SOME OBSERVATIONS ON HUNTINGTON'S CHOREA*

By

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THE first distinctive account of this condition was given by George Huntington, a physician of Long Island, in 1872. Since then our knowledge regarding aetiology has not advanced greatly, though the hereditary nature of the illness and the fact that it is transmitted as a Mendelian dominant by both sexes has been established.

Histological examination has revealed the physical basis of the disease to be degenerative changes in the cerebral cortex, basal ganglia, subthalamic region and brain-stem (Denny-Brown, 1946). A mass of statistics has been accumulated regarding the geographical distribution, the age of onset and the incidence of the disease in the population (Davenport and Muncey, 1916; Critchley, 1934; Minski and Guttman, 1938). The incidence in England and Wales has been calculated by Pleydell (1954) as 6·5 per 100,000 population, giving an estimated total of 2,600 cases.

Therapeutic progress has been hampered by lack of knowledge regarding aetiology. Naturally with an hereditary disease prevention is the ideal and a strong plea for eugenic control was made by Spillane and Phillips (1937). Reid and Palm (1951) produced statistical evidence to suggest that not only do choreics usually marry before symptoms appear, thus nullifying the effects of natural selection, but also that they are on the whole more fertile than their non-choreic siblings. As regards symptomatic treatment, there was little advance until 1952, when Goldman reported favourably on the use of procaine amide. In 1955 the use of reserpine was reported (Lazarte *et al.*) and also the treatment of two cases of Huntington's Chorea with B.A.L. (Neilson and Butt). It should be mentioned that these treatments were directed primarily against hyperkinesis rather than the mental state of the patient. This paper presents some observations on these various forms of symptomatic treatment and also the results of some biochemical investigations.

MATERIALS AND METHODS

First Trial

Four patients were selected for this trial, the mean age being 50·4 years and the range from 48 to 54 years. These patients were all female and all had a strongly positive family history. In two patients the illness was advanced; they were more or less restricted to bed on account of severe ataxia and were incapable of intelligible speech. The other two were up and about but showed well-marked arm and trunk movements. It was intended to run a double blind controlled trial of reserpine using a finger dexterity test as an index of improvement. This test consisted of a wooden board with 24 holes in it into which had to be fitted 24 wooden pegs (the apparatus was designed by the occupational

* Based on a paper read at the Winter Meeting, Scottish Division, R.M.P.A., held at Bangour Village Hospital in December, 1956.

https://doi.org/10.1192/bjp.103.432.507 Published online by Cambridge University Press

therapists). Six "normal" subjects were tested and were found to take 1 minute (±10 seconds) over the test. Preliminary trials with three of the Huntington's Chorea patients gave scores ranging from 2 to 10 minutes. The other patient (B.B.) was incapable of doing the test. Another patient later refused to do the test and these two patients (C.M. and B.B.) had therefore to be scored on the number of involuntary movements observed over timed periods of two minutes each day. The other two patients (E.M. and C.R.) were given two runs of the test each day and the mean of these two times was taken for the daily scores. From these daily figures weekly mean scores were obtained for the period of the trial. For the first period of three weeks each patient received procaine amide, starting with 1 g. daily and working up over 5 days to 1 g. q.d.s. During the next three weeks two patients received reserpine 1 mg. t.d.s. and the other two identical placebo tablets. The drugs were then reversed during the following three weeks and during the last week of all, all drugs were withheld.

Second Trial

Subsequent to the controlled trial two patients (C.M. and B.B.) were put on larger doses of reserpine (2 mg. t.d.s.). A film was taken during this period of C.M. for comparison with one taken in the pre-trial phase. Two other patients (E.M. and C.R.) were treated with reserpine (1 mg. b.d.) and Meratran (pipradol hydrochloride) 1 mg. daily. After a month the drugs for these four patients were withdrawn for a period of three weeks as a means of evaluating their effect on the patients' hyperkinesis. The drugs were then re-introduced in the same dosage as before. Finally three additional patients in other wards were tried on reserpine 1 mg. t.d.s.; of these two patients are still on the drug while in the case of the other patient the drug had to be withdrawn on account of side-effects. Details of all seven patients are given in Table I.

