Review Article

J. med. Genet. (1966). **3**, 298.

Huntington's Chorea

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Huntington's chorea is an hereditary disorder of the central nervous system characterized by the appearance in adult life of progressive chorea and dementia, and inherited in single autosomal dominant fashion with complete penetrance. The essential pathological features of Huntington's chorea are a primary loss of cells in the caudate nucleus and the putamen, and similar involvement of the cerebral cortex, particularly that of the frontal lobes. Often there is secondary hydrocephalus with gross dilatation of the ventricles. The clinical symptoms do not always correspond with these neuropathological features which are generally regarded as lacking specificity.

I: History

The disease was first recognized and described in America by Waters (1848), Lyon (1863), and others, before George Huntington gave his famous account of it. It came to be associated, however, with the name of Huntington, and rightly so, for his description of 'Hereditary Chorea' in 1872 aroused the admiration of no less a personage than Sir William Osler, for its accuracy, brevity, and vividness. An excellent account of the relation of George Huntington to earlier descriptions of the disease is given by De Jong (1937).

Waters recognized the disease to be 'markedly hereditary'. Huntington, with deep insight and acute observation, interpreted the mode of transmission of the disorder and wrote:

> 'The hereditary chorea . . . is confined to certain and fortunately a few families, and has been transmitted to them, an heirloom from generations away back in the dim past. It is spoken of by those in whose brain the seeds of the disease are known to exist, with a kind of horror, and not at all alluded to except through dire necessity, when it is mentioned as 'that disorder' . . . When either or both parents have shown manifestation of the disease . . . one or more of the offsprings almost invariably suffer from the disease, if they live to adult age; but if by any chance these children go through life without it, the thread is broken, and the grandchildren or great grandchildren of the original shakers may rest assured that they are free from the disease . . . Unstable and whimsical as the disease may be in other respects, in this it is firm, it never skips a generation to manifest itself in another . . .'

Thus, from Huntington's description of the mode of inheritance even before the rediscovery of the Mendelian laws in 1900, Huntington's chorea became the example *par excellence* in the medical literature and in medical texts to illustrate dominant inheritance with complete penetrance.

The disease is believed to have been brought to the United States by immigrants from England who landed in Boston Bay and subsequently settled in East Hampton, Long Island, where George Huntington's grandfather is said to have first identified the disease in 1797, and where George Huntington as a boy made his first observation in a mother and her daughter (Huntington, 1910). Although immediately after Huntington's description, many reports of the disease followed from England, France, Germany, and the rest of Europe and the world, the disease remained dramatically linked to the United States. Huntington's description and the reports of Davenport and Muncey (1916) and Vessie (1932) who followed the descendants of the original settlers for many generations were so striking that Critchley (1934) wrote:

> 'The story of Huntington's chorea has well been described as a true American tragedy more sinister and far more interesting than anything imagined by Theodore Dreiser.'

Davenport and Muncey traced 962 affected individuals from the New England area to four family groups who came to Salem and Boston in the 17th century, mainly from the east coast of England: three brothers who settled in New Haven, two other brothers in East Hampton, one immigrant

TABLE I

REPORTED PREVALENCE OF HUNTINGTON'S CHOREA IN VARIOUS COUNTRIES

Area Surveyed	Prevalence Rate per 100,000 Population	Investigator
England:		
East English Counties	0·2–1·2	Critchley (1934)
London	1·8	Minski and Guttmann (1938)
Cornwall	5·6	Bickford and Ellison (1953)
Northamptonshire	6·5	Pleydell (1954, 1955)
Germany:		
Rhineland	3·2	Panse (1942)
Australia:		
Tasmania	17·4	Brothers (1949)
Victoria	4·5	Brothers and Meadows (1955)
Queensland	2·3	Parker (1958)
Japan:		
Aichi Prefecture	0·4	Kishimoto *et al.* (1959)
U.S.A.:		
Minnesota State	5·4	Pearson *et al.* (1955)
Lower Peninsula of Michigan	4·1	Reed and Chandler (1958)
Rochester, Minnesota	6·7	Kurland (1958)
Canada:	3·8	Kurland (1958) (estimated from death records)
Province of Quebec	2–4	A. Barbeau (1966) personal communication

to Greenwich, and one of the founders of Southold, Long Island, who came to America in 1635*. Although it was not known that these families were related, the possibility was not held as unlikely.

Vessie described a family of two brothers who emigrated from Bures, a small village of Suffolk, to America, and produced 11 generations of choreics. He thought that the daughter of one of these original settlers in Boston Bay moved with her husband and family to East Hampton and became the parent stem of the Long Island group of Huntington's chorea. His searches led him to old records which showed that the other brother's wife, who might have been the choreic partner, was hanged for witchcraft at a public execution in Boston in 1653. Vessie suggested that the so-called witches whose trials and death at Salem became notorious were victims of Huntington's chorea. (According to Dr Muncey 'the name chorea came from the dancing mania which prevailed extensively throughout Europe in the middle ages. This mania was an epidemic in which thousands of persons became possessed with a common delusion and danced through the country like raving maniacs.')

* The original records of these 'classical' families with Huntington's chorea, on which Dr Elizabeth B. Muncey worked under the direction of Dr C. B. Davenport, have recently been compiled and published with a minimum of editing, in a limited mimeographed edition by the Dight Institute for Human Genetics of the University of Minnesota, Minneapolis. They are being sent on request to those persons who are presently engaged in research and genetic counselling in Huntington's chorea.

It seems that France also has contributed her share of Huntington's chorea genes to the New World. Hattie (1909) traced a family from Halifax, Nova Scotia, to Huguenot ancestors who fled from France because of religious persecution after the evocation of the edict of Nantes in 1685; and Barbeau, Coiteux, Trudeaux, and Fullum (1964) traced 123 cases of Huntington's chorea of French-Canadian origin to a single common ancestor who emigrated from France to Montreal in 1645.

Huntington's chorea has now been reported from all over the world. In the British Isles in addition to the focus on the east coast of England, apparently another focus is known to have existed for a long time in Scotland, in the Moray Firth area, particularly in a small fishing village on the east coast of Ross which was probably settled about 300 years ago (Lyon, 1962).

II: Epidemiology

Prevalence and Geographical Distribution. Although there are several estimates of the prevalence of Huntington's chorea from many countries and continents, these are not strictly comparable because of the diversity of methods employed by different investigators in the collection of their cases. Published prevalence rates per 100,000 population are summarized in Table I, but these require some further explanation.

The early investigations of Critchley (1934) and Minski and Guttmann (1938) for the Eastern counties

in England and for London comprise cases collected from admissions to hospitals and various mental institutions. These rates, therefore, are understandably very low because they refer to only a portion of the population. The unusually high figure for Tasmania represents an ascertainment artefact in a small population, not unlike that of the fascio-scapulo-humeral muscular dystrophy in Utah: in one family group there were 105 known cases of Huntington's chorea, all descendants of the original member who migrated from Somerset to Tasmania in 1853. Parker's figure of 2·3 for Queensland is, by the author's own admission, an underestimate from an incomplete survey (Parker, 1958). The extremely low figure of Kishimoto, Nakamura, and Sotokawa (1959) for the Aichi prefecture, with a population of approximately 4 million, is difficult to explain. Apparently for a long time the disease was thought not to exist in Japan and it was first reported from there only in 1927. In the United States, Reed and Chandler (1958) purportedly ascertained all cases in the lower Michigan peninsula which has 94% of the population of the State. The prevalence rate of 4·12 which they found is not too different from that estimated by Pearson, Petersen, Lazarte, Blodgett, and Kley (1955) for the State of Minnesota. Kurland's estimate for Rochester, Minnesota (1958), is based on only two cases of a brother and a sister. The rate for Canada was calculated by Kurland from mortality data covering a twenty-year period and that for the province of Quebec is a tentative one, based on a still continuing survey.

