However, it is clear that this drug, in the dosage given, has no significant influence upon tremor. It is also apparent, from an analysis of the subjective impressions of patients who were receiving the remedy, that almost as many patients were improved by the dummy as were improved by chlorphenoxamine. Hence if we base our assessment of the value of chlorphenoxamine in Parkinsonism upon the subjective impressions of the patients and upon our attempts to assess muscular rigidity objectively, our results do not indicate that, in the dosage we employed, this drug is of any real value if added to the previous treatment which the patient was receiving.

However, the objective evidence of the "hand test" did indicate that the patients' ability to open and close one hand rapidly was significantly improved by the administration of this drug. In our experience, too, this remedy is remarkably free from side-effects. On the basis of the hand test alone, therefore, it seems that there is some justification for suggesting that chlorphenoxamine is worthy of trial in cases of Parkinsonism if given along with other more powerful remedies. However, it is clearly not a powerful or highly effective remedy, and the results of our trial would justify equally the conclusion that, in the absence of any subjective improvement in the patients receiving treatment or of any measurable effect upon rigidity, the drug is of no therapeutic value.

Summary

A controlled trial of chlorphenoxamine hydrochloride in the treatment of Parkinsonism, using the double-blind technique, is described. Twenty-one patients began the trial and 17 completed the full course of treatment. Subjectively seven of these 17 patients improved more with chlorphenoxamine than with the dummy remedy, six improved more with the dummy, and four were unable to differentiate between the two treatments. Objective clinical assessment failed to reveal any significant effect of chlorphenoxamine upon rigidity and tremor, but this drug did produce a significant improvement in the ability to open and close the hands rapidly. No significant side-effects were observed in this series of cases.

We thank Dr. H. G. Miller for permission to include in this trial several patients who were under his care, and Mrs. Doris Weightman for assistance with the computations. We are also grateful to Dr. Arnold Worlock and to Evans Medical Supplies Ltd., who supplied the chlorphenoxamine and the dummy tablets.

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A new British Standard (B.S. 3330:1961) for polythene splints and appliances for external orthopaedic use has been prepared at the request of the Ministry of Health to ensure that correct materials are used in the making of the appliances, and to deal with those features of design which are independent of the clinical needs of each individual patient. The standard deals with appliances made of low-density polythene sheet, with or without a lining of cellular urethane. Basic information required for the fabrication of the appliances and notes on cleaning appliances are given in appendices. Copies may be obtained from the British Standards Institution, Sales Branch, 2 Park Street, London W.1 (price 5s. each. Postage extra to non-subscribers).

METHYL PHENIDATE IN PARKINSONISM

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It has been shown by Cole and Glee (1956) that the state resembling Parkinsonism which can be induced in the monkey by reserpine can be relieved by the sympathomimetic drug methyl phenidate hydrochloride ("ritalin"). Schneider and Holden have found that surgically induced tremor in the monkey can also be reduced by this drug (Carter and Maley, 1957). This suggests that the action of methyl phenidate is not specific to the reserpine-induced state and that it might be equally effective in similar types of disorder due to other causes. Glow (1959) reported that rats given reserpine go into a catatonic state, characterized by rigidity of the limbs and rhythmic alternating tremor of the head and neck; intraperitoneal methyl phenidate abolished the tremor and allowed the animals to run about and respond to their environment in a normal manner. In both monkeys and rats the effect of the injection of methyl phenidate was almost immediate and lasted some hours; the animals then reverted to the previous "reserpinized state."

In man, one of the main toxic effects of reserpine is to induce a clinical condition resembling Parkinsonism, and when given to patients with Parkinsonism the drug is reported to cause a marked though transient exacerbation of this disorder.

In view of these observations, and as methyl phenidate is satisfactorily absorbed when taken orally and is relatively non-toxic, we decided to try this drug in patients with Parkinsonism.

Accordingly, a pilot investigation was first carried out in which the drug was given intravenously to four male patients. This was followed by a more extended double-blind trial, in which the drug and control tablets were given orally to out-patients. Finally, those patients who in the blind trial were better on methyl phenidate were given various doses of the drug orally, either with or without their pre-existing medication, so as to find out the optimal dosage.

