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CLINICAL REVIEW

Huntington's chorea: a centenary review

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Historical introduction

In 1872 a recently qualified doctor of 22 gave an address to a medical academy in Middleport, Ohio, a mining town on the Ohio river, and 3 months later his paper 'On Chorea' was published in the *Medical and Surgical Reporter* of Philadelphia. The main part of this consisted of an account of rheumatic or Sydenham's chorea, but the last part was devoted to an hereditary chorea with mental changes commencing in middle life which is transmitted from generation to generation and runs a remorselessly progressive course. The account given was graphic, lucid and succinct, and soon attracted attention so that hereditary chorea has since been known as 'Huntington's chorea', after the author of the paper. William Osler (1889) who was interested in hereditary chorea praised Huntington's article. Although Huntington was not the first to describe late-onset hereditary chorea, his account is so excellent that there has never been any demand to change the name of the disease except perhaps to call it 'Huntington's disease' (Whittier, 1969) rather than chorea as some patients do not show chorea. The first description of an hereditary chorea in America was that of Waters (1841) in Dunglison's *Practice of Medicine* and this may have been seen by Huntington, although the latter's experience of the disease was gained in his father's and grandfather's practice in East Hampton on Long Island, and he later recounted seeing patients with the disease when riding with his father on his rounds in his practice (Huntington, 1910). Lund (1860) and Lyon (1863) also gave accounts of a chronic hereditary chorea of middle life. Stevens (1972) has recently reviewed the early literature of this disease in England and drawn attention to a description of chorea by Elliotson in 1832 that seems to be an early description of Huntington's disease. He attributed the lack of recognition of the condition prior to 1830 to the shorter life span before then and the smaller population of the United Kingdom. Consequently there were many fewer cases as the average age of onset of the disease (35·5 years, Bell, 1934) was similar to the average age at death. Even today the condition is rare and many general practitioners have never seen a case.

The important papers by Vessie (1932) in America, and Critchley (1934) in England, summarized the history of the disease up to the early 1930s in these countries and the interested reader might like to refer to these and also to *Neurographs* (1908) from which the two illustrations (Figs. 1 and 2) of George Huntington as a young man and as an old man are taken. Vessie found that the majority of cases presenting in New England were descendants of three individuals from Bures in Suffolk, who emigrated from Colchester, England, in 1632, and he was able to trace nearly 1000 cases spanning twelve generations in 300 years from these three.

Other historical descriptions are those of Barbeau *et al.* (1964) who traced 173 cases of French Canadian

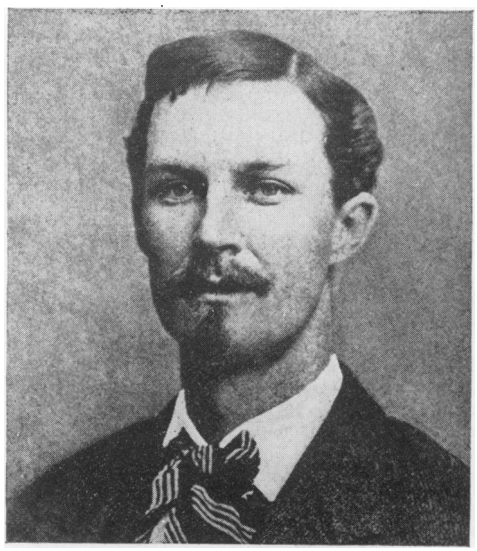

FIG. 1. Photograph of Huntington as a young man (from *Neurographs*, 1908).

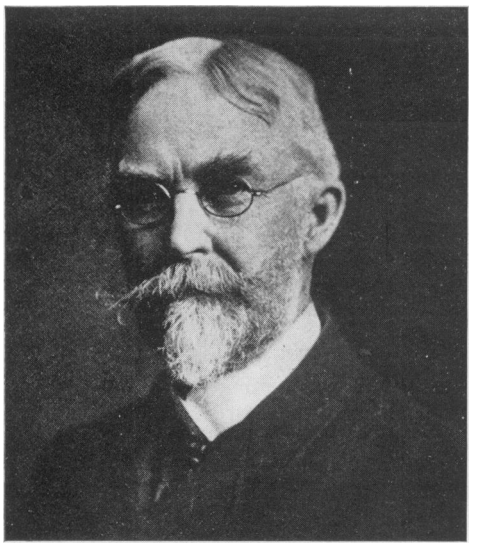

FIG. 2. Photograph of Huntington as an old man (from *Neurographs*, 1908).

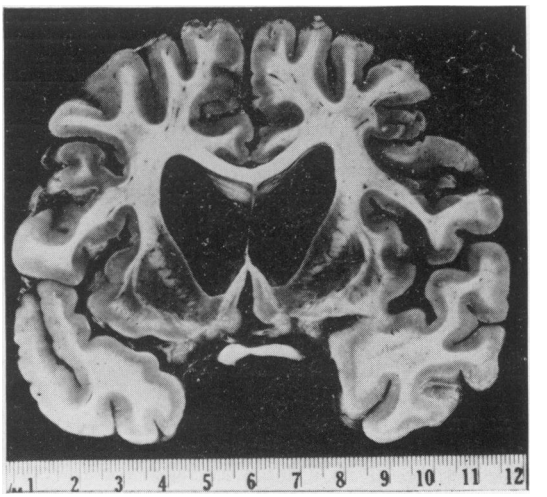

FIG. 3. Coronal section of a brain in an advanced case of Huntington's chorea showing atrophy of basal ganglia and cortical gyri, and dilated lateral ventricles.

origin in Quebec to a woman who emigrated to Montreal from France in 1645, and of Brothers (1949) who found that all eighty-six cases traced in Tasmania had a common ancester in a woman of Huguenot stock, who emigrated with her family of thirteen children from Somerset in 1848.

