The mutation rate to Huntington's chorea

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SUMMARY The problems of estimating the mutation rate to Huntington's chorea, or the proportion of new mutants among all sufferers, are discussed. The available survey data are reviewed. The prevalence of sporadic phenotypes, which include new mutations, is probably less than 2.5%. New mutants probably make up around 0.1% or less of all sufferers.

The purpose of this review is to establish that genuinely sporadic cases of true, heritable, Huntington's chorea are extremely rare. The diagnosis of the disease can cause immeasurable distress and hardship to both the sufferers and their relatives and offspring. For example:

A young man had the consequences of Huntington's chorea explained to him following the diagnosis being made in his father. This young man broke off his relationship with his intended wife, stopped all attempts to further himself at work, and made no plans for the future. He became deeply depressed. He refused to have anything to do with anybody who might have helped him. The diagnosis made in his father was made in error and his father actually got better. This man refused to change his belief about the diagnosis in his father and its consequences and also refused to change his now depressed life-style. He would not discuss this with anybody and is very obviously a likely candidate for suicide. This man's life has probably been ruined for ever by the label 'Huntington's chorea' being applied to his father. Although of course the suffering in the patient would have occurred even if the diagnosis had been applied correctly, it was in this case completely needless.

Recently, as many as one in five of those diagnosed as suffering from Huntington's chorea at certain clinics has had no known family history (Carter, personal communication, 1976). Diagnosis of such a grave inherited disorder without reasonable demonstration of its heritable nature in each case is hard to justify. That it has so often been justified seems to

reflect a widespread belief that the symptomatology never appears unless a mutant gene is present, and that the mutation rate is extremely high. We wish, in this review, to collect together all the data we have been able to find that bear on these beliefs. We shall contend that, at the most, fewer than one patient out of a hundred can be expected to be a new mutant. In view of this, we believe that when no family history can be established for a patient otherwise seemingly typical, a label that is less socially catastrophic than 'Huntington's chorea' should be attached to the patient's disease. Lyon¹ suggested 'non-hereditary chronic adult chorea', but any name for the condition that does not imply a hereditary nature would do. 'Chronic adult chorea' is simple and adequate.

Phenotype and genotype

In any serious heritable disease the frequently obscured distinction between phenotype and genotype is extremely important, because a single phenotype may have diverse causes. For example, teratogenic drugs can cause morphological abnormalities indistinguishable from those produced by mutant alleles at certain loci. There may also be dominant and recessive alleles at various loci, all capable of causing a particular phenotype. So far, admittedly, only a dominant genetic factor is known to produce Huntington's chorea, but until the underlying lesions are identified and understood, it is hardly possible to rule out other causes. Thus, no matter how distinctive the phenotype of a patient, their genotype can, at present, only be established through study of the inheritance of that phenotype. Since laymen, insurance assessors, and others, undoubtedly interpret the diagnosis 'Huntington's

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chorea' as a genotype we believe the medical profession should also so limit itself.

Thus, when discussing sporadic cases we must ask two questions. Firstly, of patients who show the classic symptoms of Huntington's chorea how many in fact carry the mutant gene? Secondly, of those patients who carry the gene (as confirmed subsequently or at the time of the diagnosis by family history) how many are new mutants? This makes apparent that the absolute mutation rate is of little importance medically. What matters is the rate of mutation relative to the prevalence of the disease. Unfortunately, neither figure is easy to estimate, and the data to provide a reasonably precise point estimate do not exist at present. The next section discusses why this is so.

