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SOME NEW ASPECTS OF THE RELATIONSHIP OF CHEMICAL STRUCTURE TO BIOLOGICAL ACTIVITY*

By Dr. D. W. WOOLLEY

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ALTHOUGH for many years it has been recognized that relationships exist between the chemical structures of certain compounds and their pharmacological properties, those interdependencies¹ which have been observed have served more to correlate existing data in many isolated sectors of the field of drug action than to serve as guideposts on the road of medicine and research ahead. Therefore it has seemed desirable to examine some of the facts recently uncovered in nutritional research in an effort to gain new vantage

points from which to survey the field of the relationship of chemical structure to biological activity. From these vantage points it may be possible to see some of the roads along which future progress may be made.

Much of the material from which conclusions will be drawn in this paper had its origin in the observation of Woods,² who in 1940 reported that the bacteriostatic action of sulfanilamide was reversed competitively by *p*-aminobenzoic acid. These two antagonistic substances are very closely related structurally, since they differ only in the fact that the sulfonamide group of the former is replaced by a carboxyl group in the latter. The hypothesis was

* Received for publication October 27, 1944.

¹ Thus while many studies have been made of the relationship of such factors as the length of side chains to a given biological activity in a series of compounds, these studies have followed the original empirical discovery of an active member of the series.

² D. D. Woods, *Brit. Jour. Exp. Path.*, 21: 74, 1940.

ence in mean gain between adjacent dose levels to be statistically significant with a probability of 5 per cent.

In the course of these studies it was discovered that the maximum height (or length) to which the odontoblast cells of the incisor teeth would develop in a given length of assay was related to the dose level of vitamin C. In this procedure the size of the odontoblasts is measured in microns by microscopic examination of sections of decalcified teeth cut longitudinally through the pulp cavity in such a way as to expose the plane from the dental papilla to the crown of the tooth containing the most fully developed odontoblast cells.

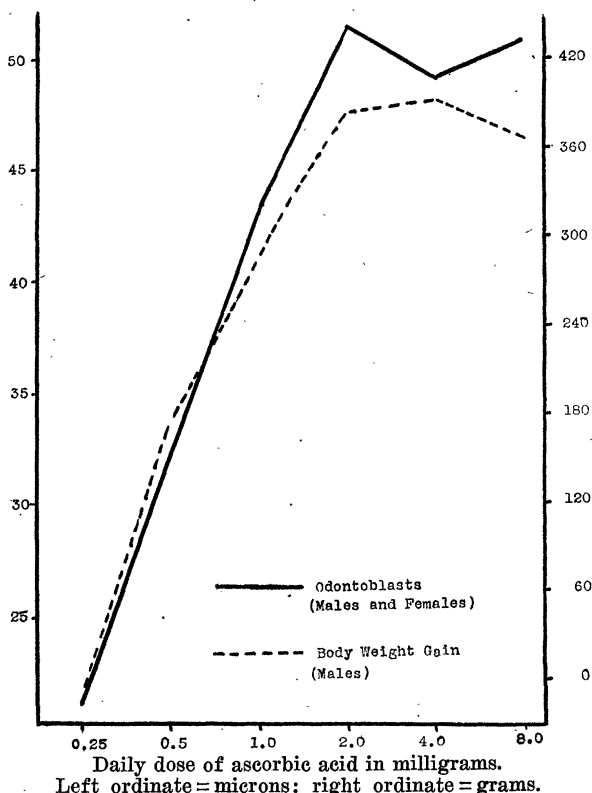


FIG. 1

When such readings were plotted against log dose of ascorbic acid, the relationship was linear between intakes of 0.5 mg and 2.0 mg ascorbic acid. No difference was found between males and females in this characteristic. Replicate tests have given the same relative results though average cell development may differ in different trials. Readings are reproducible by different technicians working independently.

Most important of all is the fact that the variability between animals treated alike is relatively low. In our eight-weeks tests the coefficient of variation in odontoblast development was 12 per cent. as compared to 29 per cent. in the case of live weight gains. The effect on numbers of animals required per treatment

which this reduction in variability has is considerable. To obtain a significant mean difference of 10 per cent. between groups would require 10 animals per group in the case of the odontoblast assay as against 65 animals were growth the criterion.

It is noteworthy that the levels of vitamin C between which response by either method bears a relationship to dose are the same. The upper level (2 mg) agrees with that for maximum bone healing reported by Bourne.²

In our experience no macroscopic scurvy is found up to eight-weeks duration of assay in young pigs where the daily vitamin C intake has been 0.5 mgms or greater. We have taken this as the minimum level of ascorbic acid suitable for bioassay, on the premise that guinea pigs that are deficient in ascorbic acid to the extent of producing visible lesions can not be depended upon to show either predictable nor reproducible development in the characteristic being used as the criterion of vitamin C intake.

Fig. 1 shows the response by guinea pigs to ascorbic acid as measured (1) by growth and (2) by odontoblast development. For these particular tests the linear relationships were:

For growth : $y = 296.9 + 818.72 x$, when $x = \log$
log dose.

For odontoblast: $y = 8.0 + 34.09 x$, when $x = \log$ dose.

Tests are still in progress to determine the minimum length of assay period permissible. Thus far it appears that at least a six weeks feeding period should be used. Assays on three- and four-week periods have not given linear response between dose level and cell development.

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² *Jour. Physiol.*, 101: 3, 327, 1942.

BOOKS RECEIVED

- BUCKY, PAUL C. *The Precentral Motor Cortex*. Illustrated. Pp. xiv + 605. The University of Illinois Press. \$4.50. 1944.
- LOEB, LEO. *The Biological Basis of Individuality*. Pp. xiii + 711. Charles C Thomas. \$10.50. 1945.
- PANTH, BHOLA D. *Consider the Calendar*. Illustrated. Pp. 138. Bureau of Publications, Teachers College, Columbia University. \$1.25. 1944.
- POPE, CLIFFORD H. *Amphibians and Reptiles of the Chicago Area*. Illustrated. Pp. 275. Chicago Natural History Museum. 1944.
- Problems in the Utilisation of Small Coals*. Illustrated. Pp. 294. British Coal Utilisation Research Association. 1944.
- SEVAG, M. G. *Immuno-Catalysis*. Illustrated. Pp. xv + 272. Charles C Thomas. \$4.50. 1945.
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