In the century since Huntington's publication the literature of this disease has grown enormously and articles have appeared on it from almost every part of the world except the Soviet Union and Communist China. A full bibliography of these is being compiled by Dr Bruin and Dr Baro—members of the research group of the World Federation of Neurology. This federation organized a centenary meeting in Columbus, Ohio, in March 1972 when seventy-two communications were read. The sessions at this symposium were devoted to various aspects of the disease including pathology, clinical manifestations, early detection, genetics, biochemistry, experimental models, social consequences and therapeutic management. In this article these subjects will be dealt with similarly.

Pathology

The pathology of Huntington's chorea was first described by Jelgersma (1908) and Alzheimer (1911). More recent accounts are those of Dunlap (1927), Stone & Falstein (1938), McMenemy (1963), and McCaughey (1961). Although there is shrinkage of the brain as a whole the most conspicuous finding is atrophy of the caudate nucleus and putamen. The brain shows gyral atrophy especially marked in the frontal lobes, and there is compensatory dilatation of the lateral ventricles especially in the anterior horns where the loss of substance in the heads of caudate nuclei leads to a concavity in the outer floor that is stated to be diagnostic of the disease whether seen on pneumoencephalography (Blinderman, Weidner & Markham, 1964) or in a morphological specimen (Fig. 3). The corpus callosum is usually thin but the globus pallidus is often spared.

Microscopically, cell-loss is the most obvious feature, the smaller cells in the caudate and putamen being affected more than the large cells. This is usually accompanied by a proliferation of protoplasmic astrocytes with fibre formation in relation to the blood vessels. Deposition of iron in the basal nuclei is not uncommon (Klintworth, 1969) and the cells may contain an excess of lipofuchsin. Changes in the other nuclei occur in the substantia nigra, thalamus, subthalamic and dentate nuclei. In the cerebral cortex the ganglion cells of the third and fourth layers are affected, but glial changes are less obvious. McMenemy said that symptomatology and pathological findings do not always agree and others have noticed that it is impossible to distinguish the rigid form pathologically. In childhood forms, however, the changes are generally greater with involvement of the dentate nuclei, while in advanced age there is less cell-loss.

Typical clinical picture

Huntington's chorea is characterized by an insidious development of fidgetiness grading into choreiform movements often over several years accompanied by a progressive change in the personality leading eventually to dementia; psychotic

TABLE 1. Mean age of onset, duration, and age of death in Huntington's chorea

Author	Age at onset			Both sexes	Mean duration (years)	Age at death	
	Year	Males	Females			Males	Females
Bell	1934	36	35	35·5	13·7	53	52
Panse	1938	36·5	35·5	36	13·5	52	52
Reed & Chandler	1958	34·5	36	35	16	52	52
Dewhurst, Oliver & McKnight	1970	37·8	39·9	39		51·7	55·3
Brothers	1964			37·5	7–18	51·2	51·7
Cameron & Venters	1967			43·2	10·5	54·6	54·6
Bolt	1970			42·5	14·6	56·7	56·7

features frequently occur and are usually the reason for admission to a mental hospital (Bolt, 1970). The average age of onset in 460 cases was ascertained by Bell in 1934 to be 35·5 years, but more recent surveys have given a later average age of onset (Brothers, 37·5 years; Bolt, 42·5 years; Dewhurst, Oliver & McKnight, 39 years; Cameron, 43·2 years; Heathfield, 44·2 years) (Table 1). From these it seems that the age of onset in the post-war generation is rather later than in the previous one and an average age of onset of 40 years is not an overstatement. Cameron prefers the term 'age of manifestation' to 'age of onset' as in many patients the exact age of onset is impossible to establish. More important than the average age of onset is the wide scatter in individual patients, from 5 years to 75 years or more, which is shown in the histogram (Fig. 4).

The mental and physical abnormalities usually occur together but choreic movements may precede the personality disorder, or irritability, slovenliness or neglect of the person and the household may begin before the movements.

Chorea

The involuntary movements in this disease may be termed choreo-athetotic as they are rather slower than those of Sydenham's chorea; they sometimes follow a particular pattern in an individual patient. Characteristic are small twitchings of the mouth and eyebrows and twisting and lordotic movements of the trunk, with individual twiddling of the fingers when walking, and of the toes. The chorea eventually becomes generalized and interferes with voluntary movement and from having previously been disguised as quasi-purposive movements, causes the patient to drop what he is holding and to fall down. The severity varies but movements usually become gradually more severe and most patients finish their years with very severe choreic movements; but a number develop terminal ridigity (see below). In the early stages the movements may resemble repetitive tics and the patient may make repeated clicking and snorting noises and repetitive utterances. Dysphagia is a common feature of the advanced stage of the disease, and some patients choke to death.

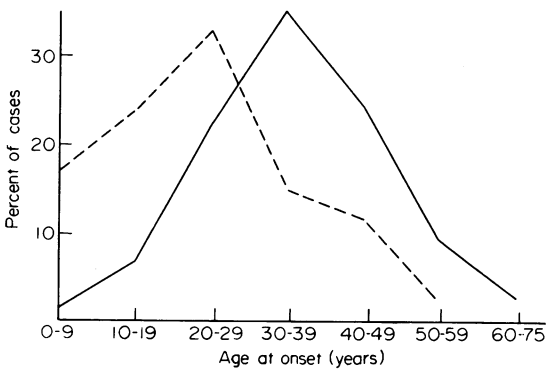

FIG. 4. (— — —) Age of onset of rigid-akinetic cases of Huntington's chorea, compared to that of the combined cases of Bell (1934), Reed & Chandler (1958), and Panse (1938) (————). From Myrianthopoulos (1966).

