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 accurred 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 enzymes by the compound in question, and apparent changes in the quality of smell with the concentration are the result of (nearly) total inhibition of some of the enzymes; (4) reversibility of most odors corresponds to the reversibility of many enzyme inhibitions, but there is the possibility of nonreversible inhibition by other compounds, which corresponds to the persistence of certain odors.

As I have no means for carrying out physiological experiments and, moreover, have not conceived of any tests which might be termed crucial for this hypothesis, it is being offered as a mere speculation.

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Errata

In the article "Hemophilia in the Female Dog," by Kenneth M. Brinkhous and John B. Graham (*Science*, 1950, **111**, 723), the caption for the fourth column in Table 2, on page 724, should read: "Prothrombin utilized during 1st hr."

In the article "The Availability of Various Manganese Oxides to Plants," by G. W. Leeper (*Science*, 1950, **111**, 463), two lines should be inserted after the word "failed" (col. 2, par. 2): "to distinguish between them. However, a solution of quinol in water with no added electrolyte gave quite a . . ."

Book Reviews

The Nature of Physical Reality: A Philosophy of Modern Physics. Henry Margenau. New York-London: McGraw-Hill, 1950. 479 pp. $6.50.

In this very interesting book Prof. Margenau, a theoretical physicist by profession and a philosopher par excellence, presents his views on the philosophical foundations of modern physics. Although as a rule there are as many opposing philosophical systems as there are people thinking about them, they can usually be divided into groups bearing well-established names. Thus we learn that "Planck and Einstein are critical realists, Eddington and Weyl moderate idealists, and Bohr and Heisenberg vaguely display the colors of positivism" (p. 12). In this sense the author of the book can probably be described as the proponent of the Neo-Kantian school of thought, inasmuch as he states (p. 58) that

> clear cognizance of the distinction between *synthesis and integration* on one side, and *imaginative supplementation* of the perceptually given on the other, has been apparent in *the Kantian and Neo-Kantian* school of thought, and much of the emphasis conferred upon this point by that school is now *indispensable as a condition for comprehending modern science.*

With this *modus operandi* the author enters into a detailed discussion of the fundamental notions of space and time, and their union in the form of Einstein-Minkowski's four-dimensional world. This is followed by an interesting presentation of the basic problems of statistical mechanics and their bearing on the philosophical interpretation of the laws of probability. The last third of the book is devoted to the problems of quantum theory, causality, and the exclusion principle. It is in this part that a philosopher will become particularly aware of the enormous impact made upon his traditional problems by the factual discoveries of science. Being an expert in the field of theoretical physics, the author presents his material with great clarity, entering into a discussion of such ultramodern problems of physical theory as the current difficulties of quantum electrodynamics and the problem of elementary particles.

On the whole, this book presents an invaluable source of information for a philosopher who would like to get the authoritative up-to-date picture of the advances of modern physics. On the other hand, the reviewer is not quite sure about the use that can be made of his book by the professional physicists, but it is probably because he belongs (p. 13) to

> the ranks of the exterminator brigade, which goes noisily about chasing metaphysical bats out of scientific belfries.

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Lehrbuch der Theoretischen Physik: Physik der Vorgänge-Bewegung, Elektrizität, Licht, Wärme, Bd. I. Walter Weizel. Berlin W35, Germany: Springer-Verlag, 1949. 771 pp. DM 56.90 bound, 53 paper-bound.

This is an excellent text, written with the thoroughness that comes from a deep understanding of the unity and coherence of classical theoretical physics. This is not to say that the subject is considered as finished and complete. The limitations are carefully pointed out and, where appropriate, hints are given as to the successes of quantum theory to be treated in the second volume, which is to deal with the theory of matter.

The present volume includes classical mechanics, elasticity, hydrodynamics, electrodynamics, optics, relativity, and thermodynamics. Each of these fields is treated thoroughly. Although the material is presented in concise form the treatment is not sketchy; sufficient detail is always given to enable the reader to follow the line of argument without difficulty. The subject of mechanics, for example, is covered in 138 pages, starting with the motion of a particle, then discussing motion of a system of particles, introducing the Lagrange equations of the first and second kind for free and constrained