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Active Constituent of Local Anesthetic Solutions.

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Such local anesthetics as are salts of weak bases and strong acids—and most local anesthetics come under this chemical classification—have repeatedly been shown to be more effective, particularly for surface anesthesia, anesthesia of isolated nerves, etc., when their solutions have been hydrolyzed to some degree by the addition of alkali. This and other similar evidence led to the theory that the base is the only active constituent of such solutions.¹

This theory has been put to direct test by comparing the local anesthetic activity of solutions of an anesthetic base alone with that of solutions containing the same concentrations of base plus varying concentrations of the anesthetic salt. The anesthetic activity was measured by the time required to anesthetize to a strong break induction shock the nerve of a sciatic-gastrocnemius preparation from *Rana pipiens*; the time for recovery after removal from the anesthetic solution was also sometimes recorded.

The presence of the salt (hydrochloride) has been found to make no difference in the time required to anesthetize with γ -4-morpholine-propyl benzoate, one of a series of recently synthesized local anesthetics² (Table I). However, in all cases, as in this one, the presence of salt results in a shift of pH towards the acid side, and this might alter the sensitivity of the tissue or otherwise modify the

TABLE I.

| Frog | Concentration of the anesthetic in mols per liter | | pH | Time to anesthesia Min. |
|------|---|------|-----|-------------------------|
| | Base | Salt | | |
| 1 | .004 | 0 | 8.1 | 10 |
| 1 | .004 | .004 | 6.9 | 10 |
| 2 | .004 | 0 | 8.1 | 12 |
| 3 | .004 | 0 | 8.1 | 8 |
| 3 | .004 | .004 | 6.9 | 8 |
| 4 | .004 | .004 | 6.9 | 8 |
| 5 | .002 | 0 | 8.1 | 60 |
| 5 | .002 | .002 | 6.9 | 60 |

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¹ Trevan, J. W., and Boock, E., *Brit. J. Exp. Path.*, 1927, **8**, 307.

² Gardner, J. H., and Haenni, E. O., *J. Am. Chem. Soc.*, 1931, **53**, 2763.

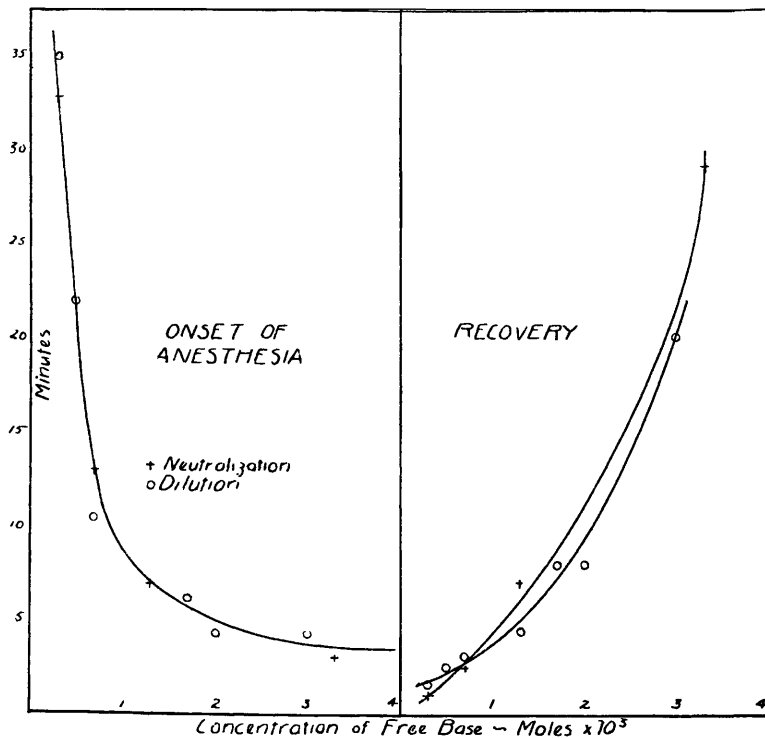


FIG. 1.

effectiveness of the anesthetic in such a way that, for instance in the example given, a total anesthetic concentration of 0.008 mols per liter had the same activity at pH 6.9 as 0.004 mols at pH 8.1.

This possibility is eliminated, however, by the results plotted in Fig. 1. To a portion of 0.004 molar procaine hydrochloride solution, enough sodium hydroxide was added to liberate the base completely, and a series of solutions containing various concentrations of the base was prepared by dilution. Another series of solutions of various concentrations of the base was prepared by neutralizing to varying degrees other portions of the original procaine hydrochloride solution (pH of series, 5.1-9.6). In the figure the 2 series of solutions fall on the same curve when the time to anesthetize is plotted against the concentration of free base, and coincide almost as closely when the time for recovery is used as the measure of anesthetic activity. It is evident that neither the total anesthetic concentration nor the pH but the concentration of free base is the variable in the 2 series determining the anesthetic activity.