Mental changes

Patients with Huntington's chorea may be normal mentally before the onset of this disorder and may be leading an active professional life; a number however, have psychopathic traits (see below). The first mental symptoms are usually irritability, aggressiveness and impulsive behaviour. Later, outbursts of violence may occur alternating with periods of short-lived depression. When the patient knows his family history and realizes that he has the disease he may become more profoundly depressed and make suicidal attempts, sometimes successfully. At a later stage apathy and neglect of the person occur followed by incontinence. Attempted suicide is rarer in the later stages. Other psychotic features may occur in individual patients such as simple schizophrenic reactions or paranoia, and more rarely hypomania is a feature. In many patients the psychosis predominates and the underlying cause is missed until choreiform movements become very evident, but even then they may be attributed to 'schizophrenic mannerisms'. In the later stages patients become profoundly demented.

Duration

Rate of progression and the duration of the disease are also variable and vary in different series. Dewhurst, Oliver & McKnight found the duration to be 15·6 years in females and 13·9 years in males, and Bolt found the average duration to be 14·6 years whereas Cameron found it was only 10·5 years.

Age at death

The average age at death in most series is stated to be 55 years although Dewhurst & Oliver have found that the average age of death in males was lower than in females, 51·7 years compared with 55·3 years, and that females were admitted to hospital from the time of onset after a shorter interval than males—6 years compared with 14 years.

Clinical variants

Whilst the above clinical picture of Huntington's chorea is very typical, there are some variations which may now be discussed.

Patients without chorea

Patients with a progressive dementia without choreiform movements have been described in choreic families (Curran, 1929; Worster Drought & Allen, 1929; Bolt, 1970). Such cases are rather rare but mild choreiform movements can be overlooked. All cases of presenile dementia should be carefully examined for the presence of choreiform movements which may be slight and affect only the hands, trunk or facial muscles.

Patients without dementia

Two cases of progressive non-familial chorea without dementia were described by Lyon (1962b), and a number of similar cases have been seen by other neurologists. Alcock (1936) described the pathology of two cases of senile chorea in which there was loss of nerve cells in the basal ganglia but the cerebral cortex was intact. Absence of dementia and psychosis is very important in prognosis for these features are more disabling than involuntary movements. The author has examined several cases of elderly choreics with a family history, in whom dementia was minimal.

Non-progressive cases ('formes frustes')

In certain instances Huntington's chorea may be so mild as to pass unnoticed by the relatives. Chandler, Reed & De Jong (1960), and Heathfield (1971) have examined elderly parents of patients with florid forms of the disease and found them to show mild but definite signs of it; in these the disease did not progress. It is not known how common these mild non-progressive cases are.

Terminal rigid form

In the terminal stage of the disease some patients cease to have chorea and develop a condition resembling Parkinsonism (Denny Brown, 1962); although they may continue to show a few fragmentary jerkings of the head and face, movements in the limbs and and trunk cease altogether. Rigidity often begins in the upper limbs and shows in lack of swinging the arms when walking and with slowness of pronation movements of the forearm. Mild 'negative features' of Parkinsonism occur in many cases of Huntington's chorea (Martin, 1967).

Juvenile form

The juvenile form, with onset before 20, occurs in about 8% of cases (Bruyn, 1967), but onset in childhood, under the age of 10, occurs in a much smaller percentage (1–2%). The average duration of the disease is shorter in juvenile cases and reference will be made later to the puzzling fact that in these younger cases transmission from the father is three to four times as frequent as from the mother. Clinically the disease is different from the adult form in that choreiform movements are rather rare while akinesia, ataxia and extra-pyramidal rigidity are usual. Intellectual deterioration leads eventually to severe dementia, and epilepsy occurs in 40% of cases. As described by Westphal (1905), a progressive Parkinsonian syndrome occurs with severe rigidity, dystonia and dysarthria. If the family history is not known these juvenile cases are very likely to be misdiagnosed as suffering from Wilson's disease, Friedreich's ataxia or a juvenile form of Parkinson's disease.

Rigid form in adults

The rigid form in adults (Westphal variant) occurs at a somewhat earlier age than the choreic form and should be distinguished from terminal rigidity (see above). It is not transmitted more often from the father than the mother. Rigidity begins in the proximal muscles, and coincidental pyramidal signs are common; a tremor of the hands aggravated by movement may also occur. Epilepsy is not a feature of this form, nor of adult cases with chorea. The Westphal form not infrequently occurs in siblings.

Other neurological signs

Other neurological signs include pyramidal tract signs in about a third of the cases—often mistakenly attributed to cervical spondylosis—and a few patients show cerebellar ataxia. Associated muscular wasting in a family with this disease was described by Sumner (1962). Abnormalities of eye movements in Huntington's chorea have been known for some years and are illustrated by Cogan (1956), as 'doll's eye' movements. Starr (1967) found that the abnor-

mality is one of loss of rapid eye movements (saccadic movements) and that slow eye movements (following movements) were unaffected. A similar abnormality occurs in supranuclear ocular palsy (Steele, Richardson & Olszewski syndrome, 1964). One of Starr's cases showed degeneration of the oculomotor nucleus with loss of cells and gliosis at necropsy. Dix (1971) also discussed the abnormalities of ocular gaze in this and other neurological disorders affecting the upper brain-stem.

