THIOURACIL IN THE PREVENTION OF EXPERIMENTAL DIETARY CIRRHOSIS OF LIVER[1]

IN the light of recent extensive studies on animals, the ratio $\frac{\text{Methionine}}{\text{Cystine}}$ may be considered as the leading etiologic dietary factor in the prevention or production of liver cirrhosis.[2] Increased intake of methionine has a beneficial effect, whereas greater relative supply of cystine accelerates the appearance of cirrhotic changes in the liver of rats. In all these experiments the amount of both methionine and cystine in the diet is kept within physiological limits. The injury caused by cystine can be overcome not only by methionine, but by choline as well.

The prominent part played by the sulfur-containing amino acids, methionine and cystine, in the pathogenesis of hepatic cirrhosis, stimulated the investigation of the properties of other organic sulfur compounds.

In preliminary investigations, carried out in 1942, thiourea was given to rats in doses of 50 mg daily as supplement to a cirrhosis-producing diet containing Casein (SMACO) 8, Crisco 38, sucrose 48, salt mixture 4, cod liver oil 2, with the daily addition of thiamine (20 γ), riboflavin (25 γ), pyridoxine (20 γ) and Ca. pantothenate (100 γ). Thiourea proved to be poisonous, with death within 24 hours[3]—in a large number of the experimental animals. In many of the surviving rats the food intake remained low with rapidly progressive loss in weight. In view of these complications no definite conclusions could be reached, although the observations at autopsy in rats that survived 100 to 150 days seemed to indicate a distinct prophylactic effect of thiourea on liver cirrhosis.

With the recognition of thiourea and similar compounds, such as thiouracil, as specific drugs which interfere with the formation of thyroxine in the thyroid gland,[4] their possible relation to hepatic injury required further study. It is well known that in man lesions of the liver are common in hyperthyroid conditions. Conversely, it could be anticipated that lowering of the thyroid function achieved by thiourea, thiouracil and similar compounds might have a beneficial effect on the liver, perhaps owing to the decreased metabolic rate, including the metabolism of methionine.

Two sets—14 each—of adult male rats were put on the following diet: Casein (SMACO) 8, Crisco 38, sucrose 50, salt mixture 4, with 0.1 per cent. thiouracil in one group and no thiouracil in the other. Vitamins were given as supplements: thiamine (20γ), riboflavin (25 γ), pyridoxine (20 γ), Ca. Pantothenate (100 γ) daily and three drops of percomorph oil with 5 mg of mixed tocopherols (Distillation Products) weekly. In addition each animal in both groups received 50 mg of cystine daily with the purpose of accelerating and aggravating the cirrhotic changes in the liver. As customary, the experimental period was 150 days and those rats that survived were then killed. The final diagnosis of hepatic injury was based, without exception, on microscopic examination. Minor but definite cirrhotic changes were given the connotation of one +, whereas more severe cirrhosis was defined as ++ to ++++, with proper consideration for its varying degree in different lobes.

From the tabulation of all the pertinent data collected (Table 1) it becomes evident that admixture

TABLE 1

Group (Each 14 animals)	Weight loss > 50 gm	Weight loss < 50 gm	No weight loss	Dead before 150 days	Killed at 150 days	Fluids in serous cavities	Cirrhosis 0	Cirrhosis +	Cirrhosis ++ to ++++
A. Without thiouracil	9	3	2	12	2	5	1	3	10
B. With thiouracil	5	1	8	2	12	..	9	4	1

of thiouracil to the basic cirrhosis-producing synthetic diet exerts a marked preventive effect, manifesting itself not only in much lower incidence and in milder degree of cirrhosis, but also in absence of serous effusions in the peritoneal, pleural and pericardial cavities, in better survival rate and in more satisfactory weight curves. The thyroid glands in all rats of group B showed, in the gross and microscopically, the typical picture of hypertrophy and hyperplasia caused by thiouracil.[5]

The beneficial effect of thiouracil in these experiments could not be explained by major differences in food intake. Beginning with the fourth experimental week the food intake was measured in 5 to 6 animals in each group. The tabulation on page 452 gives the daily averages (in gram) per week.

The beneficial effect of thiouracil (0.1 per cent. in the diet) on the prevention of cirrhosis of the liver and concurrently on the general well-being of the

[1] This investigation was aided by a grant from Wyeth Incorporated.

[2] See literature, P. György, *Am. Jour. Clin. Path.*, 14: 67, 1944.

[3] See also J. B. Mackenzie and C. G. Mackenzie, *Proc. Soc. Exp. Biol. and Med.*, 54: 34, 1943.

[4] J. B. Mackenzie, C. G. Mackenzie and E. V. MacCollum, SCIENCE, 94: 518, 1941; C. G. Mackenzie and J. B. Mackenzie, *Endocrinology*, 32: 185, 1943; E. B. Astwood, J. Sullivan, A. Bissell and R. Tyzlowitz, *Endocrinology*, 32: 201, 1943; E. B. Astwood, *Jour. Am. Med. Asn.*, 122: 78, 1943; R. H. Williams and G. W. Bissell, *New England Jour. Med.*, 229: 97, 1943.

[5] C. G. Mackenzie and J. B. Mackenzie; E. B. Astwood, J. Sullivan, A. Bissell and R. Tyzlowitz: *cf.* 3 lc.