Excluding the early English surveys and the obvious pocket of cases in Tasmania, even with the differences in methodology, it appears that the prevalence of Huntington's chorea ranges from 4 to 7 per 100,000 population. Whether the Japanese figure represents a truly low prevalence or an under-reporting artefact, it is not known. It is possible that it reflects a racial difference. It is also uncertain whether the high prevalence reported for some areas is due to pockets of familial concentrations such as occurred in the past in New England. The example of Tasmania has already been cited. Sjögren (1935) carried out an investigation in two isolated communities of north Sweden in which he found an 'astonishingly high' number of Huntington's chorea cases, 88 affected in 40 families, probably all from the same original stock. Oliver and Schiele (1945) collected the family histories of 3 separate families with Huntington's chorea in Minnesota. The striking similarities in the names of some of the people in these families alerted the investigators who traced the families as branches of one big family. Also in Minnesota, Pearson *et al.* (1955) were able to identify 170 different kindreds in whom the disease appeared. To what extent these were related is not known.

Race and Sex Distribution. Except for the low prevalence among the Japanese, there is no evidence of ethnic, racial, or geographic selectivity. Reed and Chandler (1958) traced the earliest known choreic member of 124 choreic kindreds, and while 73 of them came from several States of the United States, 51 of them were traced to Canada and 14 countries of Europe. They also found that in Michigan the proportion of Negroes affected was as expected on the basis of the Negro population of Michigan. It has been suggested that Huntington's chorea is rare among Jews. This reviewer in his capacity as a genetic counsellor has had occasion to handle a large number of counselling cases of Huntington's chorea among the Jewish population of the north-eastern United States. Based on impression alone the proportion of Jewish cases is, if anything, higher than that of non-Jewish cases.

Some discrepancies in the sex ratio have been noted, but in general it appears that both sexes are equally affected. Bell, who reviewed the literature up to 1934, collected 151 pedigrees from the literature with 991 affected cases. Of these, 551 were male, 445 female, and 35 of unknown sex. In Davenport and Muncey's (1916) series of 962 affected, there was an excess of males, 521 males to 441 females. Reed and Chandler (1958), however, among 203 affected in 124 families, found more affected females, 85 males to 118 females, a sex distribution significantly different from expectation. The difference could not be attributed to a sex difference in mean duration of the disease, but the authors noted greater mobility of males relative to females in the early stages of the study, which might have led to under-reporting of males during that period.

Age of Onset and Duration. Table II shows the mean age of onset, mean age at death, and mean duration of the disease from the data of Bell (1934), Panse (1942), Reed and Chandler (1958), and Wendt (1959). With the exception of Wendt's data the mean age of onset is between 35 and 36 years with a standard deviation of about 12 years.

The mean age of onset of Wendt's cases is considerably higher than that of the other investigators. Wendt pointed out the well-known problem that in evaluating mean age of onset considerable error is introduced when one includes individuals born in the later part of the period of the investigation be-

TABLE II

AGE OF ONSET, AGE AT DEATH, AND DURATION OF HUNTINGTON'S CHOREA

Investigator		Age of Onset			Age at Death (yr.)		Duration (yr.)	
		Male	Female	Both Sexes	Male	Female	Male	Female
Bell (1934)	No.	256	197	460*	191	158	111	93
	Mean	36·05	35·17	35·51	53·55	52·59	13·72	
	SD	12·16	12·51	12·38	—	—	—	—
	SE±	0·51	0·60	0·39	0·63	0·74	—	—
Panse (1942)	No.	225	221	446	247	226	143	128
	Mean	36·50	35·66	36·19	52·24	52·15	13·87	13·05
	SD	12·75	11·30	12·25	—	—	—	—
	SE±	0·85	0·76	0·58	0·76	0·69	0·62	0·48
Reed and Chandler (1958)	No.	86	118	204	125	137	65	88
	Mean	34·55	35·85	35·30	53·05	54·11	15·78	15·93
	SD	9·77	9·83	9·80	12·65	12·29	8·09	8·55
	SE±	1·05	0·90	0·69	1·13	1·05	1·00	0·91
Wendt (1959)	No.	377	385	762	—	—	—	—
	Mean	44·25	43·69	43·97	—	—	—	—
	SD	11·2	10·6	10·9	—	—	—	—
	SE±	0·58	0·54	0·39	—	—	—	—

*Includes 7 cases where the sex of the patient was not recorded.

cause only those with early onset will be included. This is certainly true of the cases of Reed and Chandler where the observers were in the same generation as the observed propositi, while those of Bell were taken from the literature and, therefore, somewhat selected. Panse's cases were obtained by a variety of selection procedures. In order to avoid this bias and obtain a more correct estimate of age of onset, Wendt used 762 cases born in Western Germany between 1870–1899 where valid information as to age of onset was available. The resulting estimate of the mean at 44 years, and the distribution of age of onset, are significantly higher than that hitherto reported (Fig. 1) and perhaps reflect more accurately the mean and variation of age of onset of Huntington's chorea.

The range of age of onset spans a considerable number of years, with cases recorded at 5 years on the one extreme and 70 years at the other. It appears that the age of greatest risk for developing Huntington's chorea is between 35 and 40 years. The risk is considerably smaller under 25 and over 55 years. The mean age at death is between 52 and 54 years, so that the disease has a mean duration of 15 to 16 years, perhaps a little longer in females. The longer duration figures from Reed and Chandler's recent study, no doubt, reflect a true prolongation of the life of patients in response to modern medical care and treatment.

The most common cause of death is heart disease and pneumonia following general debility from incessant choreic movements. Suicide, however, rates high as a cause of death. Reed and Chandler (1958) found that among those non-hospitalized, suicide was a cause of death in 7·8% of men and 6·4% of women.

Although generalizations about the behaviour of the disease in a family cannot be made, certain observations apparently hold. Bell, for example, found a correlation in age of onset for parent-sib of 0·5 and for sib-sib of 0·64. Reed and Chandler also found similarity among sibs in age of onset and age at death though not as high as that estimated by Bell, and regarded it as a consequence of genetic similarity. The correlation coefficient between sibs for age of onset was 0·28 and for age at death 0·47. An analysis of variance for these variables showed that the mean square between sibships within kindreds exceeded that within sibships. The authors considered these results as favouring the hypothesis

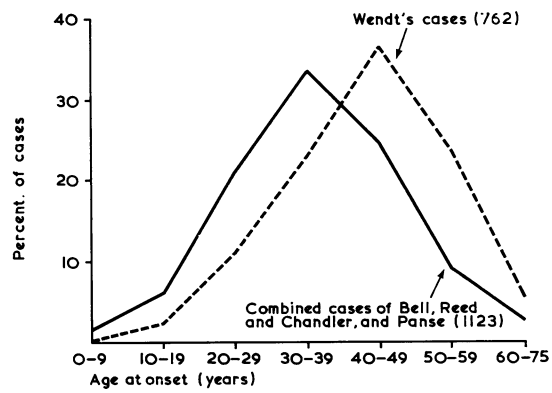

FIG. 1. Age of onset of Wendt's (1959) cases compared to that of the combined cases of Bell (1934), Reed and Chandler (1958), and Panse (1942).

that increased similarity among sibs was due to possession of common, similar 'background' genes, against which a single particular gene for Huntington's chorea manifested itself rather than that it was due to different genes for Huntington's chorea.