Psychological variants

Various types of psychoses may occur in families especially where there is a blending of psychotic and choreic stock (Brothers, 1964). Schizophrenia may be transmitted in families, and in a family I studied, the father had Huntington's chorea and schizophrenia, one son died from schizophrenia without chorea, and another had Huntington's chorea but was mentally normal, and a third had both conditions. Criminal psychopathic and depressive features may also be familial.

Associations

The associations of Huntington's chorea have in the past been over-emphasized. Except in juvenile cases the frequency of epilepsy is not greater than in the normal population. Patients suffering from this disease usually have normal intelligence before the onset. There is no evidence of a 'pre-choreic personality'. Psychopathic traits occur equally frequently in affected and unaffected siblings.

There does not appear to be any association with other medical disorders with the exception of diabetes mellitus (see below) and very rarely with hyperparathyroidism. Brothers (1964) found seven of 100 of his cases had had Sydenham's chorea in childhood.

Diagnosis

The diagnosis of Huntington's chorea is clinical and the triad of dementia, chorea and a positive family history is usually thought to be diagnostic The insidious onset of involuntary movements is unlike most of the other forms of chorea of which a few new varieties have recently been described: chorea in systemic lupus erythematosus (Paradise, 1960), polycythaemia rubra vera (Gautier Smith & Prankerd, 1967), and from the contraceptive pill (Lewis & Harrison, 1969; Riddoch, Jefferson & Bickerstaff, 1971). The tardive dyskinesias developing from prolonged administration of phenothiazines which occur especially in elderly females must also be considered in the differential diagnosis, but the involuntary movements seen as a side-effect of levodopa, which may also closely resemble those seen in this disorder, are not likely to be so confused. The hepato-cerebral syndrome, as described by Victor, Adams & Cole (1968) may also include choreo-athetoid movements. The dementia of Huntington's chorea resembles other presenile dementias although there is often more disturbance of behaviour than of intellect in the early stages unlike in Alzheimer's and Pick's disease.

Special investigations are rarely helpful in diagnosis except by exclusion, for example of polycythaemia, and although pneumoencephalography is advocated as of help in differential diagnosis by showing shrinkage of the head of the caudate nucleus as well as other signs of cerebral atrophy, this is not always present. The same remarks apply to the electro-encephalogram in which the 'flat' record reported by Hill (1948) is only present in about one-third of the cases and these are usually the most typical ones; however, when present it can be a most useful indication as it is not seen in other dementias (Scott *et al.*, 1972) (Fig. 5).

Prevalence

This disease affects all races, and its prevalence has been estimated in several epidemiological studies in Europe, America and Australia (Table 2) where the incidence of Huntington's chorea in most instances varies between 2 and 7/100,000 population. The prevalence in India, Eastern Europe and the Middle East is not known, but in Japan it is only one-tenth that of Western countries (Kishimoto, Nakamura & Sotokawa, 1959) (Table 2).

There are pockets where the disease is particularly common, these include the Moray Firth area of Scotland (Lyon, 1962a), Tasmania (Brothers, 1949), North Sweden (Sjogren, 1933, quoted by Myrianthopoulos, 1966) and around the inland sea in Venezuela (Negrete, 1962). Such areas of increased incidence are difficult to explain unless heterozygotes marry, but in some areas there is a small population artefact as for instance in Tasmania where all the known cases originated from one common ancestor. The large number of cases found in Venezuela cannot be so explained; the average age of onset of cases in that country is 23 years.

The exact prevalence of Huntington's chorea is difficult to assess and the author (Heathfield, 1967) drew attention to some of the difficulties of tracing all cases; he thought that his own incidence of 2·5/100,000 in the North East Metropolitan area was too low because of failure of doctors to diagnose a condition they have never seen in practice—the very rarity of the disease makes some physicians reluctant to diagnose it.

Early detection

Early detection may be helped by knowledge of the family history and of the expected age of onset

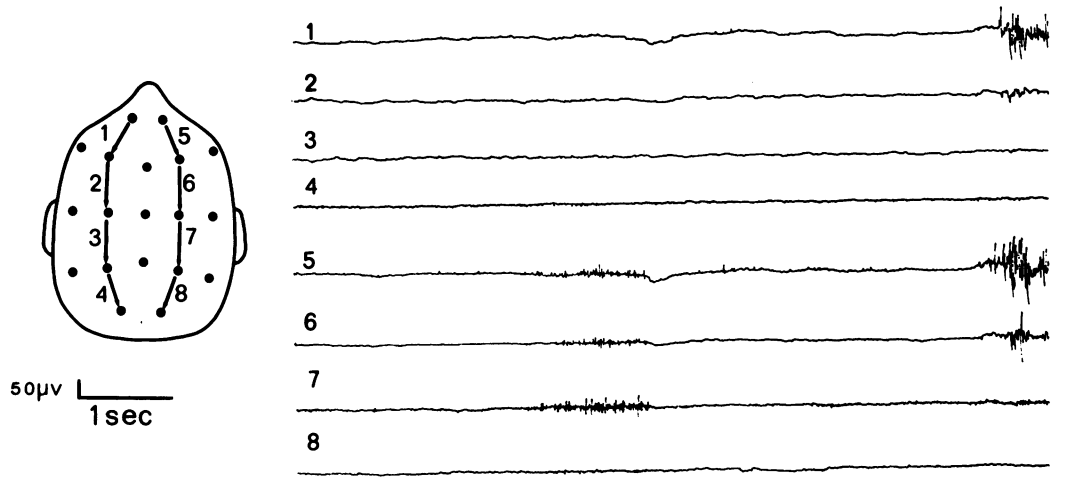

FIG. 5. Typical section of EEG of a 56-year-old demented patient with Huntington's chorea. Note complete absence of rhythmic activity and occasional bursts of muscle artefact. Reproduced by courtesy of Dr June Dickson, Severalls Hospital, Colchester.