TABLE I

Patient	Age (years)	Sex	Family History	Duration of Illness	Response to reserpine
E.S. ..	51	F.	Negative	10 years	Improved
B.B. ..	48	F.	Positive	12 years	Improved
E.M. ..	48	F.	Positive	5 years	Improved
C.R. ..	54	F.	Positive	4 years	Improved
C.M. ..	51	F.	Positive	7 years	Improved
J.B. ..	54	M.	Negative	53 years	Side effects—drug withdrawn
G.W. ..	54	M.	Positive	10 years	No change

RESULTS

First Trial

The results of this trial are shown in Figures 1–4. In two patients (Figs. 1 and 2) there is evidence of diminished hyperkinesis while on reserpine. These two were the most severely incapacitated and were scored by direct observation. The other two scored by the finger dexterity test showed no very definite response to reserpine. One patient (B.B.) appeared to improve on procaine amide. Since then this observation has not been confirmed, though a further course of procaine amide was administered.

Second Trial

Though the film of C.M. showed little change in the amount of hyperkinesis compared with the pre-trial film, yet it seemed that both C.M. and B.B.

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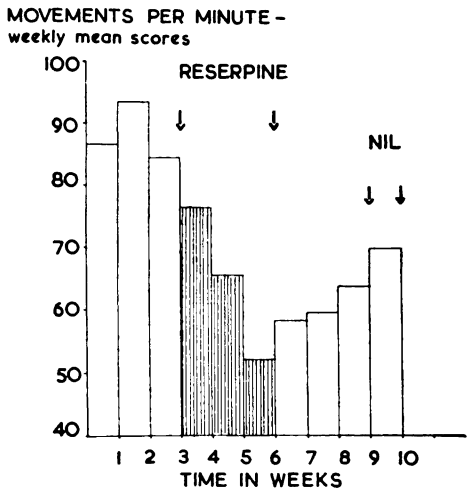


FIG. 1

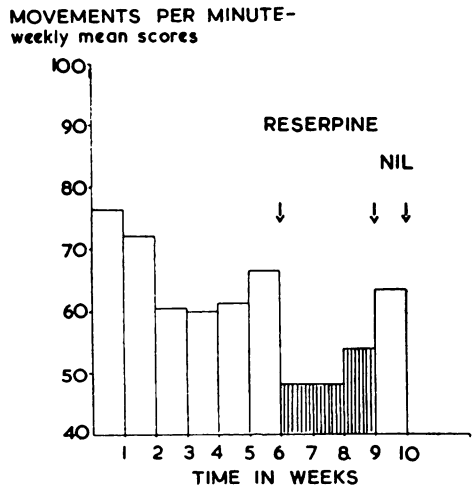


FIG. 2

showed the maximum improvement on the larger dose of reserpine (2 mg. t.d.s.). Similarly E.M. and C.R. seemed to be at their best on the reserpine-Meratran combination. The increase in the amount of hyperkinesis that was observed during the blank period when all drugs were withheld convinced the nursing staff that the patients were benefiting from their drugs. Particularly the staff commented that these patients were much less pleasant and co-operative when the drugs were withheld. Of the other three patients only E.S. showed improvement. G.W. has dyslalia rather than involuntary limb movements as his chief symptom. He did not show any significant improvement. J.B. complained of intermittent nausea, vomited twice and was troubled by aching pains in the legs and trunk. The reserpine was continued for three weeks in spite of these adverse symptoms but was then withdrawn as there had been no appreciable change in the amount of involuntary movement observed.