Methodological problems

FAMILY HISTORIES

It is more difficult than commonly realised to obtain an adequate family history. Ideally, the search should be carried out by an experienced and medically trained social worker with specialist genealogical training. Tact and experience in dealing with the relatives of those suffering from distressing neurological disorders is clearly essential, but it is also desirable that the worker should be allowed to check hospital and other records, which is not possible without medical training. The need for genealogical training is obvious but family tracing is also surprisingly expensive; in the UK it costs, for example, £6.00 for every death or birth certificate obtained. Travelling expenses may also be considerable. If less thorough methods of searching are used, a positive family history can easily be missed. For example, several times during the survey reported in Caro,² relatives strenuously denied any knowledge of hereditary madness in the family. While death certificates corroborated this, making no mention of Huntington's chorea, examination of the hospital notes made it quite clear that some of the patients concerned were, in fact, sufferers. Reports from relatives are particularly unreliable, partly because of imperfect memories and partly because of conscious or unconscious denial of the disease in the family. The last is understandable enough and has often been commented on in the literature on Huntington's chorea.² At the start of Caro's survey,² eight patients out of 50 were reported as coming from families with no known history. In no case was this found to be true on detailed search.

LEGITIMACY

As Huntington's chorea is frequently manifested only late in life, it is often impossible to check that

the natural parents of the sufferer are actually the genetic parents, because one or both may be dead. Even if the parents are alive, it may not be easy to check paternity without causing offence or running the risk of causing great distress. Thus it is very often impossible to exclude illegitimacy when an apparently new mutation has been found. It is worth noting here the experience of Wendt and Drohm.³ Of 4000 patients considered, they found one case, with choreic offspring, both of whose parents were living at advanced ages. Blood grouping, however, revealed that this patient, their only likely mutation, was undoubtedly illegitimate.

EARLY DEATH

Judged from segregation ratios, the penetrance of the gene causing Huntington's chorea is very high.⁴ Nevertheless, late manifestation is quite frequent. Wallace⁵ details the age-specific incidence rates found in the accumulated Queensland data. A more extensive series is to be found in Wendt and Drohm.³ From these, a cumulative probability distribution for the age at onset can be constructed (fig 1). Most workers have reported similar mean ages at onset with similar spreads, so this distribution should apply at least roughly to other populations. Now, suppose a person has developed the disease, but that both his parents died in good neurological health, moderately, but not especially, young, say at 64

FIG 1 Plot of $P(x)$, cumulative probability of age at onset. Probability of two subjects, one of whom is choreic, not manifesting the disease before ages x and y , respectively, is $1 - \frac{1}{2}[P(x) + P(y)]$.

(father) and 62 (mother). Then the probability that, given that one or other was a carrier, both would die healthy is 7%, a fairly substantial figure. So it is not implausible to suppose that one of them did carry the gene. Evidently, to be sure that the disease was not inherited, all relatives—sibs, uncles, aunts, parents, and grandparents—must have had clean bills of neurological health to advanced ages in the majority of cases.

BIAS

All the above factors, and others, can cause bias in the ascertainment of sporadic cases and bias in determining their genetic nature. Firstly, there is bias against the demonstration of sporadic cases. By definition such cases cannot be found by family searching, so that one efficient method of ascertainment cannot be used. Also, to prove a sporadic case we require good evidence that Huntington's chorea has not previously occurred in the family, together with proof of legitimacy and reliable diagnosis. Finally, to prove a new mutation, it is essential to have evidence that the disease is inherited, through the diagnosis of affected offspring. This is only likely to be possible retrospectively.

On the other hand, a person with worrying neurological symptoms, but no inkling that they might have an incurable inherited disorder, may be more likely to seek medical advice than a member of an afflicted family. Since family histories are usually sought only when a diagnosis of Huntington's chorea seems likely on other grounds, these patients may be as likely to enter a survey as any other proband.

Lastly, there is diagnostic bias. The elimination of this depends largely on the professional standards of the research worker. In particular it is important that in a survey as many patients as possible, and all case notes, are examined by a specialist in the disease. Stevens,⁶ for example, reported 29% misdiagnosis in the cases initially referred as probands in his extensive survey around Leeds in the UK. Similarly, Hayden *et al*⁷ quote an initial misdiagnosis rate of 40%.

