moiety are probably not in equilibrium with the carbon atoms of glucose.

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## Selenium and Liver Necrosis in the Hyperthyroid Rat

It is well known that dietary deficiencies can be seriously aggravated by the induction of a hyperthyroid state. Recently it has been shown[1-3] that selenium significantly prolongs the survival-time of rats and prevents the onset of the liver necrosis which follows the ingestion of a diet containing yeast as the only source of protein. This protective effect of selenium resembles that shown by a number of apparently unrelated substances such as methionine, cystin, vitamin E, methylene blue and methylthiouracil, the mode of action of which is not understood. Unpublished observations, made in the course of a systematic investigation into the effects of various hormonal and nutritional stimuli on the course of liver necrosis, had suggested that it might be possible to distinguish between a true protective effect and a 'non-specific', indirect effect of the substances tested by the induction of a hyperthyroid state. Methylthiouracil, for example, which protects the euthyroid weanling rat against the onset of liver necrosis, was ineffective in litter-mates made hyperthyroid by the simultaneous addition of thyroid powder to the diet. A somewhat similar effect was seen if methylene blue was given, in contrast to the persistence of the protective effect obtained if vitamin E was used. In the light of these considerations it was thought of interest to see how the induction of a hyperthyroid state would affect the protective effect of selenium in dietary liver necrosis.

Male litter-mate rats of a strain bred in the Department of Anatomy, Birmingham, were weaned on the twenty-first day of life, the first day of the experiment, and were fed the 'necrogenic yeast diet' of Lindan and Himsworth[4] to which thyroid powder and sodium selenite had been added. The dose of selenium was kept constant at a level of 0·00002 per cent, but the level of thyroid powder was increased from 0·2 per cent (Exp. 1) to 0·3 per cent (Exp. 2) and 0·5 per cent (Exp. 3). All animals were kept in individual cages with raised screen floors, and were allowed to die spontaneously. The survival times and the incidence of liver necrosis are presented in Table 1. It can be seen that the induction of hyperthyroidism significantly accelerated the onset of liver necrosis, but that despite the presence of even a severe hyperthyroid state (Exp. 3), the small amount of selenium given prevented the development of dietary liver necrosis. Although the difference in the survival times of the rats fed the highest amount of thyroid powder with and without selenium was not significant, the absence of liver necrosis was striking. This protective action of selenium, in the presence of varying degrees of hyperthyroidism, is suggestive of a direct effect of selenium, and is best interpreted as the alleviation of a true deficiency. In view of the observations of Bunyan, Edwin and Green[2] on the protective effects of trace elements other than selenium, it would be of interest to see what effect the induction of a hyperthyroid state would have on the action of these trace elements.

Table 1. The Effect of Varying Levels of Thyroid Hormone with and without Selenium on the Survival Time (in days) of Litter-mate Rats fed the 'Necrogenic Yeast Diet'.
(Incidence of liver necrosis in parentheses)

| Level of thyroid hormone | No. of animals | Necrogenic diet | Necrogenic diet plus thyroid hormone | Necrogenic diet plus thyroid hormone plus sodium selenite (0·00002 per cent) |
|---|---|---|---|---|
| Exp. 1: 0·2 per cent | 7 | 40·4±5·42 (7/7) | 25·0±1·02 (7/7) | 59·4±9·48 (1/7) |
| Exp. 2: 0·3 per cent | 7 | 29·3±1·25 (7/7) | 19·6±0·68 (7/7) | 33·9±3·54 (0/7) |
| Exp. 3: 0·5 per cent | 8 | 23·3±2·33 (8/8) | 16·7±0·50 (8/8) | 20·5±2·19 (0/8) |

Another point of interest is the effect of supplements of selenium on the course of the hyperthyroid state itself. Although the addition of thyroid powder to the diet significantly ($P < 0·001$) hastened the onset of liver necrosis in all the animals, increasing the dose of thyroid powder from 0·2 to 0·3 or 0·5 per cent had no significant effect on the survival times if each group was compared with the untreated litter-mate controls. (The spontaneous decrease in the survival times of the untreated controls of Exps. 1–3, seen in Table 1, is purely accidental.) This is in contrast to the obvious decrease in survival times found with increasing doses of thyroid hormone, if selenium is given in the diet as well. By comparison with the litter-mates given thyroid only, the regression was significant at the 5 per cent level using a 'two-sided' test. This observation again suggests that selenium acts by alleviating a dietary deficiency, and underlines the caution which is indicated if the effects of the pure, uncomplicated hyperthyroid state are to be clearly assessed.

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