Similar observations have been made in a few cases by Kindler (1943), Quimby and Werner (1949), Wilson *et al.* (1958), and Goolden (1958). The paucity of such cases suggests that the adult thyroid may not be susceptible to radiation cancer. The papers by Quimby and Werner (1949) and Duffy (1957), reporting follow-up studies on patients who had received x-ray therapy for hyperthyroidism, lend credence to this hypothesis.

Summary and Conclusions

The incidence of thyroid cancer as a cause of death in necropsy and surgical material and its association with the various types of surgically treated goitre have been calculated.

Potential aetiological agents have been discussed and the following conclusions formulated: (1) Thyroid carcinoma is a rare finding at necropsy. (2) The incidence of carcinoma in specimens available for histological examination in this series is 4.1%. (3) Malignant change is more often associated with non-toxic nodular goitre than with toxic nodular goitre. (4) The diagnosis of thyrotoxicosis does not exclude the possibility of malignancy. (5) The frequency with which thyroid cancer is being diagnosed in surgical material is increasing. This is due to an increase in the total number of operations and to an increase in the number of operations for nodular goitre. (6) The use of anti-thyroid drugs in Northern Ireland does not appear to have influenced the increase of thyroid cancer. (7) The data at present available appear to give no indication that the adult thyroid gland is susceptible to radiation cancer.

I thank Professor J. H. Biggart for his advice and continued interest during the preparation of this work. I am indebted to Dr. J. E. Morison for his permission to include the material from the laboratories, Belfast City Hospital; and to all the consultants and general practitioners, whose names are too numerous for individual recognition, for their co-operation in answering the questionnaires.

REFERENCES

- Anglem, T. J., and Bradford, M. L. (1948). *New Engl. J. Med.*, **239**, 217.
 Astwood, E. B. (1943). *J. Amer. med. Ass.*, **122**, 78.
 — (1956). *Pediatrics*, **18**, 501.
 Beahrs, O. H., Pemberton, J. de J., and Black, B. M. (1951). *J. clin. Endocr.*, **11**, 1157.
 Cattell, R. B., and Colcock, B. P. (1953). *Ibid.*, **13**, 1408.
 Cole, W. H., Majarakis, J. D., and Slaughter, D. P. (1949). *Ibid.*, **9**, 1007.
 Cope, O. (1952). *New Engl. J. Med.*, **246**, 408.
 —, Dobyms, B. M., Hamlin, E., jun., and Hopkirk, J. (1949). *J. clin. Endocr.*, **9**, 1012.
 Crabtree, H. N., and Hunter, D. C. (1953). *Arch. Surg. (Chicago)*, **67**, 175.
 Crile, G., jun. (1953). *New Engl. J. Med.*, **249**, 585.
 — and Dempsey, W. S. (1949). *J. Amer. med. Ass.*, **139**, 1247.
 Dailey, M. E., Soley, M. H., and Lindsay, S. (1950). *Amer. J. Med.*, **9**, 194.
 Dalgard, J. B. (1954). *Nord. Med.*, **52**, 1659.
 Doniach, I. (1953). *Brit. J. Cancer*, **7**, 181.
 Duffy, B. J., jun. (1957). *J. clin. Endocr.*, **17**, 1383.
 Fisher, E. R., and Fisher, B. (1951). *Amer. J. Surg.*, **82**, 202.
 Friedell, M. T. (1941). *Arch. Surg. (Chicago)*, **43**, 386.
 Goolden, A. W. G. (1958). *Brit. med. J.*, **2**, 954.
 Greene, R. (1957). *Ann. roy. Coll. Surg. Engl.*, **21**, 73.
 Herbst, W. P. (1924). *Ann. Surg.*, **79**, 488.
 Hermann, E. (1951). *Schweiz. med. Wschr.*, **81**, 1097.
 Hershey, C. D. (1958). *Arch. Surg. (Chicago)*, **76**, 407.
 Hinton, J. W., and Lord, J. W., jun. (1945). *J. Amer. med. Ass.*, **129**, 605.
 Horn, R. C., jun., and Dull, J. A. (1954). *Ann. Surg.*, **139**, 35.
 Jude, J. R., Zimmerman, J. McK., and Ward, G. E. (1958). *Arch. Surg. (Chicago)*, **77**, 757.
 Kilpatrick, R., Blomfield, G. W., Neal, F. E., and Wilson, G. M. (1957). *Quart. J. Med.*, **26**, 209.
 Kindler, K. (1943). *Z. Krebsforsch.*, **54**, 153.
 Lerman, J., Jones, H. W., and Calkins, E. (1946). *Ann. intern. Med.*, **25**, 677.
 Levitt, T. (1954). *The Thyroid*. Livingstone, Edinburgh.