'Biotype' Concept. The behaviour of the disease in various families with respect to age of onset and other variables was recognized long ago by Davenport and Muncey (1916), who coined the term 'biotypes' or various strains of the disease as they occur in families. By this they meant that several members of a fraternity may show a characteristic symptom complex. This is certainly a colourful term and it may have served a useful purpose in the past. But it must be admitted that it was created on impression alone, and the few examples that Davenport and Muncey cite to support it, though appropriate, are neither numerically nor critically sufficient to justify its use in connexion with Huntington's chorea today. Chandler, Reed, and DeJong (1960) were not able to confirm biotypes in families in their Michigan study. They found that the biotype concept might apply in some families but not in others. The manifestation of component traits of the disease was variable in members of separate generations. In general they found that the disease was more severe when the onset was early (between ages 15–40 years) than late; that in those with early onset emotional disturbance was often more prominent and preceded chorea and intellectual deterioration by many years; and that with older age of onset, chorea and dementia were more often the initial components. The biotype concept will be discussed again later on.

III: Huntington's Chorea of Childhood

Although Huntington's chorea is considered a disease of adult life and has been so defined in this review, the occurrence of what is called Huntington's chorea in children below the age of 10 has been recognized quite early and reported many times. It will be given special consideration here not only because of its early age of onset but also because of its peculiar clinical picture which makes it almost a distinct clinical syndrome.

The occurrence of this disease before the age of 10 years is quite rare though well recognized among neurologists. Jervis (1963) in a review of 2282 Huntington's chorea cases from the literature found that less than 1% had onset below the age of 10, but Müller-Küppers and Stenzel (1963) state that in Western Germany there are about 60–70 cases at any one time. It is possible that many cases of chorea in children are not recognized because the neurological symptoms resemble those of Wilson's disease, and this diagnosis or that of post-encephalitic parkinsonism is often made. Interest in chorea of childhood has been revived recently through the reviews of Bittenbender and Quadfasel (1962) and Jervis (1963), from which we have drawn heavily.

The disease in these children presents a clinical picture which is considerably different from that of the adults. Choreic movements are absent in the majority of cases and instead of hypotonia there is muscular rigidity and tremor. Seizures are almost always present and the children deteriorate mentally quite early. A few necropsies have been reported and it appears that the pathology is typical of Huntington's chorea (Jervis, 1963). The main lesions are in the caudate and the putamen, with much lesser or no involvement of the pallidum. There is astroglial proliferation in the involved areas and cyto-architectural changes in the cortex, and sometimes in the cerebellum, due to neuronal destruction. The peculiarities of rigidity, seizures, and mental defect are only partially explained by the pathology.

It is not surprising, therefore, that the clinical recognition of the disease is difficult and sometimes impossible. Of the 28 cases assembled here from the literature (Table III) less than half were given the original diagnosis of Huntington's chorea. Sometimes the diagnosis is based solely on the presence of Huntington's chorea in other members of the family (Jervis, 1963), and sometimes it is not made in spite of the family history (Bittenbender and Quadfasel, 1962). Often the diagnosis remains in doubt until pathological examination is made. It must be noted that in all reported cases there was definite or highly suspect history of Huntington's chorea in the family.

The mean duration of the childhood disease in 18 of the 28 cases collected from the literature, about whom information concerning the age at death is available, is 8·34 years, significantly shorter than that of the adult disease. It has been suggested that these cases represent extreme cases of anticipation. It is unfortunate that this concept still persists in medical and genetic literature; it has been convincingly demonstrated to be an artefact depending mainly on the manner in which families with a trait showing variability in age on onset are selected (Myrianthopoulos, 1963). In the particular case of Huntington's chorea, Penrose (1948) showed that the difference in age of onset in parent-child pairs is 8·82 years giving a parent-child correlation of age of onset of 0·59, and that the standard deviation of 12·38 years has a sufficiently wide range of age of

TABLE III

CASES OF HUNTINGTON'S CHOREA WITH ONSET DURING THE FIRST DECADE OF LIFE

Author	Age in Years at Onset	Age in Years at Death	Original Diagnosis	Hyperkinesis	Rigidity	Mental Defect	Seizures	Family History
Peretti (1885)	6	19	Huntington's chorea	+	+	?	?	+
Jolly (1891)	8	?	Huntington's chorea	+	−	?	+	+
Bielschowsky (1922)	6	15	?	+	+	+	+	+
Entrés (1925)	6	15	Wilson's disease	?	+	?	+	+
" "	5	15	Wilson's disease	?	+	?	+	+
Freund (1925)	7	?	Wilson's disease	+	+	+	−	+
Owensby (1925)	4	9	Huntington's chorea	+	−	+	−	+
Spielmeyer (1926)	7	15	Wilson's disease	−	+	+	+	+
" "	5	15	Wilson's disease	−	+	+	+	+
Runge (1927)	7	13	Huntington's chorea	−	+	+	−	+
Corberi (1929)	9	17	Huntington's chorea	−	+	+	−	+
Lion and Kahn (1938)	7	?	Huntington's chorea	?	?	?	?	+
Hempel (1938)	5	19	Wilson's disease	−	+	+	+	+
Panse (1938)	6	17	Huntington's chorea	−	+	?	+	+
" "	7	?	Huntington's chorea	−	+	?	−	+
Reisner (1944)	5	?	Post-encephalopathy	+	+	+	+	+
Pleydell (1955)	3	12	Huntington's chorea	?	?	?	?	+
" "	6	14	Huntington's chorea	+	−	+	?	+
Ford (1960)	8	?	Huntington's chorea	+	−	+	−	+
Mackenzie-van der Noordaa (1960)	6	?	Huntington's chorea	−	+	+	−	+
Campbell, Corner, Norman, and Urich (1961)	9	18	Post-encephalopathy	−	+	+	+	+
Bittenbender and Quadfasel (1962)	6	15	Parkinsonism	−	+	+	+	+
Barrows and Cooper (1963)	4	?	'Exotic disease'	−	+	+	+	+
Jervis (1963)	7	12	Spastic cerebral palsy	−	+	+	+	+
" "	9	?	?	+	−	+	+	+
" "	4	8	Brain tumour	−	+	+	+	+
" "	4	7	?	−	+	+	+	+
Müller-Küppers and Stenzel (1963)	7	?	Atypical Huntington's chorea	−	+	+	−	+

onset to allow relatively frequent occurrence of pairs of cases in which onset differs by as much as 25 years. It is very unlikely that maternal factors are at all involved in determining early onset in childhood cases of Huntington's chorea. R. Byers (1966, personal communication) observed onset of the disease before the age of 10 years in two half-sibs, children of a choreic father by two different mothers.

These, then, are clinically peculiar cases of children born to choreic parents in families with Huntington's chorea, in which the disease is transmitted in the classic autosomal dominant fashion, but who have rigidity rather than chorea, seizures, mental deterioration, onset in the first decade, and duration significantly shorter than that of the adult disease (Table IV). What should these cases be called? By the classical diagnostic standards these children cannot be given the diagnosis of Huntington's chorea. Clinically they do not show what Huntington described, neither do the majority of them have chorea. Many cases are considered as having some other disease in spite of the family history, and only after pathological examination can a reasonably definite diagnosis be made. There is hardly a doubt that the pathological process is identical to that of Huntington's chorea and that the same principal genetic mechanism is responsible for the manifestation of the childhood as well as for the adult disease. Yet the practice of calling these cases 'Huntington's chorea of childhood' sounds incongruous, and there is a temptation to try one's

TABLE IV

MEAN AGE OF ONSET AND DURATION AND SPECTRUM OF CLINICAL INVOLVEMENT IN HUNTINGTON'S CHOREA

Category	Mean Age of Onset (yr.)	Mean Duration (yr.)	% With Seizures	Chorea	Rigidity
General case of Huntington's chorea	34–36	13–16	3·4	+	−
Rigid and akinetic form (all ages)	22·5 ± 1·4 (N = 67)	11·1 ± 0·5 (N = 35)	16	±	+
Cases with onset in first decade		8·3 ± 0·7 (N = 18)	56	−	+

hand at the dangerous task of inventing new names. Barrows and Cooper (1963) half-heartedly suggest the term 'Huntington's disease', but while this makes the label less specific, it is hardly an improvement since it involves Huntington's name in a process which he neither saw nor described. With the blessing of some neuropathological colleagues I venture the admittedly cumbersome term 'striato-cortical degeneration of children in families with Huntington's chorea'.

