

The History of Huntington's Chorea

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Huntington's chorea is an inherited disorder characterised, in the majority of patients, by the appearance in adult life of progressive chorea and dementia. As it is inherited as an autosomal dominant, with apparently full penetrance, all the carriers of the gene who live long enough will eventually develop the disease. Pathologically there is neuronal degeneration in the cerebral cortex and caudate nucleus with cerebral atrophy and ventricular dilatation. The clinical picture and mode of inheritance are distinctive, and it is therefore surprising that the condition was not widely known until George Huntington described it in 1872.

This article reviews the early accounts of inherited and adult chorea. The possible existence of Huntington's chorea in England and Wales in the early nineteenth century is discussed and an attempt is made to calculate the number of choreics who would have been alive at that time and thereby to explain why the disease was not generally recognised.

EARLY USE OF THE TERM CHOREA

The word chorea is derived from the Latin *choreus*, pertaining to dancing, and the Greek *χορός*, meaning chorus or an organised band of dancers and singers. It was first used, in a medical sense, when the name *chorea sancti viti*, or St Vitus' Dance, was applied to the epidemic dancing disorders of the Middle Ages. The first use of the word to denote an organically determined disorder has been attributed to Paracelsus, 1493–1541 (von Hohenheim, 1658), who sub-divided chorea into three categories; chorea naturalis s. coacta, chorea lasciva, and chorea imaginativa s. aestimativa. The category of chorea naturalis contained patients who 'only felt an involuntary impulse to allay the internal sense of disquietude' and who made no attempt to dance, whereas those with chorea due to voluptuous desire or imagination presumably did tend to dance and were clearly suffering from non-organic disorders. From the writings of Paracelsus it is not possible to recognise any particular disease entity as being chorea naturalis, although Bell (1934) has suggested that some patients in this group may have had Huntington's chorea. There is little doubt, however, that Sydenham (1686) was describing rheumatic

chorea when he wrote on *chorea sancti viti*, although it is perhaps unfortunate that, when describing the disorder that now bears his name, he should have used the old term *chorea sancti viti*, which previously had been used to describe a non-organic disorder. That this subsequently led to confusion is clear when it is seen that James (1745), in his *Medicinal Dictionary*, listed dancing mania and Sydenham's chorea together and Cullen (1791) apparently believed that the two conditions were related. A brief review of the dancing disorders and the early use of the term chorea is given by Bell (1934) and a more detailed account has been published by Bruyn (1968).

'HEREDITARY' SYDENHAM'S CHOREA

In the late eighteenth and early nineteenth centuries the role of inheritance in the aetiology of dancing mania was occasionally considered, two examples from the British literature being Armstrong's (1783) description of 'singular convulsive fits in three children of one family' and the detailed account of the Leaping Ague of Forfarshire by an unknown author using the pen name 'The Inquirer' (1807). During this period numerous accounts of organic chorea in children also appeared, mainly to commend cures whose success depended on the self-limiting nature of the condition, and such detailed study of this condition eventually led Addison, Babington and others (Babington, 1841) to comment on the association between rheumatism and Sydenham's chorea. That the disease was hereditary had already often been suggested.

Among the earliest to suggest that chorea of any sort could be inherited was Bernt (1810), but it seems probable that he was only aware of the familial aggregation of cases of Sydenham's chorea since the example he gave clearly refers to chorea with onset in early life. He wrote: 'Desperriere describes an example of this hereditary tendency in two sisters; for each of them approaching in turn, their first menstrual period, was gradually seized by Chorea Sti. Viti and their mother, too, at the same moment of puberty before the beginning of menstruation had been subject to strong affection of the nerves and weakness of the body.' This description of chorea affecting siblings and possibly affecting a parent during youth, is similar to that given by others, including Mongenot (1815), Rufz (1834), Addison (1837), Todd (1842), Webster (1850) and Sée (1850). It has been suggested that these authors were aware of hereditary adult chorea, but all were in fact concerned with familial aggregations of chorea with onset in childhood and not adult life.

EARLY DESCRIPTIONS OF ADULT CHOREA

During the period when it was being suggested that Sydenham's chorea could be inherited, several reports appeared in which adult chorea was mentioned,

one of the earliest being that of Cullen (1791) who described a man of 42, with chorea, who was cured by 'strong electric shocks directed through the whole body'. This patient clearly did not have chronic chorea for he was apparently cured, but there are several reports of chronic adult chorea from the same era. An early and impressive description is by Coxe (1805), of a man aged 40, who suffered from progressive chorea for some years and later became fatuous in his manner. Coxe examined the brain, noting greatly dilated ventricles containing 'at least twelve ounces of very transparent fluid' and concluded that the state of hydrocephalus had evolved over a considerable time. This very remarkable observation of chronic adult chorea with mental changes and ventricular dilatation is strongly suggestive of Huntington's chorea. Coxe made no reference to the family history, although from his comments he appears to have seen other patients with chronic chorea.