- Majarakis, J. D., Slaughter, D. P., and Cole, W. H. (1953). *J. clin. Endocr.*, **13**, 1530.
 Martin, H. (1954). *Cancer*, **7**, 1063.
 Means, J. H. (1937). *The Thyroid and Its Diseases*. Lippincott, London.
 Payne, R. L., Crane, A. R., and Price, J. G. (1947). *Surgery*, **22**, 496.
 Purves, H. D., and Griesbach, W. E. (1947). *Brit. J. exp. Path.*, **28**, 46.
 Quimby, E. H., and Werner, S. C. (1949). *J. Amer. med. Ass.*, **140**, 1046.
 Registrar-General for Northern Ireland (1956-8). *Annual Reports for 1955, 1956, 1957*. H.M.S.O., Belfast.
 Rogers, W. F., Asper, S. P., and Williams, R. H. (1947). *New Engl. J. Med.*, **237**, 569.
 Ross, D. E. (1956). *Surg. Gynec. Obstet.*, **103**, 171.
 Shallow, T. A., Wagner, F. B., and Colcher, R. E. (1956). *Surgery*, **39**, 252.
 Sokal, J. E. (1953). *New Engl. J. Med.*, **249**, 393.
 — (1954). *J. Amer. med. Ass.*, **154**, 1321.
 Steiner, P. E. (1950). Cited by Dailey *et al.* (1950).
 Taylor, G. W. (1947). *New Engl. J. Med.*, **236**, 207.
 Vanderlaan, W. P. (1947). *Ibid.*, **237**, 221.
 Ward, G. E., Hendrick, J. W., and Chambers, R. G. (1950). *Ann. Surg.*, **131**, 473.
 Willis, J. (1959). *Brit. med. J.*, **2**, 550.
 Wilson, L. B. (1921). *Ann. Surg.*, **74**, 129.
 Wilson, G. M., Kilpatrick, R., Eckert, H., Curran, R. C., Jepson, R. P., Blomfield, G. W., and Miller, H. (1958). *Brit. med. J.*, **2**, 929.
 Zimmerman, L. M., Wagner, D. H., Perlmutter, H. M., and Amromin, G. D. (1950). *Arch. Surg. (Chicago)*, **60**, 1183.

CHLORPHENOXAMINE HYDROCHLORIDE IN PARKINSONISM A CONTROLLED TRIAL

BY

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The multiplicity of drugs available for the treatment of the Parkinsonian syndrome bears testimony to the fact that no single remedy has been found to be universally successful. Recent reports from the United States (Doshay and Constable, 1959; Magee and Currier, 1960) have suggested that chlorphenoxamine hydrochloride ("clorevan") is a useful addition to the remedies available, but up to the present time no results have been reported of controlled trials of treatment using this remedy and utilizing the double-blind technique. In this paper the results of such a trial conducted in a small series of patients are reported.

Chlorphenoxamine is closely related chemically to diphenhydramine hydrochloride ("benadryl") and has a chemical structure as follows:

Doshay and Constable (1959) reported that the drug appeared to be beneficial in 53% of a total of 169

patients who received it and who had failed to respond adequately to other forms of treatment. Magee and Currier (1960) concluded that the drug was of value in all of the clinical varieties of Parkinsonism, and they too found that approximately half of the patients to whom the drug was given were improved. In these two series of cases, however, no attempt was made to carry out a controlled trial, and the possibility of subjective error in the assessment of the results of treatment was therefore considerable. In each of these previous reports it was noted that chlorphenoxamine was much more successful in the control of akinesia and of rigidity than in the alleviation of tremor, which was not influenced to any significant degree. Magee and Currier pointed out that the drug did not seem to be as effective as benzhexol hydrochloride ("artane") and procyclidine hydrochloride ("kemadrin"). In their view the primary value of the drug was as an adjuvant to other antispasmodic agents. They pointed out, as did Doshay and Constable (1959), that the drug was remarkably free from side-effects, the most severe being dizziness, which was encountered in a very small proportion of patients. It was also noted that the drug could safely be given along with large doses of other remedies without producing any cumulative ill effect.

Material and Methods

Twenty-seven patients with Parkinsonism accepted the invitation to take part in this trial, and after a full initial clinical assessment the purpose of the trial was fully explained to them. The only criteria for the selection of cases for inclusion in the trial were: (a) the diagnosis of Parkinsonism of the idiopathic or post-encephalitic types was incontrovertible; (b) the patients were already receiving a stable therapeutic regimen; and (c) it was important that the patients to be included in the trial should live near enough to the Royal Victoria Infirmary to be able to attend regularly for clinical assessment of the results of treatment. Of the initial 27 patients, 23 were accepted for inclusion in the trial; 4 were discarded because they did not fulfil the above criteria. Of the 23 patients who began the trial, 2 subsequently failed to attend for reassessment and the trial was continued with a total of 21 patients. Of these, 15 were suffering from paralysis agitans and 6 from post-encephalitic Parkinsonism. Eleven of the patients could be classified as being severely disabled by the disease, and the remaining 10 were moderately disabled.