TABLE 2. Table of prevalence

Country	Area	Authors	Year	Prevalence/ 100,000
U.K. England	London	Minski & Guttman	1938	1·8
	Northampton	Oliver	1970	6·3
		Pleydell	1955	6·5
	Bedfordshire	Heathfield & McKenzie	1971	7·5
	Essex (NEMRHB)	Heathfield	1967	2·5
	Leeds	Stevens	1972	4·3
	Cornwall	Bickford & Ellison	1953	5·6
Scotland	S.W. Scotland	Bolt	1970	5·6
	Moray Firth	Lyon	1962a	560
Germany	Rhineland	Panse	1938	3·2
Spain	Cadiz	Ordonez	1970	1·4
U.S.A.	Minnesota	Pearson *et al.*	1955	5·4
	Michigan	Reed & Chandler	1958	4·1
	Rochester (Minn.)	Kurland	1968	6·7
Canada	Quebec	Barbeau (Myrianthopoulos, 1966)	1964	2·4
S. America	Venezuela	Negrete (Went 1972)	1970	'Very high'
Australia	Tasmania	Brothers	1949	17·4
	Victoria	Brothers	1964	4·8
	Queensland	Parker	1958	2·3
		Wallace & Parker	1972	6·3
Japan	Aichi	Kishimoto	1959	0·4

from that in older siblings. The mothers of some large choreic families may be able to sense which children will develop the disease, and later events prove them to be correct. Pre-clinical psychological testing has not yet been proven to be of value (Palm, 1972).

Petit & Milbled (1972) applied the observations of Starr that rapid eye movements might be impaired in this condition and by using a test of conjugate eye movements in clinically unaffected individuals, found that abnormalities might be detected in them some years before chorea developed; they found such abnormalities in six out of eighteen offspring of choreic patients. Patterson, Bagchi & Tost (1948) suggested the EEG might be of predictive value but Chandler (1966) studied their cases 18 years later and found that the EEG had been of no value in prediction. Scott *et al.* (1972) found that EEG changes occur late in the course of the disease and are related

with cerebral atrophy, especially of the frontal lobe —the more typical the case the more likely the patient is to show a 'flat' record.

Klawans, Paulson & Barbeau (1970) described a predictive test based on the observation that levodopa aggravates choreiform movements in patients with this disease and produces them in patients treated for Parkinsonism. They thought that stimulation of the striatal dopamine receptors might be involved in the production of the movements and that these receptors might be hypersensitive in asymptomatic heterozygotes and that levodopa might bring out undetected chorea in them. They compared the effects of oral levodopa in two groups —offspring of choreics and controls. Three out of eleven children of choreics developed facial twitches and limb dyskynesias but none of the controls. Klawans & Paulson gave levodopa in progressively increasing doses up to 2·5 g daily for 10 weeks, and Barbeau combined 800 mg of levodopa with a peripheral dopa-decarboxylase inhibitor (R.O. 44602). In their latest report (Klawans & Paulson, 1972) they found that ten out of thirty children developed involuntary movements. It has not yet been proven that individuals developing chorea with this test will develop the disease later nor that those in whom the test is negative may not develop it in time. The authors advise that this test should only be used in individuals who have come for genetic counselling and signed a specific consent form. If this predictive test proves reliable it should be of considerable value in eliminating the disease.

In future one can hope carriers will be detected by a specific biochemical test or by chromosome abnormalities not shown by present techniques; amniocentesis may then be used to diagnose heterozygotes *in utero*.

Genetics

Huntington recognized that the disease was transmitted directly from parent to child and that it never skips a generation. After the laws of Mendel were rediscovered (1900) it became clear that Huntington's chorea is invariably transmitted as a Mendelian dominant, and that the gene has full penetrance (Davenport & Muncey, 1916). Half of any one generation may be expected to inherit the disease and many investigators have confirmed that there is an 0·5 expectation in affected children if corrections are made for age.

New information on the heredity of this condition was added by the observations of Bruyn (1967) and Merritt *et al.* (1969), later summarized by Barbeau (1970), that in the juvenile form the father is the affected parent three to four times more frequently than is the mother—in dominant conditions the affected person usually has an equal chance of inheriting it from either parent. Barbeau found that in a series of thirty-three cases of juvenile Huntington's chorea the father was the affected parent in twenty-six and the mother in only seven. This finding has been confirmed by other workers. Merritt *et al.* (1969) found that in 106 patients with onset before the age of 21 years, eighty-four had inherited from their father and twenty-two from the mother. Several explanations have been suggested for this, and the likely one is that the X chromosome has a modifying effect upon the choreic gene, this is supported by the fact that choreic children have been born from an affected father from two different mothers; other possibilities are that choreic mothers are less fertile than choreic fathers, and that paternal cases have an earlier age of onset, but there is little support for either of these explanations.

Allowing for possible errors such as early death of parents, illegitimacy and failure to detect mild chorea in elderly patients, *mutation* is rather rare in this disease. Julia Bell (1934) was able to trace only six examples amongst 151 families. Stevens & Parsonage (1969) reported a family in which mutation probably occurred and gave criteria for its acceptance, but even in their family there is some doubt for a brother of the 'mutant' suffered from dementia, furthermore the average age of onset in their family was later than usual, and cases of chorea in a previous generation could have been missed.

