rat 23, that lost weight steadily and became moribund on the 20th day, when it was sacrificed. Two animals were placed on the stock diet after 18 days of 5 per cent cystine feeding.

*2. Pathological Findings.*—Four animals were sacrificed during the first 8 days. Their liver cells were markedly vacuolated and often hypertrophied. The fat content of these livers was elevated. Mitotic figures were present in three of the livers, but were not abundant.

The livers of the five rats sacrificed after 2 to 6 weeks of 5 per cent cystine feeding showed a high fat content, and hypertrophy and vacuolization of the cells. Necrosis and intracellular hyaline bodies were present in 4. In 3 there were hemosiderin laden mononuclear cells arranged in clumps about the portal areas. Hemorrhage occurred in two, and cirrhosis in one of this group. The sera of rats 18 and 23 showed an icteric index of 100 and 12 respectively. In the former there were acute pericholangitis and bile plugs in the liver cell canaliculi.

The kidneys of rat 23 were the only ones showing any abnormality. This lesion is very similar to that described previously by many workers as the result of cystine poisoning or of choline deficiency. It was characterized by hemorrhage into the capsule and interstitial tissue of the cortex, necrosis of the tubules in the cortex, and many casts in tubules. The testes of this animal were immature, while those of the other animals of this group were normal.

Two animals were changed from the 5 per cent cystine to the stock diet. The livers were normal, except for moderate vacuolization and hypertrophy of the hepatic cells, even after 3 weeks of stock diet (rat 19). Mitotic figures were noted in rat 5. The liver fat content was normal in both instances.

## *Control Experiments*

There were four animals on the 5 per cent and four animals on the 10 per cent casein control diets. The livers of these rats showed cellular hypertrophy and fatty infiltration, associated with slight to moderate increases in the fat content. Occasional mitotic figures were seen. In the liver of one of these rats (No. 1), a few scattered necrotic cells were noted. No periportal hemorrhagic necrosis, cirrhosis, or proliferating bile ducts were seen. One rat from each of the control groups was subsequently changed to the stock diet. The livers of both showed some cellular hypertrophy and vacuolization.

## DISCUSSION

The present studies confirm previous reports of severe liver damage and fatty infiltration resulting from excess dietary cystine. In addition, the present experiments show that cirrhosis develops on more prolonged cystine feeding. The acute lesion consists of a hemorrhagic necrosis which shows a considerable tendency to localize in the portal area. This bears a striking resemblance to the hepatic lesion of eclampsia (Fig. 1). The only other methods by which this type of lesion has been produced experimentally, have been by feeding selenium to rats or by applying Goldblatt clamps to the renal arteries of pregnant dogs and rabbits (23).

Following the hemorrhage and necrosis, connective tissue and bile duct proliferation, as part of the repair process, lead to portal cirrhosis. Cirrhosis of the liver with bile duct proliferation occurred in 5 of 6 animals on the 10 per cent cystine diet for more than 14 days. It was also found in 1 of 2 rats on the 5 per cent cystine diet for more than 40 days.

The livers of all rats that were changed from the cystine diet to the stock diet showed hypertrophy and vacuolization of the cells. Mitotic figures were greatly increased in number. In spite of this apparent liver cell regeneration, in one instance there was a definite portal cirrhosis.

Cirrhosis of the liver caused by excess dietary cystine is unlike that produced by poisons such as carbon tetrachloride, chloroform, or arsenic. However, there are many similarities in the histopathogenesis of the hepatic lesions resulting from excess dietary cystine and those found in selenosis. In both, the acute or earliest lesion consists of a periportal hemorrhagic necrosis while cirrhosis develops later. Thus it was important to be certain that selenium was not a factor in the present experiment. As described under Methods, the cystine used in these experiments was found to contain no selenium. According to Smith (24), as little as 10 parts per million of selenium in a low protein, low fat diet produces cirrhosis in the albino rats of an age group comparable to this series. However, the first death in Smith's series of 22 rats occurred in 20 days, while in the present series it is to be stressed that 69 per cent of the rats on the 10 per cent cystine diet were dead by the 10th day, many dying on the 3rd or 4th day. Furthermore, when 10 parts per million of selenium was fed in a low protein, high fat (41 per cent) diet, the only pathological findings in the livers of 21 rats, 18 of which survived 120 days, was midzonal fatty degeneration in the cells, with many mitotic figures. The fat content of the diet in the present experiment was 25 per cent. From these considerations it is most unlikely that selenium is a factor in this experiment.

