HUNTINGTON'S CHOREA

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Introduction

In Britain over 4,000 people currently suffer the symptoms of Huntington's chorea. Around 20,000 more stand a one in two or one in four chance of developing the condition in later years, the average age of onset being roughly 40. For those who are experiencing its distressing physical and psychological effects (which are characterised by involuntary 'choreic' movements and progressive mental deterioration), for those living in the shadow of being at high risk of becoming Huntington's chorea victims and for their relatives by marriage the burden is potentially devastating. In all approaching 50,000 individuals are affected.

This genetically transmitted form of early onset cerebral degeneration[1] owes its name to an American, Dr George Huntington, who as a young man in 1872 presented a paper entitled 'On Chorea' to the Meigs and Mason Academy in Ohio, USA. The subject of his lecture was chorea minor, more generally known as Sydenham's chorea or St Vitus's dance; a disorder of the nervous system usually associated with acute rheumatism in young people and characterised by involuntary movements involving the muscles of the face, neck and limbs. In the last few paragraphs he drew attention to hereditary chorea (which he had observed amongst patients in his father's practice) in such a lucid manner that the disease became named after him despite the fact that it was initially described several decades earlier.

Indeed, Huntington's chorea can be traced back in history for several centuries. For example, Vessie (1932) claimed to have found nearly 1,000 cases spanning twelve generations over 300 years, all of whom he believed to have been related to three emigrants from Bures in Suffolk who settled in New England in 1632. Even though the accuracy of this work is now in question other researchers have conducted similar studies with comparable results. Barbeau *et al* (1964) linked 173 French Canadian subjects to a choreic woman who emigrated from France to Montreal in 1645.

Historical records also indicate that in the past there was considerable hostility directed towards Huntington's chorea sufferers. This is perhaps not surprising in view of their sometimes bizarre symptoms and its familial occurrence; 'bad blood' was and is feared and vigorously avoided by basically agrarian communities. In the seventeenth and eighteenth centuries females from choreic families were reportedly persecuted as witches. Even in the nine-

1 Together with Pick's disease, Alzheimer's disease and Creutzfeld-Jakob disease, Huntington's chorea is sometimes classified as a 'pre-senile dementia'.

teenth century, New York 'megrims'[2] were treated with little sympathy or understanding.

George Huntington concluded his paper with the remark 'I have drawn your attention to this form of chorea, not that I consider it of any great practical importance, but merely as a medical curiosity, and as such it may have some interest'. Today his words are surprising, given improved understanding of the impact and severity of the disease. But even so Huntington's chorea (sometimes known as Huntington's disease, chronic progressive chorea and familial or hereditary chorea) remains relatively obscure; and the fundamental nature of the biochemical lesion which underlies it is still unknown. No curative or preventive treatment is as yet available.

The purpose of this paper is to describe the nature of Huntington's chorea and to indicate broadly its costs to both society and affected individuals. The latter are usually high because the disease manifests in middle life when people normally experience their peak occupational and familial responsibilities. In fact such is the severity of the disablement it causes in its terminal stages that despite its rarity NHS and social service caring costs alone are estimated to be in the order of £4 million per annum.

The role of the pharmaceutical industry in conducting research into uncommon conditions is also examined, as are the possibilities regarding future improvements in genetic counselling services and methods of identifying the genetic aberration responsible for Huntington's chorea. New research into the characteristics of cells from affected subjects together with the recent advent of techniques of DNA recombination and analysis means that, in theory at least, screening for Huntington's chorea should become possible in the 1980s. Whether in practice control of this disease by prenatal diagnosis and the abortion of 'at risk' foetuses will be introduced will depend on the social and economic restraints placed on this area of potential innovation.

The nature of Huntington's chorea

A progressive and ultimately fatal disorder of the central nervous system, Huntington's chorea is in all probability transmitted from generation to generation by an as yet unidentified single autosomal dominant gene.[3] This means that there is a 50 per cent

2 A megrim is a severe, one sided (hemicranial) headache or migraine. But the word has in the past also referred to conditions like 'the staggers' (OED) and presumably also to choreic movement.

3 That is, a dominant gene located on a chromosome other than those of the sex chromosome pair.

chance of the child of a 'carrier' parent being him or herself a bearer of the defective gene. Both sexes are equally affected. The condition is always expressed in those with the aberrant gene (except in instances where premature death from other causes intervenes), unlike the case with the more common recessive hereditary diseases.

It is usually impossible to define the precise age of onset. For example, early behavioural effects may be noted by close relatives but outside observers may either be unable to detect them or regard them as individual personality traits. Only when overt symptoms (against the background of a positive family history) emerge can a firm diagnosis be attached, and even today this can prove to be a difficult process.

Such considerations, combined with the effects of general increases in life expectancy, help to account for discrepancies in various researchers' estimations of the mean age of manifestation of Huntington's chorea. Table 1 shows that pre-war studies put the figure at around 35 years but more recent investigations indicate that it is rather later, something over 40 years.

However, in practical terms this estimate is of limited value because of the wide range of symptom onset ages implied by the solid line in Figure 1. Some victims (around 2 per cent) are aged under ten whilst others (perhaps 10 per cent) survive free of discernable impairments until the seventh decade of life. The broken line in Figure 1, which shows the probability of subjects 'at risk' developing Huntington's chorea after a given span of symptom free survival, is of more vital importance.

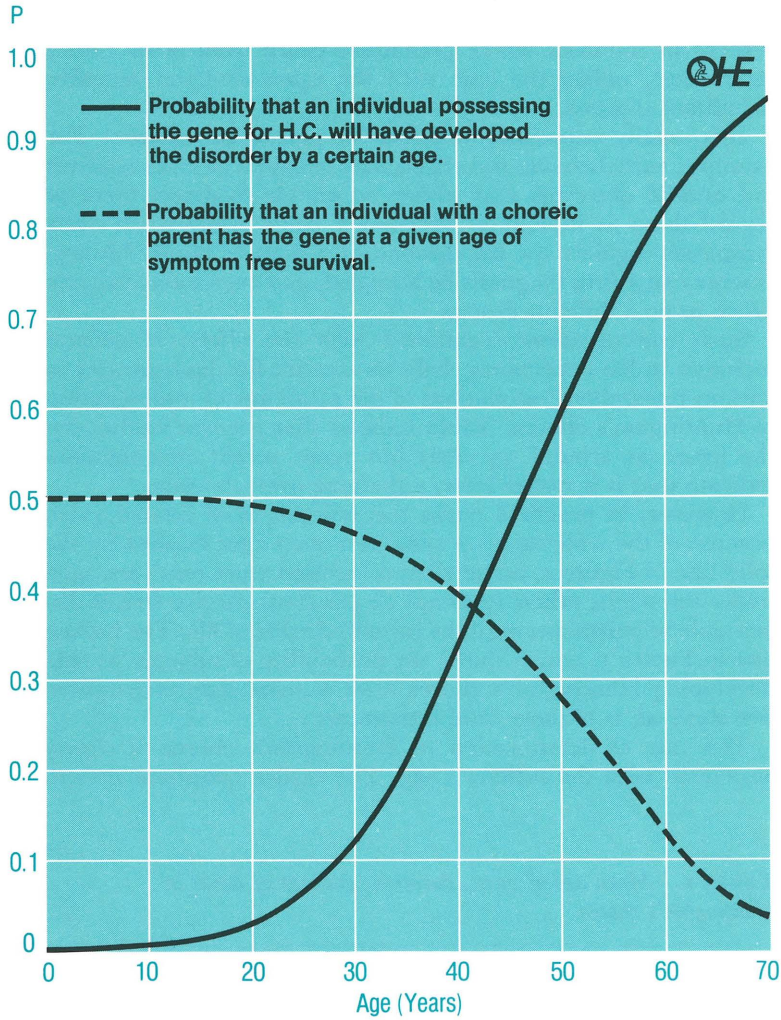
The rate of deterioration in Huntington's chorea is closely associated with the sufferer's age. The earlier symptoms present

Table 1 *Mean age of onset, duration, and age of death in Huntington's chorea*

	Age at onset				*Mean duration (years)*	*Age at death*	
Author	*Year*	*Males*	*Females*	*Both sexes*		*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

Source Heathfield 1973.

