Editorial

NEUROLOGICAL THERAPEUTICS

It has occasionally been said of organic diseases of the nervous system that while constituting a most interesting field of study in applied physiology and pathology, they are therapeutically destitute. An ardent neurologist might have replied that treatment in organic neurology at all times compared favourably with that in organic medical diseases, such as chronic conditions of the heart, liver and kidneys. We utter a truism in adding that all advance in knowledge of the aetiology, pathology and diagnosis of a disease inevitably leads to increased understanding of the possible means of treatment. It is to these aspects of organic disease of the nervous system that most neurological research has been directed, with many brilliant results. Nevertheless, in reviewing the progress of neurology during recent years, it is evident that increasing attention has been paid to treatment per se and that the advances have been considerable. Several diseases, formerly considered almost untreatable apart from general care and management, are now subjected to direct attack.

Foremost among these is that form of progressive syphilitic meningencephalitis, popularly though unfortunately known as 'general paralysis of the insane.' The application of malarial therapy undoubtedly inhibits the malady in the majority of early cases with the result that after a number of years, varying from two to six, the cerebrospinal fluid becomes normal, losing its increased protein content, positive Wassermann reaction and Lange curve. Patients are known among the first to be treated in this country—some 14 years ago—who still survive and in some instances remain useful members of society. An average of the available statistics indicates that approximately 35 per cent. of all cases treated—irrespective of the stage of the disease—show good and lasting remissions, while in a fair proportion of the remainder improvement or arrest of the disease occurs. Compare this with the prognosis invariably given prior to the introduction of malarial treatment
—that following a progressively increasing dementia the disease would prove fatal within three years.

The prognosis with malarial therapy varies with the stage of the disease at which it is possible to apply the treatment—the earlier in the malady, the better is the outlook. Many cases, however, do not come under observation until they are admitted under certificate to a mental hospital and when the brain may have already suffered irreparable damage. For this reason statistics confined to early cases would show an even higher recovery rate. Many factors in the treatment still await further elucidation. For instance, what is the exact mechanism by which malaria counteracts the syphilitic disease? Is improvement in the latter due to leucocytosis, pyrexia, antibody-formation, increased metabolic action or general vasodilatation? As far as our present knowledge goes, increase in the large mononuclear cells and possibly the occurrence of an immunizing reaction against the stroma of destroyed red blood corpuscles appear to play a considerable part. Again, from the clinical aspect, why do some cases—even early in the disease—fail to react to malaria therapy and why do others eventually show negative Wassermann reactions in the blood and cerebrospinal fluid and yet deteriorate clinically?

Other methods of inducing pyrexia have also been tried, such as relapsing fever, various bacterial vaccines injected intravenously, saprovitan, injections of milk, sulfosan and radiothermy (electropyrexia), but malaria therapy still appears much superior to all. As regards radiotherapy, claims have already been made that the method is at least equal to malaria in its immediate clinical results. Further observations a few years hence, however, will decide this question. At the outset, the claim must be received with reserve, as the benefit in degenerative syphilitic encephalitis accruing from malaria therapy appears not necessarily to depend exclusively on the pyrexia, good results having been reported by Wagner-Jauregg and others when the induced malaria has been entirely or almost afebrile.

Another organic disease viewed until recently with comparative therapeutic helplessness to which it is now possible to apply some direct treatment is progressive muscular dystrophy. Many years ago the observation was made that the urine of patients suffering from myopathy contained creatin—a substance not excreted under normal conditions. It would appear that the muscles affected by the dystrophy are unable to retain creatin, whether of exogenous or endogenous origin.
The administration of an amino-acid in the form of glycine or glycocoll was found to give rise to definite clinical improvement. Its mode of action is probably twofold: by promoting creatin formation, and by enabling the muscles to retain and metabolize the creatin. The chief obstacle to a widespread application of the treatment is the present high cost of the substance glycine, large doses varying from 10 to 30 gm. a day being necessary. Glutamic acid or monosodium glutamate may be used as substitutes, and gelatin contains 20 per cent. of glycocoll. Treatment with the latter in doses of 100 gm. per day given with orange or lemon juice is worthy of extended trial at relatively small cost.

