HUNTINGTON'S CHOREA—SOME BIOCHEMICAL AND THERAPEUTIC ASPECTS*

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INTRODUCTION

HUNTINGTON'S Chorea presents us with a good "model" of brain disease in that we know the extent of the contribution of heredity, in contrast to a condition such as schizophrenia regarding which many authors (cf. Alanen, 1958) would be prepared to defend the concept of pseudo-heredity. Secondly the disease carries a fairly uniform prognosis, and finally it results in a distinctive disturbance of motor function which permits of some accuracy in diagnosis and some criterion for objective measurement.

One might therefore consider that Huntington's Chorea presents us, as psychiatrists, with an obvious challenge. In another hereditary condition, phenylketonuria, the error in metabolism has to a large degree been elucidated. If we cannot advance our knowledge of the aetiology of a relatively sharply-defined condition such as Huntington's Chorea then our prospects of understanding the more complex problems of the functional psychoses seem remote indeed.

Looking up the literature, one is struck by the paucity of papers reporting research into aetiology. It is true that there have been some excellent epidemiological investigations such as those of Pleydell (1954) for Northamptonshire, Brothers and Meadows (1955) for Victoria, Australia, and Reed and Chandler (1958) for Michigan. A particularly interesting paper by Reed and Palm (1951) pointed out that subjects with Huntington's tend to have larger families than their disease-free siblings, thus evading the natural tendency for diseased stocks to breed themselves out.

In the therapeutic field there was little advance until 1952 when Goldman reported on the beneficial effects of procaine amide. Goldman had noticed that one of his patients had been much improved following an injection of local anaesthetic for dental extraction.

He did not use any objective techniques of measurement, but this defect was remedied by Merskey (1958) who likewise found improvement in a proportion of his patients treated with procaine amide. Similarly positive results were reported by Ganguli (1956), whereas other authors such as Lazarte *et al.* (1955), Demyer and Dykes (1954), Pleydell (1954) and Forrest (1957) had been unable to demonstrate any striking therapeutic benefit.

Another form of treatment, the administration of dimercaprol (B.A.L.), was

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reported by Nielsen and Butt (1955). The analogy was with Wilson's Disease and these authors reported high values for the serum copper in two cases. However, normal serum and urinary copper levels were reported by Forrest (1957).

In 1955 Lazarte *et al.* reported on the beneficial effects of reserpine in Huntington's Chorea, while Brodie *et al.* (1956) showed that serotonin-releasing activity is restricted to tranquillizers of the rauwolfia group. This suggested the possibility that there might be some aberration in serotonin metabolism in Huntington's. Meanwhile Armstrong and Robinson (1954) had shown that there is an aberration in indole metabolism in phenylketonuria apart from the more obvious failure in the hydroxylation of phenylalanine to tyrosine. Subsequently Pare *et al.* (1957) reported low levels of circulating serotonin and urinary 5-hydroxyindole acetic acid in subjects with phenylketonuria and suggested that impaired 5-hydroxy-tryptophan synthesis might be more closely related to mental changes than the more obvious accumulation of phenylalanine in the blood.

In 1957 one of the present authors reported the detection of what were believed to be abnormal amounts of urinary indoles from four subjects with Huntington's Chorea. The present paper reports further investigations into this problem and the results of a clinical trial comparing reserpine and trifluoperazine (Stelazine).

Biochemical Investigation

1. *Material and Methods*

Three male subjects, diagnosed as suffering from Huntington's and fulfilling the criterion of a positive family history, were put on a standard diet. By standard we mean a diet that was the same for each patient and the same each day. The diet was high in protein and gave approximately 2,500 calories per day. It was arranged in co-operation with Mr. Godfrey, the Regional Catering Officer. Fluid intake and urine output was measured during the experimental period. As these values do not correlate with the amount of urinary indoles they will not be further considered. After the patients had been on the diet for four days the 24-hour urine samples were collected for a period of nine days. During this period the following experimental procedures were effected; intravenous administration of 25 mg. of 5-hydroxy-tryptophan on day 3; oral administration of 2 g. of dl-tryptophan on day 5; and oral administration of 1·2 g. of l-tryptophan on day 8. Aliquots from the 24-hour urine samples were subjected to chromatography.

The two-way ascending technique described by Jepson (1955) using isopropanol-ammonia and butanol-acetic acid, was employed. Whatman No. 20 paper was used and 100 microlitres of untreated urine was applied with a micrometer pipette to the point of origin. Two papers were prepared from each urine aliquot and with each batch two reference papers were run. These were prepared by applying 10 mcl. of a standard mixture to the point of origin. The standard contained 5-hydroxy-tryptophan, 5-hydroxyindole acetic acid, indole acetic acid, tryptophan and tryptamine—1 mg./ml. of each substance.