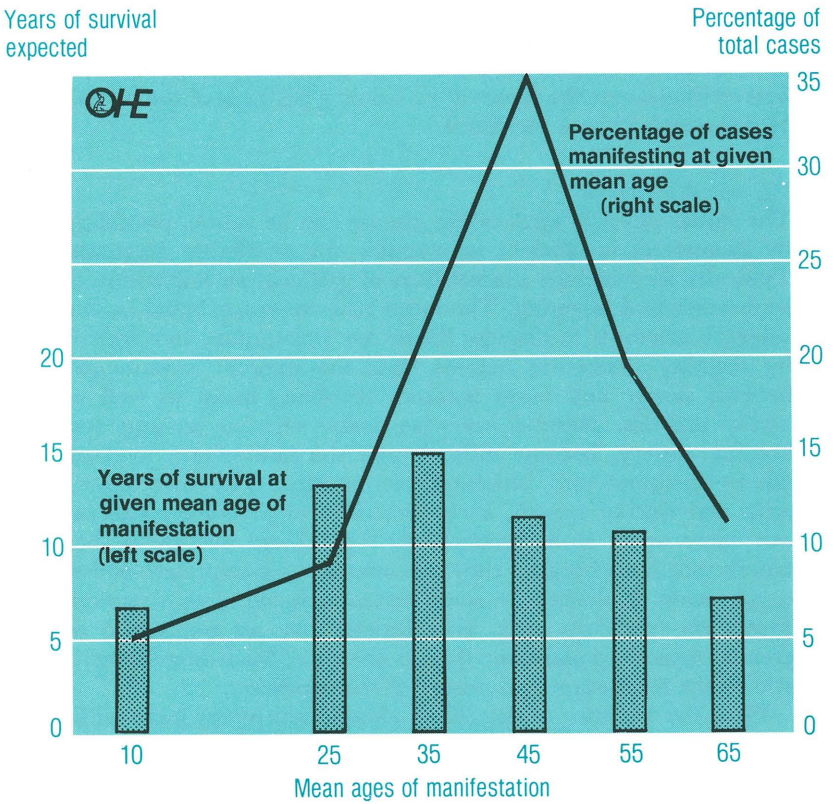
Figure 1 *Age and the risk of Huntington's chorea*



Source After Harper *et al* 1979.

the shorter the duration, at least up to around the age of fifty when other factors likely to cause death come into play. As Figure 2 outlines, onset at ten years will on average allow a child a possible six or seven years of further life whilst onset between thirty and forty indicates an approximate fifteen years before death (Spokes 1978).

Figure 2 *Manifestation and survival in Huntington's chorea*



Source After Spokes 1978.

Within families affected by Huntington's chorea the disease's expression normally shows considerable consistency in terms of symptoms, age of manifestation and speed of decline presumably in part because of the influence of genetically determined modifying factors. Yet some of the data available suggest that there is a gradual process of anticipation, with succeeding generations tending to have progressively earlier onsets. In certain cases this may be a phenomenon associated with intensified observation of 'at risk' siblings (Kurland *et al* 1973). But there is firm evidence, reviewed later in this paper, for anticipation via the paternal line in cases of childhood Huntington's chorea.

This would imply that, for the aberrant gene to remain in the population, a small number of new cases resulting from spontaneous mutation take place. However, information in this area

is scant, in part because of the absence of comprehensive records of the condition's distribution on an individual by individual basis. Perhaps, in future, improved regional and possibly national genetic registers will allow an accurate determination of the rate of mutation, if indeed such events do genuinely occur. Current best estimates put the figure at or below 5 per cent of the overall Huntington's chorea incidence.

Physical aspects

The initial physical signs of the disease can be subtle, providing by themselves insufficient information for a reliable diagnosis. Typically they include unsteadiness of gait and an impression of restlessness and fidgeting. The latter may be exacerbated by the subject's attempts to disguise his or her involuntary movements by feigning deliberate actions. But the choreic movements[4] become slower and more marked, involving facial as well as bodily muscles. Normal everyday tasks, such as writing and holding cutlery, become difficult and the individual's working life is disrupted and ultimately terminated. The involuntary jerks and slurred speech, a characteristic of hereditary chorea, can cause acute embarrassment to the sufferer and his or her family, not least because they are sometimes interpreted as due to an excess of alcohol. In some instances patients with marked dysarthria (difficulty with articulation) give an impression of greater mental impairment than is the case. Such impediments add to the frustration and misery of the condition.

With the advance of the illness choreic symptoms increase in severity, ultimately involving all muscles normally under conscious control. The involuntary movements subside during periods of relaxation and sleep but worsen when an individual tries to undertake a deliberate movement or is agitated. Walking, eating and even sitting can gradually become difficult or impossible due to the victim's constant twitching and lurching. Death by choking sometimes occurs as a result of dysphagia (difficulty in swallowing) whilst minor injuries from falls are common.

More serious than the latter, subdural haematomas may result from blows to the head, this being a particular risk in Huntington's disease because of brain atrophy and the consequently raised chance of accidental brain displacement. Clots formed in the subdural space enlarge because of the absorption of cerebrospinal fluid and may cause headaches and/or add to the mental symptoms being experienced by the victim. Often subdural haematomas are only identified during post-mortem examination.

4 Choreic movements are irregular and sporadic in fashion, occurring in any of the skeletal muscles in a fixed pattern.

Many Huntington's chorea sufferers in the later stages of their affliction become emaciated despite the fact that they display enhanced appetites and may be given special high calorie diets. The cause of this is unknown although recent research into energy expenditure and weight control in man may help to explain this observation.

Psychological and behavioural consequences

Huntington's chorea has been associated with many types of mental distress and/or disorder. Not all the individuals who display its physical symptoms will undergo such experiences but many do so, some even before any form of chorea is observable. In the early stages the psychiatric sequelae of the disease range from schizophreniform syndromes on the one hand to personality changes on the other. The latter may take the form of 'moody', obstinate behaviour, perhaps punctuated with periods of illogical anger and even violence. Cases of irrational jealousy, paranoia and sexual disinhibition have also been commonly reported, whilst suicide rates in choreic families in America are seven times that nation's average (Summary Report of the American Commission for the Control of Huntington's Disease and its Consequences, 1977). Ultimately a state of profound dementia may occur, especially in early onset cases.

The reasons for these linked psychological and behavioural effects are likely to involve both endogenous pathological and exogenous social and allied factors. For instance, terminal dementia is a clear result of the destruction of brain tissue whilst schizoid traits could well be linked to alterations in neuro-transmitter (for example, dopamine) distributions. Similarly reported increases in sexual activity (and fertility) might result from changes in the production of sex-associated hormones (Bird *et al* 1976) as well as from the disinhibiting effects of less specific brain changes.

By contrast the knowledge of being 'at risk' of or having a condition like Huntington's chorea is likely to lead to significant reactive symptoms. The attitudes of others towards the disease and the handicaps it generates may act in a similar manner. Depression is one possible consequence (and is often the cause of suicide in the initial stages of Huntington's chorea) whilst hostility and frustration in the face of unsympathetic or patronising treatment might be another. Yet it must also be emphasised that with appropriate support and personal opportunities such problems can be avoided or overcome.

Huntington's chorea in the young

Even amongst adults the classical picture of onset in middle life with choreic movements and progressive dementia is clearly

subject to substantial variation. Amongst those aged under 30 or so, the observed pattern of illness is normally so different that it may be divided into two subtypes clinically distinct from the adult form, juvenile Huntington's chorea and the Westphal variant.