The frequency of heterozygotes for chorea in Michigan was calculated by Reed & Chandler (1958) to be 1 in 9900, 2·5 times the prevalence rate. They calculated this by a simple formula, Reed's formula, and Stevens (1972) in Leeds found a similar frequency of heterozygotes and by comparing various methods has found that Reed's formula is reliable. From this work it seems that there were 1·5:1 affected heterozygotes. However, all studies of prevalence suffer from lack of full information as to the incidence of the disease in the population. Mutation rates can be calculated from the number of heterozygotes if relative fertility is first calculated. Reed & Nell (1959) found the mutation rate to be 1 in 200,000/generation. In Japan the mutation rate has been calculated as 3·3/1,000,000, but the disease has a low prevalence in that country (Kishimoto *et al.*, 1959).

The relative fertility of choreics as compared with their non-choreic siblings is high. Reed & Palm (1951) found the ratio to be 1·8:1, but thought that this might be due partly to selection of large families for study and to voluntary limitation of family size by unaffected individuals. Subsequent workers have confirmed that choreics have a slightly greater fertility than normals and no evidence for lack of genetic 'fitness' has been found. Conflicting figures have been given by different authors, and these are very hard to prove.

Twin studies

Myrianthopoulos & Rowles (1960) described monozygotic female twins who developed the disease at the age of 22 years. They proved the zygosity of these twins by fingerprint and blood group studies as well as by their physical characteristics. Myrianthopoulos (1966) analysed previous twin studies and found that of nine identical twin pairs, eight were concordant and one discordant, but in the discordant pair the unaffected twin was aged 40 years when last seen and there was thus still time for the disease to develop. Proof of zygosity has often been lacking in earlier papers. Oepen (1969) described monozygotic sisters in one of whom chorea predominated and the other Parkinsonism, monozygosity was proved by skin transplant.

When two individuals with Huntington's chorea, or two heterozygotes, marry, the probability of the offspring developing the condition is 75%. Such a family was reported in a cousin marriage by Eldridge (1972) who drew attention to the high rate of affected grandchildren, many of whom died young. A quarter of the children of such a marriage will be homozygous.

No chromosome abnormalities have been found in this condition (Benirsche & Hoefnagel, 1961). Genetic linkage studies which are proceeding in Baltimore by Lindstrom, McKusick and associates, using genetic markers and computer analysers, have so far not produced any positive findings. Previous studies have not revealed any association of the disease with any blood group (Pleydell, 1954).

The theory of 'anticipation' according to which the disease has an earlier onset in succeessive generations is now discredited, and examples are thought to have been due to observer error, but some families with a suggestive history of it are still occasionally reported (Singer, 1962).

Biochemistry

Studies of the biochemistry of Huntington's chorea has in past years led to several cul-de-sacs, but the discovery of the role of the catecholamines and their metabolic precursors in Parkinson's disease has opened up new lines of enquiry which may prove rewarding.

In the 'pre-levodopa era' research concentrated on analogies with Wilson's disease in which an abnormality of copper metabolism had been found. This led first to a number of publications pointing to a disorder of trace metals and subsequent publications disproving these. The authors of these papers and others described the beneficial effects of chelating agents but subsequent publications denied them. Copper, iron, calcium, magnesium and strontium have all been involved in one part or the other of this double process, and there is now no convincing evidence for a disorder of any of these substances (Neilson & Butt, 1955; Kenyon & Hardy, 1963; Haslam, 1967; Fleming, Baker & Stewart, 1967; Bruyn, Mink & Calfe, 1965; Perry, 1961; Courville, Nusbaum & Butt, 1963).

McMenemy (1961) speculated that an autoimmune disorder might be present in this and other diseases in which large numbers of nerve cells die and abnormalities of gamma globulins in the serum were described by Bruyn & Lequin (1964) and Cowie & Gammack (1966), but these were thought to be non-specific by Maughan & Williams (1966); and Cowie (1969) was unable to confirm her previous findings. It now seems unlikely that a disorder of immunity plays a significant role although this subject does not seem to be as fully exhausted as the heavy metal seam.

More recently attention has been focused on abnormalities of amino-acid metabolism. Although Oliphant, Evans & Forrest (1960) found no abnormalities of amino acid excretion in the urine, Bruck *et al.* (1968) found slight abnormalities of several amino acids in the CSF, and a slightly increased pyruvic acid in the serum. The most convincing findings were those of Perry *et al.*, 1969, who found abnormally small amounts of six essential amino acids in the serum in nineteen patients with Huntington's chorea. They thought that the low levels might reflect the basic biochemical error underlying this disorder. The amino acids affected were proline, alanine, tyrosine, and the three branched-chain amino acids — valine, leucine and isoleucine. Although previous workers had found no abnormalities of serum amino acids (Bruyn, 1966; Oepen & Bickel, 1964), Ottoson (1972) has confirmed Perry's findings.

Perry *et al.* (1972) have since extended their studies to fresh brains obtained at necropsy and found substantially diminished amounts of amino acids in the putamen and substantia nigra in this disorder; in particular a very low level of gamma-amino butyric acid (GABA) in these nuclei; his studies are proceeding. A major difficulty in this disorder is to know whether the biochemical findings are primary or secondary.

The discoveries of the role of dopamine as a chemical transmitter in the nervous system and abnormally low levels of dopamine in the substantia nigra in Parkinson's disease, together with the beneficial effect of its precursor levodopa in treatment of it have led some workers to postulate an analogously opposite condition in Huntington's chorea. Klawans & Rubovits (1972) for example suggested that an antagonism exists between cholinergic and anti-cholinergic mechanisms in this condition and found that benzhexol aggravated the

involuntary movements while physostigimine, which has a central anti-cholinergic action, improved them. These authors also thought that a balance between dopamine and acetylcholine is important in Huntington's chorea as well as in Parkinsonism.

