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BY ANTIMETABOLITES I. PANTOTHENIC ACID  
DEFICIENCY PRODUCED BY ( 2-METHYL PANTOTHENIC  
ACID IN MICE

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# ON THE NUTRITIVE STUDIES OF PANTOTHENIC ACID BY ANTIMETABOLITES

## I. PANTOTHENIC ACID DEFICIENCY PRODUCED BY $\omega$ -METHYL PANTOTHENIC ACID IN MICE

By

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A deficiency syndrome of mice after daily oral administration of pantoyltaurine for three to four weeks at a level of 200 mg per kg body weight was observed by Snell *et al.* (1) in 1943.

This result was not confirmed by Woolley and White (2) who reported that mice (and hamsters) were resistant to this analogue of pantothenic acid. Similarly, no symptoms of pantothenic acid deficiency were noted by Unna (3) after oral administration of pantoyltaurine to rats. Brackett *et al.* (4) induced a deficiency disease in chicken with pantoyltauramide-4-chlorobenzene which was reversed by pantothenic acid.

Recently, Drell and Dunn (5) have demonstrated the inhibition of growth mice using  $\omega$ -methyl pantothenic acid, which was reversed by simultaneous administration of pantothenic acid.

In the present study the writer used  $\omega$ -methyl pantothenic acid as an antagonist of pantothenic acid and studied its inhibitory actions.

### Materials and Methods

#### 1. Sodium *DL*- $\omega$ -methyl pantothenate

This analogue was prepared by the method described by Drell and Dunn (6).

#### 2. Diets and feeding techniques

The composition of the pantothenic acid-free basal ration is shown in Table 1. Sodium  $\omega$ -methyl pantothenate and calcium pantothenate were mixed with the basal ration at the levels shown in Table 2.

#### 3. Animals

Male mice of DD-strain were placed in individual cages at the time of

weaning (body weight was about 11 g) and were fed the designated (in Table 2) experimental diets for 16 days inducing pantothenic acid deficiency and then the diets were changed to the basal diet (0:0).

The animals were weighed from one to three times weekly.

Table 1. Composition of the pantothenic acid-free basal ration.

Component	Amount
Casein (purified)	18.0 g
L-Cystine	0.3 "
Sucrose	70.7 "
Salts mixture (McCollum salt No. 115)	6.0 "
Soybean oil	5.0 "
<i>Vitamin mixture</i>	
Thiamine chloride	0.5 mg per 100g diet
Riboflavine	0.5 "
Pyridoxine hydrochloride	0.5 "
Niacine	5.0 "
<i>p</i> -Amino benzoic acid	20.0 "
Choline chloride	50.0 "
Ascorbic acid	40.0 "
Biotin	0.05 "
Folic acid	0.02 "
$\alpha$ -Tocopherol	5.0 "
Vitamin A	2000 U.S.P. Units
Vitamin D	200 "

### Results and Discussion

As shown in Table 2 and Fig. 1, the weight gain of mice fed with a pantothenic acid-free diet decreased proportionately to the level of supplementary inhibitory analogue,  $\omega$ -methyl pantothenic acid, in virtue of the data before the 16th day. As may be noted in the experimental results, the physiological effects depended upon the ratio of  $\omega$ -methyl pantothenic acid to pantothenic acid rather than upon the absolute amounts of analogue. The growth of the animals on the diets in which ratios were 1500:0, 500:0, 300:0, respectively, were apparently inferior to the control on the ground of significance (Significance level; 5 per cent), furthermore 500:0 was inferior to 500:5 and 300:0 was inferior to 300:5 or 500:5.

Test of significance shows that there were no differences between 500:5, 300:5, 0:0 and the control respectively. Therefore, "interference ratio"\* appears to be approximately 100:1 - 60:1 (300:5) for the male mice. The ratio was fairly consistent with that of Drell and Dunn.

\* Drell and Dunn defined as the ratio of inhibitor to vitamin at which survival time is not increased compared to the vitamin deficient control.

After the 16th day all groups of animals were changed to 0:0 ratio, however the group of 300:0, 500:0 and 1500:0 were not recovered practically in weight gain. But the other groups increased weight.

The earliest symptoms observed which at the ratio of 1500:0, 500:0 and 300:0 were ruffling of the hair particularly on the head and neck after about eight days and scanty of the hair of the head extended an alopecia and dermatitis on the margin of eyes and tail as shown in Plate 1 (Fig. 1). The majority of these animals showed a nervousness and convulsive walking was observed in some of them. As above mentioned the experimental diets of 1500:0, 500:0 and 300:0 ratios were replaced to the basal pantothenic acid-free diet, but one third of these animals exhibited a remarkable convulsive walking within three weeks. All animals of 1500:0 ratio died in this period. These facts indicated that the effect of the large dose of the analogue was not recovered by replacing the diet with the analogue free diet. Seven weeks later the alopecia which was observed on the heads of some mice extended to almost the entire body except a part of the head and the joint of the limbs and the tails as shown in Plate 1 (Fig. 2). The animals exhibited the deficiency syndrome, alopecia, were fed pantothenic acid containing diet (3 mg per 100 g diets) supplemented with 100 mg inositol (100 mg per 100 g diets),

**Table 2.** Weight changes of male mice on diets with and without pantothenic acid and  $\omega$ -methyl pantothenic acid.