Methods of estimating the mutation rate

DIRECT ENUMERATION

An obvious method of finding the proportion of sporadic cases and new mutations among the affected population (from which it is only a small step to calculate the absolute mutation rate) is to count all sufferers on a particular day, noting whether they inherited the disease or not, and whether they have passed it on to their offspring. There are great problems in putting into practice this ideal scheme. Firstly, it is very hard to ascertain Huntington's

chorea completely in a defined population, or even to estimate the degree of underascertainment that has occurred. When ascertainment is incomplete, the problems of bias mentioned in the previous section necessarily arise. Secondly, as discussed above, deciding if a case is genuinely sporadic is far from easy. Finally, the determination of the mutants among the sporadic cases can only be done retrospectively by observing their offspring. (Obviously, we feel that the clinical title given to the sporadic cases should not be Huntington's chorea until the inheritance is proven.) Unfortunately, a fully retrospective study cannot be easily undertaken, because many familial cases are only recognised after they have occurred, through study of the offspring. A similar increase in the efficiency of detection of sporadic cases retrospectively will not take place. Furthermore, in a retrospective study there is no opportunity to check the accuracy of diagnoses, an important factor if the study extends more than a few years back from the present day.

INDIRECT ESTIMATION

It might seem from the foregoing discussion that direct enumeration of sporadic cases and mutations is not the best way of determining their frequency. An alternative method, first suggested by Haldane,⁸ is superficially attractive, but in practice turns out to have just as many difficulties. The method assumes that the population under study is in genetic equilibrium between steady selection against an unfavourable allele and mutation of the normal allele to it. A simple mathematical expression relates the mutation rate, the prevalence of the mutant allele in the population, and the selective difference between the two forms. Some care is needed in defining these qualities but, if the selection and prevalence are known and the assumption of equilibrium is admitted, the mutation rate can be calculated. (See Charlesworth and Charlesworth⁹ for details.)

The method has been used with success for some other genetic diseases in man.¹⁰ In the case of Huntington's chorea, it seems very unlikely that selection against the mutant allele has been constant for long enough to allow equilibrium to be approached closely.¹¹⁻¹³ Selection is mostly social in form, operating through reduced marriage rates, increased fecundity, social ostracism, etc. It is unlikely to be constant in every generation of a lineage, and the whole pattern of selection is likely to change as societies change. At best, fitness can only be measured in 20th century societies. It seems unreasonable to expect selection in, say, Tudor Britain to conform to the same pattern: but if selection is relatively weak (of the order of 10% difference

TABLE 1 Estimates of fitness, prevalence, and mutation rate

Authors	Region	Date	Fitness	Prevalence per million	Mutation rate
Kishimoto <i>et al</i> ¹⁴	Aichi Province, Japan	1956 (?)	0.65	3.8	0.7 × 10 ⁻⁶ indirect
Marx ¹⁵ and Pearson <i>et al</i> ¹⁶	Minnesota USA	1955	1.16	54.0	—
Reed and Neel ¹¹	Michigan, USA	1940	0.85	40.0	{ 5 × 10 ⁻⁶ direct 10 × 10 ⁻⁶ indirect
Panse ¹⁷	Germany	(?)	1.18	32.0	—
Shokeir ¹⁸	Canada	1974	1.18	84.0	—
Mattsson ¹⁹	Sweden	1965	0.97	47.0	{ 5 × 10 ⁻⁶ direct 0.7 × 10 ⁻⁶ indirect
Wendt and Drohm ³	Germany	1950	0.95	22.0	1.5 × 10 ⁻⁶ indirect

between the genotypes) then about 20 generations are required before the population will be near the equilibrium. Also, the weaker the force of selection the more sensitive the estimate of mutation rate becomes to errors in the estimate of selection. Surveys concur in finding that the genetic fitness of sufferers from Huntington's chorea is not very different from the rest of the population (table 1). However, a potential advantage of the method is that it is relatively insensitive to small errors in the prevalence rate, and therefore to small numbers of sporadic cases, resulting from non-genetic causes, misdiagnosis, etc.