The former involves between the 3 and 5 per cent of the total population of Huntington's chorea sufferers who develop symptoms in the first two decades of their lives. Of these it is believed that a minority, perhaps only 1 per cent of the global number of cases, are aged under 10. However, difficulties in identifying subjects could have led to underestimates of this figure, not least because the parents of the tiny minority of small children so affected will probably remain symptom-free until after their offspring are ill or dead. Wilson's disease is an example of a diagnosis which might be made in error.

In typical juvenile Huntington's disease choreiform movements are rare or even absent while rigidity, hypokinesia (diminished speed of movement) and epilepsy (especially before the age of ten) are prominent features. Patients deteriorate mentally at an early stage and dementia is more marked than in the adult form. The mean duration is significantly shorter with death occurring within about seven years of onset.

Several researchers have found that an unexpectedly high proportion of child victims inherited the condition via their fathers. For example, Barbeau (1970) reported that of a sample of thirty-three approximately three-quarters had a male choreic parent. All similar surveys have concurred, giving estimates in the 70 to 80 per cent region. Such observations are clearly at variance with what would be expected in a condition showing classical autosomal dominant inheritability, where parents of either sex would be expected to be found on a fifty-fifty basis.

Attempts have been made to understand these findings along the lines that either there are differential paternal and maternal fertility rates or that children carrying the choreic gene who would potentially show symptoms in the first two decades of life stand a raised chance of dying *in-utero* if the mother is choreic (Jones and Phillips 1970). This last assumes a lethal interaction between mother and foetus. There is no empirical support, however, for either explanation.

A currently preferred hypothesis is that anticipation via the male line may be explicable in terms of an inheritable sex-related modifying factor capable of governing relevant aspects of the disease's expression (Bird *et al* 1974). This view is supported by the results of a study by Bird and his colleagues in which it was shown that affected offspring of males with Huntington's chorea die at an earlier age than their fathers, whereas offspring of females with the disorder die at an age not significantly different

from their mothers. Further investigation of this area might eventually provide some practical means of altering the condition's course.

The second sub-type of Huntington's chorea occurs in young adults but not children. It was first described by Westphal in 1905 and is thus known as the Westphal variant. Tremor is an early symptom which later manifests itself as exaggerated trembling when a voluntary movement is made. Muscle rigidity, which is usually only evident in the Westphal and juvenile forms and in some terminal cases of adult chorea, can lead to bradykinesia (extreme slowness of movement). And another striking abnormality in Westphal cases is the inability to move the eyes, thus limiting the sufferer to a fixed 'dolls eye' gaze.

Occurrence

As with any relatively rare condition, epidemiologists have been faced with considerable problems when attempting to study the occurrence of hereditary chorea. To the need for large initial population samples can in this case be added factors like the difficulty of accurate diagnosis; the fact that some families may deliberately conceal the condition for fear of stigmatisation; and the complication that in less sophisticated areas with short average life expectancies and early initial child bearing the condition may not manifest itself in every generation despite continued transmission of the associated gene(s).

It is thus not surprising that the studies listed in Table 2 were mainly conducted amongst European populations. (Even the investigation by Negrette – 1970 – in Venezuela related to a community in which the introduction of Huntington's disease was traceable to a German sailor who settled there in mid-nineteenth century.) However, the Japanese findings recorded in the Table suggest that the disease is not evenly distributed across all ethnic groups[5], although in this context the history of Japan and the attitudes adopted within the traditional culture towards those thought of as undesirable could well be significant.

Nevertheless, if deficiencies in the available research, like inadequate age-standardisation of the subject populations, are temporarily ignored then the consensus finding appears to be that,

5 Huntington's chorea has been found amongst New York Jews and the South African Cape Coloured community but here again mixing with European blood has taken place on some scale. Yet it is interesting to note that if it is assumed that European findings do apply to other racial groups then the estimated world population of sufferers is in the order of 300,000 whilst a further million or so individuals are at risk of future illness.

in European stock at least, the prevalence of manifest Huntington's chorea normally ranges between 4 and 7 per 100,000 total population. Only a few studies, such as Shokeir's (1975) investigation of the Canadian Prairies' provinces of Saskatchewan and Manitoba which gave an estimated rate of 8.4 per 100,000, have recorded significantly higher figures. And in most cases the latter are explicable in terms of unusually high local concentrations, a common phenomenon in the case of rare familial traits.

For example, all the cases identified by Brothers (1949) in Tasmania were traceable to a particular English woman from Somerset. Whilst Caro's (1977) work in East Anglia, which indicated a rate of over 9 per 100,000, appears to show that selective population movements led to an increase in concentration of choreic subjects in certain centres. This is most notably so in Lowestoft where 11 families were identified, giving a prevalence rate of some 30 per 100,000.

If the figure of 7 manifest cases per 100,000 is applied to the overall UK population it indicates a total of about 4,000 active Huntington's chorea sufferers. However, this estimate is only an approximate guide to the burden imposed by the disease because it is based on limited data which might mis-state the occurrence of symptomatic distress.[6] Also it does not include those individuals who are currently well but who might at some later point develop hereditary chorea.

A rising trend?

A number of commentators have as a result of examining the reproductive records of choreic families suggested that individuals carrying the critical gene(s) display increased fertility. Large families appear to be relatively common whilst the unaffected brothers and sisters of choreic subjects tend to have fewer offspring. Reed and Palm (1951) found a ratio of 1.8:1 in the number of children parented by choreic and non-choreic siblings. Their results are broadly supported by the more recently collected data shown in Figures 3a and 3b, derived from research conducted in Wales (Harper *et al* 1979).

The reasons for such a phenomenon may relate to both the physiological impact of Huntington's chorea and its social and psychological consequences. For instance, decreased sexual inhibition, perhaps coupled with a lack of competence in avoiding unwanted births or a decline in a subject's sense of having anything to gain from limiting family size, could play just as significant a role as increased libido in accounting for the raised fertility of some choreic individuals. Whilst ironically their unaffected

6 The Association to Combat Huntington's Chorea (Combat) estimates that the number of affected individuals is nearer 6,000 (over 10/100,000).

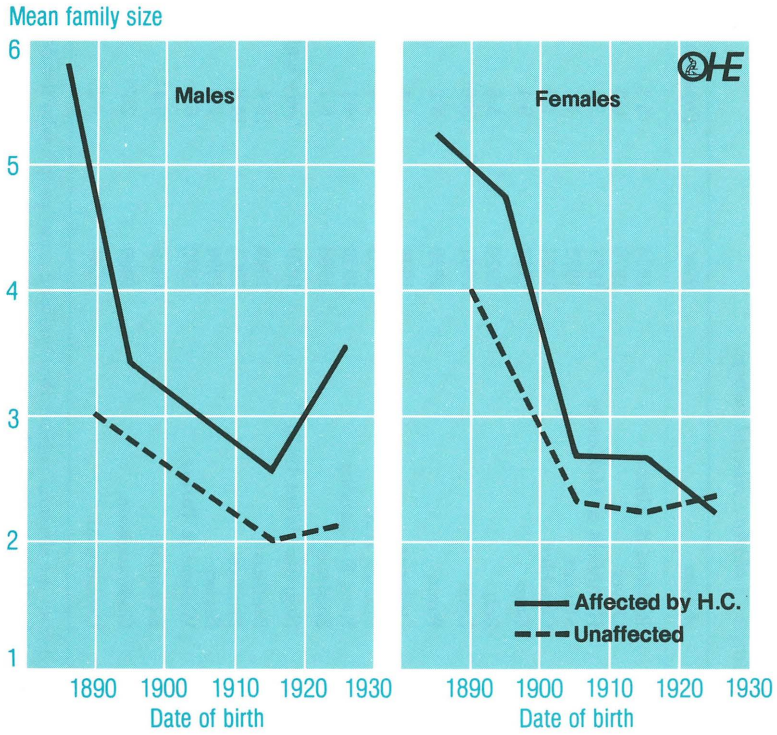
Table 2 *Prevalence rates per 100,000 population for Huntington's chorea: selected surveys*

