THE NERVE-MODULUS FOR ANESTHETICS

FOR some years this laboratory has examined the quantitative effects of local anesthetics upon nerve action-potentials. Full details of apparatus and methods will be published elsewhere. It was found that for sciatic nerve of *R. Pipiens*

$$T \log R = Z$$

when:

T is the elapsed time in minutes between the application of the anesthetic and a decrease in action potential of 80 per cent.

R is the ratio $\frac{\text{molarity—minimum effective molarity}}{\text{minimum effective molarity}}$

Z is a constant.

We propose to call the quantity Z the nerve-modulus for local anesthetics. It was found closely to approximate 5.50 for five local anesthetics of unrelated chemical structures.

In the determination of local anesthetic-potency it is a common practice to use the minimal effective concentration (Mm) as a criterion of potency. Mm is frequently determined by successively testing solutions of decreasing concentrations. Because the relationship between block-time and molarity is hyperbolic the experimental determination of the minimum effective concentration presents practical difficulties. The use of the modulus Z renders this procedure unnecessary as from it the minimum effective concentration can be readily calculated.

Thus

$$\text{Log } R = \frac{Z}{T}$$

$$R = \log^{-1} \frac{Z}{T}$$

and

$$R = \frac{M_1 - Mm}{Mm}$$

$$Mm = \frac{M_1}{1 + \log^{-1} \frac{Z}{T}}$$

or more conveniently (and because $Z = 5.50$)

$$Mm = \frac{M_1}{1 + \text{antilog} \left(\frac{5.50}{T}\right)}$$

Thus in comparing an anesthetic with procain the ratio:

$$\frac{M_1 \left(1 + \log^{-1} \frac{Z}{T_2}\right)}{M_2 \left(1 + \log^{-1} \frac{Z}{T_1}\right)} = P$$

When:

M_1 = molarity of procain
M_2 = molarity of anesthetic tested
T_1 = block-time for procain
T_2 = block-time for anesthetic tested
Z = modulus or 5.5
P = potency (relative to procain)

Consequently the minimum effective concentration of procain and the unknown may be compared without the determination of the Mm of either. When anesthetics differing widely in potency are compared it is not usually possible to use equimolar concentrations in testing them, because an effective concentration of one will be either too concentrated or too dilute for the other.

The modulus permits direct comparison of solutions of unlike molarities. To correct the block-time for differences in nerve-diameters the standard nerve diameter was arbitrarily taken as 500 micra. The block-time for a given molarity was found to vary as the square of the diameter of the nerve. Therefore it is a simple matter to correct an observed block-time to that for a standard nerve of 500 μ. In practice a concentration of anesthetic is selected that causes 80 per cent. block in from 3.5 to 12 minutes. Higher concentrations give inaccurate results because when excess anesthetic is present the molar/time relationship is not valid. Lower concentrations yielding long block-times are inconvenient for the same reason that renders the determination of Mm difficult. When a number of determinations of T have been made for one or more values of M the times are corrected to standard diameter, averaged, and Mm calculated. The validity of Mm can then be checked by direct experiment. When this is done, 45 minutes is arbitrarily taken as the time in which a decrease in the action potential must be observed in order for the concentration to be considered minimal. In the five anesthetics tested Mm calculated from Z closely corresponded with the experimentally determined values.

For anesthetics having prolonged action such as Nupercain the calculated Mm was found to exceed the determined Mm. These anesthetics block nerve-conduction for much longer periods than those for which the modulus was found to hold, recovery-time in some instances being as long as 3 or 4 hours contrasted with 30 minutes or less for anesthetics such as cocain and procain. The modulus proves useful in making rapid preliminary tests of new compounds. When it is found that the recovery time after 80 per cent. block is longer than 30 minutes, the calculated Mm should be checked by direct experiment before attempting to use the modulus to calculate the relative potency P. Further experiments are in progress.

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THE QUANTITATIVE RELATIONSHIP OF RIBOFLAVIN TO CATARACT FORMATION IN RATS

NUTRITIONAL cataract in rats due to avitaminosis was first described by Day, Langston and O'Brien.[1]

[1] P. L. Day, W. C. Langston and C. S. O'Brien, *Amer. Jour. Ophth.*, 14: 1005, 1931.

Later Bessey and Wolbach[2] described other ocular changes due to Vitamin G deficiency but reported that cataract occurred in only a small percentage of their animals. El Sadr[3] observed both the corneal opacity, vascularization and cataract reported by the above workers. Day, Darby and Langston[4] subsequently identified riboflavin as the cataract preventive factor.

