The Effect of Biotin upon \( p \)-Dimethy lamino azobenzene Carcinogenesis*

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In a previous report, we (2) have shown that although addition of liver extract at a level of 3 per cent to a diet favorable to production of hepatic carcinoma by \( p \)-dimethylaminoazobenzene resulted in great retardation of tumor development, addition of the extract at a level of 15 per cent afforded appreciably less protection. This effect was attributed to biotin, since the 15 per cent liver extract diet contained approximately 0.2 \( \mu \)gm. of biotin per gram. (This estimate is based upon assay of another lot of liver extract because the lot used in the 15 per cent diet was exhausted.) With a daily food consumption of 10 gm. per rat, this would provide 2 \( \mu \)gm. per day, an amount found by du Vigneaud and his associates (1) adequate to accelerate tumor development on a protective diet. In order to ascertain whether or not our interpretation was valid, another experiment was set up.

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### METHODS

In general, our procedures were identical with those employed in the earlier experiments. However, the concentration of the carcinogen in the diets was reduced was present in our 15 per cent liver extract diet. Except for the differences already mentioned, diets 15R and 16R were identical with our original diets 15 and 16.

As in the earlier experiment, the rats’ livers were palpated at weekly intervals, and as soon as it was certain that a tumor was present the animal was killed and section taken for microscopic confirmation. Administration of the carcinogen ceased only with death of the animals.

### RESULTS

The results obtained in this experiment are shown graphically in Fig. 1, and should be compared with Fig. 21 of our earlier paper. In both figures the ordinates represent cumulative tumor incidence in per cent, and

### TABLE I

| Diet 15R | 4850 gm. 2nd basal diet  
| 150 gm. carcinogen solution  
| (2% in cottonseed oil) |
| --- | --- | --- |
| Diet 16R | 4700 gm. 2nd basal diet  
| 150 gm. Liver Extract, Lilly  
| 150 gm. carcinogen solution  
| (2% in cottonseed oil) |

* Merck’s crystalline biotin (synthetic).

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the abscissae represent latent period in days. Death of tumor-free rats is indicated by a short line perpendicular to the graph of each diet, and the number adjacent to each curve is that of the diet concerned.

In Fig. 21 of our earlier paper (2) it is seen that 3 per cent of liver extract in the diet (No. 16) gives striking retardation of tumor development as compared with the control diet (No. 15), but 15 per cent of liver extract (No. 30) gives appreciably less protection.

In the present experiment, as shown by Fig. 1, the latent period of tumor development is somewhat prolonged and the slope of the curves is less steep, undoubtedly a result of reduction by one third of the concentration of the carcinogen in the diet. There is, however, a striking similarity between the curves for diets 38 and 30, and there seems little doubt that our explanation of the course of events noted with diet 30 is correct.

The results with diet 37 indicate that although biotin will accelerate liver tumor development on a diet that in itself protects against carcinogenesis, it will not have this effect when added to a diet that favors early carcinogenesis.

Not shown by the curve for diet 16R is the death of the last two rats in the experiment, both of which died tumor-free, one on the 615th day and the other on the 628th day.

Table II permits additional comparison of the original and subsequent experiments. The data in the first three lines have been taken from our earlier paper. It will be seen that the mortality rate during the period before the first tumor developed (ascertainable from columns 3 and 4) on diets 15R and 16R was no less than that on the original diets 15 and 16. Hence, the reduction of carcinogen content for the diets was fruitless, and had the undesirable effect of prolonging the latent period of tumor development.

**SUMMARY**

Fifteen per cent of liver extract in the diet had given less protection against \( p \)-dimethylaminoazobenzene carcinogenesis than had 3 per cent, presumably because of the biotin content of the former diet. To test this point four diets were used: (1) control (favorable to early carcinogenesis); (2) control plus biotin; (3) control plus 3 per cent liver extract; and (4) control plus biotin plus 3 per cent liver extract. The biotin level in diets 2 and 4 approximated that of the 15 per cent liver diet. The curves of tumor development on diets 1, 3, and 4 were similar to those on the control, 3 per cent liver extract, and 15 per cent liver extract diets, respectively, of the earlier experiment. Diet 2 did not show accelerated tumor development. Thus, addition of biotin to a protective diet probably accelerated carcinogenesis, but addition of biotin to a diet favorable to early carcinogenesis did not have this effect.

**REFERENCES**


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