In 1825 Jeffreys described a man whose chorea started at the age of 54 and persisted until his death at 81. He did not become demented, but, as can happen in Huntington's chorea, he lost 40 lb in weight which Jeffreys attributed to 'the constant exercise from involuntary motion'. This patient was a relative of the author, so it is reasonable to conclude that, if any similar cases had occurred in the family, they would have been mentioned. In 1827 Clutterbuck stated that he had seen chorea affecting a woman far advanced in age, but he did not give any details, and Thompson (1841), in a discussion on chorea in general, noted that the condition is most common between the ages of 7 and 15, but that no age is exempt and that he had seen it at all ages 'from 40 to 50 and even up to 70 and 80'. He goes on to say 'in advanced life it is mostly complicated with other affections such as hemiplegia, rheumatism, paralysis, mental affections, etc'. The mention of chorea associated with hemiplegia and paralysis probably indicates that Thompson had seen patients with chorea caused by cerebrovascular disease, but the mention of 'mental affections' raises the possibility that he may have seen Huntington's chorea. This possibility is increased when it is seen that he included an hereditary disposition among the various factors that determine the occurrence of chorea. In 1850, Sée noted that chronic and incurable chorea, with associated character change and memory disturbance, occurred principally in older people. He quoted references to similar descriptions by others and mentioned three cases of his own, without commenting on the family histories. The patients he does describe as having hereditary chorea all appear to have suffered from chorea minor, rather than chronic adult chorea. Crawford (1850) and Hale (1853) both describe further adult patients with incurable chorea.

These examples, being mainly from the British literature, clearly indicate that chronic adult chorea occurred in the first half of the nineteenth century,

but the relative scarcity of reports suggests that the condition may have been even less common than it is now; furthermore, it seems likely that most of these patients were suffering from Huntington's chorea, although it is possible that other causes of chorea in later life have been included.

EARLY DESCRIPTIONS OF INHERITED ADULT CHOREA

The inherited form of chronic adult chorea was not generally recognised until after Huntington's (1872) description, but a number of earlier descriptions were produced. The first was by Elliotson in 1832. He noted that St Vitus' Dance was usually a benign condition but that 'when it occurs in adults it is frequently connected with paralysis or idiotism and will perhaps never be cured. It is very rare for you to remove the affection if it occurs in an adult and if it occurs in a local form. It will sometimes take place in one arm only, or in the head, or some of the muscles of the face, so that the person makes faces continually. In cases of this description I have never seen the affection cured. It then appears to arise for the most part from something in the original constitution of the body, for I have often seen it hereditary.' Despite the brief comment on local chorea, and the associated ambiguity, it seems that Elliotson is describing what we now call Huntington's chorea. No earlier description has been found. In 1841 Waters's detailed report of chronic adult chorea 'which is markedly hereditary' appeared. There is no doubt that the entity he described was Huntington's chorea. Sinkler (1889) gave a complete reprint of Waters's paper and concluded that the cases may well have been those seen by Huntington some years later. The next description of the disease is said to have been by Gorman in a thesis in 1846. The thesis has been lost, but mention of it remains in the 1848 edition of Dunglison's textbook. In 1860 Lund described two families in some detail and again there is little doubt that he was familiar with Huntington's chorea. This work is in Norwegian and has only been recognised in recent years, a translation being provided by Ørbeck (1959). In Scandinavia the disease is sometimes referred to as Lund-Huntington's chorea. A further description was provided by Lyon in 1863, who gave details of three affected families. Finally, in 1872, Huntington described the disease in more detail and with less ambiguity than most of the other authors; in fact the description was so good that it moved Osler (1908) to comment that 'in the history of medicine there are few instances in which a disease has been more accurately, more graphically or more briefly described than that in which Dr Huntington calls attention to an hereditary chorea which prevailed at the eastern end of Long Island where both his father and grandfather had practised'. After such a eulogy from Osler it



Fig. 1. John Elliotson (1791–1868) MD, FRCP, Physician to St Thomas's Hospital from 1817 to 1834, Professor of Medicine at University College from 1832 and Physician at University College Hospital from 1834. He was recognised as an astute diagnostician and teacher, but fell from grace when he became interested in Mesmerism. His colleagues found this so objectionable that the Council of the Royal College of Physicians interceded; whereupon, in 1838, he resigned his posts as Physician and Professor and, instead, practised Mesmerism and phrenology for the rest of his professional career (Munk, 1878).

would be churlish to quibble about the name of the disease which, if historically inaccurate, has the advantage of being universally recognised. Attempts to introduce new names, such as Lund-Huntington's chorea, have nothing to commend them, particularly if neither author has any claim to priority.