After completing the two runs and drying, the first paper was exposed to U.V.L., and then to Ehrlich's reagent. The second paper was treated with sulphanilic acid reagent. On the basis of these reactions, Rh. values and comparison with the reference papers spot identification was attempted. The spot areas were then measured using a straight arm planimeter.

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2. *Results*

These are shown in Table I.

TABLE I

Daily Excretion of Indole Substances
(Area in sq. cm.)

	Day	Patient	Trypto-phan	Kynur-enine	Q.F.B.	X	5-H.T.	5-H.T.P.	Z	5-H.I.A.A.
	1	B	3·3		2·4					
	1	J	2·8		2·1	3·0				
	1	L	2·3			2·0				
	2	B	2·4	2·6	2·0					
	2	J	3·2	2·7	1·9	2·8				
	2	L	2·8			2·2				
25 mg. 5 H.T.P. I/V	3	B	3·0				2·0	3·2		
	3	J	2·8		2·4		1·6	3·2		
	3	L	3·3			2·4	1·6	2·9		
	4	B	2·5	5·0				2·8		
	4	J	2·8	4·8				2·7		
	4	L	3·4			1·6	1·4	2·9		
2 gm. DL-T.	5	B	3·0			2·0			2·9	
	5	J	3·2	3·5		2·2			2·8	
	5	L	3·0			2·4			2·7	2·5
	6	B	3·0			1·6			2·8	
	6	J	2·6	4·2	2·9	1·9			2·2	
	6	L	2·6			2·2			2·3	
	7	B	2·3	3·0		1·7			2·8	2·9
	7	J	3·0	2·4		1·8			2·2	3·0
	7	L	2·4			2·4			1·8	2·0
1 gm. L-T	8	B	2·9	4·2		2·6			1·6	
	8	J	3·0	5·0		2·4			1·2	
	8	L	2·0			2·0				
	9	B	2·6	3·2		1·6				1·8
	9	J	3·8	4·4	1·9	1·4				1·6
	9	L	3·2		1·6	1·6				1·8

The designations Q.F.B. and X require some explanation. The identity of Q.F.B. (quickly fading blue) is in dispute. Riegelhaupt (1958) who first gave it this name found the spot more frequently in schizophrenic urine. Rodnight and Aves (1958) consider it to be a skatole derivative, whereas G. A. Buscaino (1958) suggests that it may be a methoxy tryptamine. One of us (A.D.F.) has found Q.F.B. quite often in normal urine. Spot X is, probably, anthranilic acid on the basis of the position, blue fluorescence with U.V.L., and yellow-orange colour with Ehrlich's reagent.

The administration of 5-H.T.P. was followed by the appearance of 5-H.T. in the urine and also unchanged 5 H.T.P.

Dl-tryptophan administration resulted in the appearance of spot Z and, after an interval of 2 days, 5-H.I.A.A. Z lies at 4 o'clock to the tryptophan spot, gives a blue-purple colour with Ehrlich's, fading quite quickly to a grey colour. There were no responses to the other tests and this spot was thought to be 5 methoxy tryptophan.

The administration of l-tryptophan was followed by the expected appearance of 5-H.I.A.A.

The next table (Table II) records the spot areas of urinary indoles from two normal male controls on the same standard diet. The only experimental procedure was the administration of 1·2 g. of l-tryptophan by mouth. As can be seen from the table, that substance Q.F.B. was detected in urine from one of these controls. The ingestion of l-tryptophan was followed by the appearance of 5-H.I.A.A. in both subjects.

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TABLE II

Indoles Excreted by Two Normal Subjects
(Area in sq. cm.)

	Day	Subject	Trypto-phan	Q.F.B.	X	5-H.I.A.A.	Kynur-enine	5-H.T.
	1	F	2·4				2·2	
		E	2·2					
	2	F	2·6				1·8	
		E						
1 g. L-T	3	F	2·5	1·2			1·6	
		E	2·8		2·0			1·4
	4	F	2·4	1·4		2·0	1·2	
		E	2·2		2·4	1·8		

THERAPEUTIC OBSERVATIONS

1. *Materials and Methods*

The same three male patients as were involved in the biochemical study were included in the therapeutic trial. During the first week each patient received nicotinic acid 100 mg. t.d.s. During the next three periods, each of two weeks, the subjects received either trifluoperazine (5 mg. tablets), lactose tablets or reserpine (1 mg. tablets) three times per day. The dosage schedule was one tablet t.d.s. for two days, two tablets t.d.s. for two days and three tablets t.d.s. for ten days. The drug sequences were arranged in the usual latin square. Methods of measuring changes in the level of motor co-ordination and the degree of interference from involuntary movement, were as follows:

(a) *Peg Board Test.* This consisted of a flat wooden board containing 24 holes into which had to be fitted 24 wooden pegs. Two trials were given each morning and the time taken to complete the test was recorded with a stop-watch.

