

tyrosine molecule abolished the constrictor action entirely.

The conclusion drawn from these findings is that constriction of the blood vessels of the

rabbit's ear is dependent to a large degree upon traces of epinephrine and tyrosine-containing compounds of special configuration.

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### Prevention of Experimental Dietary Hepatic Cirrhosis by Goitrogenic Substances.

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In previous observations<sup>1</sup> thiouracil, and to some extent thiourea, exerted a beneficial effect in the prevention of dietary cirrhosis of the liver in rats. In animals receiving thiourea the food intake was generally very low and their weights showed a rapidly progressive decline. In contrast, the general well being of rats fed the same basal ration mixed with thiouracil (0.1% in the diet) remained undisturbed. The weight losses sustained were smaller than in the control animals without any appreciable difference in the average food intake in the two groups.

The beneficial effect of thiourea and thiouracil in the prevention of experimental dietary cirrhosis has been related to their effect on thyroid function, specifically to the decreased metabolic rate including the metabolism of protein. Decreased turnover of proteins pertains also to that of their constituents, including methionine, which is one of the key substances in the pathogenesis of dietary hepatic injury.<sup>2</sup>

It is difficult to furnish direct proof for the correctness of this assumption. The demonstration of strict parallelism between goitrogenic activity and preventive effect on hepatic cirrhosis may serve as indirect circumstantial evidence. The superior effect of thiouracil over thiourea is in good accord with these

considerations. In this connection it seemed advisable to include propyl-thiouracil and aminothiazole in these investigations. Propyl-thiouracil is at present probably the most effective goitrogenic agent available. Aminothiazole, when first used, was reported to be very effective in the treatment of hyperthyroid conditions.<sup>3</sup> However, pharmacological<sup>4</sup> and more recent clinical studies<sup>5</sup> are at variance with this conclusion and support the view that aminothiazole is less effective and more toxic than propyl-thiouracil or even thiouracil.

*Experimental.* During the course of our studies extending over several years it became evident that even without any change in the basic composition of the experimental cirrhosis-producing diet the results, such as incidence and severity of cirrhosis, food intake, weight changes, and survival time, may vary at various times. These variations—admittedly within narrow limits—are probably due to changes in the composition of the fat used (perhaps in addition to obscure climatic influ-

<sup>3</sup> Perrault, M., and Bovet, D., *Annales d'Endocrinologie*, 1945, **5**, 86; *Lancet*, 1946, **1**, 731; Bovet, D., Bablet, J., and Fournel, J., *Ann. de l'Inst. Pasteur*, 1946, **72**, 105.

<sup>4</sup> Astwood, E. B., Bissell, A., and Hughes, A. M., *Endocrinology*, 1945, **36**, 456.

<sup>5</sup> Morgans, M. E., *Lancet*, 1947, **1**, 519; Williams, R. H., *Arch. Int. Med.*, 1947, **80**, 11; McConnell, J. S., Frost, J. W., Wilber, R. W., and Rose, E., *Am. J. Med. Sc.*, in press.

<sup>1</sup> György, P., and Goldblatt, H., *Science*, 1945, **102**, 451.

<sup>2</sup> See literature. György, P., *Am. J. Clin. Path.*, 1944, **14**, 67.

ences), all other experimental conditions being fairly strictly controlled. These observations necessitate the liberal use of controls in experiments in which the effect of a particular substance on the production of dietary hepatic injury is being investigated. In the present report the effect of 6-propyl-thiouracil and of 2-aminothiazole has been studied in two consecutive experiments. In each experiment one group of control animals was placed on the basal experimental ration without goitrogenic substance, to be compared with a second test group of rats receiving the same basal diet supplemented with propyl-thiouracil or aminothiazole. Young adult male rats with an initial weight of 150-225 g were used throughout.

The basal diet consisted of casein (G.B.I.) 8, Crisco 40, sucrose 48, salt mixture 4, with the admixture of 0.05% propyl-thiouracil or 0.05% aminothiazole in the corresponding group of each experiment. Each animal received daily 20  $\mu$ g thiamine chloride, 25  $\mu$ g riboflavin, 20  $\mu$ g pyridoxine, and 100  $\mu$ g calcium pantothenate, all dissolved in 1 cc of water. Three drops of percomorph oil furnishing 3750 units of vitamin A and 540 units of vitamin D, and 3 mg of mixed tocopherols (Distillation Products) were given weekly. In addition all animals 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 marked with +, whereas more severe cirrhosis was defined as ++ to +++++, with proper consideration for its varying degree in different lobes.