HUNTINGTON'S CHOREA IN THE EARLY
NINETEENTH CENTURY

The preceding sections have shown that organic chorea has been recognised since the middle of the seventeenth century, and the chronic adult form since the end of the eighteenth or the early years of the nineteenth. Yet the hereditary form was not described until 1832, or, if the brief account by Elliotson is not accepted, until 1841, and was not widely recognised until after 1872. Hitherto there has been no explanation for this apparent ignorance of the disease before the middle of the nineteenth century. There can be no doubt that the condition existed, since there are a few reports in the literature of families where the disease occurs in various branches of a pedigree which itself can be traced back to the eighteenth century or earlier (Tilney, 1908; Barbeau *et al.*, 1964). Several thriving journals were in existence in the early nineteenth century and references to chorea were common. Inherited disease had been known since the time of Hippocrates (Chadwick and Mann, 1950) and it had been suggested early in the nineteenth century that chorea minor could be inherited. Indeed, it is tempting to suggest that Pargeter's (1792) surprisingly modern views on inherited diseases could refer to Huntington's chorea, for he wrote:

'Lunatic ancestry . . . when madness exists in the blood of families and shews itself regularly in the several branches of the pedigree ill-concerted alliances will always keep up the general tendency to the disease. What then shall be said of those, who either from ambitious or lucrative motives, stifle the feelings of honour and humanity, and sordidly submit to form connections which entail miseries on their posterity, more grievous than death itself? Such matrimonial contacts should be avoided, and, if possible, prevented by every one which is a well-wisher to society; indeed I feel no reluctance whatever, in pronouncing those who engage in, and those who encourage and promote such alliances, to be, in the strictest sense, enemies to their country. If the symptoms do not immediately appear, but lie dormant for a time, we are justified, I think, in deeming those persons at least *amentes* if not absolutely *maniaci*.'

Yet the hereditary nature of chronic adult chorea was not generally recognised until over eighty years later.

Chronic adult chorea undoubtedly existed in the early nineteenth century and many of the patients described were probably suffering from Huntington's chorea. As the importance of inheritance in the aetiology of diseases was recognised, why was the hereditary nature of chronic chorea not recognised? An attempt to answer this question is made below by presuming that the

prevailing conditions in the past concealed the florid picture of the inherited disease.

It is possible, using data available on the structure of the population in the early nineteenth century and information collected recently by the author on patients with Huntington's chorea in the area of the Leeds Regional Hospital Board, to calculate the number of choreics and the number of unaffected carriers who were alive in England and Wales at that time. (Details of the methods used and the assumptions made are given in the appendix.) The year 1841 was chosen, as this is the first year for which fairly reliable information about the different age groups is available. The population was then much younger and the expectation of life at birth was lower, being 40·2 years for males and 42·2 years for females, compared to 68·4 years and 74·7 years respectively in 1966 (Registrar-General, 1968).

In Huntington's chorea heterozygotes exist in two forms—as choreics and as asymptomatic carriers who have yet to reach the age of onset of chorea. From Table 1 it can be seen that the frequency of heterozygotes in the popula-

TABLE 1

| England and Wales | | |
|---|------------|------------|
| | 1966 | 1841 |
| Population | 47,135,510 | 15,914,100 |
| Heterozygotes | 5,164 | 1,614 |
| Choreics | 1,967 | 419 |
| Unaffected carriers | 3,197 | 1,195 |
| Ratio of carriers/choreics | 1·62 | 2·85 |
| Choreic frequency ($\times 10^{-5}$) | 4·17 | 2·63 |
| Heterozygote frequency ($\times 10^{-5}$) | 9·13 | 9·86 |

