An Interaction of Dieldrin with Thiamine* (33344)

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Lee *et al.* (1) have reported that dieldrin toxicity is accentuated in rats raised on rations containing low levels of protein, whereas in our laboratory we have observed that dieldrin accentuated an essential fatty acid deficiency in the rat (2). In extending these studies to include other nutritional variables it seemed probable that a thiamine deficiency should influence dieldrin toxicity. Both these stresses affect the central nervous system and it seemed possible that one stress might potentiate the other. The present paper summarizes experiments designed to study this interaction.

Materials and Methods. Litter mate groups of 4 males or 4 females from our closed colony of randomly bred Wistar rats were raised for 12 weeks on the following semisynthetic rations: 1, a control, nutritionally adequate, ration; 2, a ration containing a marginal level of thiamine; 3, the control ration containing 20 ppm of dieldrin; and 4, the deficient ration containing 200 ppm of dieldrin. The control ration contained 4000 μg and the deficient ration 800 μg of thiamine hydrochloride/kg of ration. The rats were weaned onto these rations at 4 weeks of age and a total of eight (4 ♂ and 4 ♀) rats were used for each ration. The rations were fed *ad libitum* and no effort was made to prevent coprophagy. The animals were weighed weekly and observed carefully for the appearance of any gross symptoms of toxicity or nutritional stress. The present paper summarizes the data from two such experiments.

The semisynthetic ration contained 22% protein as casein, 5% fat as corn oil, 69% carbohydrate as dextrin, and 4% salts. A more detailed description of the composition of this ration is given in a previous publication (2). Dieldrin (analytical standard grade) was added to the ration dissolved in corn oil. We have observed in other experiments with this strain of rat that a dietary level of 20 ppm of dieldrin did not influence growth, but did induce convulsions in some rats after a 10–12-week feeding period.

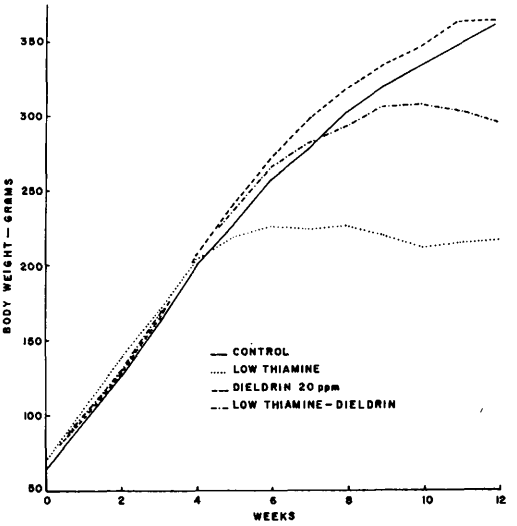

FIG. 1. Growth curves of male rats raised on rations containing low levels of thiamine and/or dieldrin.

Results. Inspection of the growth curves for male rats (Fig. 1) suggests that dieldrin affords some protection against thiamine deficiency. A statistical analysis of body weights at 9 weeks indicated a significant interaction ($p < .01$) between the two experimental variables. With female rats a comparable but not as dramatic a response was observed. Addition of dieldrin to the low-thiamine ration resulted in a higher maximum body weight and delayed the onset of weight loss associated with the nutritional deficiency. Dieldrin produced no significant changes in growth when added to the control ration.

To analyze the nature of this interaction comparisons have been made within a litter of the influence of the following variables on the 9-week body weights: (i) Low thiamine in the absence of dieldrin (Rations 1 and 2);

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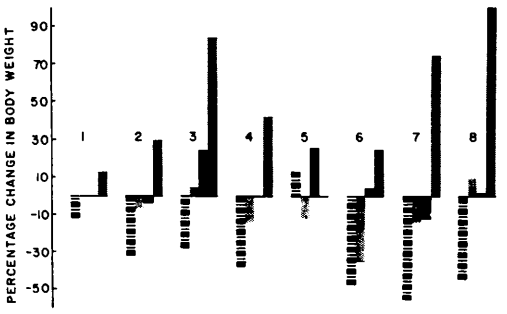

FIG. 2. Percentage change in body weight at 9 weeks produced by the thiamine deficiency in the control (unevenly striped bar) and dieldrin fed (dotted bar) rats, and by dieldrin in the control (solid bar) and thiamine-deficient (evenly striped bar) rats.

(ii) Low thiamine in the presence of dieldrin (Rations 3 and 4); (iii) Dieldrin in a nutritionally adequate ration (Rations 1 and 3); and (iv) Dieldrin in a thiamine-deficient ration (Rations 2 and 4). The percentage change in body weight produced by these variables is plotted for each litter for the 8 male litters (Fig. 2). With one exception a consistent pattern was observed in all litters, with the thiamine deficiency producing a smaller growth depression in the rats fed dieldrin and dieldrin producing an appreciable stimulation in the growth of rats subject to a thiamine deficiency. In two litters dieldrin increased growth in the control rats, but this was not a consistent effect. The dieldrin reduced the degree of nutritional stress in the thiamine-deficient rats.