Bearing these points in mind, table 1 shows the estimates of the fitness of sufferers that we have been able to find. Where the fitness of the mutant genotype is greater than that of the normal genotype, genetic theory implies a continuing increase in its frequency and the data can shed no light on the mutation rate, which may be arbitrarily small. None of the several papers in which estimates of the mutation rate were made considered that their figures merited much consideration. Reed and Neel's estimate¹¹ (note a correction in Charlesworth and Charlesworth⁹) is quite high. Those of Kishimoto *et al*¹⁴ and Mattsson¹⁹ are among the lowest human mutation rates ever postulated. In no case has the society been sufficiently static to justify the minimal necessary assumption of constant selection over the last eight to 20 generations (say, 200 to 500 years). Furthermore, the estimates of fitness are very inaccurate. Their formal confidence limits would more or less coincide with the range of possible values. For example, if Wendt and Drohm's³ figure for fitness were 0.98 instead of 0.95 their estimate of mutation rate would more than halve.

Observed cases of mutation

At this point we would like to reiterate that bias in surveys towards or away from familial cases, if it exists, is very likely to be reflected also in clinical practice. However, a very conservative estimate of the rate at which sporadic cases will appear in clinical work can be obtained by comparing the

number of cases seen with the total number of families in the survey, rather than the total number of cases. This estimate is an extreme upper bound; it would reflect clinical reality only if families in surveys were always represented by a single member known to the medical profession. This is not the case. As stated above, a more plausible estimate is that obtained by comparing the number of sporadic cases seen with the total number. Table 2 lists those reports, whether or not they are based on survey data, that reported suspected mutants. It is immediately clear that published reports of sporadic cases are rare; in Bell's data, for example, only three of 190 families trace to an apparently sporadic case.²⁰ Most of the family trees span three to five generations. In Hayden's study,⁷ 80% of present sufferers could be connected in a single lineage. Evidently, if sporadic cases are common, they rarely leave offspring. It seems simpler to believe that they are rare.

FIG 2 Frequency distribution of different pedigree lengths.

TABLE 2 Possible cases of mutation

Author	Legitimacy	Medical histories of relatives	'Probability'	Other details	Comments
Bell ²⁰ quotes Geratovitsch (1927) and Smith (1898) and Seip (1928)	No	Choreic offspring; parents died healthy, 80, 73	0.01	Bell reports on 151 pedigrees, including 991 cases	Plausible cases, but legitimacy unproven and the pedigrees are rather old
Haugerud ²¹	Yes	Choreic offspring; parents died healthy, 93, 87	0.001	Choreic offspring; parents died healthy, 79, 88; two healthy sibs	Not from a survey; no affected offspring. Haugerud assumes a germline mutation in one parent to explain the observations
Lyon ¹	No	Parents healthy, 64, 62; grandparents died healthy, maternal 54, 52, paternal 69, 72. No trace in earlier generations or parental sibs. Pair of sibs affected	0.07	Father died healthy, 84. Mother suffered '12 year invalidity' of unspecified nature	Unlikely, mother might have been sufferer anyway
Minski and Guttman ²²	No	Parents died healthy, 57, 55; psychoses in other relatives	0.17	Survey included 140 cases in 34 families; diagnosis explicitly doubtful	Improbable
Pleydell ²³	No	Parents died healthy, 70, 71; 7 sibs and 6 parental sibs also healthy at time of report	0.01	Oliver ²⁷ expands the survey to include 18 families, 13 live cases (the putative mutant was dead)	Plausible but legitimacy unproven
Reed and Neel ¹¹	No	Parents healthy at 65, 65; 4 normal sibs; no kin reported by family	0.04	Reed and Neel report 6 other possible cases, but in these one or both parents died young. Survey includes 196 lineages, 231 live members at survey date	Possible; Reed and Neel point out that the length of their series is enough to expect a few cases like this. Heredity unproven
Stevens and Parsonage ²⁴	No	Parents died healthy, 86, 86; also 7 sibs died healthy; 3 grandparents known to have died healthy	0.001	114 lineages included in survey, 133 members alive at survey	Plausible but legitimacy unproven
Wallace ¹³	Yes	Father died healthy, 74; mother alive at time of survey; also 8 unaffected sibs	0.005	46 kindreds in survey, 111 alive at survey date	Most plausible case

Probability is calculated as explained in the legend to fig 1.