IV: Rigid and Akinetic Forms

Rigidity, which is seen in children instead of chorea, also occurs in adults with Huntington's chorea. It may be the most prominent symptom, especially when the onset is early (Denny-Brown, 1962). The rigid form of the disease is not rare and it was noticed by Hamilton as early as 1908, but apparently it has been better known and more often reported by European than English-speaking neurologists. Panse (1942) found that among his cases 6% had rigidity and an even higher proportion had akinesia of parkinsonism. He estimated that the rigid form might constitute as high a proportion as 12 to 14% of all cases. As with the childhood form, in rigid cases the diagnosis of Huntington's chorea may be impossible to make on clinical grounds alone.

Bittenbender and Quadfasel (1962) collected 62 cases from the literature and added 8 cases from their own observations, one of which had onset before the age of 10. All cases were characterized by rigidity which in some dominated the clinical picture from the beginning and in others developed later. It was commonly associated with tremor and cog-wheeling and often developed into torsion dystonia. The mean age of onset of these cases is 22·5 years (Table IV, Fig. 2) and differs significantly from that reported for the general case of Huntington's chorea. The duration of 11·1 years, while higher than that of the childhood form, is lower than that of the general case. Seizures are present in 16% of the rigid cases and in only 3·4% of all cases (Entrés, 1925): they are present in 56% of childhood cases. The pathology apparently is not differentiating, though some investigations stress the loss of cells in the pallidum and fibres within the pyramidal tracts. Thus, the clinical picture of the rigid form of the disease appears to be intermediate between that of the childhood form and the general case of Huntington's chorea.

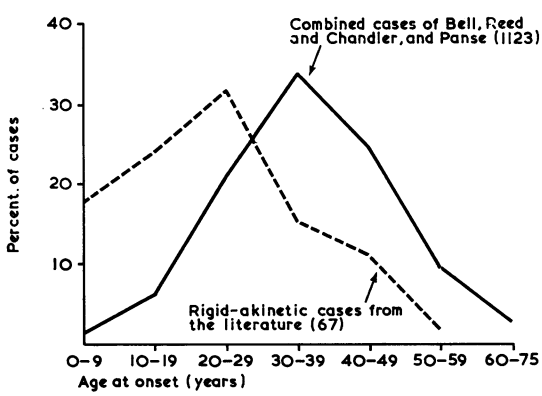

FIG. 2. Age of onset of rigid-akinetic cases of Huntington's chorea compared to that of the combined cases of Bell (1934), Reed and Chandler (1958), and Panse (1942).

Since the nature of the gene action and the pathways through which it works are unknown in Huntington's chorea it is not possible to explain adequately this extreme variation in phenotype. Yakovlev is quoted by Bittenbender and Quadfasel (1962) as holding the somewhat obscure opinion that rigidity and other variants of Huntington's chorea 'reflect a genetically predetermined selective vulnerability of the neural substrata'. The authors take this to be an example of the 'biotype' concept. The same concept is invoked by Müller-Küppers and Stenzel (1963) to account for the peculiar symptomatology seen in the childhood form.

This is not quite what Davenport and Muncey meant by 'biotypes' of the disease. They coined this term on the basis of observations that the symptomatology of the disease appears to be different in different families, and they cited examples of families which showed a specific complex of symptoms—not an isolated symptom or a single case—among their affected members. While the early onset and the rigid form are found sometimes in more than one case in the same family (Bittenbender and Quadfasel, 1962; Jervis, 1963), in the majority of cases they appear to be isolated occurrences indicating intrafamily variation, which Davenport and Muncey also noted and described in detail. To cite one of the earliest examples (not included in Table III), Facklam (1898) reported the case of a 46-year-old man who developed chorea at age 40. His father and grandfather were also affected and two sibs were already showing signs of the disease. Of his four children three died in infancy and the fourth, a daughter at age 10, was already showing early signs of the disease.

It appears to this reviewer that the wide variation in clinical symptoms, ranging from hypotonia to rigidity, sometimes with tremor and cog-wheeling, from chorea to akinesia, coupled with a wide range of age of onset and duration, may well fit within the concept of a continuum of hereditary

neurological disorders as elaborated by Myrianthopoulos and Smith (1962). These authors outlined a clinical, pathological, and genetic continuum of pyramidal and extrapyramidal disorders, and described transitional types between the main components of these entities. It is true that much of the phenotypic variation in the main and transitional components of the continuum was reflected in pathological changes, while in the childhood and adult rigid forms of Huntington's chorea the pathological changes do not seem to be different from those of the general case. But the microscopical pathology of Huntington's chorea, as was pointed out earlier, lacks specificity, and subtle variation, which may reflect variations in phenotype, cannot be recognized.

V: Heredity

As mentioned earlier, the hereditary nature of the disease was recognized by the earliest observers, and Huntington made definitive and accurate statements about the mode of inheritance. Nothing new has been added since Huntington's time. The disease is transmitted from parent to offspring in autosomal dominant fashion with full penetrance. Only in extremely rare instances has it appeared in offspring whose parents survived to old age without manifesting symptoms of the disease. With a disease of such a wide range of age of onset, however, such cases are expected to occur. Bell cited six such cases in her collection of 151 pedigrees from the literature. She also noted that in her material affected fathers had a preponderance of sons among their affected offsprings but this was not true with affected mothers. Segregation analysis was done by Sjögren (1935), Panse (1942), and Reed and Chandler (1958). All these investigators found excellent agreement with 0·5 expectation under dominant inheritance when corrections for age of onset were made.

Twin Studies. Systematic twin studies of Huntington's chorea have not been made but there are many published reports of twins with the disease. About two dozen cases of twins with chorea have been reported; 9 of these were allegedly in identical twins though in only one case was the monozygosity of the twins adequately documented. Russell (1894) described male twins who had chorea with equivocal signs of mental deterioration at the age of 27, a little earlier in one of the twins. Their identity was based on their remarkable likeness in appearance. Another family in which there were male twins discordant for Huntington's chorea was reported by Rosenthal (1927). The affected twin had symptoms at the age of 29, though chorea was not diagnosed until 10 years later. At the age of 40, his co-twin was still not affected. No evidence of zygosity was presented. Popenoe and Brousseau (1930) published a brief report in which they merely stated that they observed identical twin males, age 60, both affected with Huntington's chorea. Rosanoff and Handy (1935) reported female monozygotic twins affected with Huntington's chorea in whom symptoms appeared at age 35. The twins were described as being so similar in features and build that they could not be told apart and their records became very much mixed. Entrés (1940) reported two twin cases. The first was of female twins whom the author regarded as definitely monozygotic. They both became affected at age 41 and died at ages 54 and 56. The second was of male, presumably monozygotic twins, both of whom showed choreic symptoms at age 45 and died at ages 64 and 65. Jelgersma (1957) reported the case of twin sisters concordant for Huntington's chorea. One twin, 57 years old, was choreic since age 45 and mentally deteriorated. Her twin sister was affected with Huntington's chorea and died during an apoplectiform attack at age 54. Apparently, the deceased twin was never seen by the author, but he expressed the opinion that there were strong indications that the twins were identical on the basis of their striking resemblance. Parker (1958) described the occurrence of Huntington's chorea in male twins who were identical in appearance. In both, involuntary movements commenced at the age of 43 years and the twins died within three months of each other. Myrianthopoulos and Rowley (1960) reported monozygotic female twins concordant for Huntington's chorea in whom the first symptoms appeared at the age of 22 years, within a very short time of each other. The zygosity of the twins was determined by comparison of physical characteristics, fingerprints, and blood groups, and a probability figure in favour of monozygosity was calculated by the method of Smith and Penrose (1955). Thus, of the presumably monozygotic twin pairs, 8 were concordant and 1 was discordant for the disease. In the latter, however (Rosenthal's case), the unaffected twin was last seen at age 40, still well within the age of risk.