Other types of hepatic damage by dietary means have recently been reported. György and Goldblatt (25), found in the livers of rats on a diet deficient in the vitamin B complex and supplemented by $B_1$, $B_6$, and riboflavin, changes characterized by fatty degeneration, focal and massive necrosis, hyperemia, and hemorrhage. This differs from the cystine lesion in that it is central in distribution, resembling acute yellow atrophy. Rich and Hamilton (26) described a portal cirrhosis of the liver, with practically no necrosis and no hemorrhage, occurring in rabbits on a yeast deficient diet. Connor and Chaikoff (27), reported very fatty livers in dogs that received a high fat diet and large doses of alcohol. Four of sixteen animals on this régime showed portal cirrhosis. Later, these workers (28), reported cirrhosis of the liver in dogs on a high fat diet alone. In this case, however, the scarring was diffuse rather than portal in distribution.

Renal lesions in albino rats resulting from excess cystine have been described by many workers, and it is difficult to explain why only one rat in this series of 30 presented abnormal kidneys. Addis, MacKay, and MacKay (29), however, found no renal lesion in young rats after prolonged feeding of 1 per cent cystine in a diet containing 17.3 per cent protein. Longwell, Hill, and Lewis (30), after feeding 0.3 to 0.6 per cent cystine to young albino rats, noted only renal hypertrophy after the larger dose of cystine. Cox and Hudson (31) were able to prevent the hemorrhagic renal lesion in albino rats resulting from 0.3 per cent cystine in the diet by incorporating 20 per cent yeast in the diet. They also observed considerable variation in this reaction to cystine among different strains of rats.

Although the diet employed in these experiments was low in protein and high in fat, recent unpublished data indicate that severe liver damage also results from 10 per cent cystine fed in a (*a*) low fat, low protein diet, (*b*) low fat, high protein diet, (*c*) low fat, low protein, high yeast diet, and (*d*) McCollum stock diet.

## CONCLUSIONS

1. Cystine fed to young albino rats as 10 per cent of the diet resulted in: (*a*) Portal hemorrhagic necrosis, resembling eclampsia, within 3 or 4 days. (*b*) A high mortality rate. (*c*) Fatty infiltration of hepatic cells in all rats surviving the initial acute lesion. (*d*) Cirrhosis of the liver in rats surviving more than 2 weeks.

2. 5 per cent dietary cystine produced marked fatty infiltration of the liver, followed by portal hemorrhagic necrosis. Cirrhosis was present in one of the two rats on the diet for 6 weeks.

3. The livers of rats fed 5 or 10 per cent cystine diets followed by the

McCollum stock diet, showed evidence of residual cellular damage, and of regeneration as shown by mitotic figures.