Litter made group No. 5 (Fig. 2) deviates from the usual pattern, with the rat raised on the low-thiamine ration showing a higher body weight at 9 weeks than the rat raised on the control ration. This response was not due to any unusually low body weight of the control rat. With this litter also, dieldrin did not produce any increase in growth in the thiamine-deficient rat. This pattern was also observed in several litters of female rats and one might conclude that dieldrin increases growth in thiamine-deficient rats taken from litters which show a growth depression with this level of thiamine in the diet. In fact, with the 16 litters used in these experiments a good correlation ($r = 0.85$) is observed between these two factors (Fig. 3).

Discussion. This result was somewhat unexpected for it seemed probable that this combined stress would prove to be more debilitating to the rat. The protective effect of the dieldrin cannot be explained by an increase in food intake. Some limited observations in this study and more extensive observations in other experiments suggest that this dietary level produces a slight reduction in food intake if it produces any effect.

Certain antibiotics show a thiamine-sparing action which is related to the production of the vitamin by intestinal flora (3). This occurs primarily in the large intestine and the thiamine produced is not available to the rat unless the feces are recycled (4). The amount of thiamine produced is not sufficient to meet the requirement of the rat, but its presence becomes evident when dietary thiamine is withdrawn. Deficiency symptoms are observed much sooner in rats when coprophagy is prevented. The thiamine-sparing action of certain antibiotics is related to this phenomenon since this type of response is not observed in axenic rats nor in rats when coprophagy is prevented (3). Apparently the antibiotic influences the intestinal microflora

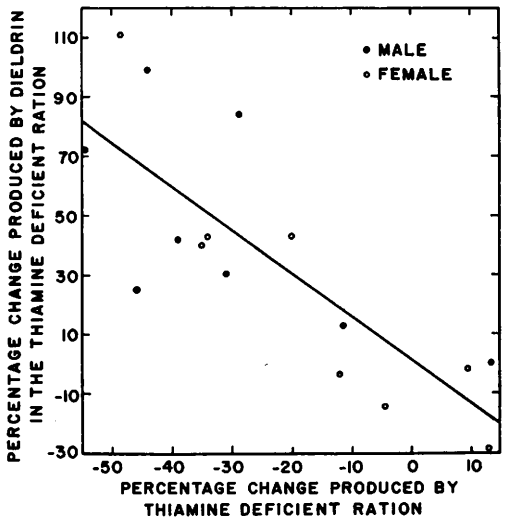

FIG. 3. Correlation within a litter between response to thiamine deficiency and influence of dieldrin in the thiamine-deficient rat. Comparison made of body weights at 9 weeks.

in some fashion so that the level of fecal thiamine is increased. The antibiotic may eliminate certain strains of microorganisms with those surviving being more proficient producers of thiamine. Antibiotics also show a comparable effect in riboflavin and pyridoxine deficiencies (5).

One might propose a similar mode of action for dieldrin, but this would also imply that this chemical is exerting some selective effect on the intestinal microflora. A toxic chemical such as dieldrin may well have some bactericidal effect, but there is no evidence to suggest that its action is particularly selective. Also, in some preliminary experiments, dieldrin has not shown any sparing effect in riboflavin and pyridoxine deficiencies. A proposed experiment with axenic rats should throw some light on this situation.

Another possibility could be that dieldrin improves the efficiency of thiamine utilization. This could be effected by stimulation of absorption or by inhibition of metabolic breakdown which would decrease turnover rate and conserve tissue levels of the nutrient.

These data also illustrate a genetic effect. There is a marked variation among litters in their response to the low thiamine ration and the degree of the dieldrin response is greater in those litters which are more susceptible to the thiamine stress. If one assumes that the variation in response to the nutritional stress is genetic in nature, this interrelation might be explained on the basis of an effect of dieldrin on the intestinal production of thiamine. If the onset of the nutritional deficiency promotes coprophagy those animals more subject to the stress could benefit more from an increase in the level of fecal thiamine.

Summary. A dietary level of 20 ppm of dieldrin increased growth in rats raised on rations containing low levels of thiamine, or conversely, the low dietary intake of thiamine produced a smaller growth depression in rats ingesting dieldrin. There was a marked variation among litters in their response to the nutritional stress and the dieldrin produced a more pronounced response in those litters which were more susceptible to the thiamine deficiency stress.

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The Inhibition of the Maturation of Newly Synthesized Bone Collagen by β-Aminopropionitrile in Tissue Culture* (33345)

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One of the principal manifestations of lathyrism in animals is the increased solubility of tissue collagens, or more precisely, the increased ease with which collagen can be extracted from tissues and the increased quanti-

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