Cytological Studies. There is no evidence that Huntington's chorea is due to a gross chromosomal defect, though again systematic studies have not been made. Benirschke and Hoefnagel (1961) mention briefly that chromosome counts from peripheral blood cultures in one case of a male patient with Huntington's chorea were normal; and A. Barbeau (1966, personal communication) found

the karyotypes of six cases done at various times to be normal. The genetic mechanism responsible for Huntington's chorea must be considered as a point mutation whose spatial relations and pathways, through which it produces its effects, are still unknown.

Genetic Epidemiology. The frequency of the dominant gene for Huntington's chorea can be estimated from the prevalence rates given by the various investigators. Not all heterozygotes, however, can be identified, since the onset of the disease is late and many individuals are carriers of the Huntington's chorea gene at the time of the investigation though without showing any symptoms. Reed and Chandler (1958) estimated that the frequency of individuals heterozygous for the dominant gene for Huntington's chorea was $1{\cdot}01 \times 10^{-4}$ or 1 in 9,900. This is about $2\frac{1}{2}$ times higher than the prevalence rate of the disease found by these investigators, of 1 in 24,000. The gene frequency is, of course, one-half the heterozygote frequency.

A mutation rate based on these data could be calculated for the gene if reproductive disadvantage compared to the general population could be identified and measured. However, it is difficult to detect such a reduction in genetic fitness. It has been the impression among earlier investigators that affected persons of both sexes tend to have very large families. This is strengthened by the observations of Davenport and Muncey (1916), Vessie (1932), and the investigations of Pearson *et al.* (1955) in Minnesota. Bell (1934) gained the same impression from inspection of her pedigrees.

Panse (1942) calculated that the fertility of choreic patients compared to that of their non-choreic sibs was 1·18. Reed and Palm (1951) made a striking comparison of the fertility of two brothers from the State of Minnesota, U.S.A., one affected and one normal, each of whom had 10 children. At the time of investigation, the affected brother had 787 descendants of whom 716 were living; the normal brother had 186 descendants, 167 of whom were living. In other words, the normal brother had fewer than one-quarter the descendants of his affected brother. The mean number of children born to affected persons in this family was $6{\cdot}07 \pm 0{\cdot}9$ as compared to $3{\cdot}33 \pm 0{\cdot}5$ children born to unaffected sibs of choreics. This makes the relative fertility of choreics 1·89 that of their non-choreic sibs, and the difference is statistically significant.

Reed and Neel (1959) pointed out that the extremely high relative fertility of choreics found by Reed and Palm might have been due to the selection of a large, and consequently fertile choreic kindred, which might not be representative of choreic kindreds in the State of Minnesota, and that if choreics have higher fertility than normals, then this would be an instance of a rare dominant gene in the process of replacing its normal allele. Their own results, however, were in the same direction when normal sibs were used for comparison. By an elaborate procedure they estimated the relative fertility of choreics to be slightly higher than that of their non-choreic sibs, $1{\cdot}12 \pm 0{\cdot}12$, which is not too different from that reported by Panse; but they also found that the fertility of the non-choreic sibs was significantly lower than that of the general population, of the order of $0{\cdot}77 \pm 0{\cdot}08$. They suggested as possible explanation for this the fact that the sibs of choreics limit their reproduction because of the occurrence of chorea in the family. This makes the fertility of the carriers of the Huntington's chorea gene 0·81 that of the general population. Taking into consideration the relative fertility of the heterozygote, Reed and Neel (1959) estimated the upper limit of the mutation rate for the Huntington's chorea gene to be 5×10^{-6}, or 1 in 200,000 chromosomes per generation. Kishimoto *et al.* (1959) found that the relative fertility of their choreic patients was 0·65 when compared with that of their healthy cousins, but it does not appear as if the appropriate corrections for age were made. Using this fertility figure they estimated a mutation rate of $3{\cdot}3 \times 10^{-7}$ per locus per generation, which reflects the reported low prevalence of the disease in the Aichi prefecture.

VI: Neurological and Behavioural Disorders in Choreic Families

The occurrence of other neurological and behavioural disorders and abnormalities in choreic families has been discussed many times but its significance is still not very clear. Davenport and Muncey (1916) observed, among the 3000 relatives of their choreic patients, many nervous traits, including seizures, feeble-mindedness, hydrocephaly, Sydenham's chorea, etc. They considered the frequency of these defects to be rather high for the size of the population. Bell (1934), on the other hand, found no evidence that chorea was associated with other degenerative conditions. Leese, Pond, and Shields (1952) reported nervous and excitable behaviour in members of one choreic family, and Chandler *et al.* (1960) observed parkinsonism, cerebellar syndromes, spastic quadriplegia, dementia, and other defects in many choreic families. It has not been possible to decide whether or not these represented true or chance associations. Leese

et al. (1952) suggested that social factors might lead to selective mating between persons with Huntington's chorea and those with other physical or psychotic disabilities, resulting in the appearance of abnormalities in families with Huntington's chorea.

The story is different with the choreics themselves. Huntington described at length the tendency of affected individuals towards insanity and suicide. Later investigators and more recently Chandler *et al.* (1960) observed in choreic patients mental defects, convulsive disorders, alcoholism, behaviour abnormalities, suicide, criminal tendencies, and insanity. Mental deterioration is one of the cardinal signs of the disease. According to Bell (1934), men with chorea stand a better chance of retaining near normal or slightly disordered mentality than women. It is at times difficult to assess the degree of dementia, for as Parker (1958) pointed out, the patients' difficulty in communication due to impaired speech, might be confused with dementia. However, patients progress to develop severe dementia, suspicious behaviour, delusions, and schizophrenic reactions. The high frequency of suicide among such patients has already been referred to. A large proportion of choreics are in institutions: in Minnesota, Pearson *et al.* (1955) found that 45% of affected were in institutions, and in Michigan, Reed and Chandler (1958) found that 23·5% were so placed.

VII: Identification of Subjects who will Subsequently be Affected

The aetiology of Huntington's chorea remains unknown. Intuitively, it must be considered as a metabolic defect mediated by the action of an autosomal dominant gene. The deviations from normality, however, that occur in patients with Huntington's chorea, are either too small and vague to be quantified or cannot be presently evaluated in relation to the neurological damage which they produce. For this reason, the detection of the genetic carrier before he manifests any symptoms of chorea is, unfortunately, not as yet possible. This is downright tragic in such a devastating disease as Huntington's chorea, as anyone who has followed the course of the disease in an individual or in a family will readily admit, especially since onset is usually after reproduction has been completed. Efforts towards the detection of the genetic carrier have been made in several directions but without much success. A few still hold considerable promise and may eventually prove to be of value in genetic counselling.

