the specific receptors, but produces an increase of the dopamine concentration in the synapse by some other means. I shall discuss the probable mechanisms of action tomorrow, but would like to point out now that, irrespective of the possible mechanism, the dopamine probably originates from the pre-synaptic fibre.

On the biochemical evidence we assume that the dopamine content of the substantia nigra is lowered in Parkinsonism. One can reason that when it is very low, amantadine will have little effect, since it is dependent on dopamine from the pre-synaptic fibres for its action. Under these conditions one may also expect very little, if any, enhancement of the effect of L-dopa.

If the severity of Parkinson's syndrome can be relat d to the degree of destruction of the pre-synaptic neurones only (this may not be a valid assumption), I would expect that amantadine would be of more value in the treatment of milder cases and of little value in the treatment of severe cases. I would also expect a more pronounced synergism between amantadine and L-dopa in mild or moderate cases then in severe ones, although synergism will also depend on the dose of L-dopa. Some of the clinical results produced here do seem to confirm at least the first part of my reasoning.

PEARCE: If this is so, one would expect the response to amantadine to be directly related to the duration of the disease.

OFFERMEIER: If the damage to the dopaminergic system is the major cause of this disease, I think the effectiveness of amantadine—if it does not act directly on those receptors—would be inversely related to the amount of dopaminergic fibrous destruction. Therefore, the greater the destruction of the dopaminergic system, the less effective amantadine would be, if this is the only aspect of its activity. How is the degree of destruction related to the duration of Parkinsonism?

PEARCE: I think it reasonable to assume that with increasing duration there is increasing neuronal depletion. Indeed, Dr. Levin has said that this may be the reason why certain patients are refractory to L-dopa. In fact, we have clinical evidence which goes against that (see Table 1).

Dr. P. B. JØRGENSEN (Newcastle-upon-Tyne): Prof. Offermeier assumes that people with Parkinson's disease of greater severity or

longer duration respond less well to amantadine, whereas our evidence and that of Dr. Parkes is contrary to this. We have found that moderate and severe cases responded significantly better than mild ones, and with increased duration of disease there is also a better response to amantadine.

Table 1. Effect of Duration of Disease on Response

Maximal % Improvement	*Duration of Illness (mean)*[a]	
	L-dopa	*Amantadine*
0–25	3 years	3.5 years
26–50	6 years	4 years
51–75	5 years	3 years
76–100	—	—
Number of patients	19	19

[a] Post-encephalitics excluded

SYMMETREL WITH ANTIDEPRESSANTS AND OTHER DRUGS

Dr. F. GERSTENBRAND (Vienna): With antidepressant drugs we have experiences in two groups. First, some Parkinson patients are depressed and require specific antidepressant in addition to anti-parkinsonian therapy. We now have experience in six patients on conventional antiparkinson treatment later combined with Symmetrel. The Symmetrel had a remarkable effect on the Parkinson symptoms but none on the depression. So it was necessary to add an antidepressant to the conventional antiparkinson and Symmetrel treatments. After the addition of dibenzepin hydrochloride, the depressive symptoms improved markedly in two of the six cases after three to four weeks, and a further two showed significant improvement. In none of these cases did we see side-effects from the combination. Two cases obtained no real benefit, however. One is still under observation, but it is not possible to give a final assessment.

From our experience with L-dopa, we know that it induces, in some Parkinson cases, a depressive reaction at first; and from the literature we know that this can be very marked and dangerous. In patients receiving L-dopa, we therefore prescribe dibenzepin as well. But we never combine L-dopa with stronger antidepressants.

I should also like to comment on the question of Symmetrel in combination with conventional drugs. Nearly all our patients are already receiving these. We are not inclined to stop them, and so leave our patients without treatment, in order to give them Symmetrel. The majority therefore receive both.

The conventional antiparkinson drugs we use most often are phenglutarimide or biperiden for rigidity and akinesia; orphenadrine in cases of arteriosclerosis; and a combined antihistamine/anticholinergic preparation where tremor is the major symptom.

The combination of L-dopa and Symmetrel may be required when L-dopa alone is not sufficient (we use 1.5 to 2.5 gm of L-dopa daily) or the side-effects are too great. We treated 12 patients with this combination and found improvement marked in three. Satisfactory in four, slight in another four, and no change in one.

It is important to remember that L-dopa treatment needs as much as three to four months before a final conclusion can be reached about dosage and efficacy. With Symmetrel, by contrast, it is often possible to decide after two days. I would allow about two weeks to decide whether a combination with Symmetrel is effective or not. L-dopa treatment is much more trouble to us than Symmetrel.

DISCUSSION

CHAIRMAN: Looking at this through the eyes of a clinician, I can see no clear picture of the action of combinations of drugs. We have a lot of conflicting clinical observations, and things which we cannot explain. For example, some very severely disabled patients may respond dramatically to amantadine alone. All sorts of combinations of events have been reported clinically, and we shall not see daylight until the fundamental mechanisms are clearly understood.

