Comments and Communications

Dimenhydrinate vs. Diphenhydramine

The recent comments by Mark Nickerson (*Science*, 1950, **111**, 312) are pertinent ones; he suggests that, in view of the lack of evidence for any pharmacological action of 8-chlorotheophylline, it would seem improbable that dimenhydrinate (i.e., diphenhydramine-8-chlorotheophyllinate) should possess therapeutic properties differing appreciably from those of the antihistamine component, diphenhydramine. This point is even more valid in view of clinical demonstrations of the antinauseant and antiemetic effects of several antihistamine drugs in some of those conditions for which dimenhydrinate has been advocated, viz., motion sickness, nausea, and vomiting of pregnancy.

However, with reference to the treatment of radiation sickness it has been claimed (Tillisch, J. H. *Proc. Staff Meet. Mayo Clin.*, 1949, **24**, 477) that dimenhydrinate is more effective than other more potent antihistamines, and some specificity of action for this drug in depressing the vomiting center is suggested. Quite recently, evidence has been presented favoring the slight protective action of 8-chlorotheophylline in airsickness (Chinn, H. I., and Oberst, F. W. *Proc. Soc. Exp. Biol. Med.*, 1950, **73**, 218) although the same study failed to disclose any superiority of dimenhydrinate over diphenhydramine. Most recently, however, experiments have been described (Chen, G., and Ensor, C. R. *J. Pharmacol. exp. Therap.*, 1950, **98**, 249) showing the equivalent effectiveness of diphenhydramine and dimenhydrinate, and the lack of effectiveness of 8-chlorotheophylline in protecting dogs against apomorphine-induced vomiting.

A few months ago we undertook some preliminary experiments to ascertain any possible antiemetic specificity for dimenhydrinate as compared to diphenhydramine. In a group of three cats the reliable emetic dose of apomorphine was determined as 50–75 mg subcutaneously; with this dose emesis occurred invariably within 5–6 min. We determined next that, depending on the amount of emetic injected, dimenhydrinate by mouth 15 min prior to apomorphine protected the respective animals in a dosage of 50–100 mg.

These quantities of dimenhydrinate and diphenhydramine were compared for protective action, alternating the drug used and allowing adequate recovery intervals, and also retesting with apomorphine from time to time to detect any acquired resistance to the emetic action. In a series of 15 trials dimenhydrinate gave complete protection in 13 instances; in the other 2 instances vomiting occurred in 14 min and 48 min. In a series of 12 trials diphenhydramine gave complete protection in only 2 instances; in the other 10 instances vomiting occurred in 20–90 min.

These preliminary results suggest to us some superiority for dimenhydrinate over diphenhydramine. In view of the fact that equal quantities were tested, and that the antihistamine base represents only about 55% of the weight of dimenhydrinate, it would seem that the antiemetic action of the latter drug is not predicated solely on the basis of its antihistamine component. Since diphenhydramine does offer some protection—in that vomiting is appreciably delayed as compared to untreated animals—it may be that, as a result of different absorption and excretion rates, higher blood or tissue levels are maintained for a longer period with dimenhydrinate than with diphenhydramine.

Later experiments have suggested a high degree of protection with 8-chlorotheophylline, but these results cannot yet be considered significant, since it is apparent that the animals have now developed some resistance to the emetic action of apomorphine.

A continuation of these experiments on a larger number of animals will be described in detail at a later date.

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On the Theory of Odors

I cannot resist the temptation to add one more hypothesis on the nature of the sensation of smell to speculations of others on this subject. Several characteristic traits of this sense can be accounted for without infringing on basic physical principles if it is attributed to the inhibition of certain enzymes contained in the olfactory organs. Suppose that a system of enzymatically catalyzed reactions represented schematically, for instance, by $A \rightarrow A' \rightarrow A''$; $B \rightarrow B' \rightarrow B''$; $C \rightarrow C' \rightarrow C''$; etc., is causally related to the olfactory nerve signals. Each step, as $A \rightarrow A'$ or $A' \rightarrow A''$, is catalyzed by a separate enzyme, and each of the compounds A′, B′, C′, etc., in a number related to the number of basic smells, is capable of causing a signal in a distinct nerve when its concentration is altered. This particular reaction scheme is of course not essential to the following. What is essential is some mechanism by which changes in concentration of several active enzymes are converted into distinguishable nerve signals. The effect of a compound possessing the property of odor is the inhibition of one or more of these enzymes, causing a shift in relative concentrations of A′, B′, C′, etc., and thus producing signals in the nerves that respond to these compounds.

This proposal has the merit of accounting for a number of known traits of the sense of smell: (1) high smell sensitivity becomes plausible because the quantities of the enzymes involved may be exceedingly minute; the intensity of smell becomes related to the extent of inhibition; (2) the wide range of compounds having odor becomes understandable because enzymes are frequently inhibited by a great variety of compounds and yet show definite selectivity in this respect; (3) complex odors are seen to be the result of inhibition of several of these