**Results.** From the tabulation of all the pertinent data collected (Table I, Exp. I) it becomes evident that propyl-thiouracil when added to the basic cirrhosis-producing synthetic diet exerted a marked preventive effect, manifesting itself not only in much lower, almost negligible incidence (8 out of 10 experimental animals were free from cirrhosis) and in milder degree of cirrhosis, but also in

| *<br>Exp. | Supplement           | No. of<br>animals | Wt loss |       | No wt<br>loss | Avg wt<br>loss, % | Dead<br>before<br>150 days | Killed<br>at<br>150 days | Fluid in<br>serous<br>cavities | Food<br>intake,<br>g | Cirrhosis |   |               | Ceroid |               |
|-----------|----------------------|-------------------|---------|-------|---------------|-------------------|----------------------------|--------------------------|--------------------------------|----------------------|-----------|---|---------------|--------|---------------|
|           |                      |                   | >50 g   | <50 g |               |                   |                            |                          |                                |                      | 0         | + | ++ to<br>++++ | 0      | Trace<br>to + |
| I.        | A. None              | 12                | 8       | 3     | 1             | -29.6 $\pm$ 21.7  | 6                          | 6                        | 5                              | 7.5 $\pm$ 0.95       | 0         | 1 | 11            | 6      | 6             |
|           | B. Propyl-thiouracil | 10                | 0       | 9     | 1             | -11.0 $\pm$ 5.1   | 0                          | 10                       | 0                              | 3.9 $\pm$ 0.23       | 8         | 1 | 1             | 10     | 0             |
| II.       | A. None              | 15                | 3       | 3     | 9             | -8.4 $\pm$ 26.0   | 4                          | 11                       | 10                             | 5.8 $\pm$ 0.93       | 1         | 1 | 13            | 10     | 5             |
|           | B. Aminothiazole     | 15                | 2       | 8     | 5             | -7.1 $\pm$ 20.5   | 2                          | 13                       | 2                              | 6.0 $\pm$ 0.62       | 4         | 2 | 9             | 5      | 10            |

absence of serous (partly chylous) effusions in the peritoneal, pleural, and pericardial cavities, in far better survival rate and in more satisfactory weight curves. It was especially impressive to the observer that these better weight curves were obtained with a food consumption only 52% of that of the control animals fed the same diet without propyl-thiouracil. The animals receiving propyl-thiouracil exhibited a perfect fur and were altogether in an exceptionally good general condition.

As would be expected, in the absence of cod liver oil<sup>2,6</sup> and in the presence of hydrogenated fat (Crisco),<sup>7</sup> ceroid was found in the livers even of the control animals in only limited quantity or not at all. Even these irregularly occurring traces of ceroid were missing in the animals fed the diet containing additional propyl-thiouracil. In contrast, the fat content of the liver judged on the basis of histologic examination and not by the more reliable chemical analytical data appeared to stay elevated in both the control animals and in the experimental animals receiving propyl-thiouracil.

The incidence of acute or subacute necrotizing nephrosis<sup>2</sup> happened to have been low in the present group of control animals, only 2 rats out of 12 showing these changes. In the light of this low incidence in the control group, the fact that no renal changes were observed in the group of rats receiving propyl-thiouracil is of interest but of no statistical significance. Atrophy of the testes with suppressed spermatogenesis was seen in 7 out of 10 rats in the control group (A) and in 8 out of 10 in the corresponding group (B) fed propyl-thiouracil. Thus, the injurious effect of the diet on the gonads remained uncorrected by propyl-thiouracil.

In contrast to the remarkable preventive effect of propyl-thiouracil as documented by the data of Exp. I (Table I), aminothiazole in the dose given (0.05%) seemed to influence only very slightly, if at all, the production of

dietary hepatic injury in rats (Exp. II, Table I). The slight reduction in the incidence of cirrhosis in the group of rats fed aminothiazole might indicate some beneficial effect but it is of no statistical significance. The only significant change brought about by aminothiazole was with regard to the occurrence of effusions in the various serous cavities: instead of 10 animals out of 15 in the control group (A), only 2 out of 15 in the experimental group (B) exhibited such pathologic manifestations.

Again, in contradistinction to the effect of propyl-thiouracil, aminothiazole exerted no significant influence on ceroid production or on food intake, survival rate, and weight changes of the experimental animals. The liver fat estimated histologically appeared to be high in both the experimental (B) and control animals (A). There was no difference in the incidence of renal or testicular changes between the groups not receiving and those receiving aminothiazole.

