

Reports and Letters

Chemical Model of Drug Action

Orienting experiments were performed to test a working hypothesis on the mode of action of some drugs. The hypothesis is based on the observation that a striking number of drugs that display a great variety of effects contain certain functional groups at the same distance of about $5\frac{1}{2}$ Å from each other (1) as the distance between two turns of the α -protein helix (2). The fact that these functional groups (hydroxyl and amine) are capable of hydrogen bonding suggests that the molecules of such drugs might be able to attach themselves by hydrogen bonds to proteins, thus changing the native hydrogen bonding arrangement and the shape of the protein molecules. If the protein is an enzyme, and if the change is great enough and occurs at a sufficiently critical point of the enzyme molecule, an alteration of its specificity may result. Drug action could be the consequence of such alteration in an enzyme.

Should this picture correspond to reality, the hydrogen bonding of properly spaced functional groups would account for the (nonspecific) ability of drugs that possess these functional groups to attach themselves to proteins. Other structural features—benzene rings, alkyl chains, acyl groups, and so forth—must then be held responsible for the specific action of each drug by preferentially adhering to one or the other particular enzyme in a way that essentially changes the shape of the enzyme molecule. Further hydrogen bonding, electrostatic interactions, appropriate spatial fit of the two molecules, and other factors may play a role in this specific drug-enzyme interaction.

The difficulty of seeing clearly in the interaction of complicated drug molecules with complex proteins prompted us to reduce the experimental situation to its bare essentials. Our first orienting experiments were therefore designed to provide information on whether a simple molecule that possesses only the requisite two functional groups at $5\frac{1}{2}$ -Å distance and thus serves as a model for all drugs with such functional groups is able to associate with amino acids and simple peptides by hydrogen bonding. To this end, the drug model was brought to equilibrium be-

tween water and a lipophilic solvent, and it was determined whether, other things being equal, the presence of an amino acid or peptide in the aqueous layer shifts the distribution of the drug model in the direction of water.

As a lipophilic solvent, we used chloroform. As the drug model, we selected diethylaminoethanol (DEAE) for the following reasons: (i) it is easily available in high purity; (ii) it has the desirable water-to-chloroform distribution ratio of about 1 to 2, and (iii) since it is a base, it is readily estimated by titration. (Our method was *pH* titration.) The conditions of the experiment were fixed in such a way that 100 mg of amino acid or peptide were added to 10 ml of water, the *pH* of the resulting solution was measured, 10 ml of chloroform and 50 mg of DEAE were added and stirred to equilibrium, the chloroform layer was extracted with excess standard HCl, and the amount of DEAE in it was determined by back-titrating the excess. We worked on the chloroform layer because the insolubility of amino acids and peptides in it provides a simpler situation than that provided by the aqueous layer, which contains amino acid or peptide in addition to DEAE. In order to eliminate *pH* effects, the experiment was repeated without amino acid or peptide, using a buffer solution of the same *pH* as was measured originally for the amino acid solution; the distribution of DEAE between water and chloroform obtained at this *pH* was taken as the blank with which its distribution in the presence of amino acid or peptide was compared.

Each experiment was performed 12 times, and the average of the results was taken; the maximum deviations of individual values from the average were generally 8 percent either way.

It was found that, under the conditions established for these experiments, the following figures represent the mole-percent of each amino acid and peptide that is bound to DEAE: glycine, 1; alanine, 1; glycyl alanine, 40; glycyl glycyl glycine, 50; alanyl glycyl glycine, 55; leucyl glycyl glycine, 61. Since the comparison with the blank excludes *pH* effects, we believe that these figures do indeed show the effect of hydrogen bonding be-

tween DEAE and the various amino acids and peptides used. Whether our findings can be generalized to other amino acids, peptides, and proteins on the one hand, and to actual drugs on the other hand, and whether any definite stoichiometric relationships exist in this binding is the subject of further research now in progress that will be reported from time to time.

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References and Notes

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2. L. C. Pauling and R. B. Corey, *Proc. Natl. Acad. Sci. U.S.A.* 37, 204 (1951).
3. This investigation was supported by a grant from the John J. Pender Cancer Fund.
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Intracellular Recording from Moving Tissues with a Flexibly Mounted Ultramicroelectrode

Intracellular recording with Graham-Ling-Gerard microelectrodes (1) (tip diameter less than 0.5 microns) has proved useful for studying the electric activity of excitable tissues. However, muscle studies have been hampered because the movement that accompanies activity often dislodges the electrode, damaging the cell and occasionally breaking the electrode. This problem is particularly acute in cardiac muscle. Heretofore, the attempt has been to immobilize the tissue with respect to a rigidly mounted electrode (2, 3). This report describes a technique for flexibly mounting an ultramicroelectrode (UME) so that it moves easily with an unrestrained tissue without being dislodged (4). When this mounting is used, recordings of intracellular activity that were previously difficult or impossible to obtain can be made routinely. For example, consistent recordings can be obtained from a heart moving as much as 2 cm.

A piece of 1 mil (0.001 in.) bare tungsten wire several inches long is pushed into the large end of a microelectrode until the wire end jams in the tapering region of the electrode. This force fit is tight enough to hold the electrode tip on the wire after the portion of the UME that is larger than the wire has been broken off. The break is made by holding the tapered region firmly with the thumb and forefinger of each hand and gently bending the electrode until it breaks. If excessive force is applied, the tip may also snap off. The necessary force is usually not excessive if the break is made near the jammed end of the wire. The