(b) *Test I* represented the time taken to tie a neck-tie. Patients with Huntington's generally have considerable difficulty with motor tasks of this sort and it was anticipated that this task might be a good index of changes in the level of involuntary movement. The task was performed pre-trial and at fortnightly intervals and the time taken was noted.

(c) *Test II* was a simple weaving task devised by the O.T. Department. Whereas both the time taken and the level of accuracy were recorded, yet in fact these values correlated quite well and for the sake of simplicity the time taken for the task was used as the index of change. This task was likewise performed pre-trial and at fortnightly intervals.

RESULTS

The mean daily times for the peg-board test are shown in Figures 1–3.

Figure 1 shows the results in patient J. There is improvement in the test times toward the end of the first week with further improvement during the trifluoperazine (Stelazine) period. Scores deteriorate during treatment with placebo and reserpine.

Figure 2 refers to patient B. Again improvement during the first week is followed by relapse in the placebo and reserpine periods. Improvement in the test times occurs during treatment with trifluoperazine.

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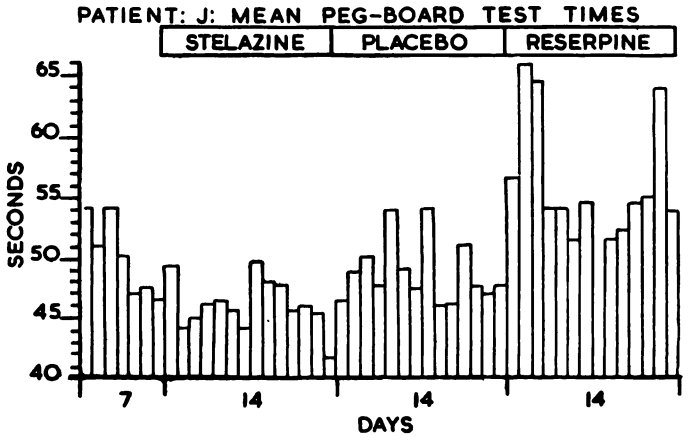


FIG. 1

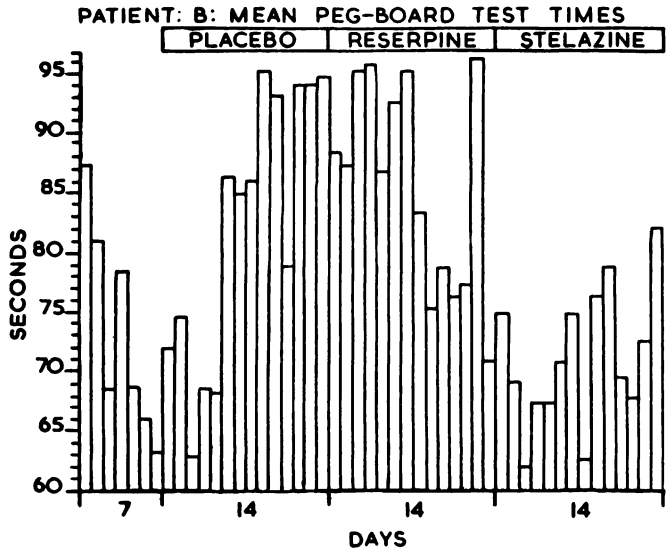


FIG. 2

Figure 3 refers to patient L. He was not very co-operative and, as you can see, on several occasions he refused to do the test at all. The test scores were recorded at the end of the first week and during the second week, while on reserpine.

The peg-board test was performed twice daily by two normal subjects for 14 days. The mean scores on the 14th day were 79 per cent. and 80 per cent. respectively of the mean scores on the first day. Applying these crude criteria to patients J. and B., it appears that their best times on trifluoperazine were 76 per cent. and 71 per cent. of their starting times. These figures are, in fact, not much different from those that might have been predicted on the basis of practice effect in the two normals.

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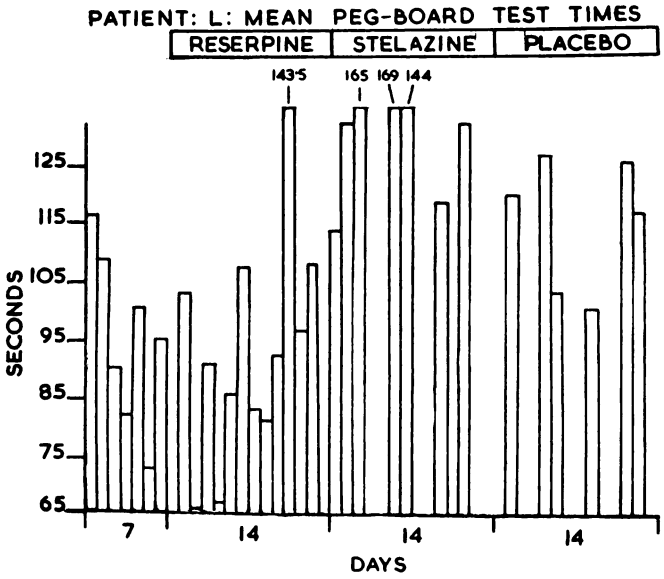


FIG. 3

However, the practice element in tests I and II were minimal and from Table III it is clear that the test scores during the trifluoperazine period were again lower than in the other two drug periods. Rather surprising perhaps are the low scores recorded during the first week when the patients were receiving nicotinic acid.