Homovanillic acid (HVA) the principal metabolite of dopamine, is considerably reduced in the CSF in most cases of Parkinsonism but normal, or only slightly decreased, in Huntington's chorea.* Hornykiewicz (1972) examined the brains of choreic patients and found somewhat lower levels of dopamine in the caudate nucleus although the other catecholamines were normal and its level in the other nuclei, including substantia nigra, was normal. He thought that a disturbance of the balance of dopamine between the putamen and the caudate nucleus might be responsible for the hyperkinesia in this disease in contrast to the hypokinesia of Parkinsonism in which dopamine is decreased in the substantia nigra and globus pallidus.

Other studies of dopamine and its end-products in the serum, CSF and urine, are proceeding (Barbeau, 1972; Goodall, 1972; Chase, 1972) and it is to be hoped that a clearer picture will emerge from these. The subject is, however, very complex as levodopa has many metabolic products.

Abnormalities of carbohydrate metabolism were found in six out of ten randomly selected patients by Podolsky, Leopold & Sax (1972). The six had diabetic glucose tolerance curves although their fasting glucoses were normal, they also responded abnormally to administration of arginine (a substance used to induce insulin secretion but which usually fails to do so in diabetics) with an increased level of blood insulin to over twice normal. The affected patients had had their chorea on an average of 8 years as compared with an average of 4 years in the four with normal glucose metabolism but there were no other clues as to why they were diabetic. The authors considered that there might be an abnormal genetic linkage between Huntington's chorea and diabetes as in Friedreich's ataxia; alternatively the latter could be due to hypothalamic damage which has been reported in the disease.

Bolt & Lewis (1972) reported the results of liver function tests and liver biopsies in twelve patients. They found that the disease is commonly accompanied by minor abnormalities of the pathology in the liver and disturbances of the liver function tests. The histological changes were chiefly pleomorphism and anisocytosis of the liver cells with a relative increase of mitoses; increased amounts of fibrous tissue and reticulin occurred in some cases. The abnormalities of liver function tests together with the abnormal histology suggested that the liver cells have a shortened survival time and this had been postulated in the neurones of the basal ganglia by McCaughey (1961). Because of the regenerative capacity of the liver its integrity is preserved until a late stage.

Another interesting finding is a low output of androgens in the urine (Oepen, 1972).

Drug-induced dyskinesias

The drug-induced dyskinesias are of interest in the aetiology of choreiform movements. The commonest side-effect of phenothiazine drugs is a Parkinsonian syndrome which occurs with chlorpromazine and fluphenezine after continued medication for some weeks and which may be partly genetically determined (Myrianthopoulos *et al.*, 1962); a small group develop dyskinesias with the first doses as a 'sensitivity reaction'—retrocollic spasms, oculogyric crises and acute Parkinsonian crises may then occur.

The labioglossal dyskinesias first described by Sigwald, Bouttier & Courvoisier (1959) and later by Hunter, Earl & Janz (1964), affect elderly women twice as commonly as men. They occur after administration of phenothiazine drugs for years, and for this reason they have been called 'tardive dyskinesias' by Faurbye (1964) and Crane (1968). They are common, with an incidence of 35% in females and 15% in males in a mental hospital population according to Brandon, McClelland & Protheroe (1971). They affect the mouth, lips and tongue, although choreic movements of the fingers and feet may also occur. A similar group of involuntary movements is seen in patients treated for Parkinson's disease with levodopa.

Similar syndromes of dyskinesia have been produced in experimental animals (monkeys) with both levodopa and phenothiazine drugs (Bird *et al.*, 1969). The morbid anatomy of these conditions is not yet fully ascertained but there is evidence that a lesion of the substantia nigra in combination with other lesions is responsible (Christiansen, Moller & Faurbye, 1970). The movements are irreversible although partly ameliorated by other tranquillizing drugs of rather similar composition. Both excessive doses of levodopa and substances that act by depleting the dopamine content of the brain produce the movements, and tetrabenazine, which is also known to act by dopamine depletion, will relieve them. The labioglossal dyskinesias occur more commonly in patients in whom brain damage has occurred, either from cerebrovascular disease, leucotomy or electroconvulsive therapy. It is too early yet to say what link these iatrogenic and experimental dyskinesias have with Huntington's

* Curzon, Gumpert & Sharpe (1972) have recently reported lowered HVA levels in the CSF correlating negatively with the severity of the symptoms.

chorea but the movements may be strikingly similar and both respond to the same drugs, such as tetrabenazine and thiopropazate.

Socio-psychological aspects

The onset of Huntington's chorea in the mid-thirties usually comes as a shattering blow to the family. The marital partner has often not fully appreciated the implications of the disease and the symptoms make the patient difficult to live with. The fear that the children may become affected then begins to dawn and if these are already married, and there are grandchildren, the implications become even worse.

