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ACETYLCHOLINE

Professor F. R. Fraser's Croonian Lectures, the last of which appears in our columns this week, give a lucid and well-documented account of the present state of knowledge of the therapeutic uses of acetylcholine and related substances, and afford an opportunity for discussing briefly a few points in connexion with one of the most interesting chapters in modern physiology. Experimental work has shown that acetylcholine is liberated in nerve endings in many parts of the body, including the terminals of all the parasympathetic and somatic motor nerves and the preganglionic fibres of the whole autonomic system. There are excellent reasons for believing that acetylcholine is probably concerned with the transmission of the nerve impulse in this region; but it would be unwise to conclude as yet that it is the sole mechanism involved and that no other agencies play a part. Be that as it may, those properties which make acetylcholine highly suitable as a nerve transmitter make it highly unreliable as a therapeutic agent. The transmitter must be a very unstable substance which can be disposed of with great rapidity, so that the peripheral response of the organ to the nerve impulse should not be unduly prolonged. As Professor Fraser has pointed out, when acetylcholine is administered to man by any route it is rapidly destroyed by the specific enzyme cholinesterase in the blood and in the tissues, so that its effects, even when given in comparatively large doses, are uncertain and evanescent and usually disappear completely in a few seconds or minutes. It is improbable, therefore, that much can be expected from the use of acetylcholine in the treatment of high blood pressure or of intestinal atony. To overcome the difficulties enumerated one may use other and more stable choline esters which act for longer periods or else employ drugs of the eserine or prostigmin type which inhibit the action of cholinesterase, preserve naturally formed acetylcholine, and, so to speak, make it available for therapeutic purposes.

Professor Fraser discusses the use of carbaminoylcholine (doryl) and of acetyl-β-methylcholine (mecholy). Both substances have been tested in vasospastic conditions, but although symptoms were relieved no permanent effects have been noted on the blood pressure in cases of hypertension. It is claimed that attacks of paroxysmal tachycardia may be brought to an end by injections of these drugs, but anyone with experience of the natural history of this condition would hesitate to dogmatize about the relation of the treatment to the result. Apart from possible uses in ophthalmology, it seems well established that doryl especially is useful in overcoming post-operative intestinal atony and retention of urine due to weakness of the bladder wall. Of the anticholinesterases studied prostigmin has proved to be the most useful, both for its stimulating action on the bowel and, more especially, for its dramatic ameliorative effects in myasthenia gravis. Eserine, although it has the same general actions, is less satisfactory for systemic purposes as it produces in man severe cardiovascular depression, vomiting, headache, and general malaise. Although the muscular weakness of myasthenia gravis can now be readily controlled no final conclusion has yet been reached as to the underlying disturbance. There is at present no proof of either insufficient formation or excessively rapid destruction of acetylcholine at the nerve endings in muscle. On the other hand, recent observations by Dr. Mary Walker indicate that in this disease a substance may be formed at the motor endings which resembles curare in blocking the transmission of the impulse from nerve to skeletal muscles. When a myasthenic patient exercised the arms (after the blood supply to them had been blocked) to the point of exhaustion Walker found that on release of the circulation weakness developed in the muscles of the rest of the body, suggesting that some chemical agent had been freed from the ischaemic limbs. Further observations on these points will be awaited with much interest.

There is still no direct evidence that acetylcholine is concerned with the transmission of impulses in the central nervous system. The researches of Schweitzer and Wright,[1] however, show that both acetylcholine itself and anticholinesterase drugs act directly on the spinal cord in cats, and it has now been confirmed[2] that prostigmin given intrathecally produces striking changes in reflex activity in man. A recent paper by Schweitzer and Wright[3] throws further light on this complex problem. They examined the pharmacological actions of two derivatives of the dimethylcarbamic ester of hordenine —namely, the hydrochloride and methiodide. Both substances are anticholinesterases; they are equally potent *in vitro* and have identical actions on muscle and other peripheral organs; yet they

[1] *J. Physiol.*, 1937, **89**, 165, 384; **90**, 310.
[2] Kremer, M., Pearson, H. E. S., and Wright, Samson. Ibid., 1937, **89**, 21 P.
[3] Ibid., 1938, **92**, 422.

differ fundamentally in their central effects, the hydrochloride being convulsant and the methiodide a central depressant. Further experiments[4] suggest that these differences are to be attributed mainly to the physical (rather than chemical) properties of the substances concerned. The hydrochloride gives rise in the body to a derivative containing tertiary nitrogen, which is lipoid-soluble, and so can probably penetrate into the interior of the nerve cells; the methiodide, on the other hand, gives rise to a water-soluble derivative containing quaternary nitrogen, which is perhaps compelled to remain outside the surface membranes of the nerve cells. More extensive investigations suggest that this general rule probably applies to the anticholinesterase group as a whole so far as their action on the central nervous system is concerned. These conclusions will have to be taken into serious consideration when any theory of central transmission is ultimately promulgated.