Results of Pilot Investigation: Intravenous Methyl Phenidate

For this part of the investigation, four male patients were chosen who manifested different forms of the disorder. Two were severely incapacitated, having been confined to wheel-chairs for some years; their movements were greatly impaired and were accompanied by very marked tremor and rigidity. The other two patients were much less severely affected and were still carrying on their respective occupations; the main disability in one was a dysarthria and in the other a coarse tremor of the right upper limb with minimal rigidity.

Each patient received a total of 30-40 mg. of the drug intravenously on each of one or two days, and this was usually given in two divided doses over a period of less than three hours. It caused a striking reduction in the rigidity, so that where rigidity impaired movements the

range and freedom of movement were greatly increased. One patient was able to get up from lying and to stretch his arms above his head, neither of which he had been able to do before. Subjectively the limbs felt less tense, and the patients performed spontaneous movements, the absence of which is usually such a typical feature of Parkinsonism. In the patient, however, in whom dysarthria was the main trouble and rigidity was relatively unimportant, there was a transient increase in tone in both upper and lower limbs on the side affected by Parkinsonism when a total dosage of 30 or 40 mg. was given. This passed off within 10 minutes and the limbs were then looser than normal as in the other patients. This transient hypertonia was not seen after a single dose of 20 mg. Speech appeared to be improved following methyl phenidate in all three patients in whom it was affected, becoming louder and clearer.

The drug had no beneficial effect on tremor, and in one patient the tremor became worse. The drug produced a lightening of mood in all four patients, with marked euphoria in two. In one, however, an initial period of cheerfulness was followed by a feeling of drowsiness and complaint that he felt "dopy"; at this time the patient was quieter and more subdued than usual. Beyond this complaint and the presence of the transient hypertonia in one patient, there were no unpleasant side-effects other than slight lightheadedness or dizziness. Obvious effects of the drug lasted about two and a half hours after intravenous injection, but less obvious effects were still present a few hours later. One patient had insomnia on the night after the injection, and he noticed that his limbs were still definitely less rigid than normal the next day.

In view of the success of the drug in lessening rigidity and improving movement, and the likelihood that it would produce no undesirable side-effects when given in oral dosages limited to 20 mg., we decided to carry out a more extended trial to determine whether it would have a place as an adjuvant to other forms of medication in the long-term treatment of Parkinsonism. As it seemed clear that it had none of the beneficial effect on tremor of benzhexol hydrochloride, we did not feel justified in depriving patients of this drug for a number of weeks while the trial was in progress. Hence it was decided to test the value of methyl phenidate added to the existing medication.

Extended Trial of Oral Methyl Phenidate

Twelve unselected out-patients with Parkinsonism were given the drug by mouth in addition to their usual medication. They attended the hospital once every four weeks, when they gave a report, were examined, and received a supply of tablets for the following month. The whole trial lasted 16 weeks for each patient, though one of the 12 gave up taking the tablets during the third month, complaining that they made her feel too ill. The tablets for any one month consisted either of 20 mg. of methyl phenidate or of excipient without any drug; neither the patient nor the doctor who assessed the patient knew which tablets were being given. In fact, each patient spent two months on methyl phenidate and two months on control tablets, the order in which these four were given differing from patient to patient. The patients were told to take two tablets on getting up and two after their midday meal; they were thus taking 40 mg. of methyl phenidate a day when on this drug. To avoid insomnia, the tablets were not given later in the

day, and it was thought best to give them after lunch rather than before, because of the tendency of the drug to diminish appetite.

The patients were told that they were being asked to try out a new drug for Parkinsonism. They were asked at the end of each month how they had felt and whether they had noticed any change from the previous month. Sometimes they did note marked differences and asked for an explanation; they were told that for each of the four months they were receiving a slightly different form of the new drug, so as to see which was the best.