Country	*Area*	*Authors*	*Year*	*Prevalence/100,000*
England	Cornwall	Bickford & Ellison	1953	5·3
	Northampton	Oliver	1970	6·3
	Bedfordshire	Heathfield & McKenzie	1971	7·5
	Leeds	Stevens	1972	4·3
	East Anglia	Critchley	1934	1·2
	East Anglia	Caro	1977	9·4
Scotland	South-West Scotland	Bolt	1970	5·6
	Moray Firth	Lyon	1962	560[1]
Germany	Rhineland	Panse	1938	3·2
Spain	Cadiz	Ordonez	1938	1·4
USA	Minnesota	Pearson *et al*	1955	5·4
	Michigan	Reed & Chandler	1958	4·1
	Rochester (Minn)	Kurland	1968	6·7
South America	Venezuela	Negrette (Went 1972)	1970	'very high'[2]
Australia	Tasmania	Brothers	1949	17·4
	Victoria	Brothers	1964	14·8
	Queensland	Parker	1958	2·3
	Queensland	Wallace & Parker	1972	6·3
Japan	Aichi	Kishimoto	1959	0·4[3]
Iceland		Gudmundsson	1969	2·7[4]
Poland		Cendrowski	1964	4·1

1 The population for this study was very small and was calculated from the electoral register thus omitting many people who should otherwise have been included. Thus, although widely quoted, the estimate is of little general value.
2 In a study of 165 families living in the area surrounding Lake Maracaibo, west of Caracas, 28 active cases (2.07 per cent of the population) were identified and historical research revealed over 200 choreic deaths.
3 Until 1927 Huntington's chorea was thought to be non-existent in Japan and it is still considered to be very rare.
4 Only a small series was used for this study and ascertainment may have been incomplete.

Source Heathfield 1973; Kurland *et al* 1973.

Figures 3a and 3b *Family sizes in choreic and non-choreic siblings*



Source Harper *et al* 1979.

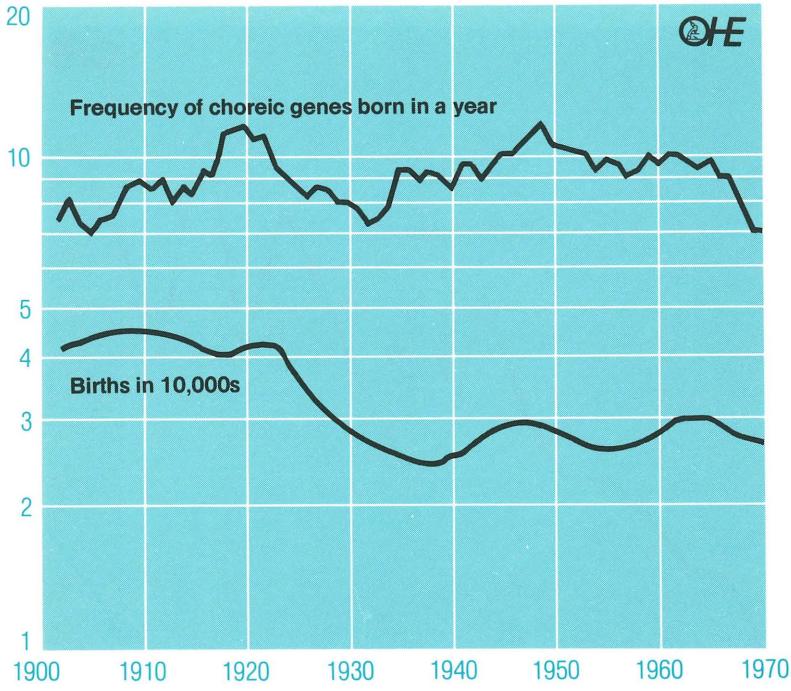
relatives may, because of their uncertainty about the future and the retention of 'normal' behavioural responses, be more likely to limit their procreative activities.

Such findings suggest that, in periods when the mass of the population's fertility is being restricted, the incidence rate of Huntington's chorea per head of population may rise. Figure 4, again drawn from the research of Harper and his colleagues in Wales, implies such a shift.

Similarly Figure 5, compiled from the Registrar General's statistics, shows a marked rising trend in the overall numbers of deaths attributed to hereditary chorea in the last two decades. This could be indicative of a both proportional and absolute growth in the number of gene carriers, although in this case the information available is far from conclusive.

One set of difficulties relates to the change of coding in 1968, before which date Huntington's chorea was not classified as a single disease entity. And the apparent mortality increases in

Figure 4 *Frequency of gene carrier births compared with all births in Glamorgan and Gwent, 1900–70*



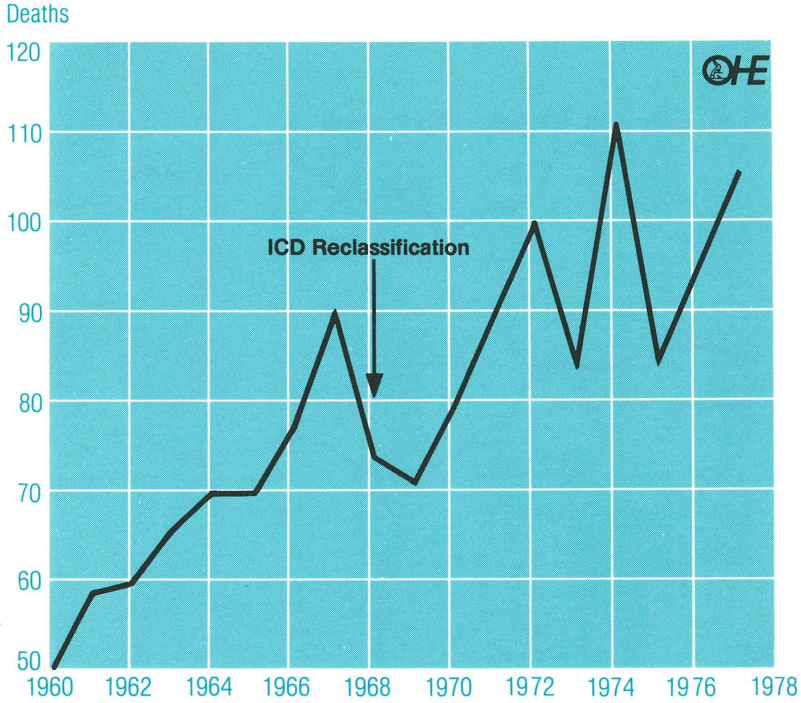
Note 5-year moving averages.
Source Harper *et al* 1979.

recent years are also clearly linked to improved diagnosis and more honest recording, although even in 1977 only 106 deaths were attributed to the disease. The epidemiological studies reviewed in this section imply an expected figure of at least 300. Reasons for this discrepancy relate to the fact that hereditary chorea is often not the certified cause of its victim's deaths, which may rather be attributed to intervening or associated states like broncho-pneumonia, cardio-vascular disease or subdural haematoma.

Brain changes in Huntington's chorea

The most outstanding pathological aspect of hereditary chorea is the extent of brain atrophy found on post-mortem examination. Neuronal loss associated with the condition was first noted by

Figure 5 *Increase in mortality of cases due to Huntington's chorea, England and Wales, 1960–77*

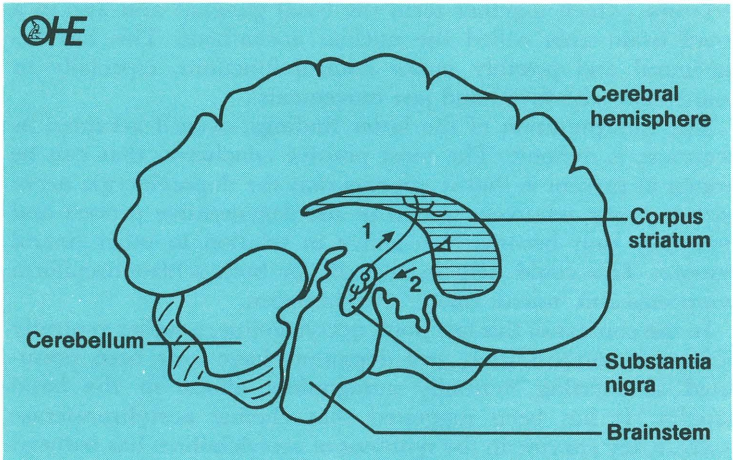


Source Registrar General, various years.