Again, the institution of treatment as early as possible in the course of the disease is essential, as improvement depends upon the condition of the muscle-fibres at the time treatment is started. Amelioration cannot occur in atrophied muscles in which the nuclei of the fibres are already disintegrated and no form of treatment could be expected to prevent further degeneration. There can be no question concerning the initial improvement in cases of myopathy treated with glycine, but it remains to be seen how far this therapeutic method is able to avert the usual progress of the malady.

The recent discovery that injections of physostigmine and its analogue prostigmin lead to temporary abolition of the muscular weakness in myasthenia gravis is distinctly encouraging. It has also been found that atropine given at the same time as the prostigmin prevents the colic and nausea resulting from the latter substance without impairing its action on the muscles. The optimum dose of prostigmin appears to be 5 c.cm. (2.5 mg.) given with 1/100 gr. of atropine. Improvement in the affected muscles begins in about one hour and lasts up to six hours, and two injections a day may be given. The effect of the prostigmin is said to be due to its property of delaying the destruction of acetylcholine at the motor nerve-ending by the choline esterase normally present in the blood. If it is a fact that nervous impulses set free acetylcholine or some analogous substance at the nerve-endings, it would appear that in myasthenia gravis there is an insufficient supply of this substance. Prostigmin, by delaying the destruction of acetylcholine, tends to compensate for the deficiency.

On this hypothesis, defective innervation resulting from a disability of the lower motor neurone—whether in the anterior horn cells, in the nerve-fibres or in the nerve-endings—should tend to be compensated by an injection of prostigmin. From
experiments in cases of neuritis and anterior poliomyelitis this indeed appears to be the case. Consequently, an even wider field of experimental therapeutics is revealed.

It might be said that it is inconvenient to give a patient one or two hypodermic injections each day. Nevertheless, it is routine in diabetes for the patient to measure and inject his own doses of insulin; sufferers from myasthenia may similarly be educated to give their own injections of prostigmin and atropine.

As with glycine, the cost of prostigmin is a difficulty, and various substitutes have been suggested and tried—e.g. physostigmine salicylate in doses of from $\frac{1}{8}$ to $\frac{1}{6}$ gr. given in water by the mouth and preceded by 15 to 20 minims of tincture of belladonna. In the hands of one observer this method was said to be followed by improvement in 20 minutes, reaching a maximum in from one to two hours and lasting about five hours. Some faintness and a weak pulse during the first two hours were concomitant symptoms. It is evident that individual patients have different degrees of tolerance to physostigmine by the mouth, as other observers failed to observe the improvement in myasthenia from this method while noting epigastric pain, chilliness, nausea, vomiting and a weak pulse in the cases treated. Potassium chloride in large doses (10 to 12 gm.) given by the mouth in a tumblerful of water has also been tried. The use of this substance is based on the observation that it has a stimulating effect on ganglion cells and that it raises their excitability to pre-ganglionic stimuli and to acetylcholine. Improvement in the myasthenic symptoms lasts about two hours. Diuresis occurs constantly after each dose of the potassium chloride and unpleasant symptoms may be nausea and mild diarrhoea. In smaller doses, however, it may serve as a useful adjunct to prostigmin treatment, as some patients complain of undue fatigue after the effects of the latter substance have worn off. A dose of from 4 to 6 gm. of potassium chloride taken shortly before the action of prostigmin has passed relieves the feeling of exhaustation and tends to prolong the period of improvement.

Idiopathic narcolepsy is yet another disease of the nervous system to which improved treatment is now applicable. The use of ephedrine in this disorder was a distinct advance on the older methods of prescribing caffeine and thyroid extract. More recently Prinzmetal and Bloomberg in America have reported even better results with benzedrine sulphate. This
substance is related both to epinephrine and ephedrine and has a greater stimulating effect on the central nervous system than the latter. It is further of comparatively low toxicity. Almost complete relief of the narcoleptic attacks occurred in every instance of the disease treated, with considerable improvement in the cataplexy when present. Using control cases, the authors named considered that benzedrine was three times as effective as ephedrine and that even small doses of the former produced complete relief of symptoms in cases which were not relieved by large doses of ephedrine. The dosage of benzedrine varies from 10 to 30 mg. morning and afternoon, with a smaller dose early in the evening according to the effect on the normal night sleep. Further experience confirms the claims made for this substance in narcolepsy; indeed, it is usually advisable to omit the evening dose owing to the development of nocturnal insomnia.

From the observations made above, it may be deduced that the immediate future of therapeutics in organic neurology lies mainly in the researches of biochemistry and experimental pharmacology.