The assessment of the drug was based primarily on the patient's report. An attempt was made to supplement this with a more objective assessment, by clinical examination, and by using a battery of tests to try to detect and evaluate changes in the speed and dexterity of movement. Strength of hand-grip was tested with a dynamometer, and the acts of clenching and unclenching the fist, flexing and extending the elbow, knee, and ankle, 12 times each, were timed. The patients were also timed while they made a pile of six pennies, placing one on top of the other, one at a time, with each hand, and, again, while they removed 16 wooden pegs from holes in one side of a large board, turned the pegs upside down, and placed them in 16 holes on the other side of the board. Specimens of their writing (name and address) were taken on each occasion, and they also had to draw spirals and to attempt to guide a pencil down a zigzag groove 2 cm. wide without hitting the sides.

The results of this fairly elaborate objective assessment were unsatisfactory and disappointing. It was clear that times obtained in the tests of speed bore little or no relation to the speed of movement; many of the patients became stuck and unable to move at various points in the tests, and the length of these interruptions was much more variable, and often longer, than the total time taken by the test when it was performed

Results of extended trial with oral methyl phenidate.

uninterruptedly. Even apart from this, the movement and tremor in Parkinsonism are notoriously variable and easily influenced by emotional factors. It was clear that these tests gave little quantitative indication of changes occurring from month to month. They will therefore not be reported further.

Results of Trial

The results of the trial are summarized in the Chart. The patients' reports were rated for their overall opinion of the action of the tablets into three categories: definitely improved, definitely worse, and a third category, including both reports of no effect and mixed effects, good and bad. Similar ratings were made for the effect of the tablets on tremor, freedom of movement, and speech, including in each of the three groups only those patients in whom these were initially affected.

It is noteworthy that in this group of disabled patients, eagerly searching for drugs to help them, there was an unexpectedly slight degree of improvement reported with the control tablets. Only one of the 12 reported feeling generally better on them, while five of the same group felt a definite improvement while on methyl phenidate. None of the patients reported any definite improvement while on the control tablets in their individual ratings for freedom of movement, tremor, or speech, although at least half noticed improvement in movement and tremor on methyl phenidate. In only seven of the patients was speech affected, and only one of these reported any change while on methyl phenidate. This patient was the most severely dysarthric of the seven, and his speech was greatly improved while on the drug, as was obvious not only to himself but to the examining doctor. It became much louder, clearer, and altogether more intelligible.

Apart from any direct effect on motor function, a number of other differences were reported during the trial. Some of these may have been due to the pre-existing medication, or the combined effect of this with the drug, but in many cases these effects were quite clearly associated with the period during which methyl phenidate was being given, and did not occur with the control tablets. Among such effects were changes in mood (10 patients), sweating (3), subjective weakness (3), blurring of vision (2), dryness of the tongue (2), feeling generally unwell (2), palpitations (1), and anorexia (1). Two patients reported having transient symptoms immediately after taking the tablets—one of throbbing in the temples and the other of a "fluffy feeling with a kind of pins-and-needles all over." Four patients had no side-effects apart from those on mood.

The effect of the drug on mood was striking, although not all patients reported the same kind of change, and two noticed no effect on mood at all. Seven patients were stimulated, and three were adversely affected. However, in two of the latter group there was no real evidence of a swing of mood. They were the two patients already mentioned who felt generally unwell on methyl phenidate, one of whom gave up the trial during the third month for that reason. The third patient reported that she felt quieter mentally and more contented and that the pills made her tired and sleepy for about 10 minutes after she had taken them. There was no such report by her during the periods on the control tablets, so that this effect must be regarded as a genuine effect of the drug. The seven patients whose mood was lightened by the drug felt less tired and

had more energy than before; they wanted to be "on the go," and some were frankly restless or excited. In two of the patients the increased cheerfulness was very marked. Some of the patients found this upward swing of mood the best single effect of the drug, while others did not like it.