TABLE 3 Survey data on incidence of sporadic cases

Author (i)	Total live cases	Prevalence (/10 ⁻⁶)	Total families	Sporadics	Criteria including sporadics (ii)
Bolt ²⁶	154	52	Unavailable (73) (iii)	4	a
Caro ²	54	92	35	0	
Hayden <i>et al</i> ⁷	153	22	Unavailable (72) (iii)	8	b
Mattsson ¹⁹	362	47	110	9	a
Oliver ²⁷	27	63	18	0	
Reed and Neel ¹¹	231	40	196	7	b
Shokeir ¹⁸	162	84	58	5	b
Stevens ⁶	133	42	Unavailable (63) (iii)	0	
Wallace ⁵	111	63	46	1	See table 2
Wendt and Drohm ³	1032	22	Unavailable (489) (iii)	0	c

Notes

- (i) Surveys providing no useful information on the occurrence of sporadic cases have been excluded. References are exhaustively listed in Kurtzke *et al*²⁸ up to that date. The prevalence figures above are representative of those found in North European derived populations. Prevalence seems to be much lower in Japanese and Negro populations.
- (ii) Criteria for including sporadic cases vary.
- (a) Both parents healthy to older than 60; otherwise classic picture; no other familial evidence.
- (b) Both parents died healthy at any age; otherwise classic picture; no other familial evidence.
- (c) Wendt and Drohm³ state "... nicht einen Fall gibt, den wir mit Sicherheit als Neumutation ansprechen könnten". Their criteria were thus a demonstrated new mutant.
- (iii) Figures in brackets are estimated numbers of families using the overall mean ratio of live cases to families from surveys where the data are available. The conclusions in the text are unaltered even if the maximum ratio is used instead of the mean.

Here it is worth commenting on a procedure of Wallace¹³ and Shokeir.¹⁸ They give tables showing the frequency distribution of different pedigree lengths. These have the general shape of fig 2. Both authors suggest correction of the curve to obtain the true number of sufferers, as shown by the dotted line. This technique, which obviously considerably raises the number of 'sporadic' cases, among whom phenocopies and mutations are to be sought, is incorrect for a number of reasons. The curve in fig 2 is the product of two curves describing (1) the true distribution of lengths of choreic pedigrees, given perfect knowledge, and (2) the ease with which information can be gathered about a particular generation. (1) is determined by the detailed pattern of selection in every generation. This distribution could have almost any shape. In any case, it can be seen by examining published pedigrees that the pattern of fig 2 will be almost completely determined by factor (2). For example, among the pedigrees in Caro,²⁵ all peter out through lack of information rather than definite knowledge of the origin of the disease through mutation. If Shokeir¹⁸ or Wallace¹³ had been more successful in tracing their pedigrees back to a mutational event, they would surely have reported the fact. Given this state of affairs, extrapolation from fig 2 as shown is completely unjustified, since the theoretical shape of the curve is unknown.

Table 3 lists surveys which are recent and reasonably extensive, and in which ascertainment was more or less as exhaustive as possible. Although these surveys refer to different times, they also refer to different places and estimates derived from them are therefore independent. Provided that the character and prevalence of Huntington's chorea is not changing rapidly, and that ascertainment efficiencies do not follow grossly different patterns in the different studies, the data from these studies may legitimately be averaged. The information these surveys collectively yield as to the proportion of sporadic Huntington's chorea cases will now be considered.