Studies of Pre-morbid Personality. The first efforts have been directed toward identifying some kind of pre-morbid personality. Minski and Guttmann (1938) noted that many relatives of their 50 cases, who showed minor motor abnormalities, appeared to have a type of psychiatric personality consisting of irritability, quick-temperedness almost to the point of violence, were stubborn, domineering, opinionated, and easily offended. Although they found these traits difficult to interpret, they suggested that psychiatric examination might be of help in singling out potential patients. Tusques and Feuillet (1937), Laane (1951), and others, have described schizophrenia and other psychotic reactions preceding the onset of choreic symptoms by many years. Evard (1936) considered the occurrence of schizophrenia in choreic families as a 'phenotypic polymorphism' of Huntington's chorea. Myrianthopoulos and Rowley (1960) described the onset and development of schizophrenia in one of the sisters of their twin cases. They thought it possible that these psychotic episodes might be prodromal manifestations of chorea and that this sister might later develop the disease. At the time of writing, she has not. Brothers and Meadows (1955) administered psychological tests to a small number of children from Huntington's chorea families, but these yielded insufficient data on which to base a firm hypothesis. However, tests of an unaffected descendant of a choreic patient, age 37, with three Wechsler tests, were remarkably similar to those of affected cases. This person showed organic symptoms of the disease two years later. Palm (1953), using the Wechsler-Bellevue test, the MMPI (Minnesota Multiphasic Personality Inventory), and the Rorschach test on 23 clinically normal children of choreic patients, found no basis for prediction from the results and no correlation of the results with EEG findings (see later).

Electroencephalographic and Electromyographic Studies. Another approach has been through the recording and interpretation of the electrical potentials of the brain and those of the motor units. Patterson, Bagchi, and Test (1948) investigated whether or not the offspring of choreics show EEG abnormalities as blood relatives of some epileptics do, and if so, to what extent EEG abnormalities might be made the basis for prediction in non-affected children who show such abnormalities. For this investigation they selected 26 subjects from 9 families, ranging in age from 6 to 41 years, each of whom had one affected parent. These were first subjected to a variety of examinations and tests, including a neurological examination, and were found to be essentially normal and free from neurological deficit. On EEG tracing, 19

(79·1%) had abnormal records, particularly in the motor region; 5 (19·2%) had borderline records; and 2 (7·7%) had normal records. The EEG abnormalities consisted mainly of dominant slowing of waves, sudden slow or fast bursts of high voltage, abortive bilateral spike and wave formations, and exaggerations of these findings during hyperventilation. Many had spike and wave patterns without history of convulsive disorder. There was no specific EEG pattern except for slowing activity and general disorganization.

These findings were significant on two counts: first, because there was an abnormality in a high proportion of the offspring of choreics, and second, because there was no consistent similarity between these EEG patterns and those of 21 choreic patients who showed generalized low-voltage fast activity. The difficulty in interpreting these findings was recognized by the authors, especially since Gibbs, Gibbs, and Lennox (1943) reported that 16% of a large control group had abnormal EEGs. The authors assumed that very slow or fast EEG waves, episodic slow bursts, and marked hyperventilation had the greatest composite weight in prediction and suggested that if the EEGs were taken every 5 to 10 years, they might be found to deteriorate in half of the group and eventually resemble those of affected cases, when they became affected.

The work of Patterson *et al.* raised high hopes that it might provide a promising lead in the detection of the pre-morbid state, but very shortly after Harvald (1951) was unable to substantiate these findings. Harvald tested 25 adults over the age of 20 who were offspring of parents with Huntington's chorea. Two of these showed unmistakable signs of Huntington's chorea, which had not been discovered previously. Both showed low-voltage, fast activity without other signs of EEG abnormality. The remaining 23 showed no clinical symptoms of Huntington's chorea. Of these, 16 had completely normal EEGs; one showed low-voltage fast activity; five showed doubtful minor changes; and one had abnormal EEG with moderate changes. Harvald considered his series as not differing from the general population with respect to EEG pattern, and expressed the opinion that by means of current EEG techniques it is not possible to predict the morbidity among the offspring of patients with Huntington's chorea.

Leese *et al.* (1952) also criticized Patterson's work on the grounds that his criteria for abnormality were too loose, especially since some of the offspring were too young, and that most of the abnormalities found were unlike those seen in Huntington's chorea. On the other hand, when they administered EEG tests to 21 members of one choreic family which they investigated, they were able to substantiate the findings of Patterson *et al.* Of these records, five were abnormal; five were probably abnormal; six were doubtfully normal; and five were normal. The doubtful and the abnormal records were of either low-voltage, fast activity, or contained an excess of theta and beta rhythm. They found that these abnormalities tended to become more pronounced in older than in younger groups. Out of 12 unaffected sibs of the propositus, three or four had such a record. The authors noted that three out of eight (or three out of five over the age of 20 years) of Patterson's and one out of 23 of Harvald's normal subjects also had this kind of tracing, and commented that though non-specific EEG abnormalities were relatively common in presumably normal subjects in the general population, this particular pattern was rare and it was unlikely that it would occur by chance alone in the reported cases.

Palm (1953) came closer to the 1 : 1 ratio expected under dominant inheritance when he obtained EEG records on 25 clinically normal children of choreics from a single family. Twelve (48%) of these were abnormal or borderline while the remainder were normal. The abnormalities consisted of low-voltage, fast activity and some asymmetry and disorganization. Palm suggested that the individuals whose records showed these abnormalities might be incipient choreics.

Actually, there is no great disagreement in the EEG findings of these investigators, especially when low-voltage fast activity is considered sufficient to classify a record as abnormal (Table V). The EEG in most Huntington's chorea patients has relatively little normal alpha activity but shows generalized low-voltage fast waves, or low-voltage, poorly formed, irregular, and asymmetrical slow wave sequences (Patterson *et al.*, 1948; Hill, 1948; Pond, 1952; Palm, 1953). The suppression of the usual cortical rhythm has been attributed to the atrophic process in the frontal cortex and the basal ganglia (Gerebtzoff, 1941; Hill, 1948), which is pathognomonic of Huntington's chorea. Apparently these destructive processes disrupt the cortico-striato-thalamic circuits, thus abolishing or suppressing the cortical alpha activity. The EEG picture in Huntington's chorea patients, however, cannot always provide a good baseline, since normal EEGs have been occasionally obtained in advanced cases of Huntington's chorea (Palm, 1953).

While the EEG work initiated by Patterson *et al.* may not have fulfilled the expectations that it had initially raised, it may not be completely without

TABLE V

FREQUENCY OF EEG ABNORMALITIES IN CLINICALLY NORMAL CHILDREN OF PATIENTS WITH HUNTINGTON'S CHOREA

Investigator	No.	Abnormal		Borderline		Normal	
		No.	%	No.	%	No.	%
Patterson *et al.* (1948)	26	19	79·1	5	19·2	2	7·7
Harvald (1951)	23	2	8·7	5	21·7	16	69·6
Leese *et al.* (1952)	21	5	23·8	11	52·4	5	23·8
Palm (1953)	25	—	—	12	48·0	13	52·0

promise. Interpretation of EEG records depends largely on anatomical and physiological parameters, as well as those of time and age, many of which are unknown or poorly understood, and these may have contributed to the uncertain outcome of the investigations described above. In the opinion of this reviewer the whole problem of the role of EEG as a predictive instrument in Huntington's chorea merits thorough reappraisal and continuation under more refined and better controlled conditions. In the long run, the EEG technique may prove to be a useful adjunct to more precise studies using biochemical determinations.