Group A (No thiouracil)

Rat 40*: 6.6 – 8.2 – 7.4 – 7.3 – 7.3 – 7.0 – 6.7 – 7.7 – 6.5 – 5.9 – 5.5 – 4.8 – 4.2 – 2.6†
Rat 43*: 8.3 – 9.7 – 9.4 – 9.2 – 8.5 – 7.5 – 6.3 – 9.2 – 2.9†
Rat 44*: 9.0 – 11.2 – 11.7 – 12.2 – 10.8 – 9.7 – 7.0 – 9.4 – 7.6 – 6.3 – 7.0 – 6.0†
Rat 45*: 8.6 – 10.4 – 10.0 – 8.1 – 9.0 – 8.3 – 7.3 – 10.2 – 8.0 – 6.0 – 6.2 – 5.1 – 5.1 – 4.8 – 4.1 – 3.4 – 0.7†
Rat 53*: 5.2 – 6.9 – 6.6 – 5.9 – 6.3 – 6.3 – 5.4 – 6.4 – 5.3 – 1.4 – 4.4 – 4.4 – 5.5 – 2.7 – 2.3 – 2.0†
Rat 68*: 6.3 – 7.4 – 7.4 – 6.7 – 6.4 – 7.6 – 6.5 – 7.7 – 6.4 – 7.0 – 7.4 – 6.9 – 8.4 – 6.0 – 5.2 – 6.3 – 6.5†

* Cirrhosis.

Group B (With thiouracil)

Rat 55**: 8.8 – 7.8 – 6.6 – 5.6 – 5.8 – 6.5 – 6.2 – 6.6 – 6.7 – 6.3 – 7.1 – 7.4 – 7.9 – 7.5 – 7.3 – 7.1 – 7.4†
Rat 59‡: 6.1 – 5.7 – 7.0 – 6.8 – 6.6 – 8.0 – 5.7 – 7.6 – 6.2 – 6.1 – 5.9 – 5.6 – 6.4 – 7.5 – 5.8 – 6.3 – 7.7†
Rat 60‡: 7.2 – 6.9 – 6.6 – 7.0 – 6.6 – 4.9 – 4.5 – 7.5 – 6.7 – 6.0 – 5.7 – 5.2 – 5.9 – 6.7 – 5.8 – 6.6 – 6.1†
Rat 63‡: 6.6 – 6.1 – 6.4 – 6.3 – 5.9 – 6.0 – 4.7 – 8.0 – 6.2 – 6.1 – 6.5 – 6.4 – 6.0 – 6.1 – 7.4 – 7.9 – 8.1†
Rat 64‡: 6.6 – 7.2 – 7.0 – 5.1 – 5.5 – 6.3 – 5.7 – 6.4 – 5.9 – 6.5 – 5.5 – 5.5 – 5.5 – 6.4 – 6.5 – 7.7 – 8.6†

** Mild cirrhosis.
‡ No cirrhosis.

Average daily food intake: Group A: 6.7 gm. Group B: 6.5 gm.

animals kept on a severe cirrhosis-producing regime is in good accord with the protective action of sulfanilamide against the hepatic cirrhosis due to chronic poisoning with carbon tetrachloride.[6] Both sulfanilamide and thiouracil inhibit the formation of thyroxine in the thyroid gland[5] and their effect on the liver might be based on this common denominator. Methionine protects the liver not only from purely dietary (trophopatic)[7] but also from postnecrotic (toxipathic)[7] cirrhosis, such as is caused, for instance, by carbon tetrachloride.[8] It can be assumed that the possible saving effect of lowered metabolic rate on methionine may, therefore, manifest itself not only in trophopathic but also in toxipathic cirrhosis.

The clinical implications of the above observations are obvious: Thiouracil presents itself as a supporting measure in the treatment of cirrhosis in combination with a diet rich in protein and methionine. The high incidence of injurious manifestations following thiouracil therapy does not militate against its use in cirrhosis for which condition any possible improvement in prognosis, even if only on account of prevention of progress of the disease, would represent a distinct advantage. Constant clinical observation, with repeated blood counts (leukopenia), is indispensable. It may be surmised that jaundice, seen in very few cases as a toxic complication of thiouracil medication in the clinic, is more the expression of allergic reaction than direct hepatic injury. How far these experiments on animals will prove to be valid in therapeutic clinical studies, only experience will teach.

Conclusions. Thiouracil mixed to a cirrhosis-producing synthetic diet in amount of 0.1 per cent. has a preventive effect on the production of cirrhosis in rats.

PAUL GYÖRGY

DEPARTMENT OF PEDIATRICS,
SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA

HARRY GOLDBLATT

DEPARTMENT OF PATHOLOGY,
SCHOOL OF MEDICINE,
WESTERN RESERVE UNIVERSITY

SCIENTIFIC APPARATUS AND LABORATORY METHODS

THE APPLICATION OF GEOPHYSICAL OSCILLOGRAPHS TO MULTIPLE RECORDINGS IN PHYSIOLOGY

THE simultaneous recordings of several physiological phenomena is facilitated by the use of appropriate pick-up units that convert the events into electrical signals which are capable of actuating galvanometers, oscillographs, inkwriters or other recording devices. When a number of phenomena such as blood pressure, respiration, blood flow, body temperature, the activity of the heart, the activity of nerve fibers, the contraction of muscles, etc., are to be accurately and simultaneously recorded, severe instrumental difficulties arise because of the variety of pick-up units that are required for the recording of these several phenomena. The ideal recorder should be compact, permanently aligned, sensitive; yet rugged and simple to operate. Under these conditions atten-

[6] J. C. Forbes, B. E. Leach and G. Z. Williams, *Proc. Soc. Exp. Biol. and Med.*, 51: 47, 1942.
[7] H. P. Himsworth and L. E. Glynn, *Lancet*, I: 457, 1944.
[8] P. György, J. Seifter and R. M. Tomarelli. Unpublished experiment.