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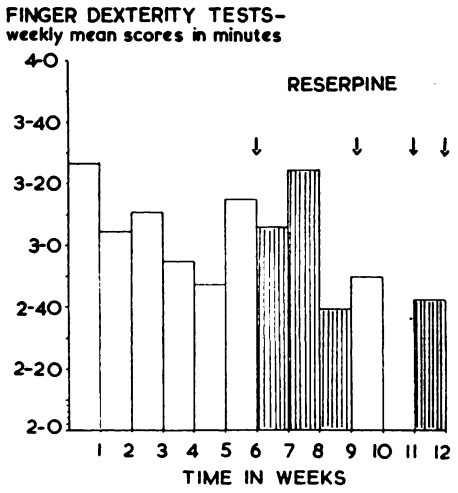


FIG. 3

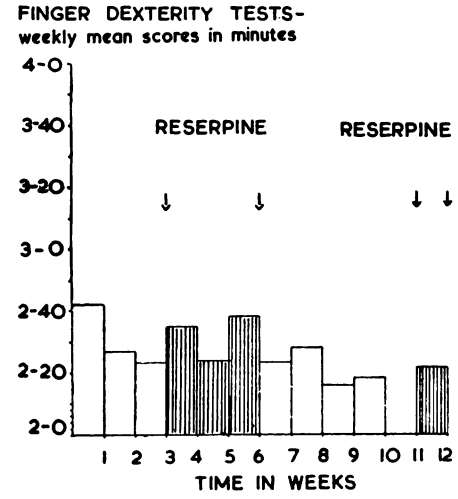


FIG. 4

BIOCHEMICAL INVESTIGATIONS

The serum copper levels in the first four patients were compared with values obtained for eight non-choreic controls (four normal volunteers, four schizophrenic patients). All the results fell within the normal range. Twenty-four hour urine specimens were then collected (using suitable precautions to avoid metallic contamination) and the copper content estimated. These results also fell within the normal range (see Table II).

As it had been noted that the trial patients seemed to show more hyperkinesis before meals than afterwards it was postulated that low fasting blood sugars might be related to this phenomenon. Accordingly the fasting blood sugar was estimated in six patients and in two patients glucose and insulin tolerance curves were also performed. The only abnormal result was the insulin tolerance

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curve in case B.B., the blood sugar falling from a fasting level of 78 mg./100 ml. to 17·5 mg./100 ml. at 1 hour and 42 mg./100 ml. at 2 hours (0·1 units soluble insulin per Kg body weight). It was felt that this finding might reflect hepatic deficiency and liver function tests were therefore performed in seven patients. In two patients the flocculation tests were abnormal (B.B.: thymol turbidity 3 units, thymol flocculation +ve, serum colloidal gold 4 units; E.S. thymol turbidity 6·5 units, thymol flocculation +ve, zinc turbidity 11·0 units, serum colloidal gold 4 units). The serum proteins and serum bilirubin levels were within normal limits.

TABLE II

Patient	Fasting Blood Sugar (Per cent.)	Serum Copper (Per cent.)	24-hour Urinary Copper Excretion	Liver Function Tests
G.W.	85 mg.	—	—	Normal
J.B.	—	—	—	Normal
E.M.	77 mg.	150 mcg.	22 mcg.	Normal
C.R.	89 mg.	130 mcg.	28 mcg.	Normal
C.M.	74 mg.	130 mcg.	26 mcg.	Normal
E.S.	67 mg.	—	—	Hepato-Cellular Damage
B.B.	70 mg.	160 mcg.	11 mcg.	Hepato-Cellular Damage

Finally the urine was examined for amino-acids (3 patients) and for indole excretion compounds (7 patients). No abnormal amino-acids were found in the urines examined. Early morning urine specimens from seven patients were examined for urinary indoles using a technique based on that described by Jepson (1955). Urine was examined both before and while the patients were under treatment with reserpine. The confirmatory tests used for serotonin (5-hydroxy-tryptamine), indole-acetic acid and 5-hydroxy-indole-acetic acid were the same as those described by Jepson in the article already quoted. The results of this investigation are shown in Table III. Urea and Indoxyl sulphate, which are normal urinary constituents, were found in each case and have not been included in the Table.