Dewhurst, Oliver & McKnight (1970) discussed the socio-psychiatric consequences in 102 patients, eighty of whom were eventually admitted to mental hospitals, nine were in other hospitals, and thirteen were in the community. They found a high incidence of psychiatric symptoms antedating the diagnosis, and also found a preponderance of psychiatric symptoms as the first symptom—fifty-seven patients presented with these and only sixteen with neurological symptoms, although twenty-nine patients had both. 60% of the patients were still in the reproductive period at the time the diagnosis was made. Self-aggression was common, one patient committed suicide, ten others made suicidal attempts, and thirteen patients mutilated themselves; there were nineteen cases of alcoholism. In twenty-three (38%) of the married patients, the marriages broke up and divorce or separation occurred. Sexual aberrations were common in both sexes; in women promiscuity commonly led to illegitimacy, and in males various abnormalities occurred including indecent exposure, hyper-sexuality, promiscuity and homosexual assaults. Criminality occurred in eighteen patients: the offences included assault, offences against property and cruelty to children. Of the 172 children at risk, twelve were known to be illegitimate, seventeen were seriously neglected and nine had been subjected to offences of extreme violence. Heathfield (1967) draws attention to the neglected state of the homes of some patients. Oliver (1970) also studied the mental and social disorders in the clinically unaffected siblings of the patients in his Northamptonshire series. There were 150 of these compared with sixty affected offspring. He found that seventeen had died under the age of 11, and nine between the ages of 11 and 21; two others committed suicide. He thought that the childhood deaths were probably partly due to undiagnosed childhood forms of the illness but one child had been murdered, and in others assault and neglect had led to premature death by accident or disease. Ten children were abandoned, nine were known to be illegitimate, five became alcoholics, three criminals, ten were divorced, six were responsible for illegitimate children and one abandoned her own child; nine had severe neuroses. Dewhurst (1970) emphasized that personality disorders in this disease are more often due to adverse environmental factors than to genetic ones, as they occur equally in affected and unaffected siblings.

Whittier (1963) has also been interested in the social effects of the disease and is Medical Advisor to the Committee to combat Huntington's disease (CCHD), a society formed by relatives and patients in America with the object of spreading information about the disease and to pressurize the medical profession. A branch has been formed in England and is now linked with the Central Council for the Handicapped with lay and scientific sub-committees. Leaflets giving a simple accurate account of the disease were started at the Mayo Clinic by Pearson *et al.* in 1955; contrary to expectation they were much appreciated by patients and relatives and did not cause undue emotional trauma but often allowed individuals to verbalize their anxieties and helped them to refrain from procreating. The CCHD has issued a similar leaflet in America and Stevens has prepared one for the English group. The research committee on Huntington's chorea of the World Federation of Neurology is an active body that meets annually.

Bolt suggested registration of cases of Huntington's chorea, and Oliver and I are in favour. A wider appreciation of the disorder and its mental and social consequences by doctors in general is badly needed.

Genetic counselling is important as there are many misconceptions about the disease by general practitioners and wrong advice is often given. The genetic counsellor has the advantage of knowing the full facts as far as they can be known and is able to put these to the patient or his relatives to enable them to decide what they should do; the geneticist does not suggest a line of action but only outlines the risks. Some problems arising in this disease were discussd by Cameron & Venters (1967) who analysed the statistical risks to children at various ages and also calculated the risk of grandchildren being affected. They drew attention to problems of marriage, education and employment, and stressed that in children of choreics intellectual capacity should be fully used to enable them to find pensionable employment as an insurance should they become affected later.

Treatment

In the absence of a known cause treatment is at present empirical, and although some improvement in involuntary movements may be obtained with new pharmacological preparations these affect

neither the course of the disorder nor the dementia; indeed the situation today is hardly different from that in Huntington's time. Drugs used are chiefly those of phenothiazine constitution such as chlorpromazine, fluphenazine and thioproperazine—these are dopamine-depleting drugs which will cause Parkinsonism when given in an excessive dose. For several years thioproperazine was the favoured drug in this country and Lyon (1962c) established its value in a controlled therapeutic trial, however many patients did not benefit and others relapsed after initial improvement. Tetrabenazine appears the most effective drug used at present and was the subject of a controlled trial (Swash *et al.*, 1972); it is given in a dose of 100–150 mg daily. Gumpert, Sharp & Curzon (1972) also confirmed its value, and Jewesbury (1972) has been impressed by its value in some cases.

Whittier & Korenyi (1968) treated a large number of patients with fluphenazine and found it of considerable value: others have been less impressed. Perphenazine has also been proved to be of value in diminishing choreic movements in a trial conducted by Fahn (1972). Haloperidol is the drug most often used in the United States although many neurologists in the United Kingdom have found it disappointing. Chelating agents have been used and include BAL and penicillamine; but neither has proven to be of long-lasting therapeutic value. Anti-serotonin agents have recently been prescribed on the hypothesis that there is hyperfunction of serotonin in the basal ganglia in this disease, but neither methysergide (an anti-serotonin agent) nor parachlorophenylalanine, which inhibits the synthesis of serotonin, were of benefit (Weiner *et al.*, 1972; Chase *et al.*, 1972). Mesoridazine, a compound related to thioridazine, is stated to be of value in enabling patients to gain weight (Lehnhoff, 1972). Levodopa aggravates the involuntary movements in Huntington's chorea but may be helpful in rigid cases although over-dosage may lead to the appearance of choreiform movements (Barbeau, 1969).

Stereotaxic neurosurgery introduced by Spiegel & Wycis (1953) is now mainly of historical interest, for although an occasional patient may benefit from this form of surgery, the dementia and chorea often occur together and the former may be aggravated by the treatment. Furthermore, many patients often lack insight into their involuntary movements, hence little is gained by removing them.

Conclusion

The essential nature of this disease remains obscure despite the large number of publications since the original description 100 years ago. Future studies of aminoacid, and in particular catecholamine, metabolism may well elucidate the basic fault and with this knowledge the clinician will be able to both treat the individual patient and prevent the disease developing in the children. Because the disease takes many years to become apparent it may well eventually prove to be even more rewarding for prophylaxis than such conditions as phenylketonuria in which the biochemical disorder leads to symptoms shortly after birth. Until its nature is better understood the doctor looking after a patient with Huntington's chorea has the sad task of watching its remorseless course and fortifying him and his family against events to come.

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