Alzheimer at the start of the twentieth century. Since then other investigators have shown that the areas most affected are the basal ganglia (see Figure 6), which may be reduced in weight by as much as 50 per cent at the time of death, the cerebellum and the brain stem adjacent to the substantia nigra (Spokes 1979a). The basal ganglia are known to play a key role in controlling movement and muscle tone.

Nerve cell destruction is particularly marked in the juvenile form. By contrast, late onset cases suffer less than average losses. Many researchers have attempted to elucidate the neurochemical changes which accompany Huntington's subjects' brain atrophy, such work having received particular encouragement after the success achieved by Cotzias and his co-workers (1967) in the treatment of Parkinson's disease. Parkinsonian symptoms are a partial mirror image of those of hereditary chorea. For instance, in Parkinsonism there is a slowness of, or even inability to initiate, movement coupled with symptoms like muscle rigidity leading to the characteristic mask-like face: the opposite is so in all but a

Figure 6 *Section through the medial surface of the brain*



The corpus striatum and substantia nigra are known collectively as the basal ganglia.
1 Nigrostriatal dopamine pathway.
2 Striatonigral GABA pathway.
The arrows indicate direction of nerve impulse flow.

Source Spokes 1978.

tiny minority of terminal chorea sufferers. The discovery of deficiencies of the neurotransmitter dopamine[7] in the basal ganglia of the brains of individuals dying of Parkinson's disease followed by the introduction of therapeutic regimes including the dopamine precursor L-DOPA led to hopes of similar advances in the control of Huntington's chorea.

As yet no such breakthrough has been made. And the neurochemical findings to date must be treated with some caution, not least because variations in expected levels of transmitter concentrations may be affected by the process of brain atrophy or perhaps by independent aspects of a subject's condition like intervening depressive illness. However, a number of promising lines of investigation have emerged.

For example, post-mortem studies published in the first half of the 1970s (Bernheimer *et al* 1973; Bird and Iverson 1974) indicated that dopamine levels in the basal ganglia of familial

7 Dopamine is one of many chemical substances known as neurotransmitters which mediate the transmission of electrical impulses across the many junctions between nerve cells (synapses). The neurotransmitter diffuses across the synaptic gap and enters a receptor site. Interaction of the transmitter with the receptor may cause excitation or inhibition of the nerve cell.

chorea sufferers were normal. But more recently Spokes (1979b) reported a significant increase in the substantia nigra and corpus striatum (which together form the basal ganglia) and also in a small brain area called the nucleus accumbens. This has behavioural and possibly motor control functions, especially in connection with facial and jaw movements.

The interpretation of the latter findings, even if accepted as accurate, is difficult. The most positive conclusion that can be drawn at present is that it appears that the dopaminergic nerve pathways are relatively spared in the degenerative process and that they thus become over-active in relation to other neural systems. This could help to account for both schizophreniform symptoms and 'mirror image' Parkinsonism.

In the context of this last point acetylcholine, another centrally acting neurotransmitter, and dopamine have long been postulated as exerting mutually antagonistic effects in the basal ganglia. It has been suggested that choline acetyltransferase (CAT), a key enzyme in the synthesis of acetylcholine, has reduced activity in choreic brains. This could exacerbate an imbalance with dopamine.

Abnormal distributions of a wide range of other neurotransmitters have also been reported. They include noradrenaline, serotonin, and the neuropeptide known as 'substance P'. But perhaps the most important and interesting neurochemical findings in Huntington's chorea relate to the inhibitor gamma-aminobutyric acid (GABA) and its biosynthetic enzyme glutamic acid decarboxylase (GAD). It appears that both are present in significantly reduced concentrations in the basal ganglia of choreic brains, where GABA-ergic neurones should form a major pathway between the area known as the corpus striatum and the substantia nigra. It is quite probable that the death of these cells reduces the inhibition of the associated dopaminergic system resulting in choreiform movement.

Underlying causes

The fundamental aetiology of the brain atrophy and associated biochemical changes seen in Huntington's chorea is unknown. One theory was that like Wilson's disease it may be caused by the build-up of a metal, in this case ferric iron (Klintworth 1969), in the brain tissues. But in fact this tendency is displayed in other neurological disorders and thus cannot be considered specific.

Other commentators have speculated on the link between the schizophrenias and Huntington's chorea. Clearly there are some symptomatic overlaps, both conditions responding to medicines which block dopamine reception or release in areas like the nucleus accumbens (Bird *et al* 1979). It would be misleading to overstate the significance of such links but recent research has

indicated that, at least in some forms of schizophrenia, a virus-like agent may be involved (Crow *et al* 1979). It was identified in the cerebrospinal fluid of 18 out of 47 schizophrenic subjects and also in 2 out of 3 cases of familial chorea. It has been hypothesised that the virus-like agent could promote neural atrophy and/or other changes in genetically predisposed sub-populations.

Findings which might support this model were obtained in a study by Husby *et al* (1977) in the United States. Half of a large group of patients with well-documented Huntington's chorea showed the presence of antineuronal antibodies in their blood; that is antibodies which were probably engaged in some form of immune response to the subject's own neural tissues. They were also present in 13 of 56 first-degree 'at risk' individuals against 2 of 60 normal controls.

However, the most important aspect of this study was the finding that antineuronal antibodies were present in 6 of 20 spouses. It is possible that this finding reflected the presence of a relatively common neurotropic virus in chorea sufferers and those living in close contact with them. The latter may, theoretically, be repeatedly exposed to the virus but as they do not have appropriate genetic make-up will never develop Huntington's chorea.

Finally, a rather different hypothesis regarding the aetiology of Huntington's chorea may be based on the observation that when kainic acid, which is structurally similar to naturally occurring glutamic acid, is injected into the brains of animals changes very similar to those found in the human disorder occur. This provides not simply a useful test model for further studies; it also suggests that some mechanism associated with glutaminergic neural pathways in the brain may be the site of the key biochemical lesion in hereditary chorea. Therefore it is an important field for further investigation.

Therapeutic implications

Present medical treatment aims to alleviate the symptoms of chorea and mental distress but cannot, at this stage, halt the progression of the disease. It is only in the last decade or so that any effective relief has been found through the availability of neuroleptic drugs. Prior to the mid-1950s sedatives, particularly phenobarbitone, were commonly prescribed but were unsatisfactory. The neuroleptics, or major tranquillisers, have a powerful dampening effect on the brain. They interfere with dopamine function, decreasing the amount effectively active at the receptor site.[8] Involuntary movements can to varying degrees be controlled

8 Predominantly they cause a reduction of motor activity without a marked hypnotic effect but can induce a Parkinsonism syndrome. The phenothiazine and butyrophenone compounds are the main classes of the neuroleptic group of drugs.

by them as may states of anxiety, restlessness and excitement. In addition, tetrabenazine, which has a reserpine-like action, has been used for the suppression of chorea (McLellan *et al* 1974; Godwin-Austen 1979). However, like reserpine, it can also promote noradrenaline depletion and so depression is a side effect although it is the most widely used medicine for the control of chorea. Neuroleptics such as chlorpromazine are not similarly subject to this risk but can in time themselves promote unwanted symptoms.[9]

Recently researchers in Canada (Perry *et al* 1979) have been investigating the use of the antitubercular medicine isoniazid in the treatment of Huntington's chorea. Isoniazid has been found to act as an inhibitor of GABA aminotransferase, the first enzyme in the degradative pathway of GABA, and when given to animals in high doses it can elevate the brain GABA content. A small trial was conducted on 6 choreic patients with encouraging results, with 5 showing marked improvement in their choreiform movements and 4 a lessening of irritability and moodiness. However, it must be noted that the dose needed to maintain this therapy creates a risk of liver malfunction which could seriously damage patients' life chances in the early stage of their illness. Also, until subjected to full double-blind controlled trials, the beneficial action of isoniazid in this context remain unproven.