TABLE III

Patient	Receiving Reserpine?	Indoles Detected in Urine				
		5–H.T.	Trypto-phane	5–H.I.A.A.	I.A.A.	I.L.A.
C.M. ..	No	+	+	−	+	+
	Yes	+	+	−	+	−
B.B. ..	No	+	+	+	+	−
	Yes	+	+	−	+	−
C.R. ..	No	+	+	+	−	−
	Yes	+	+	−	−	−
E.M. ..	No	+	+	−	−	−
	Yes	+	+	−	−	−
E.S. ..	No	+	+	+	+	−
	Yes	+	+	−	+	−
G.W. ..	No	+	+	−	−	−
	Yes	+	+	−	−	−
J.B. ..	No	+	+	−	−	−

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Discussion

It should perhaps be made clear that the scoring techniques used in the drug trial were found to give a retesting error of plus or minus 10 per cent. Thus the figures have no absolute validity, but owing to the nature of the trial should provide an adequate measure of the difference between one phase of the trial and the next. If this is accepted then the first trial demonstrated that reserpine produced a significant reduction in the amount of hyperkinesis in two of the four patients tested. In fact the phase in the second trial when the drug was withdrawn was much more impressive. All observers were agreed that the patients were worse without their drugs. For milder cases reserpine plus Meratran seems a satisfactory combination. The findings reported here confirm those of other workers (Lazarte *et al.*, 1955; De Myer and Dyker, 1954) that procaine amide is without significant effect in reducing the hyperkinesis. In view of the negative findings regarding copper metabolism it has not been thought justifiable to try the effects of B.A.L. In fact there seem to have been no reports in the literature confirming the observations of Nielson and Butt (1955) regarding the efficacy of B.A.L.

It is difficult to assess the significance of the biochemical abnormalities discovered. Dr. Easson, who very kindly arranged for most of the biochemical tests to be performed, is satisfied that the liver function test abnormalities in cases of B.B. and E.S. are significant and indicative of cellular damage. It does not seem likely that dietary deficiency can explain these findings or the increased insulin sensitivity in the case of B.B. In fact it was striking what voracious appetites these patients had. The association between advanced liver disease and involuntary movements of extra-pyramidal type is now well known (Sherlock, 1956). It seems possible that further investigations into the liver functions in cases of Huntington's Chorea might be rewarding. It is even more difficult to decide the significance of the findings regarding indole excretion patterns in the seven patients examined.

Jepson (1955) in the paper quoted above suggested that 100 microlitres of normal urine would show very little in the way of indoles apart from indican, a trace of I.A.A. and an occasional unidentified spot. In fact the volume of urine used in these chromatograms was 60 microlitres though it should perhaps be emphasized that early morning samples were examined. In the course of another investigation samples of urine from patients in a general medical ward have been examined using the same technique. So far 55 samples have been examined and 17 (30·9 per cent.) were found to contain detectable amounts of serotonin. This is in keeping with the observations of Rodnight (1956) who found that the 24 hour excretion of serotonin in 12 normal adults ranged from 45 to 120 mcg./24 hours. On the other hand, Boyland *et al.* (1956) found no serotonin in the urine of 16 normal subjects even after the ingestion of 2 g. of L-tryptophan. One point of interest arising from this investigation was that 5-hydroxy-indolyl-acetic acid (5-H.I.A.A.) was detected less frequently than serotonin (5-H.T.) which is perhaps surprising as 5-H.I.A.A. is thought to be the normal excretion product of serotonin. The other point of interest is that there was no constant alteration in the indole excretion pattern during treatment with reserpine.

Summary

A controlled clinical trial of reserpine in four cases of Huntington's Chorea showed significant improvement in two cases. A more extended trial of reserpine in a total of seven cases of Huntington's Chorea showed some degree of reduction in hyperkinesis in five patients.

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Procaine amide was tried in four patients and was not found to be effective. A series of biochemical investigations on these seven patients have been reported and the possible significance of the findings discussed.

ACKNOWLEDGMENTS

I should like to thank Dr. A. K. M. Macrae, Physician Superintendent, for his encouragement; Sister F. O'Loughlan and Miss M. McLennan, A.O.T., for their very considerable assistance in running the first trial; and many other members of the staff for their help and criticism.

The placebo tablets were supplied through the kindness of Mr. R. W. Richards of *Riker* Laboratories Ltd.

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