After they had completed the blind trial, all the patients, with the exception of the two who had felt ill on the drug, were put on methyl phenidate, in most cases combined with other medication, and the dose was individually adjusted. Six of the 10 patients felt better on the drug than without it (including one ranked as having shown "mixed effects" in the blind trial). Several of these patients were extremely enthusiastic about the drug, which one called the best she had tried; another patient said that on it he felt better than he had done for years. They all wished to go on taking the drug indefinitely. The effects observed were the same as those in the main trial. The individual dosages arrived at ranged from 30 to 100 mg. daily, usually in two divided doses taken on rising and after lunch. In the four patients who obtained no benefit from the drug in the blind trial there was also no benefit with increased dosage.

Discussion

The results of this trial can be summarized by saying that half the patients tested felt better on methyl phenidate, though some of its beneficial effect was not derived from specifically anti-Parkinsonian features of its action, but from the fact that it gave the patients more energy and lightened their mood. However, there appears to be no doubt that it also increased freedom of movement and reduced tremor and rigidity in a number of these patients, and, although it improved speech in only one of the seven affected patients, its effect here was obvious and occurred in the most severely dysarthric of the group. A quarter of the patients tested were no better on methyl phenidate and a quarter felt definitely worse. The drug was obviously less effective when given orally than when given intravenously in the dosages used.

Although many of the patients reported that the tremor was improved on the drug, neither in the intravenous nor in the oral trial did any patient show the striking abolition of tremor reported in the animal experiments which led us to undertake this trial. This was disappointing; but it may not be surprising when the dosages used in the monkey and rat are compared with those which we employed. Cole and Glees (1956) injected 20 mg. subcutaneously (equivalent to 6.6 mg./kg. body weight in an average 3-kg. monkey), and Glow (1959) 10 mg./kg. in the rat. If we assume a mean weight of 70 kg. for our subjects, they were given something between one-twentieth and one-fortieth of the equivalent animal dose. Unfortunately, though the drug is relatively non-toxic, we had ample evidence of the occurrence of unpleasant side-effects even with these dosages, so that it does not seem practicable to increase the dose of the drug further, to try to reproduce in man the total abolition of tremor and rigidity with complete restoration of normal co-ordination and activity which the animals exhibited. It is still an open question whether this effect would be produced with any dosage in Parkinsonism, but it would seem well worth while for pharmacologists to try to produce a variant of the drug without its undesirable side-effects, which would be even more effective against tremor and rigidity.

Summary

Methyl phenidate ("ritalin") was given to patients with Parkinsonism. Four patients received it intravenously and 12 received it orally in a double-blind trial; those patients who obtained benefit from the drug given orally then received it in various doses, alone or in combination with other medication for Parkinsonism, in order to establish the optimal dosage.

The drug gave some patients an increased freedom of movement and reduced the rigidity; it had little effect on the tremor. The most marked effect was the improvement in mood.

Our thanks are due to Dr. E. A. Carmichael for his interest and encouragement, and to the physicians of the National Hospital who kindly allowed us to include in this trial the patients under their care. We would like also to thank Dr. C. D. Falconer, of Ciba Laboratories Ltd., who supplied us with the drug and control tablets.

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Preliminary Communications

Pyloric Stenosis: A Physiological Exploration

Pyloric stenosis is a common condition in infancy, occurring in three to four of every thousand newborn infants (Davison, 1946). The clinical syndrome is well defined, but little information is as yet available concerning the physiological changes. In the present study intragastric pressures have been measured as a reflection of the motility of the fundus of the stomach in nine infants with pyloric stenosis. The fundus as opposed to the antrum was chosen as it shows little if any activity in health, so that a more definitive change might be expected in this area. The method has shown a clear difference between normal infants and those with pyloric stenosis.

In most cases the diagnosis presents little difficulty; it rests on the finding of a typical pyloric tumour in a vomiting baby. However, Craig (1955), using accepted criteria for his physical signs, found a pyloric tumour in no fewer than 25 out of 115 symptom-free babies whom he examined when less than 2 weeks of age. Contrary to accepted opinion, he concludes that a palpable tumour in a baby during the first two weeks of life is not necessarily diagnostic of pyloric stenosis. The clinical condition of pyloric stenosis clearly must depend on a disturbance of function and not on the presence of a tumour.