Since these workers had used different rations and since their results were varied, a series of experiments was undertaken to explain the inconsistency of cataract formation in rats fed on riboflavin deficient diets.

Sixty rats were placed on the diet of Bourquin and Sherman.[5] A microbiological assay by the method of Snell and Strong[6] showed this ration to contain riboflavin in such amounts that our animals received 0.57 micrograms per day on the basis of average food consumption. Another group of fifty animals was placed on a modified ration of Bourquin and Sherman in which the B-complex was supplied by adding sufficient amounts of crystalline thiamin, pyridoxin, nicotinic acid, pantothenic acid and choline, instead of the 80 per cent. alcoholic extract of wheat. Some of these animals were supplemented with varied amounts of riboflavin while others received only the basal ration.

A third group of twenty animals was placed on a riboflavin free diet in which 14 per cent. Crisco was used as a source of fat instead of the 8 per cent. filtered butter fat used in the Bourquin-Sherman diet. The animals on this ration were supplemented with 50 gamma thiamin, 20 gamma pyridoxin, 200 gamma nicotinic acid, 100 gamma pantothenic acid and 5 milligrams choline per rat per day.

The results of these experiments variously corroborate all the work done on riboflavin deficiency as it affects the eyes of rats. Corneal opacity and vascularization occurred in all animals except those receiving adequate amounts of riboflavin. Cataract occurred in 90 per cent. of the animals on the Bourquin-Sherman diet within 9 weeks.

On the modified ration, 85 per cent. of the animals receiving between 1 and 3 micrograms of riboflavin daily developed cataract in 10 weeks. On the modified ration without the riboflavin, only 14 per cent. of the animals exhibited cataract formation. The time periods in each case were comparable, *i.e.*, cataract had developed in the animals receiving small amounts of riboflavin at a period when the negative controls were alive and exhibiting some growth but without the development of cataract.

All the animals on the third ration failed to develop cataract within twelve weeks after which they were discarded.

These results indicate that rats on a ration devoid of riboflavin do not exhibit cataract. Minute amounts of riboflavin induce cataract formation and rations containing more nearly adequate amounts are non-cataractogenic. This would explain the inconsistency reported by various workers of cataract production on rations which were deficient but not entirely riboflavin free. Our results are also in agreement with the observations of Stokstad and Manning[7] on the incidence of the curled toe paralysis syndrome in chicks. These findings demonstrated a lack of curled toe paralysis except when small amounts of riboflavin were present. A more complete report of these findings will appear elsewhere.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

A TEST-TUBE SPIRAL ABSORPTION VESSEL

A SIMPLE, efficient and inexpensive vessel for carbon dioxide absorption has been constructed and extensively used for plant respiration measurements. As seen in Fig. 1, this absorption cell has the added advantage of compactness. This feature is obtained by the use of a test-tube for the shell of the apparatus.

The nucleus around which the absorption cell is built consists of a glass spiral through which a chain of gas bubbles moves in contact with the absorbing solution. This spiral tube lengthens the path of the bubbles and thus prolongs the time of contact between the gas and the solution. By this means, increased efficiency of absorption is obtained. Apparatus built upon this principle have been described, heretofore, by Harvey and Regeimbal,[1] and also by many other designers of similar apparatus.

As indicated in Fig. 1, the apparatus includes a test-tube (b) fitted with a two-hole rubber stopper (a) through which pass a long inlet tube and a short outlet tube. The inlet tube is bent just below the rubber stopper so that its longer portion is centered in the

[2] O. A. Bessey and S. B. Wolbach, *Jour. Exp. Med.*, 69: 1, 1939.
[3] M. M. El Sadr, *Chem. and Ind.*, 58: 1020, 1939.
[4] P. L. Day, W. J. Darby and W. C. Langston, *Jour. Nutrition*, 13: 389, 1937.
[5] A. Bourquin and H. C. Sherman, *Jour. Amer. Chem. Soc.*, 53: 3501, 1931.
[6] E. E. Snell and F. M. Strong, *Ind. and Eng. Chem.* (Anal. Ed.), 11: 346, 1939.
[7] E. L. R. Stokstad and P. D. Manning, *Jour. Nutrition*, 16: 279, 1938.
[1] R. B. Harvey and L. O. Regeimbal, *Plant Physiol.*, 1: 205–206, 1926.