TREATMENT OF PNEUMONIA

We referred not long ago in these columns[5] to the great advances which have been made in the United States in the study of pneumonia and in the direction of making serum treatment for this disease generally available. One of the great organizations taking part in this campaign published two years ago a useful practical handbook entitled *Lobar Pneumonia and Serum Therapy*, which we reviewed at that time.[6] A second edition has now appeared, with a significant change in title—*Pneumonia and Serum Therapy*[7]—the word "lobar" being omitted. Implied in this change is one of the advances which have taken place in these two years and are recorded in this edition. The study of the "higher types" of pneumococcus has shown that some of these types, which more often occur in bronchopneumonia than the classical Types I, II, and III, are capable of causing a severe form of the disease; such of these infections by the higher types as have been subjected to serum treatment have been found amenable to it. Among the data assembled in this volume are the results, including some hitherto unpublished elsewhere, so far obtained in treating pneumonia due to Types V, VII, VIII, and XIV. Another new factor in the situation is the advent of rabbit therapeutic serum. It will be remembered that in this animal, according to recent observations, antibodies to the pneumococcus are produced more rapidly and in greater quantity than in the horse, and they have the advantage, owing to the smaller size of the rabbit globulin molecule, of greater diffusibility in the body. Although results with this serum continue to be encouraging, they are not considered to have reached such a stage as to justify general use. Besides reporting these new developments, and bringing up to date the imposing mass of evidence on the results obtainable with serum treatment, this volume remains an invaluable practical guide in which every detail of procedure connected with serum administration, including preliminary typing and tests for hypersensitiveness, is carefully and simply explained and illustrated by diagrams. Special emphasis is laid on the importance of blood culture as a prognostic aid and a guide to serum dosage. It is also emphasized that even in apparently mild cases "there may be a rapid or gradual transition from a condition of apparent safety to one of great gravity"; for this reason *every* case amenable to serum treatment should receive it. This is a vital question, and it is here that the American attitude differs from that usually taken here; whether this difference is justified by a lower mortality from pneumonia and a generally more favourable course followed by the disease in this country is a matter which, as we have pointed out before, calls for careful investigation and decision.

The stupendous effort which has organized the treatment of pneumonia in some of the eastern States of America and achieved such results as have been mentioned has been financed by the States themselves, by insurance companies, and by large charitable funds. It has no parallel in this country, and, as we pointed out in reviewing this subject before, serum treatment cannot be made universally available without concerted action, in which it seems that public health authorities should take a leading part. It is possible that, even if such an effort were accepted as desirable and feasible, it may become unnecessary, and indeed that the whole of the vast structure which has been built up in the United States may yet be abandoned, having served its turn. Chemotherapy, having conquered in the sphere of streptococcal infection, is turning its attention more seriously to the pneumococcus, and it is reported by Whitby[8] that an entirely new sulphonamide compound—2(*p*-aminobenzenesulphonamido)-pyridine—has a striking curative action on pneumococcal infection in mice; an account by Drs. W. A. Oliver and Maxwell Telling[9] of its effect on three cases of pneumonia suggests that this experimental action will be confirmed clinically. But for the fact that experimental results with these drugs have always hitherto

[4] Schweitzer, A., Wright, Samson, and Stedman, Edgar. *J. Physiol.*, 1938, **92**, 6 P.
[5] *British Medical Journal*, 1938, 1, 76.
[6] Ibid., 1936, 1, 758.
[7] *Pneumonia and Serum Therapy*, by F. T. Lord and R. Heffron. New York: The Commonwealth Fund; London: Oxford University Press, 1938. (4s. 6d.)
[8] *Lancet*, 1938, 1, 1210.
[9] Ibid., 1938, 1, 1391.