SCIENTIFIC MEETINGS

SOME ASPECTS OF PHARMACOLOGICAL CHEMISTRY

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ONLY the symptomatic drugs were considered in this series. The first lecture dealt with the significance of total chemical constitution and the theories of modes of drug action[1]. Examples indicating constitution-action-parallelism were quoted, but it was emphasised that much more data were required to produce a more secure basis for a rational approach. In the next lecture the work on the analgesic substances, particularly on morphine, was discussed[2]. On the third occasion the chemistry of the parasympathomimetics and parasympatholytics was considered. These drugs are based on acetylcholine, which is not strange to the organism. Acetylcholine has three pharmacological actions, muscarinic, nicotinic and under certain conditions, curare-like. As an ester, it is hydrolysed by the enzymes, cholinesterases of blood cells and plasma and transformed into the weakly active choline. Its re-synthesis may be due to the action of an acetylase, the co-enzyme of which may consist partly of pantothenic acid. Its existence was demonstrated by Feldberg and Mann in brain and by Bülbring and Burn in rabbit heart auricles. There exists also an inactive acetylcholine complex, the formation of which may partly explain the disappearance of the neurohormone. That it also occurs in plants was shown by Feldberg's discovery of acetylcholine in the stinging nettle. The instability and amphotropic properties of acetylcholine stimulated the pharmacological chemist to synthesise substances with more sustained and clear-cut action. When considering substances which, like acetylcholine, possess parasympathomimetic action, Pfeiffer's theory of prosthetic[3] distances comes to mind, postulating an optimum distance between the N-methyl group and the two oxygen atoms. Thus it can be understood why three natural drugs—muscarine, pilocarpine, and arecoline—show, on the whole, lower activities and have never gained clinical importance. Virtual changes of the acetylcholine molecule itself have produced evidence that the free aminoalkanols are very much weaker and that, for the existence of full muscarinic action, the alcohol group must be esterified and the nitrogen carry at least two methyl groups. When the chain of the alcohol or the acid is elongated, activity falls considerably. There is one exception, and that is when the aminoalkanol chain is branched, as in mecholyl which shows strong muscarinic effect. Acetic acid has been exchanged against other acidic residues, such as carbamic acid in carbachol, thioacetic acid, etc. Transformation of the choline ester into choline ethers produces more stable but less active compounds. An ether-like product was made by Fourneau (2268 F) and found to be very potent indeed. Another ether-like compound is Esmodil which contains a double bond like arecoline and croton betaine methyl ester. The latter, carrying the nitrogen on the acidic side, is very much like acetylcholine though weaker. While choline itself shows very little activity, 3-hydroxymethylpyridine, the alcohol corresponding to nicotinic acid, possesses interesting parasympathomimetic properties. Other aromatic compounds with phenolic groups in place of alcoholic hydroxy groups, show remarkable properties, especially when esterified with carbamic acid. Such substances, like physostigmine, Prostigmine (neostigmine) are

not only stable towards cholinesterase, but inhibit the action of cholinesterase on acetylcholine in a reversible manner. A similar action had been described for *bis-p*-dimethylaminobenzylacetone dimethiodide and for various alkyl phosphates, although the latter combine irreversibly with cholinesterase. The " stigmines " act against the effect of curare, but are seemingly not able to counteract the curariform action of *bis*-trimethylammonium decane.

While the nicotinic action of acetylcholine is antagonised either by ganglia-blocking agents, such as tetraethylammonium salts or *bis*-trimethyl-ammonium pentane, or on the skeletal muscle side by curariform compounds, the muscarinic action of the cholinergic neuro-hormone and parasympathomimetics is antagonised by atropine. This drug, together with similarly acting compounds, named parasympatholytics, and the papaverine and anti-histamine group, form what one may call the larger group of anti-spasmogenics or spasmolytics. There is hardly any representative of this group which does not possess a multiplicity of action but usually one predominates over the others, either the atropine-like, the musculotropic papaverine-like, or the histaminolytic. The parasympatholytics or anti-acetylcholine drugs represent mostly nitrogen-containing esters which, when Pfeiffer's theory of prosthetic distances is applied, show similar distances between the nitrogen-methyl group and the two oxygens to those of the protagonist group, the parasympathomimetics. This represents a very neat illustration of the receptor theory.

On looking through the list of drugs of the parasympatholytic group, we find that the acid part of the ester is " heavier " than acetic acid, Pfeiffer's umbrella effect being obtained by additional phenyl or hydroxy groups. The alkanolamine part need not be so complicated as the tropine of atropine, but can be represented by dialkylamino alkanols. The original tropic acid has been changed in time to mandelic, benzilic, diphenylacetic and fluorene carboxylic and dihydroanthracene carboxylic acids. Compounds prepared for different purposes, but showing, superficially, similarities with the atropine group, except for the fact that they are not esters, show varied amounts of parasympatholytic activities; but even compounds like Benadryl or diphenylpropylamines, without oxygen, still possess measurable anti-acetylcholine action in addition to anti-histamine and anti-barium activities.

References

1. Bergel, *J. Soc. chem. Ind., Lond.*, 1949, in the press.
2. Bergel and Morrison, *Quart. Rev.*, 1948, **2**, 349.
3. Ing, *Science*, 1949, **109**, 264.