I am deliberately over-simplifying, but it looks to me as though we clinicians are still in the position where there is much trial and error in our treatment. It is rather like the treatment of epilepsy, where one tries the safer drugs first. Only if they are found wanting are we prepared to use the more potent drugs, knowing that we must be on the look-out for side-effects.

MODE OF ACTION OF ANTICHOLINERGIC DRUGS

Prof. G. WEBER (St. Gallen, Switzerland): May I ask Prof. Offermeier to explain the action of anticholinergic drugs in Parkinsonism?

OFFERMEIER: I think one should keep in mind that there are separate dopaminergic and cholinergic fibres in the substantia nigra. The effects produced by these two systems are thought to be opposite. Parkinsonism can supposedly be seen as a functional imbalance in these two systems whereby the cholinergic becomes predominant. One can correct the balance, if this assumption holds, either by suppressing cholinergic transmission (with an anticholinergic drug) or by enhancing dopaminergic transmission (with L-dopa or amantadine), or both. There is some evidence that certain so-called anticholinergic drugs may also enhance the dopaminergic system, probably by inhibiting neuronal re-uptake of dopamine.

Dr. P. LEVIN (Basle, Switzerland): I am completely in agreement with the idea that there are two neuro-transmitters involved in Parkinson's disease, the acetylcholine and the dopamine, and that Parkinson's syndrome probably develops as a result of imbalance between these two systems, with excessive cholinergic and decreased dopaminergic activity. Exactly where Symmetrel fits in is not entirely clear, although we are inclined to think that it affects the dopaminergic system. I think the simplest way for us to think of it is that anticholinergics cut down excessive cholinergic activity and that L-dopa (when it is converted into dopamine by the dopa-decarboxylase enzyme system in the brain) provides an additional dopaminergic transmitter and works on the other side of the system. Up to now as many as four transmitters have been implicated in Parkinson's disease. Someone may yet come up with hypotheses built around histamine or serotonin.

STEREOTACTIC SURGERY

PARKES: Does anybody think there is a place for stereotactic surgery in the treatment of Parkinsonism?

GERSTENBRAND: At the neurological clinic in Munich, Prof. Struppler is performing stereotactic operations and giving L-dopa and Symmetrel too. They have a clear indication for stereotactic surgery: severe postural tremor. These cases sometimes respond well to a combination of L-dopa, Symmetrel and stereotactic surgery. Some neurosurgical clinics, however, are using L-dopa and/or Symmetrel only and have given up stereotactic operations.

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WEBER: Stereotactic procedures for destruction of the ventrolateral nucleus of the thalamus improve rigidity and tremor, but not hypokinesia. And in our experience a combination of stereotactic surgery with subsequent L-dopa or amantadine in patients with rigidity, tremor and hypokinesia will give better results than operation alone.

CHAIRMAN: Decreasing numbers of patients are now being referred for stereotactic surgery, but that does not mean that it has become obsolete.

Session 4 (part 1): Side-Effects

CHAIRMAN (Dr. Maurice Parsonage, Leeds): We are concerned with side-effects of amantadine—their type, frequency and prevention compared with placebo, L-dopa and other drugs, short and long term. We also hope to discuss side-effects specific to patients with Parkinsonism, such as oedema.

Dr. K. HEATHFIELD (Whipps Cross Hospital, London): Our first trial[7] involved treating 29 patients with amantadine at a dose of 200 mg daily, and this produced a statistically beneficial effect on all facets of their Parkinsonism. We found that with this dose severe side-effects from amantadine were minimal; in fact, there were rather more side-effects in the patients taking placebo. Of these 29 patients, four complained of dry mouth, three of slight drowsiness, two of giddiness (due to postural hypotension in one), two of slight blur of vision and one of sleeplessness.

All these symptoms cleared despite continued treatment. There were no severe side-effects in this series at all, apart from two patients who developed visual hallucinations. Both of these were also taking benzhexol. Their hallucinations cleared on a reduced dose of benzhexol.

BRITISH STUDY OF INCREASED DOSAGE

When we had completed the first trial, we compared amantadine with L-dopa in the same group of patients, plus some others.[8] Our regime seemed designed to bring out side-effects: we increased the daily dose of amantadine by 100 mg each week to a total of 400 mg daily, and during the same monthly period stepping up L-dopa dosage to 4 gm daily. In the second month this dosage was continued in patients who would tolerate it, but not all could. Of the 21 patients taking amantadine at this dose level, 19 developed side-effects. We did not find that the increased dose of amantadine was more effective, when compared with the previous trial, but the severity of the side-effects obviously counteracted any slight beneficial effect of increasing the dose.

Table 1 lists the side-effects on 400 mg amantadine daily. Mental symptoms of various kinds occurred in 10 cases, and we had to discontinue the amantadine in four patients, because of severe

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