The first attempts to measure motor control and co-ordination, though recent, have been admittedly crude. Parker (1958) used a sphygmomanometer test initially designed for the detection of Sydenham's chorea on a number of relations of choreics. This failed to produce a consistent abnormality which could be interpreted as a prechoreic physical sign. Baroff, Falek, and Haberlandt (1958) administered a battery of tests of co-ordination, motor control, and steadiness (degree of tremor) to a series of children and sibs of Huntington's chorea patients as well as to controls. These tests proved effective in distinguishing between normal and affected but not in identifying potential cases.

This approach paved the way, however, for the development of more sensitive instruments for motor evaluation. Falek and Glanville (1962) made use of an electronic tremometer which utilizes transducers, strain gauge, and accelerometer to record graphically fine motor movements. Recordings of vertical acceleration of a point on the hand taken from five patients with Huntington's chorea showed intermittent bursts of 1–2 seconds' duration which were considerably above the normal level of ordinary types of tremor which were observed in 54 controls (Fig. 3). Recordings of an affected mother and her two asymptomatic children, ages 14 and 19 years, showed that the record of the younger child resembled that of his mother while that of the other child was normal (Fig. 4). While it is not possible to say with any certainty at this time that the child with the abnormal tremogram is a potential choreic, extended and refined work with improved instruments, employing large numbers of patients and their immediate families to give statistically valid results may go far in resolving the problem of identification of the carrier of Huntington's chorea gene before the onset of the disease. This type of approach has been successfully used in other neurological disorders, such as Charcot-Marie-Tooth disease, for which the metabolic error has not been identified (Myrianthopoulos, Lane, Silberberg, and Vincent, 1964).

Biochemical Studies. One would reasonably assume that the most fruitful approach would be through the identification of some metabolic abnormality, first in the affected and then in the potentially affected, for there is hardly any doubt that Huntington's chorea is an inborn error of metabolism. Yet no such abnormality has been demonstrated in any biochemical studies. These efforts, however, can hardly be called systematic and at best seem to involve only a few patients. The majority of them appear to proceed from the reasonable premise that since the pathological process in Huntington's chorea affects chiefly the basal ganglia and the symptomatology resembles to a certain extent that of other basal ganglionic disorders, such as Wilson's disease and Parkinson's disease, the first line of attack should be a search for biochemical differences similar to those which are known to occur in basal ganglionic disorders.

Thus, when Nielsen and Butt (1955) reported that out of many patients with Huntington's chorea whom they treated with BAL (British anti-lewisite), two showed clinical improvement, a number of trials followed, involving the metabolism of copper and other metals. The reports concerning copper metabolism were more often than not contradictory and the copper theory is now discredited. Chhuttani Chopra, and Singh (1959) found high urinary copper in one of two brothers with Huntington's chorea, while Perry (1961) in a study of 14 urinary trace metals including copper, iron, manganese, and lead

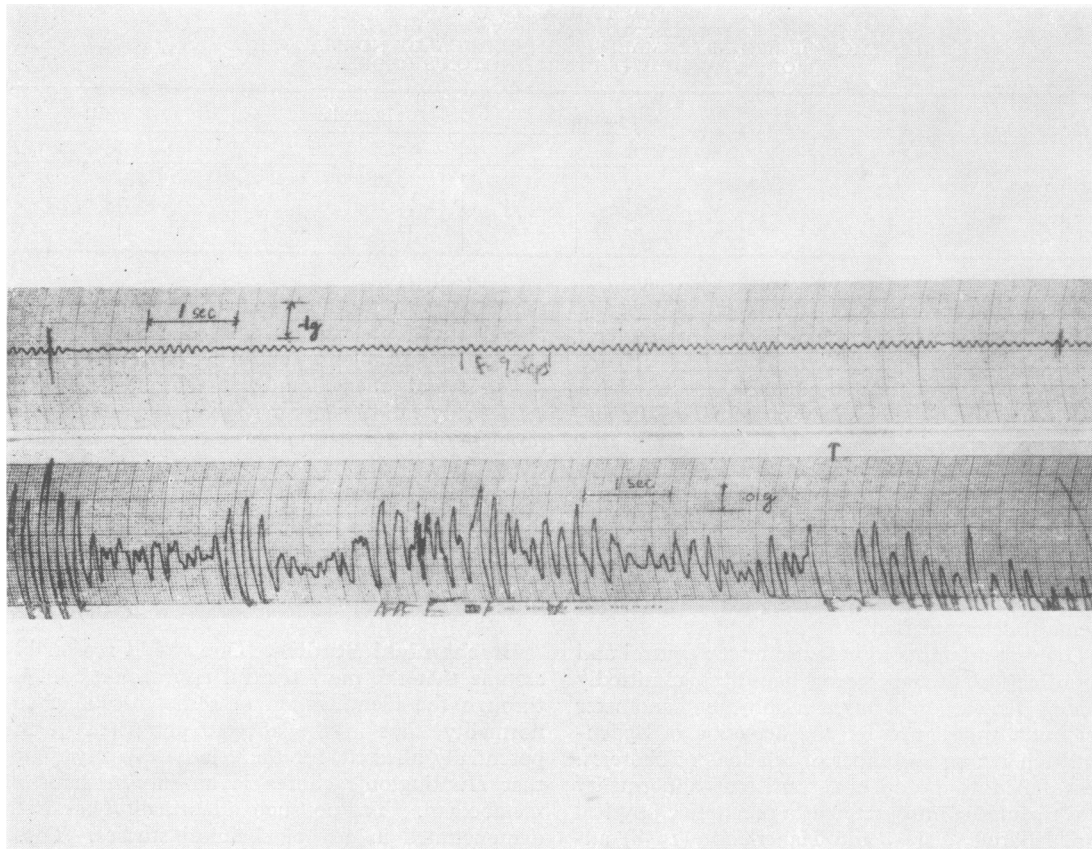

FIG. 3. Hand tremor recordings. *Top*, unaffected control. *Bottom*, Huntington's chorea patient. (From Falek and Glanville, 1962, Grune and Stratton, Inc., by permission.)

in seven patients with Huntington's chorea, six psychiatric patients, and nine normal adult controls, found no significant differences in the three groups. Courville, Nusbaum, and Butt (1963), in a spectrophotometric evaluation of 13 trace elements in three brains from Huntington's chorea patients and 18 control brains, found strontium to be increased but copper decreased. Finally in an extensive, unpublished study involving a large number of Huntington's chorea patients and their immediate relatives, initiated by Dr Benjamin Boshes (unpublished data and personal communication), in which this reviewer participated, some patients were found to have raised serum copper while others had normal values. The whole picture was one of hopeless inconsistency and was abandoned.

Our confusion and lack of understanding of the significance of trace metals levels is illustrated by the findings of serum copper levels in monozygotic female twins who developed Huntington's chorea almost simultaneously and showed the same progression (Myrianthopoulos and Rowley, 1960). On two determinations the serum copper level in one twin was 154 and 171 μg./100 ml., which is considered as abnormally high, while in the other twin it was 105 and 106 μg./100 ml., which falls within normal limits.

