SCIENTIFIC MEETING

DRUG ACTION, IONS AND NEUTRAL MOLECULES

by ADRIEN ALBERT, D.Sc. Ph.D. B.Sc., F.R.I.C.

Summary of a paper read at the Norwood Branch of the Royal Institute of Chemistry, at the Norwood Technical Institute on December 6.

MANY drugs undergo ionisation and a number do so to different degrees at different *p*H values. The most significant changes in ionisation occur around the *p*H value at which the drug is 50 per cent. ionised, i.e., the pk_A value. Ions and molecules behave differently in their effects on drug action, especially in relation to chemical reactivity, adsorption and the penetration of membranes. An example of the first difference is shown by aniline, where the molecule is nitrated mainly in the *para* position, but the ion is nitrated in the *meta* position. Again the mono-anion of ascorbic acid is easily autoxidised, whereas the di-anion and the molecule are both quite stable. A distinction is made between general and specific adsorption. In the former, the drug is rejected by water because of a relative lack of hydrophilic groups and becomes adsorbed on any surface which offers itself. In such cases the molecule is usually more highly adsorbed than the ion, because the latter is hydrated at one end. In specific adsorption the drug, which may have many hydrophilic groups, is specifically attracted to cellular receptor-groups by reason of having a complementary structure. This often takes the form of the drug being kationic and the receptor anionic, or *vice versa*. In such a case, only the ion can be adsorbed. Generally, for any one substance, the molecule penetrates much faster than the ion. The principal barrier to the penetration of an ion is the strong attraction between its charge and the oppositely charged groups on the cell membrane. However, if ions are provided with lipophilic groups, penetration is considerably improved.

In view of these marked physico-chemical distinctions between ions and molecules, it is not surprising to find that some drugs (such as the acridine antibacterials) have ions that are many times as active as the neutral molecules. Other drugs are known (e.g. benzoic acid) where the activity is proportional to the amount of non-ionised material present. Information of this kind can be gathered from reasonably simple experiments, in which firstly a given drug is examined biologically over a range of *p*H values and then a series of related substances, differing widely in pk_A values, is examined at the physiological *p*H value (*p*H 7).

Such information is of considerable practical use. Modern knowledge of inductive constants enables the pk_A of a substance to be varied at will by the insertion of appropriate groups, so that ionisation can be either increased or repressed at a given *p*H value. In some classes of drugs, such as the sulphonamides, a more complex picture is presented, where the maximum activity is obtained when the drug is half ionised. The usual interpretation of this is that the neutral molecule is required in order to penetrate into the cell, but that the ion is regenerated within the cell (according to the law of mass action) and is, of the two, the more biologically active.