*Discussion.* The present and previous<sup>1</sup> observations are in good agreement regarding the beneficial effect of goitrogenic substances on the prevention of dietary cirrhosis of the liver in rats. The parallelism between goitrogenic and "anti-cirrhotic" potency is satisfactory. Propyl-thiouracil which is considered the most powerful goitrogenic substance proved also to be superior to the other goitrogenic substances tested in its effect on the prevention of dietary cirrhosis of the liver. As regards their relative effectiveness against cirrhosis these substances are in the following order: Propyl-thiouracil > Thiouracil > Thiourea > Aminothiazole. Of course this order applies only to the quantitative conditions chosen for the present and previous experiments. Nevertheless it is of interest to note that on the basis of food intake and molecular weight propyl-thiouracil appears to be at least 5 times as potent in its effect on the prevention of hepatic cirrhosis as thiouracil. The daily dose of propyl-thiouracil amounted on the average to 1.95 mg, which in itself is good support for the assumption that propyl-thiouracil and other goitrogenic substances act with greatest probability through the intermediary of the thyroid gland. So-called lipo-

<sup>6</sup> Endicott, K. M., *Arch. Path.*, 1944, **37**, 49; Endicott, K. M., Daft, F. S., and Sebrell, W. H., *Proc. Soc. Exp. Biol. and Med.*, 1944, **57**, 330; Wachstein, M., *ibidem*, 1945, **59**, 73.

<sup>7</sup> György, P., unpublished observations.

tropic substances, such as methionine or choline, used for the prevention of hepatic cirrhosis, require relatively higher doses to be effective.

Aminothiazole was found to be without any significant benefit in doses which on the basis of food intake and molecular weight were about 3.5 times higher than those used for propyl-thiouracil.

Successful prophylaxis of hepatic cirrhosis with goitrogenic substances such as thiouracil in the previous<sup>1</sup> and with propyl-thiouracil in the present studies does not necessarily lead to the conclusion that the same approach may be successful in the therapy of this condition. As a matter of fact, in unpublished experiments thiouracil appeared to exert no effect or even a slightly deleterious one on a *pre-existing* cirrhosis in rats.

As an unexpected indirect result of our studies the excellent general nutritional state of the experimental animals receiving propyl-thiouracil deserves special attention. This observation supports the view expressed in another connection by several authors<sup>8</sup> that goitrogenic substances could play an important role in the feeding and fattening of farm animals, and especially in the feeding efficiency, an all-important economic factor. Older experiments were carried out mainly with thiouracil. Our own studies seem to give propyl-thiouracil a definite edge over thiouracil. The practical problem as to whether goitrogenic substances are stored and, if so, how long in animals receiving them with their feed, and whether the ingestion of such

animal products may exert a toxic (goitrogenic) effect on the consumer is beyond the scope of this presentation.

*Summary.* Admixture of propyl-thiouracil (.05%) with a cirrhosis-producing synthetic diet will prevent effectively the production of dietary cirrhosis in rats. This result is achieved with simultaneously reduced food intake and is manifested not only in the absence of cirrhotic changes in the liver but also in the improved general condition of the experimental animals and increased feeding efficiency.

Aminothiazole in the dose used (3½ times the equivalent of propyl-thiouracil) was without any significant effect on the production of dietary cirrhosis, on food intake, survival rate and weight changes.

For the goitrogenic substances tested efficiency in prevention of cirrhosis seems to parallel goitrogenic potency.

<sup>8</sup> Kempster, H. L., and Turner, C. W., *Poultry Sc.*, 1945, **24**, 94; Andrews, F. N., and Schnetzler, E. E., *ibid.*, 1946, **25**, 124; Glazener, E. W., and Jull, M. A., *ibid.*, 1946, **25**, 236; Mixner, J. P., Tower, B. A., and Upp, C. W., *ibid.*, 1946, **25**, 536; Reineke, E. P., Davidson, J. A., Wolterink, L. F., and Barrett, F. N., *ibid.*, 1946, **26**, 410; Andrews, F. N., Beeson, W. M., Herrick, E. R., and Harper, C., *J. Animal Sc.*, 1947, **6**, 3; Beeson, W. M., Andrews, F. N., and Brown, P. T., *ibid.*, 1947, **6**, 16; Muhrer, M. E., and Hogan, A. G., *Proc. Soc. Exp. Biol. and Med.*, 1945, **60**, 211; Van der Noot, G. W., Reece, H. P., and Skelley, W. C., *J. Animal Sc.*, 1947, **6**, 12; McMillen, W. N., Reineke, E. P., Bratzler, L. J., and Francis, M. J., *ibid.*, 1947, **6**, 305.

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### Observations on Ureteral Peristalsis in Unoperated Dogs.

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Up to the time Trattner<sup>1,2</sup> developed the hydrophorograph for the graphic recording

<sup>1</sup> Trattner, H. R., *J. Urol.*, 1924, **11**, 477.

<sup>2</sup> Trattner, H. R., *J. Urol.*, 1932, **28**, 1.

of peristaltic activity in the human ureter, investigations on ureteral peristalsis were carried out on excised ureters, or on exposed ureters *in situ* in anesthetized and operated