Treatment.—The patients were instructed to continue taking the drugs they had previously been receiving, in exactly the same dosage as before, throughout the entire period of the trial. The drugs in question included benzhexol, bengtropine methanesulphonate ("cogentin"), orphenadrine hydrochloride ("disipal"), and procyclidine in various combinations. It was arranged that throughout the period of the trial the patients should receive either chlorphenoxamine hydrochloride in a standard dose of 50 mg. three times daily, or dummy tablets which were identical in appearance and which were also to be given three times daily. Each patient was treated with chlorphenoxamine for three months and with dummy tablets for three months. The order of administration, chlorphenoxamine or dummy first, was decided from a list, based on random numbers, which was held in the hospital pharmacy. The randomization was restricted to produce nearly equal numbers starting on each treatment. Neither the doctor responsible for

assessing the clinical response to treatment throughout the course of the trial nor the patient knew whether the chlorphenoxamine or the dummy was being administered at any one time. An interval of one week separated the two three-monthly periods, so that the effect of one treatment could wear off before the second treatment was begun.

Clinical Assessment

Each patient was assessed clinically, using criteria to be described below, before starting treatment, and one month and two months later during treatment. After a further month's treatment and an interval of one week without receiving either of the remedies, they were seen again, examined, and given the second treatment. Two examinations were made one and two months later while receiving the second treatment. At each visit the patients brought back any surplus of the tablets with which they had been supplied at the last visit. By this means a rough check was kept on whether they were taking the tablets regularly as prescribed. The patients' general practitioners were kept fully informed of the nature and purpose of the trial, and agreed to leave the previous treatment unchanged throughout its course.

The clinical assessment of the patients' condition was made by recording the following information at each visit. On each occasion the assessment was carried out by one of us (P. R. U.).

Subjective Impression.—Under this heading was recorded the patient's own impression of his clinical state during the preceding month. It was stated first whether he felt that he had been better or worse or much about the same during this period, and an attempt was made to discover whether he had been better able to dress or to feed himself, whether he had been walking longer or shorter distances than before, whether fine movements of his hands and his handwriting were improved, and whether there had been any alteration in akinesia or in speech and salivation. The patient's own account was supplemented by that of relatives who attended with him or her at each interview.

Rigidity.—This was assessed objectively for each of the four limbs at each visit on the following numerical scale: grade 1, normal tone; grade 2, slight rigidity; grade 3, moderate rigidity; grade 4, severe rigidity; grade 5, gross rigidity. The patient was given a numerical score for each limb according to this graduated scale, on each attendance.

Tremor.—This was similarly assessed objectively on a numerical scale as given below: grade 1, no tremor; grade 2, occasional and slight tremor; grade 3, continuous and slight tremor; grade 4, continuous and severe tremor, but controllable and abolished by activity; grade 5, continuous, severe, and uncontrollable tremor. The presence or absence of tremor and its severity according to this scale was again assessed numerically in each of the four limbs at each attendance.

Hand Test.—In this test a recording was made of the number of seconds it took the patient to make a fist and to open the hand completely again 10 times. At each visit the number of seconds taken for first the right hand and then the left was timed with a stopwatch. It was found that a normal person could carry out this series of actions within three to five seconds, but that a patient with severe Parkinson's disease could take up to 30 seconds.

Hence at each visit three measurements were taken—namely, measurements for rigidity in the arms and legs, tremor in the arms and legs, and the hand test—and the patients' subjective impressions were also recorded.

Results

Of the 21 patients who were admitted to the trial, four failed to attend one or more of the examinations

during treatment. The results which follow are based on the 17 who completed the entire course. Of the remaining four patients, one withdrew before receiving treatment with the dummy, two were marginally better on the chlorphenoxamine, and one was marginally better on the dummy remedy for all three criteria, on the occasions when they were recorded. Subsequent analysis has shown that inclusion of the partial records from these three cases would make no difference to the conclusions of the trial, and hence the findings in these patients have been excluded from further consideration.

Pre-treatment Results

The condition of the patients on admission to the trial is shown in the first two columns of Table I. The average rigidity score was 2.25 for the right arm and 2.21 for all limbs together. Tremor was more marked in the arms than in the legs, giving initial average scores of 2.76 for the right arm and 2.02 for all limbs. The average time to make a fist 10 times was 8.53 seconds for each hand.