TABLE III

Results of Timed Performance Tests in Subjects J. and B. During Different Drug Treatments

Subject J.				Subject B.			
Date	Drug	Test 1 (Seconds)	Test 2 (Seconds)	Date	Drug	Test 1 (Seconds)	Test 2 (Seconds)
1/5/59 ..	—	20·4	360	1/5/59 ..	—	52	480
15/5/59 ..	S	22·4	420	15/5/59 ..	P	79	1,680
29/5/59 ..	P	30	420	29/5/59 ..	R	47·6	720
12/6/59 ..	R	67·6	540	12/6/59 ..	S	36·8	660

DISCUSSION

Previously (Forrest, 1957) one of us had reported the detection of excess indoluria in samples from patients with Huntington's Chorea. The criteria for excess were based on the paper by Jepson (1955). Subsequent experience had suggested that dietary factors were important and that a "loading test" using the amino acid tryptophan might bring out metabolic abnormalities. In fact there seemed, in this investigation, to be little difference between the choreics and the normals in their response to the ingested tryptophan. Whereas it is true that the choreics did excrete a greater total, as measured by spot area, the significance of this observation is obscure. Similar findings have been reported for schizophrenics (Leyton, 1958; Cafruny and Domino, 1958).

The results of the therapeutic trial indicated that as regards suppression of involuntary movement trifluoperazine proved more potent than reserpine.

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This is not consistent with the postulate that the reserpine effect is specific and related to some disturbance of serotonin metabolism in Huntington's Chorea.

However, though we used the motor phenomena as a guide to drug effects, our object was to treat the patients rather than their movements. Subject B, in fact, showed more improvement on reserpine as judged by self-assessment and the opinion of the nursing staff. Subject J showed improvement in his mental state as well as the choreiform movements while on trifluoperazine; on reserpine he became depressed and suicidal. Subject L, who showed more intellectual deterioration than the others, made little consistent response to either of the drugs. As noted previously all three patients improved during the first week while receiving nicotinic acid. This vitamin was not used with any therapeutic intent but merely because two of the patients expected pills and would have been upset if they had been withheld. The improvement in the first week was probably a practice effect. Subsequently we treated two of the patients with large doses of oral nicotinic acid but without any striking results.

The tests we used are certainly open to criticism. We have described them loosely as performance tests and admit that completion of them largely depends on the subject's attitude and motivation. It may be, in fact, that improved times on the performance tests reflected alteration in attitude to the tests rather than any specific effect on involuntary movement. That this is clearly not the whole answer is shown by the observation that patients B and L showed increased involuntary movement at rest during the placebo period.

As regards the mode of action of chlorpromazine Bradley and Elkes (1956) have suggested, on the basis of animal experiments showing a blocking effect on arousal responses to afferent stimulation, that the drug may act in relation to the afferent collaterals entering the reticular formation at the brain stem level. As regards reserpine Gross and Weiskrantz (1959) have reported experiments on delayed auditory response in monkeys which suggested that reserpine was producing a partial "sensory blockade". We therefore treated two of our choreic patients with phencyclidine (Sernyl) on the basis that this drug induces an even greater degree of "sensory blockade". Given by the intravenous route this drug is a psychoticomimetic (Luby *et al.*, 1959) while by the oral route it has been used as a tranquillizer (Bodi *et al.*, 1959). Our two patients received 5·0 mg. t.d.s., of phencyclidine by mouth and showed quite marked reduction in the amount of involuntary movement. Unfortunately drowsiness and ataxia were conspicuous side-effects. Nevertheless these different observations suggest that there may be a common factor in the mode of action of these drugs used in Huntington's Chorea, namely a partial "sensory blockade" of incoming proprioceptive impulses.

Summary

1. An investigation into the excretion of urinary indoles and the response to a test dose of l-tryptophan in three patients with Huntington's Chorea and two normal controls is described. No specific abnormality, differentiating the patients from the normals, could be detected.

2. A trial comparing the effect of reserpine and trifluoperazine on the amount of involuntary movement in three patients with Huntington's Chorea is described. Trifluoperazine seemed, in this respect, to be the more potent drug.

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