tion was about the same in 1841 as in 1966, but the frequency of choreics was much less, being slightly more than half the current figure. In other words, in 1841, there were far more unaffected carriers of the gene than choreics, a fact clearly illustrated by the ratios of unaffected carriers to choreics—2·85 in 1841 and 1·62 in 1966. These differences, which are entirely due to the different expectation of life and, therefore, the different age structure of the population, offer a ready explanation for the apparent rarity of the disease, and a possible explanation for the failure of recognition of its hereditary nature in the early part of the nineteenth century. The gene that causes the disease was no less common then than it is now, but fewer carriers of this gene lived long enough to develop chorea. Consequently, even those who survived long enough to reproduce may often have died before they had themselves manifested the

disease that they had transmitted to their offspring, which would tend to conceal the hereditary nature of the condition and would cause the fairly frequent appearance of individuals with chronic incurable chorea, but no apparent family history of the condition.

CONCLUSIONS

The evolution of the awareness of Huntington's chorea as a distinct disease entity has been a gradual process and, as Bruyn (1968) has said, its history is also the history of involuntary movements as a whole. The disease has clearly existed for many generations and may well have been included in Paracelsus' category of chorea naturalis, but recognisable descriptions of the disorder did not appear until the early nineteenth century when chronic adult chorea was defined. The hereditary nature of the disorder was probably occasionally evident even in the remote past, but, as the calculations presented in this article indicate, the chances of this hereditary basis being recognised, let alone documented, would have been small. The chances remained small until the latter half of the last century when, in a climate of increasing interest in involuntary movements, generated by previous investigators, the slowly increasing expectancy of life permitted the appearance of greater numbers of choreic individuals with obviously affected relatives.

Appendix

Methods used and assumptions made in calculating the number of choreics in England and Wales in 1966 and 1841

The calculations have been based on data on patients with Huntington's chorea collected during a survey of the Leeds Regional Hospital Board (LRHB) area. The prevalence of the disease has been calculated for 30th June 1966 as this date coincides with the date of the Registrar-General's annual estimate of the national and regional populations. On that date there were 133 choreics known to be living in the LRHB area. These choreics are listed, according to their ages on prevalence day, in Table 2. Also listed in this table are the calculated numbers of choreics in England and Wales for the years 1966 and 1841. These figures have been derived by using the formula:

$$H_{EW} = \frac{H_L \times N_{EW}}{N_L} \text{ at age } x$$

where H_{EW} and H_L represent the number of choreics in England and Wales and the LRHB area respectively and N represents the populations of the two areas, values for which are given in Table 3.

Table 1 (in the main text of this article) gives details of the numbers of heterozygotes (the carriers of the Huntington gene) which have been calculated by using the formula:

$$f = \frac{H}{\sum_x \cdot N_x \cdot P_x}$$

TABLE 2. Number of Choreics

| Age | LRHB | England and Wales | | Age at Onset |
|-------|-------|-------------------|-------|--------------|
| | 1966* | 1966† | 1841† | (P_x)‡ |
| 0-4 | 0 | 0 | 0 | 0.0034 |
| 5-9 | 0 | 0 | 0 | 0.0034 |
| 10-14 | 0 | 0 | 0 | 0.0067 |
| 15-19 | 1 | 15 | 6 | 0.0101 |
| 20-29 | 1 | 15 | 7 | 0.0705 |
| 30-39 | 19 | 282 | 101 | 0.3787 |
| 40-49 | 36 | 533 | 132 | 0.7338 |
| 50-59 | 38 | 564 | 94 | 0.9482 |
| 60-69 | 34 | 497 | 71 | 0.9884 |
| 70-79 | 4 | 61 | 8 | 1.0000 |
| 80+ | 0 | 0 | 0 | 1.0000 |
| | 133 | 1,967 | 419 | |

* Observed; † Calculated; ‡ See text for details.

TABLE 3. Population

| Age | LRHB | England and Wales | |
|-------|---------------------------|------------------------------|-----------------------------|
| | 1966 * † § (N_L) ¶ | 1966 * † § (N_{EW}) ¶ | 1841 * (N_{EW}) ¶ |
| 0-4 | 278.10 | 4,013.70 | 2,106.30 |
| 5-9 | 246.30 | 3,572.80 | 1,904.90 |
| 10-14 | 221.50 | 3,254.31 | 1,732.10 |
| 15-19 | 247.90 | 3,681.84 | 1,586.80 |
| 20-29 | 403.40 | 5,986.76 | 2,833.40 |
| 30-39 | 387.60 | 5,743.01 | 2,051.50 |
| 40-49 | 415.40 | 6,154.59 | 1,526.60 |
| 50-59 | 415.60 | 6,166.18 | 1,026.20 |
| 60-69 | 332.80 | 4,862.51 | 699.40 |
| 70-79 | 177.30‡ | 2,714.98 | 344.20 |
| 80+ | 64.30‡ | 984.83 | 102.70 |
| | 3,190.20 | 47,135.51 | 15,914.10 |