The maximum conceivable rate, admitting all cases in which the parents were known to be healthy until their deaths, or at the time of the survey, is $34/1387 \approx 2\%$ on the basis of the total number of sufferers, or $34/671 \approx 5\%$ using the total number of families. This derives from all surveys shown in table 3 except that of Wendt and Drohm³ (see note (c) in table 3). Criteria for defining sporadic cases vary slightly between reports, (see note in table 3), but this is not very important for these rough and generous estimates. Since none of these surveys regularly checked legitimacy, at least some of these cases are almost certain to arise via illegitimacy.

As there is a probability of 5 to 10% that onset of the disease will occur after the age of 60, a proportion of such apparent sporadics is in any case to be expected. (There are other sources of information than the parents' health that can shed light on whether the disease was inherited or not. This accounts for the proportion of sporadics observed being rather smaller than the probability of late onset.) Turning from apparent sporadics to likely mutations, we can include all surveys in which mutation is mentioned and would therefore have been reported if it had been seen. The most likely mutation is that of Wallace.⁵ Stevens' subject⁶ could have been illegitimate and was, in any case, dead at the time of his prevalence study. Using the reports in table 3 we obtain a frequency of mutation among sufferers of $1/2419 \approx 0.04\%$. In making this calculation we have subtracted from the total those cases in which a definite family history was not available. Considering, instead, numbers of families, the rate is $1/1160 \approx 0.1\%$ with the same correction.

To sum up: apparent sporadics appear at a rate of 1 to 5%. These fall into four classes as follows. Firstly, if family data are restricted, the affected parent may have died before showing symptoms. Secondly, the affected person may be illegitimate. Thirdly, there may exist phenocopies of the disease, or recessive genes giving the same phenotype. Finally, there are the true mutants, probably making up less than a tenth of the total.

For comparison purposes, an order of magnitude estimate of the absolute mutation rate may be of interest. Suppose the population is in a steady state. Then, if the average lifespan is 70 years, about $1/70$ or 1.4×10^{-2} must be born each year. If the prevalence of Huntington's chorea is 50 to 100×10^{-6} (see table 1), with a 15-year interval on average between onset and death, and mean onset at about the age of 40,⁴ the incidence must be 3 to 7×10^{-6} . Then, using the higher incidence figure, choreic births form about $7 \times 10^{-6} / 1.4 \times 10^{-2} = 5 \times 10^{-4}$ of all births. If 1 in 500 of these are new mutants, the mutation rate is about $\frac{1}{5} \times 10^{-6}$. If 1 in 1000 are new mutants and we take the lower incidence figure, the rate is nearer 10^{-7} . These figures are on the low side but broadly speaking comparable with previous estimates (see table 1).

Comparative data

Stephenson and Kerr²⁹ considered the available evidence on sex linked mutations in man, concluding that the average mutation rate at a given locus was likely to be substantially less than 10^{-6} per gamete, with considerable variation above and below this figure. The range of mutation rates suggested above

for the Huntington's chorea locus fits this picture, which is also in general agreement with data from mice and *Drosophila* (see, for example, Dobzhansky³⁰); but in any species the range of rates is so wide that it would be very surprising to find substantial disagreement. Any estimate between 10^{-9} and 10^{-5} would be reasonable.

Conclusions

Our fundamental belief is that it is wrong to tell the relatives of a patient suffering from a remarkably unpleasant, slow, progressive neurological disease, for which medical science can do virtually nothing, that they run a risk of also developing the disease, unless it is proven that they do so. The proportion of cases in which this question arises is, of course, irrelevant to this position. We believe that this review shows two things. Firstly, the number of cases in which a family history is genuinely negative is smaller than commonly believed; we have given reasons why this may be so. Secondly, the mutation rate to Huntington's chorea is very small in proportion to the total number of cases. Lastly, we wish to reiterate our belief that the label attached to patients who seem to suffer from a Huntington's chorea-like syndrome, but in whom the heritable nature of the disease is not proven, should not be Huntington's chorea but a neutral label.

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