Dopamine has recently been implicated in another disease involving the basal ganglia, Parkinson's disease. Barbeau, Murphy, and Sourkes (1961) found the excretion of dopamine and epinephrine significantly higher than normal in a group of 16 patients with 'striatal syndrome', including four patients with Huntington's chorea. Williams, Maury, and Kibler (1961), however, found that urinary excretion of homovanillic acid, a major terminal metabolite of dopamine, in four patients with Huntington's chorea did not differ from that

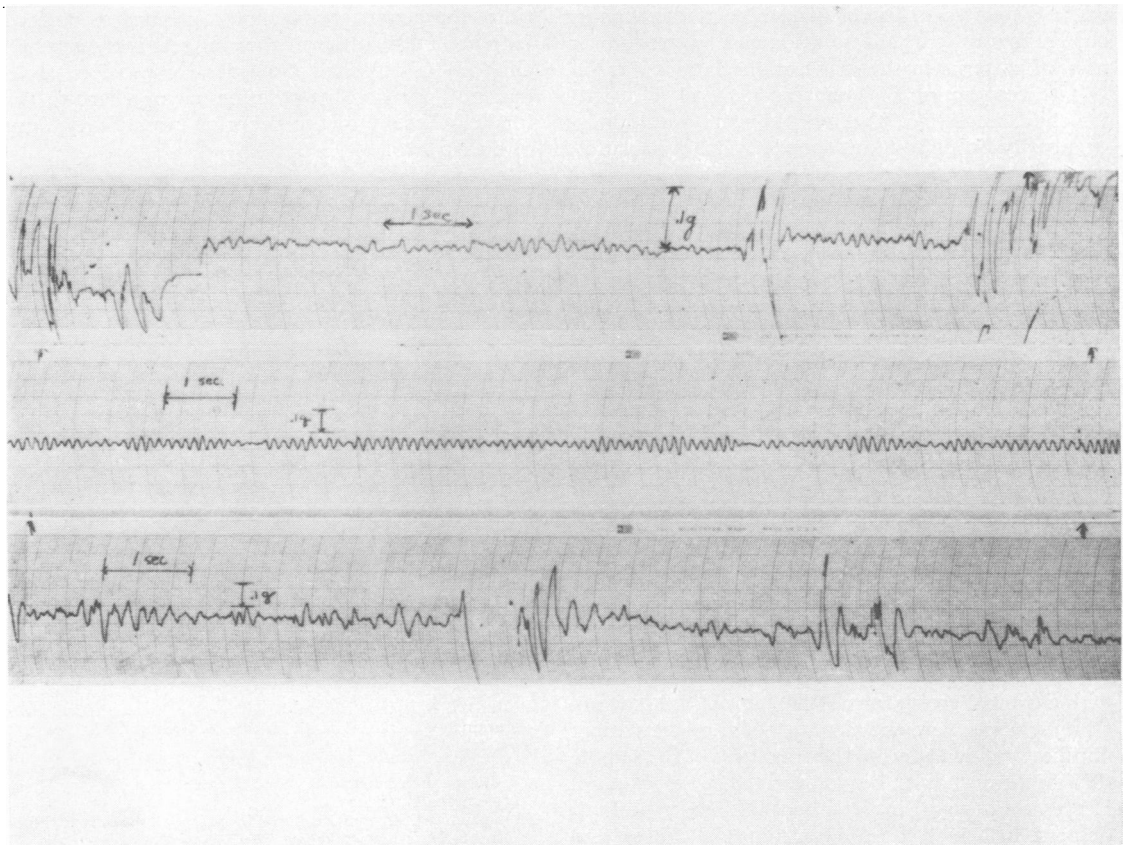

FIG. 4. Hand tremor recordings of three members of a choreic family. *Top*, mother affected with Huntington's chorea. *Centre*, unaffected son, age 19. *Bottom*, unaffected son, age 14. (From Falek and Glanville, 1962, Grune and Stratton, Inc., by permission).

of normal controls, and concluded that the metabolism of dopamine was not altered in Huntington's chorea.

Kenyon and Hardy (1963) observed that choreoathetosis and other types of involuntary movements, as well as a variety of mental states, have been described in patients suffering from disorders of magnesium metabolism, and studied the level of magnesium and calcium in the serum and erythrocytes of 20 choreic patients and an equal number of schizophrenic controls. The choice of the controls immediately casts doubt on the validity of the experiment and the findings, which were that patients with Huntington's chorea had normal serum values of these elements but raised cellular magnesium values, when compared with those of the controls. Further, those with positive family history had significantly higher cell magnesium values compared to those with no family history. This last observation is quoted for what it is worth, for the authors do not state how accurately their family histories were taken.

A variety of other trace metals (see Perry, 1961 and Courville *et al.*, 1963) and metabolites have been investigated without success. Oliphant, Evans, and Forrest (1960) measured the excretion of urinary indoles and the response of a test dose of l-tryptophan in three patients with Huntington's chorea and 2 controls. They found no specific abnormalities or differences. Deiwick and Oepen (1964) found no abnormalities in the activity of main chain enzymes in the serum of eight Huntington's chorea patients and one unaffected daughter of one of the patients; and Delbrück and Oepen (1964) found no abnormalities in the polysaccharide metabolism of seven patients with Huntington's chorea by a urine test. Oepen and Kreutz (1964) found no abnormalities in the serum cholestrol of these patients,

while Oepen and Bickel (1964) reported that paper chromatography of amino acids and sugars showed normal patterns in the urine of six patients.

The recognition of some biochemical difference which characterizes the morbid state would have eventually brought about some reasonably accurate method of detecting the carrier before the onset of the illness. However, though the metabolic basis of some inherited disorders of the nervous system, especially those of children, is now more or less understood, we are still in the dark in the vast majority of neurological disease processes which include the upper and lower motor neurone disorders, the extrapyramidal disorders, the leucodystrophies, and the cerebro-retinal degenerations.

Still another approach that would be of enormous importance and help, especially in genetic counselling, would be through well-designed association and linkage studies. Unfortunately these, too, have been only sporadic, and led nowhere. Patterson *et al.* (1948) found no significant association between Huntington's chorea and certain anthropometric measurements, colour vision, and P.T.C. tasting in 32 patients from among the families which they studied. On blood typing, 59·3% of these were of group A, a rather high percentage when compared with a control group from Michigan, U.S.A., whose ethnic origins were the same as those of the patient families, but considering the smallness of the sample this finding should be interpreted with caution. Leese *et al.* (1952) investigated one family of Irish descent in which both Huntington's chorea and colour blindness occurred. Linkage studies using as markers a full constellation of blood groups, P.T.C. tasting, colour blindness, and myopia failed to establish any linkage between Huntington's chorea and these traits.

Investigation of fingerprint patterns has not fared any better. Barbeau, Trudeau, and Coiteux (1965) examined and compared the fingerprints of 61 Huntington's chorea patients and 50 patients with Parkinson's disease with those of 100 normal controls. While there was some increase of whorls in the left second and third fingers of the Huntington's chorea patients, this finding was not consistent and the authors considered it of no diagnostic or prognostic value in Huntington's chorea.

It is somewhat disappointing that this review has to end on such a pessimistic note. The prospects for resolving the prognostic (and hence, genetic) and therapeutic problems of Huntington's chorea do not appear to be very good and they are not likely to get better unless efforts become concerted and systematic and include integrated team work in the field, the clinic, and the laboratory. In the meantime, the genetic counsellor continues to be faced with great difficulties in advising relatives, especially children of choreics. However compassionately he tries to approach his case, he has nowhere to turn for help except to the sobering probability figure of one in two.

I am indebted to Drs G. Allen, E. A. Carmichael, S. C. Reed, and S. M. Aronson for reading and criticizing the manuscript.

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Addendum

Since this review was prepared, a relevant article by Chandler has appeared in which the author reports an 18-year follow-up of 23 offspring of choreic patients, about whom Patterson *et al.* made predictions in 1948 on the basis of EEG recordings. Although 12 of the 23 have developed chorea, the occurrence of the disease in this group appears to be random rather than according to prediction. The author concludes that the EEG as used by Patterson *et al.* has little value in identifying carriers of Huntington's chorea. The original predictions, of course, were made on the basis of the criteria set by Patterson and his associates. These should also be critically examined in the thorough reappraisal of the role of the EEG as a predictive instrument.

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