A possibility for the future is that more effective and safer GABA-ergic neurone stimulants will be found. One such substance, a muscarine derivate, has already reportedly been developed in Denmark and is undergoing trials of its pharmacological potential. However, it is still uncertain for how long such a therapeutic approach would prove effective in Huntington's chorea, given the progressive destruction of the subject's neurones. This process cannot be checked and, therefore, such palliative treatments[10] cannot ward off the onset of dementia in sufferers.

Finally it is mainly of historic interest to note that the development of stereotactic surgery in 1947 by Spiegel and Wycis was a turning point in the surgical treatment of diseases of the basal ganglia. This is a method of inserting instruments into precise

9 Choreiform movements can be induced by prolonged treatment with neuroleptic drugs. Such iatrogenic disorders, known as tardive dyskinesias, produce abnormal movements not dissimilar to Huntington's chorea. In some cases the condition is irreversible. It is thought that tardive dyskinesias arise from an overstimulation of certain dopaminergic receptors which become supersensitive to dopamine as a result of chronic neuroleptic therapy. When the mechanism of drug-induced dyskinesias is fully understood it may lead to greater comprehension of some of the spontaneous movement disorders including Huntington's chorea.

10 Anti-depressants and minor tranquillisers (which in the case of the benzodiazapines may act directly on GABA receptors) can also provide some symptomatic relief.

areas of the brain through holes in the skull. It was hoped that by creating small lesions in the nervous system of patients with chorea there would be a decrease in hyperkinesis. But this technique is of limited value because the abnormal movements can never be totally abolished and there is the rare risk of paralysis or impairment of speech and intellect. Although an occasional individual benefits choreics often appear to lose awareness of their involuntary movements, sometimes even denying their existence, whilst it is possible that the more disabling aspect of progressive dementia could be aggravated by surgical intervention.

The opportunities for prevention

It may be that eventually some form of treatment for Huntington's chorea will become available that will either halt the pathological process in its initial stages or at least slow it and/or modify distressing symptoms. For example, the control of phenylketonuria, a genetically transmitted metabolic defect, by special diets for affected children indicates that some form of intervention may prove possible although in the case of hereditary chorea lifetime therapy could well be necessary. But at present it is clear from the foregoing section that no such development can be confidently envisaged.

The alternative, and currently more promising, route to control of this distressing disease is via prevention. This may be achieved by a general reduction of the fertility of choreic subjects by providing them with an improved knowledge of the condition and its consequences and eventually by the detection and abortion of gene carriers before birth. The remainder of this section discusses aspects of both these approaches.

Genetic counselling

It is only within the last decade that each NHS region has had its own genetic advisory service. The specialist centres now instituted are able to provide not just full information about the nature and transmission of inheritable disorders; they should also be equipped effectively to communicate it to often distressed and sometimes poorly educated or intellectually less able clients.

In the future such counselling skills may be backed by the accumulation of a comprehensive knowledge base regarding the distribution of individuals carrying particular conditions within the community. Computer held regional genetic registers could help to cut the chances of a diagnosis being missed and families being needlessly exposed to the distress that a condition like Huntington's chorea can cause (*Lancet* 1979). However, such progress may be seen potentially to have less desirable aspects. It is

possible that if improperly used by individuals, corporate bodies or the state, such information could damage rather than enhance the life chances of people directly involved. At a simple level, for instance, unauthorised access could damage an affected individual's chance of obtaining insurance or a mortgage. (As indeed might the spread of information to 'at risk' individuals who previously were unaware of their potential impairment.)

In the specific context of efforts intended to reduce the prevalence of Huntington's chorea, the value of genetic counselling is limited by several other considerations. One is that for the present the only effective means of limiting the disease is for 'at risk' individuals to remain childless. Simply to tell a couple that one partner has approximately a 1 in 2 or 1 in 4 chance of being affected[11] and hence that their children would stand a 1 in 4 or 1 in 8 chance of having the choreic gene still leaves prospective parents with a difficult choice.

Of course, alternatives like adoption, sterilisation and artificial insemination can be presented. But many people may decide to accept the risk outlined to them. Indeed, the purpose of genetic counselling in professional (as opposed to, say, political or administrative) terms can be seen to be to alert individuals to a certain hazard rather than to force a choice not to reproduce upon them. The criteria of 'success' in such circumstances is not necessarily whether a given disease is eliminated or not, even though such an objective may have guided the original decision to provide services.

Several studies have suggested that the behavioural impact of genetic counselling may be limited, at least in the circumstances of today's opportunities for helping possibly choreic individuals. Tyler (1979) surveyed 92 patients and their families in a predominantly industrial area of South Wales. They were found to be largely ignorant of the genetic implications of their condition. Only a third had received any information, the exclusive source being hospital consultants.

However, 65 of their 173 offspring were also studied. This latter group had more adequate counselling. As a result 41 (19 of whom were still single) believed that they should avoid having children or should limit their families to one or possibly two. Yet the remaining 24 had not been so influenced and had already produced some 38 children between them.

Such small scale studies cannot be taken as any sort of overall guide to the potential efficiency of genetic counselling in controlling the prevalence of Huntington's chorea in the modern world. The Welsh researchers believe that it may take a decade or more for them to assess its role in the long-term prevention of

11 The precise ratio may be modified by age.

chorea[12] (Harper *et al* 1979). And even if in this context it is unsuccessful counselling may be of personal value to those who receive it.

But it does seem likely that it would generate more benefit if backed by some method of identifying healthy gene carriers and, ideally, a foetal screening technique.

Presymptomatic detection of hereditary chorea

Many researchers have attempted to develop tests by which those carrying the gene(s) responsible for Huntington's disease could be distinguished from their normal siblings before their condition becomes manifest. For example, one of the earliest projects involved electro-encephalographic (EEG) examinations. Since it had already been established that those with advanced illness showed abnormal, 'flat' readings it was hoped that as yet non-symptomatic subjects could be identified. Yet these efforts finally proved unproductive (Chandler 1966).

Similar techniques based on abnormalities of eye, tongue and limb movements have been tried and found unsuccessful. Even if more refined measurements can eventually be demonstrated to have some predictive value it appears highly unlikely that they will be of sufficient discriminatory power to be of much practical value to people at risk of becoming choreic. Little optimism can be reasonably felt in connection with more recent work on measurements of GABA in the cerebrospinal fluid, erythrocyte cell membrane investigations, screening by computerised axial tomography and genetic linkage studies.

The latter, aimed at linking Huntington's chorea to other easily observed genetically determined 'marker' traits, theoretically might provide a means of calculating modified risk ratios although so far the results of enquiries have been negative. One problem has been the difficulty of obtaining relevant information about several generations of affected families.

However, a number of possibly more productive areas of investigation have emerged in recent years. For example, one relates to tests conducted on cultures of skin fibroblasts, which may to a degree be able to differentiate between choreic and non-choreic populations.[13] An alternative approach to identifying

12 By which time other alternatives may exist. One short-term reason for choreic individuals to delay starting a family is the possibility of further advances in foetal genetic screening in the 1980s.

13 Fibroblasts (cells present in connective tissue) were obtained by skin biopsy and cultured under laboratory conditions. The choreic fibroblasts divided, increased and eventually levelled-off at a significantly higher cell density than those from the normal controls. It is, therefore, conceivable that, after further observations, such a process could possibly be the basis for an intra-uterine test for detection of Huntington's chorea in the foetus (Spokes 1978).

symptom-free gene carriers has been suggested by the fact that the disease can promote relative over-activity in the dopaminergic pathways of the basal ganglia. Acting on the assumption that increases in brain dopamine could even in pre-symptomatic choreics stimulate abnormal responses Klawans *et al* (1970) administered doses of L-DOPA to a sample of 'at risk' subjects. A third showed choreic movements (reversible on withdrawal of L-DOPA), a reaction not seen in any 'normal' controls.