Methods.—The technique of measuring intraoesophageal pressures in infants has already been described (Colley and Creamer, 1958). A similar method was used for recording intragastric pressures. The pressures were measured through fine water-filled "polythene" tubes connected to Hansen capacitance manometers beside the child. Two tubes were used, fastened at the tip and with lateral recording holes spaced 3 cm. apart. The tubes were passed through the mouth and positioned so that the proximal recording hole was just below the hiatus of the diaphragm, a point which can easily be recognized by the reversal of inspiratory pressure swings. The recordings in most instances were made immediately after a feed or during and after a feed.

CASES STUDIED

Nine infants with pyloric stenosis were studied and their clinical features are summarized in Table I. The age at onset ranged from 2 to 6 weeks. All presented

TABLE I.—Clinical Data on Cases with Pyloric Stenosis

Case	Sex	Position in Family	Birth Weight		Age at Onset (Weeks)	Vomiting	Constipation	Weight Loss	Palpable Tumour	Peristalsis	Treatment
			lb.	g.							
1	M	4	8.5	3,770	6	+++	0	++	+	+	Operation
2	M	2	6.8	3,085	5	+++	+	++	+	+	"
3	M	3	9.3	4,220	2½	++	++	++	+	+	"
4	M	2	9.4	4,265	6	++	+	++	+	0	"
5	F	1	6.13	2,780	4	+	0	+	+	+	Medical
6	M	1	5.15	2,335	3	+	+	0	+	+	"
7	M	3	6.12	2,775	4	++	+	+	+	+	Operation
8	F	3	7.13	3,234	4	+	0	0	+	+	"
9	M	1	6.7	3,040	4	++	0	+	+	+	"

with vomiting, though in only four could it be described as projectile. Constipation was noted in five cases, but in two there were loose "hunger stools." Loss of weight occurred in all but two babies, and in one case resulted in the infant being 12 oz. (340 g.) below his birth weight at 3 weeks of age.

A pyloric tumour was felt in all cases and peristalsis was observed in eight. Rammstedt's operation was performed in seven cases and resulted in the immediate cessation of symptoms in six. In the other infant (Case 8) the pyloric muscle had not been adequately split and the infant continued to vomit. Two cases were treated medically with atropine methonitrate ("eumydrin").

The control group contained six cases. Three were infants who were studied because of vomiting due to causes other than pyloric stenosis—infection, air-swallowing, etc. The others included the sibling of a child who had had pyloric stenosis but was free from symptoms, a baby with Fallot's tetralogy, and an infant that was slow to gain weight but appeared otherwise normal.

RESULTS

Classification of Activity.—There is no available classification for activity of the fundus of the stomach as there is for the antrum. Two types of pressure change are seen. Most commonly this is a simple wave of pressure, usually occurring rhythmically from two to three times a minute. Where this is 5 cm. of water-pressure or less we have arbitrarily called it a type I wave; where more than 5 cm. of water-pressure, a type II wave. Occasionally these waves are superimposed on a general rise in pressure lasting up to two minutes and ranging in amplitude from 2 to 12 cm. of water-pressure. These base-line variations have been called type III waves. In every record the pressure tracings from the two recording sites in the fundus were identical.

Findings in Control Subjects.—There was no difference in the records from normal children and children vomiting from causes other than pyloric stenosis (Table II). The recordings were conspicuous for the lack of

TABLE II.—Summary of Recordings from Control Cases

Case	Vomiting	Time Activity Present	No. of Waves	Type of Waves			Amplitude (cm. Water)	
				I	II	III	Max.	Mean
A	+	27%	23	23	0	1	2	1.7
B	+	12%	5	5	0	0	2	1.4
C	+	0%	0	0	0	0	0	0
D	0	22%	4	4	0	0	3	2.3
E	0	0%	0	0	0	0	0	0
F	0	12%	5	5	0	0	2	1.4