TABLE I.—*Rigidity, Tremor, and "Hand-test" Scores; Pre-treatment Values*

Criterion	At Commencement of	
	First 3 Months	Second 3 Months
Rigidity—right arm	2.25	2.40
„ —4 limbs	2.21	2.28
Tremor—right arm	2.76	2.41
„ —4 limbs	2.02	1.84
Hand test	8.53	7.41*

* $P < 0.01$.

At the end of the first three months' treatment, as already mentioned, an interval of one week without treatment was arranged before the next examination. It was expected that any effects of treatment would not persist beyond this time. The last column in Table I shows that the rigidity and tremor figures had not changed significantly from the initial value, but the patients were taking on an average one second shorter on the hand test. Further analysis shows that this improvement could not be attributed to persistence of the effect of treatment, since the improvement was present after both chlorphenoxamine and the dummy, and there was no significant difference between those who started on chlorphenoxamine and those who started on the dummy. We believe it must have been due to the patients becoming more used to the test (practice effect). The importance of having equal numbers beginning with active treatment and the dummy is obvious if practice in performing one of the tests resulted in improvement. In this trial eight patients began with chlorphenoxamine and nine began with the dummy. These numbers are close enough for the possible bias to be disregarded.

Criteria of Success of Treatment.—For each patient and each measurement two figures are available from the examinations one month and two months after the beginning of a particular treatment. The average of these two figures was taken to represent his functional ability while taking the treatment concerned. The difference between the two averages for chlorphenoxamine and for the dummy is the number used to indicate the superiority of chlorphenoxamine in that patient. For both rigidity and tremor the results were calculated for all four limbs together, and separately for the right

arm only. The hand-test figures are the average of results on the two hands.

Analysis of Results

The results of the treatment are shown in Table II. Rigidity was on average slightly reduced and tremor slightly increased with chlorphenoxamine, but in neither case was the difference statistically significant. Com-

TABLE II.—*Effect of Treatment Upon the "Scores"*

Criterion (1)	Chlorphenoxamine (2)	Dummy (3)	Difference (4)=(2)-(3)
Rigidity—right arm ..	2.50	2.59	-0.09 $\pm$ 0.17
„ —4 limbs ..	2.35	2.38	-0.03 $\pm$ 0.11
Tremor—right arm ..	2.58	2.41	+0.17 $\pm$ 0.12
„ —4 limbs ..	1.99	1.89	+0.10 $\pm$ 0.06
Hand test ..	6.88	7.66	-0.78* $\pm$ 0.29

* $P < 0.02$.

Figures in columns 2 and 3 are averages of results one month and two months after starting the relevant treatment.

Standard errors in column 4 are based on within-patient comparisons.

parison of Table II with Table I shows that, for these two criteria, neither treatment achieved an improvement over the initial state before treatment started. For the hand test, however, a significant difference was observed, patients on chlorphenoxamine clenching a fist 10 times in 6.88 seconds, compared with 7.66 seconds on dummy, an improvement of 10% in the time taken. This difference is not produced by the practice effect mentioned above. In fact, with only one more patient beginning on dummy than on chlorphenoxamine there is very little bias due to practice effect. Compared with the initial hand-test scores, the times were faster during each of the two treatments. The initial value of 8.53 seconds was reduced by 1.65 seconds on chlorphenoxamine ($P < 0.01$) and by 0.87 second on dummy ($P < 0.05$). On analysing the subjective impressions of the 17 patients during the course of the treatment it was found that seven had improved more with chlorphenoxamine, six had improved more with the dummy remedy, and four did not differentiate between the two treatments (in two of these cases there was a slight improvement on each treatment, and in the other two no change was apparent on either). Further analysis revealed that the subjective effect of chlorphenoxamine was no better in the severe cases than in those who were moderately disabled.

Side-effects.—This trial has confirmed the almost complete absence of significant side-effects in patients treated with chlorphenoxamine hydrochloride. Throughout the entire trial period no significant side-effects were observed in any of the cases. It was, however, apparent that the addition of chlorphenoxamine hydrochloride in a dosage of 50 mg. three times daily to previous treatment, which was in several cases very substantial, did not appear to produce undue toxic reactions of any kind. Several patients who received this drug were already receiving as many as eight 50-mg. tablets of orphenadrine and two 2-mg. tablets of benzotropine daily, and others were receiving as much as 20 mg. of benzhexol each day.

Discussion

The results of this trial are somewhat equivocal. Objective assessment revealed no significant reduction in muscular rigidity in patients who were receiving chlorphenoxamine, and tremor was actually increased in some, though this increase, too, was not significant.

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.

REFERENCES

- Doshay, L. J., and Constable, K. (1959). *J. Amer. med. Ass.*, **170**, 37.
 Magee, K. R., and Currier, R. D. (1960). *J. Mich. med. Soc.*, **59**, 1364.

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 Glees (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