Group	No. of animals	Average weight and its increase						
		1st day	5th day	8th day	14th day	16th day	22nd day	31st day
Control	4	11.1	15.0 (+3.9)	16.6 (+5.5)	17.1 (+6.0)	17.3 (+6.2)	18.1 (+7.0)	18.9 (+7.8)
0:0	3	11.0	14.7 (+3.7)	15.7 (+4.7)	16.4 (+5.4)	16.6 (+5.6)	17.4 (+6.4)	18.2 (+7.2)
100:0	3	10.5	13.5 (+3.0)	13.8 (+3.3)	14.0 (+3.5)	14.1 (+3.6)	16.5 (+6.0)	17.0 (+6.5)
300:0	3	9.8	13.3 (+3.5)	13.3 (+3.5)	12.8 (+3.0)	12.5 (+2.7)	11.7 (+1.9)	12.7 (+2.7)
300:5	3	10.0	14.0 (+4.0)	14.8 (+4.8)	15.3 (+5.3)	15.6 (+5.6)	16.4 (+6.4)	17.5 (+7.5)
500:0	4	11.5	14.9 (+3.4)	14.9 (+3.4)	13.1 (+1.6)	12.9 (+1.4)	13.2 (+1.7)	13.4 (+1.9)
500:2	3	13.3	16.0 (+2.7)	16.0 (+2.7)	15.8 (+2.5)	15.7 (+2.4)	16.4 (+3.1)	18.7 (+5.4)
500:5	3	12.8	16.7 (+3.9)	17.0 (+4.2)	17.2 (+4.4)	17.2 (+4.4)	18.7 (+5.9)	20.0 (+7.2)
1500:0	3	12.3	15.5 (+3.3)	14.8 (+2.5)	13.8 (+1.5)	13.4 (+1.1)	12.5 (+0.2)	10.3 (-2.0)

and after ten days the naked animals began to grow hairs and recovered almost within two weeks as shown in Plate 1 (Fig. 3).

Drell *et al.* observed similar severe alopecia with the diet which contented inositol and so it can be considered that the alopecia is caused mainly by the deficiency of pantothenic acid.

The view that  $\omega$ -methyl pantothenic acid exhibits inhibitory effect by interfering with the utilization of pantothenic acid rather than through any inherent toxicity was introduced by Drell *et al.* According to Novelli and Lipmann (7) both phenylpantothenone and  $\omega$ -methyl pantothenic acid interfere with the synthesis of Coenzyme A. Since  $\omega$ -methyl pantothenic acid inhibits the growth of rats (8), chicken (9), protozoa (9), certain bacteria and higher plant (10) the mode of mechanism of this inhibitory action may exist in blocking of the synthesis of normal Coenzyme A.

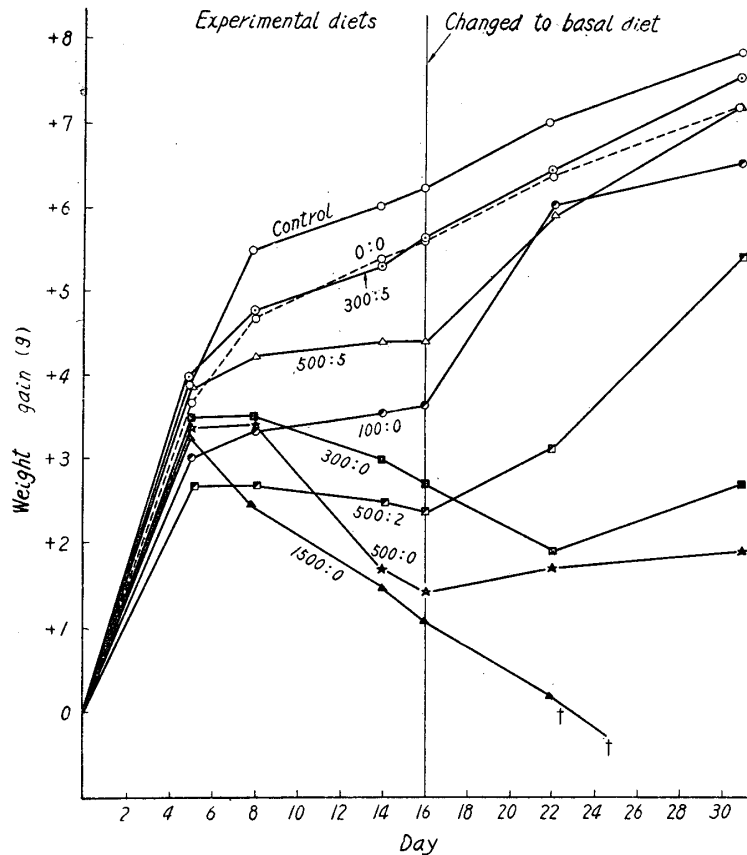


Fig. 1. Curves of weight gain

### Summary

1. It was shown that the weight gain of the male DD-strain mice diminished proportionately to the level of supplementary inhibitor analogue,  $\omega$ -methyl pantothenic acid.