Thus a predictive screening test along these lines may one day be developed, although even if this is so it is unlikely to be as accurate as would ideally be hoped and it could have some unwanted effects. Whether, for instance, the administration of L-DOPA to children or young adults over periods of ten weeks or more is sufficiently free from risk to make it acceptable practice and whether the precipitation of symptoms in affected individuals is without physical ill consequences are both unanswered questions. In addition the certain knowledge that one will develop Huntington's chorea may not be psychologically preferable to a state of symptomless uncertainty, at least for a proportion of those involved. This is especially so when such knowledge cannot even be employed to ensure that the victim's children will live on into the future free of hereditary illness.

Some form of prenatal screening would thus be extremely beneficial. Moshell *et al* (1980) of the US National Cancer Institute recently reported that examination of the cultured lymphocytes of four patients with Huntington's disease showed that they were abnormally sensitive to the lethal effects of X-rays. The authors postulated a genetically caused defect of DNA repair and argue that their observations indicate a method by which cells extracted from the amniotic fluid in 'at risk' pregnancies might be tested with the intention of determining if the foetal material contains the postulated choreic gene(s).

This is obviously a promising area for further research. But even if it does not lead to desirable results recent advances in techniques associated with DNA recombination and decoding mean that in the course of the 1980s it may in any case be possible to identify genetic characteristics consistently displayed by samples of people with hereditary chorea. Once this is achieved prenatal screening is likely to prove feasible. Hence afflicted foetuses could if the parents chose be aborted and the latter freed to start a fresh pregnancy with the chance of an unaffected child ensuing. To certain minority groups this path would seem a morally unacceptable one for anybody in the community to take. But to those whose main concern is to reduce distress caused by such hereditary illness it appears extremely attractive.

The provision of care

The progressively disabling nature of Huntington's chorea coupled with the distressing psychological effect mere awareness of the condition can have on entire families means that rehabilitation and social care must be geared to helping subjects and their relatives cope with constantly changing difficulties. Initially employment issues, such as those related to the hazards choreics face in driving or handling machinery, may predominate. But by between five and ten years after diagnosis most will have had to stop working and their problems come to centre on domestic life and the complexities of, for example, obtaining financial support via the social security system. And ultimately the need for intensive nursing care becomes overwhelming.

The impact of symptomatic chorea, coming as it normally does in middle life when an individual's career and his or her relationships with the children he or she may have are at an especially important stage, is often dramatic. It is revealing that in his observations of hereditary chorea in New York State in the 1830s Charles Waters, a pre-Huntington observer, commented that families with the disease were impoverished (Dunglison 1842). Even today in Britain, despite the provisions of the 'welfare state', they frequently face hardships at simply a material level. The mental changes the condition can directly or indirectly cause can exacerbate such disadvantages, very probably creating 'cycles of deprivation' across the generations which have their basis in social as well as genetic inheritance.

For example, a study by Dewhurst *et al* (1970) indicated that significant proportions of choreics attempted suicide (10 per cent), mutilated themselves (13 per cent), became alcoholic (19 per cent) and/or became involved in legal proceedings (18 per cent). Charges included assault and cruelty to children. About a third had suffered a broken marriage and raised rates of illegitimacy and aberrant sexual behaviour were suggested. Of the 172 offspring of the sample subjects 9 were identified as victims of extreme violence and 17 were seriously neglected. Furthermore, Oliver (1970) studied the clinically unaffected siblings of these Huntington's disease victims, finding that out of 150 such individuals 17 died under the age of 11 and that 9 did so between 11 and 21; two others were successful suicides. These latter figures show both the probable occurrence of undiagnosed disease and the prevalence of ill treatment or neglect in these choreic families.

Dewhurst (1970) emphasised the role of adverse environmental factors in the context of such findings. It should thus not be assumed that the disease itself inevitably leads to such phenomena, only that in conditions of inadequate care and support the

statistical chance of the degeneration of normal family and social life is much increased. Informed assistance may thus be of great value to both choreics and the community as a whole, although at present the availability of help seems very limited.

For instance, Tyler's (1979) research in South Wales showed that 64 per cent of those interviewed felt that they had care needs which were unmet. These included lack of opportunities for personal counselling, inadequate medical supervision and financial support and insufficient practical assistance with clothing, bedding and home adaptations. Those who had regular home visits from their family practitioners often emphasised the value of such attention and interest but many spouses said that there were not sufficient facilities available to allow them to have enough short breaks away from the constant caring for their affected partners. There is also evidence that both in this country and the United States families may often be pushed to the extremes of their endurance, with crises like attempted suicides being the precipitating factors which finally cause patients to be admitted to residential facilities.

Even after severely affected individuals enter hospital or social service care, significant problems may remain for them and their families. This is because their combined physical and mental symptoms may make them difficult patients in the environment of either a long-stay psychiatric or geriatric ward, where they are often inappropriately placed. The response to the disruption they sometimes cause may be an excessive use of sedative medicines. The lack of more suitable NHS or local authority facilities makes the provision of specialist residential caring units for choreic patients an attractive idea, especially in areas with a known high density of 'at risk' families. But resource shortages may limit the viability of such proposals and some may argue that, at present, the first priority is to improve the quality of support given to relatives struggling to cope with the problems of Huntington's chorea at home.

Social services or community nursing?

It is probable that the disturbing implications of the above findings apply nationwide. In many instances the quality of social and medical services for chorea sufferers appears inadequate, not least because of poor co-ordination of NHS and local authority provisions.

One suggestion for improving the situation is that, in localities with known concentrations of cases, specialist social workers with a particular knowledge of Huntington's chorea could be employed. Ideally they might liaise with NHS staff, like specialist health visitors, to create a more integrated and effective service capable of helping victims through the difficult transitions from

normal life through stages of partial dependence to virtually total disablement.

But the realism of such proposals may be questioned on both organisational and financial grounds. With retrenchment in social service spending (current plans indicate a reduction of about 7 per cent in real terms in 1980) and the problems of inter-professional co-operation still unresolved, it could be argued that in cases where disablement and social distress are so clearly related to an overt, degenerative disease process, the responsibility for 'maintenance rehabilitation' ought to be in the hands of a single group of health service providers holding both social and medical skills. Ideally such a professional body would span the gap between residential and traditional community care, expanding the concept of the latter in order to break down the social isolation of institutional support.

In some cases, such as mental handicap, attempts have already been made to break down the divisions between groups like social workers and nurses, so creating a new type of caring profession, but vested interests may slow such a process or even make it impossible. The alternative might be to invest development funds and efforts in one of the established professional areas so that the new group could evolve out of it. With education designed to confer counselling and social support skills and to maintain their existing expertise it is possible, for example, that a radically new and more self-confident sector of the nursing profession could emerge, one which could perhaps take over and co-ordinate current inefficient efforts in the field of supporting people and families with social disadvantages related to chronic medical disorders.

However, such speculation can do little to relieve the immediate plight of Huntington's chorea victims. In the short-term all that can be hoped for is that the spread of objective information about the condition will contribute to gradual improvements in care, although these will in particular localities inevitably depend on the goodwill and dedication of individual professionals coupled with the self-help of those affected by the condition. The Association to Combat Huntington's Chorea (Combat) is the natural focus for those wishing to channel their voluntary efforts into providing better support, an illustration of which might be the type of help offered by the Crossroads Care Attendance Scheme.

Economic aspects of Huntington's chorea

With an incidence of only about 300 new diagnoses each year hereditary chorea does not create major non-health care costs for the community. For example, the morbidity it causes at most accounts for losses of about 2,000 man/woman years per annum in the population of working age.[14] Even if this total is doubled to allow for the impact on relatives' work activities at home or in employment the resultant income losses do not at maximum represent more than £20 million. In practice in a period of surplus labour the measureable direct impact on the economy of the lost production so caused is negligible.