4. In this series of 30 rats on excess dietary cystine, a renal lesion was found in only one case.

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## EXPLANATION OF PLATE 8

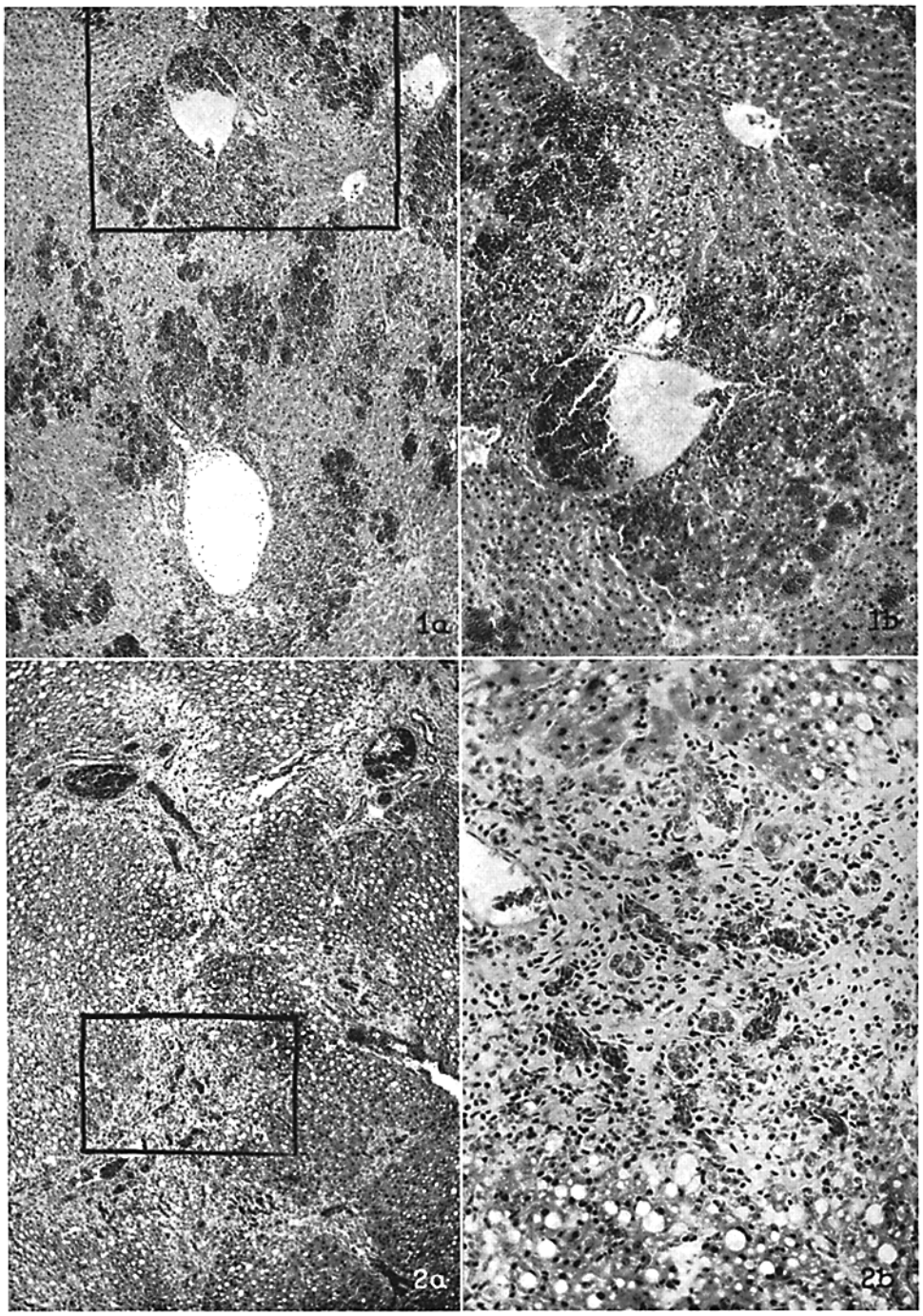
Hematoxylin and eosin stain.

FIG. 1 *a*. Hemorrhage, sinusoidol engorgement, and necrosis about portal areas of liver with hydropic vacuolization of cytoplasm of hepatic cells. Rat 40 after 4 days of 10 per cent cystine feeding. × 60.

FIG. 1 *b*. Greater magnification of area outlined in Fig. 1 *a*. × 100.

FIG. 2 *a*. Cirrhosis of the liver. Periportal fibrosis with bile duct proliferation and engorged capillaries in the scar tissue. The liver cells are slightly hypertrophied and filled with fat vacuoles. Rat 25 after 22 days of 10 per cent cystine feeding. × 60.

FIG. 2 *b*. Greater magnification of area outlined in Fig. 2 *a*. × 200.




(Earle and Victor: Cystine cirrhosis of liver)