2. The inhibitory effects depended upon the ratio of inhibitor to pantothenic acid.
3. The critical ratio, termed "interference ratio" was found to be 100:1–60:1. This ratio was near to that (100:1) described by Drell *et al.*
4. The cause of alopecia induced by  $\omega$ -methyl pantothenic acid was discussed.
5. In principle, these results supported the works and view of Drell *et al.* that the symptoms of pantothenic acid deficiency were caused by inhibitory activity of  $\omega$ -methyl pantothenic acid.

### References

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**Plate 1****Explanation of Figures**

Fig. 1. Appearances of animals :

- A) Control
- B) 500:0
- C) 500:5
- D) 300:0

Fig. 2. Alopecia :

Alopecia extended to almost the entire body except a part of head and joint of the limbs and tail, skin became scaly and falled off.

Fig. 3. Recovered animals :

Above the animal was recovered by supplementation of pantothenic acid (3 mg per 100 g diets) and inositol (100 mg per 100 g diets).

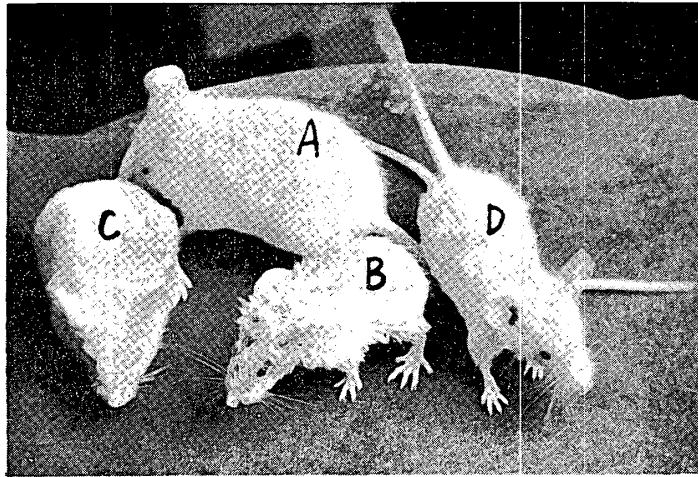


Fig. 1.

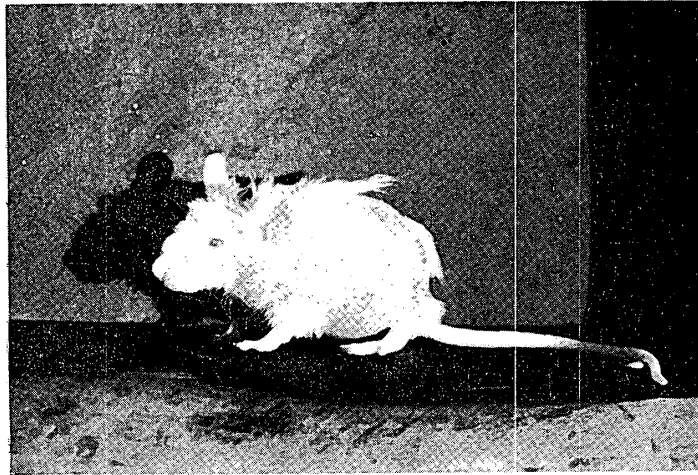


Fig. 2.

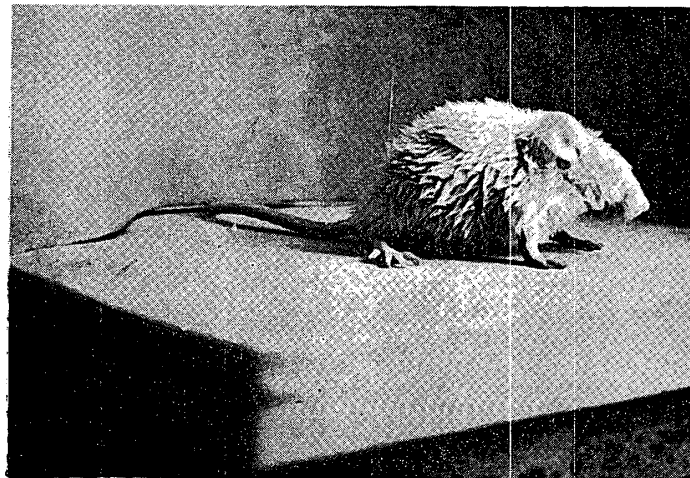


Fig. 3.