Similarly the 5,000 years of lost life which can be attributed to the disease annually are only a tiny fraction of the toll that common conditions like the cancers and circulatory disorders extract. Indeed in overall economic terms it could perhaps even be argued that premature deaths of individuals in their fifties and sixties in some ways save society costs which would have been incurred had they lived to old age.

However, on an individual 'unit cost' basis it can be shown that Huntington's chorea is an extremely expensive condition for the health and social services. For instance, in the terminal stages intensive nursing support is required. One American study (McAtee and Stevens 1972) indicated that patients suffering the disease needed up to three times the *average* attention time demanded by other patients on the wards in which they were treated. In Britain it may be estimated that there are approximately 500 choreics in institutions such as psychiatric hospitals at any one time. The *average* cost per annum of each place is currently (1979) £5,000 to £6,000 implying that the NHS hospital costs imposed by the disease are at least £2.5 million.[15]

Other social service and NHS costs such as home helps, home adaptations, home nursing, general practitioner consultations, genetic counselling and out-patients consultations probably account for a further £1 million or more, indicating a total health and personal social service expenditure of some £4 million per annum. This estimate suggests an average lifetime cost per case cost of about £15,000 (£1979), a little below Harper

14 About 70 per cent of symptomatic cases are aged between 15 and 65. Calculation assumes a total disease duration of 15 years, for 10 of which the sufferer is taken to be effectively disabled though in practice the period of total incapacity is likely to be shorter.

15 A detailed analysis would of course be concerned with marginal costs. Given the above average intensity of nursing demanded by choreic individuals the figure quoted may be taken as a reasonable guide.

et al's (1979) figure of £20,000. But the latter included an allowance for transfer payments made to sufferers and their families.

Costs of this magnitude clearly demonstrate the potential returns to the Health Service to be gained from reductions in the incidence of the condition, quite apart from the enormous intangible benefits to be gained from the control of familial chorea. Genetic counselling is an unquestionably beneficial investment, although for sufferers control of the disease at the expense of the total elimination of their genetic line appears to many to be an unacceptable price to pay. Prenatal screening programmes could avoid the latter, and therefore be more acceptable to those who at present decide to become a parent despite the knowledge that he or she may eventually develop chorea.

Future research – the responsibility for innovation

It has been suggested by a number of commentators that relatively rare conditions like Huntington's chorea are ignored by bodies such as the multinational pharmaceutical companies, which on a world-wide basis rival governments as major investors in bio-medical research (see *Pharmaceutical Journal* 1979). Some critics believe that, because the potential market size in any one country is allegedly small and the costs of getting a new medicine through safety testing are high, pharmaceutical companies would not make new curative or palliative medicines available, even if they had discovered them.

Such criticisms are unfounded in the context of hereditary chorea for a number of reasons. One is that research initiators, whether privately or publicly employed, tend to concentrate resources on areas most likely to maximise the community's social and economic benefit. This means that either very large numbers are affected by a target condition or that there is firm reason to believe a specific advance can be made in respect to a less prevalent disease. Up until recently at least neither condition applied in this case. Thus it has been a reasonable scientific policy to concentrate on wider areas like the biochemistry of the schizophrenias and techniques of genetic analysis and manipulation. Eventually such studies will lead either to chance findings relevant to rarer illnesses or fundamental advances in theory and/or methodology which might be systematically applied to understanding conditions like Huntington's chorea.

Also, if a medicine were to become available which might, say, relieve the symptoms of chorea it would not remain unmarketed. It is government or the health authorities which both in effect determine the cost of placing a product on the market and which, in most of the advanced nations of the world, decide whether it will be paid for. As the predominant purchasing agencies for medicine, the Department of Health and the National Health

Service in Britain are in a position to define what a maximum acceptable unit cost for the treatment of Huntington's chorea with such a hypothetical specific medicine would be.[16] With a total of 4,000 symptomatic sufferers and perhaps 14,000 heterozygotes carrying the relevant gene(s) in the UK alone the potential benefit from a palliative treatment or screening test for Huntington's chorea would in fact be substantial and the cost would undoubtedly be met. (World-wide there may be 300,000 manifest and approaching a million non-symptomatic cases. Hence the world market for a significant therapeutic advance would be considerable.)

The real barriers are still technical rather than economic. What those with concern for this area should concentrate on in the next few years is to ensure that all relevant advances, such as methods of screening for shared genetic factors, are applied to the choreic population as rapidly as possible. It would seem that everyone in the health care field, including government, industry and university scientists, has a common responsibility in this respect.

Conclusion

Huntington's chorea remains a distressing and irreversible condition which imposes heavy burdens on both those who suffer it and their relatives. Despite advances in palliative treatments, such as the introduction of tetrabenazine, there is still no fundamental understanding of the genetically-based abnormality which results in the brain degeneration characteristic of the disease. It is probable that, if possible at all, any development of techniques capable of preventing or controlling expression of the disease in those carrying the gene will come only after major breakthroughs in identifying the primary biochemical lesion(s) in Huntington's chorea have been achieved.

However, diagnostic tests capable of tracing pre-symptomatic choreics, ideally at a prenatal stage, are likely to become a practical possibility in the relatively near future. Combined with the support given by genetic counsellors they could provide the community with a long-term means of limiting or even eradicating the occurrence of this unpleasant hereditary affliction. It would thus seem logical to concentrate current research efforts in this latter area.

Even with today's knowledge of the condition the suffering

16 It could be suggested that manufacturers should subsidise rarer disease medicines with funds derived from 'best selling' products. This practice is sometimes adopted but increasingly strict price and profit controls world-wide have limited its practicality.

experienced by choreic families could be reduced. Improved social and related medical support might also cut any risk of bizarre manifestations of the condition, like child neglect, which relate to adverse environmental factors. One possibility is the introduction of a limited number of specialist social or community health workers who could perhaps operate within multi-district catchment areas. Another is the introduction of a small number of specialised residential units capable of dealing with the complex mix of mental and physical symptoms which often occur in familial chorea. Psychiatric or geriatric wards are often unsuitable for patients with this condition.

Day centres and day hospitals providing relief for relatives for just a few days a week can greatly reduce the strains of constant care. It is to be hoped that social service and to a lesser extent NHS retrenchments do not interfere too greatly with existing provision in this area, although the extension of such facilities to more adequate levels seems in the short term to be an unlikely prospect in many parts of the country. Initiatives from the Association to Combat Huntington's Chorea (Combat), which has recently opened a holiday home for choreics, may be of considerable value. But despite the fact that self-help groups can do much to alleviate the isolation and fears of sufferers, charitable resources are such that they cannot provide an alternative to health service funded care at a national level.

Finally, although Huntington's chorea is commonly regarded as a rare condition with a minimal economic or social impact on the community as a whole in Britain, in reality it directly affects a total of some 50,000 when sufferers, symptom-free but 'at risk' subjects and the spouses of both groups are all counted in.[17] The scale of their personal distress and, especially for sufferers in the later stages, the costs of their individual care are far larger than is sometimes assumed or implied. It would be tragic if, because of ill-founded beliefs that progress in this field would be of essentially academic rather than genuine social or economic value, advances in therapeutic or diagnostic techniques were needlessly delayed. All the major research agencies, whether state or privately funded, share a responsibility in ensuring that therapeutic and allied innovations are made as rapidly as the expansion of biomedical knowledge permits.

17 This figure includes those who are still uncertain whether or not they are carrying the affected gene(s).

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Office of Health Economics

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To undertake research on the economic aspects of medical care.
To investigate other health and social problems.
To collect data from other countries.
To publish results, data and conclusions relevant to the above.

The Office of Health Economics welcomes financial support and discussions on research problems with any persons or bodies interested in its work.