* Totals given in thousands; † Estimated population on 30.6.1966 (Registrar-General); ‡ These are calculated figures. The Registrar-General gives details for the age groups 70-74 and 75+ for the LRHB area. The present figure is derived by presuming that the proportions in the LRHB area are the same as in England and Wales as a whole; § From Registrar-General (1968); || From Mitchell (1962); ¶ See text for details.

suggested by Reed and Chandler (1958); where f is the frequency of heterozygotes, H is the number of choreics in the population, N_x is the number of people in the population at age x , and P_x is the proportion of all heterozygotes who have become choreic at age x . Values for N_x are given in Table 3 and values for P_x are given in the final column in Table 2. These latter values have been derived from data on 298 choreics, both living and dead, who have been ascertained in the LRHB survey. The figures for heterozygotes in England and Wales for 1966 and 1841 have been calculated by using the numbers of choreics calculated previously. Also given in Table 1 are details of the numbers of unaffected carriers of the gene, these figures having been derived by subtracting the known, or calculated, numbers of choreics from the calculated numbers of heterozygotes.

In performing these calculations it has been necessary to make a number of assumptions:

1. It has been assumed that all the choreics living in the LRHB area on prevalence day have been ascertained. This must be incorrect; therefore the calculated numbers of choreics for England and Wales both in 1966 and 1841 must be underestimates. The magnitude of this error is not known. As the prevalence of the disease calculated for the LRHB area is very similar to figures derived by others in similar surveys (Reed and Chandler, 1958), it seems reasonable to suppose that this error is not very large. As the error introduced by this incomplete ascertainment is the same for the calculated numbers of choreics in England and Wales for 1966 and 1841, no bias will have been introduced, unless the failure of ascertainment occurred only in particular age groups, which seems unlikely.

2. It has also been assumed that the data obtained in the LRHB area would be similar to data obtained from the whole of England and Wales, should the whole country be surveyed. This seems a reasonable assumption as there is a close similarity between the LRHB material and similar material obtained in other surveys in this country and elsewhere. This similarity exists in the prevalence (noted above), the mean age of onset (42.9 years), the mean age of death (56.9 years) and the mean duration of the disease (13.7 years), all of which compare with the figures obtained by Wendt *et al.* (1959, 1960) and Bolt (1970) who surveyed populations of similar size to the LRHB population. The heterozygote frequency of 9.17×10^{-5} for the LRHB area compares well with the only other estimate, that of Reed and Chandler (1958), who calculated a heterozygote frequency of 1.01×10^{-4} for the lower Peninsula of the State of Michigan.

3. The formula suggested by Reed and Chandler (1958) for calculating

the heterozygote frequency has a number of disadvantages, the most important of which is the implicit assumption that carriers of the Huntington gene have a similar expectancy of life, or a similar age-specific mortality rate to the general population. This is incorrect, as the carriers of the Huntington gene die earlier than their normal counterparts in the community. The authors of this method felt that the errors introduced by this formula were unlikely to be greater than 10 per cent and personal calculations (unpublished) tend to support this view.

4. In using the formula mentioned above, use is made of data on the age of onset of the disease. It has been assumed that the age of onset distribution curve would have been the same in 1841 as it is now, if the carriers of the gene 130 years ago had had a similar overall expectancy of life to that which occurs today. This assumption seems reasonable, as it can be argued that the distribution curve of age of onset is a reflection of the frequency of various modifying genes in the population and that the frequency of these genes is unlikely to have altered in the last 130 years.

5. Implicit in these calculations is an assumption that the frequency of the Huntington gene in the community would have been the same in 1841 as it is now. There is no *prima facie* reason for doubting this in view of Reed and Neel's (1959) demonstration that the reproductive fitness in this disease is only a little less than unity, an observation that implies that the carrier of the Huntington gene has only slightly fewer children on average than a normal member of the community. Thus, there is no great tendency for the gene to become more or less frequent in the population, particularly if the rare spontaneous mutations are also considered.

6. A final assumption is that, in 1841, the choreic would have lived the same length of time, on average, after developing the symptoms of the disease as he does today. There is no way of knowing whether this is so or not, and no way of introducing meaningful corrections if it should be untrue.

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