The Prevention of Huntington's Chorea.

The Milroy Lecture 1985

PETER S. HARPER, DM, FRCP
Professor and Consultant in Medical Genetics, University of Wales College of Medicine, Cardiff

When Dr Gavin Milroy endowed this lecture, I doubt if he envisaged that inherited diseases would come to form a challenge equal to that which infectious disorders posed for nineteenth-century physicians.

My subject is the genetic disorder Huntington's chorea (HC), which epitomises many of the problems that we face in medical genetics and illustrates the common ground that exists between genetics and epidemiology.

Both genetics and epidemiology are scientific disciplines with a theoretical basis that, in genetics especially, has widespread applications for all living organisms. Both are also clinical specialties, and the emergence of the medical geneticist as a specialist in his own right has been one of the major developments of the past 15 years.

In both fields prevention is the primary aim and in both the emphasis extends beyond the individual patient to the family as a whole and to the general population.

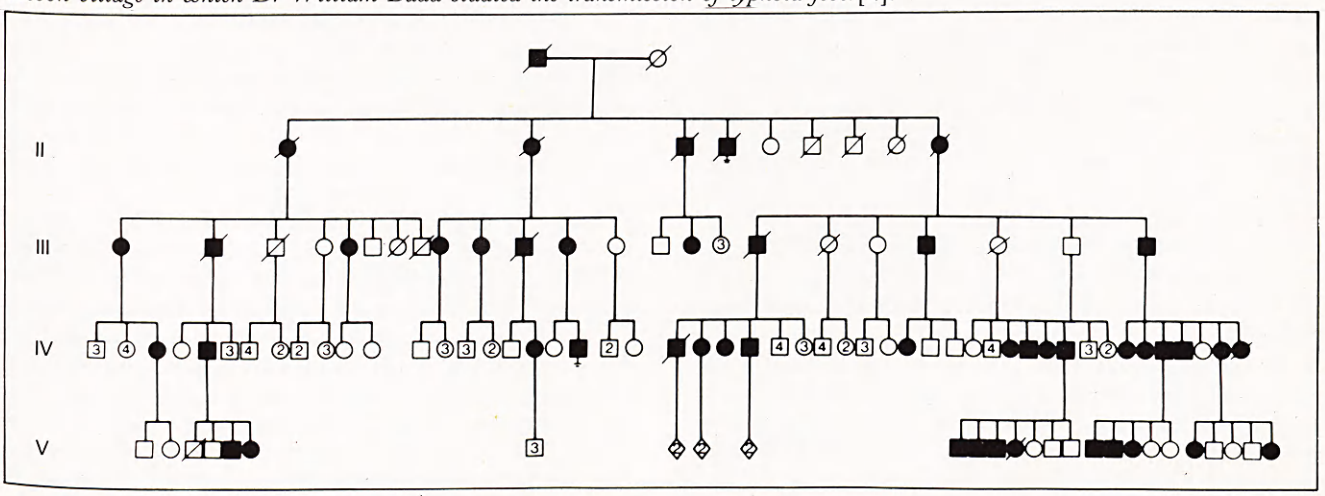
Huntington's chorea follows autosomal dominant inheritance, passing on average to half the offspring of an affected person, but sparing those of a person who remains free from the disease. It is perhaps the most serious disorder of adult life that faces the medical geneticist involved in genetic counselling and prevention, and the physician and neurologist who are still largely helpless in influencing its course[1]. The combination of progressive involuntary movements, general physical disability, serious mental deterioration and the hereditary nature of the disorder, create an overwhelming burden for most of the families in which it occurs.

The family in Fig. 1, the first with Huntington's chorea that I encountered on coming to work in Cardiff 14 years ago, epitomises the problem of prevention to be faced. All members are descended from a single individual who came to work in Wales around a century ago[2]; the house where he lived still stands in the hamlet of Mynyddislwyn, high on a ridge between two mining valleys. His descendants moved down into the valleys and almost all of them live there still, many affected with the disorder and many more at risk.

It soon became clear to me that HC was a major problem not just in this small area, but throughout South Wales, and that a major initiative was needed if its full extent was to be known.

We decided to concentrate initially on the geographically restricted area of industrial South Wales rather than attempt total ascertainment throughout the scattered rural areas of West, Mid- and North Wales. The population in our study is dense, relatively stable, with a limited number of specialist services and within easy travelling distance of our centre in Cardiff.

Fig. 1. *A large South Wales kindred with Huntington's chorea. The ancestor of this family originates from North Tawton, the same Devon village in which Dr William Budd studied the transmission of typhoid fever*[2].



At the end of the first phase of our study we found that the number of both affected individuals and apparently unrelated kindred was much greater than we had envisaged, while the number of those at high risk was close to 1,000[3,4].

The results of this study are summarised in Table 1.

Table 1. Huntington's chorea in South Wales.

Prevalence	7.6 per 100,000
Total living affected	130
Total living high-risk relatives in area	980
Annual new cases (mean 1960–70)	9.3
Mean duration of illness (onset to death)	15 years
Number of proven new mutations	0

The prevalence of HC in South Wales is indeed high in comparison with most other British surveys; leaving aside those selected for small foci of the disorder, only the East Anglian study of Caro shows a higher prevalence[5]. More important for prevention is the large number of relatives at high risk, about eight times the number of those actually affected. Only those with an age-adjusted risk of greater than 1 in 10 are included here, but this large number, around 1,000 in South Wales, illustrates how much greater an impact the disorder has than would be expected from its prevalence. Only a minority of those at risk will develop the disorder, but all will be 'affected' by it in one way or another.

The mean duration of the disorder from onset to death is 15 years, of which the last five years represent severe disability; half of our patients required long-term hospital care, with an average duration of four years, but half were cared for at home throughout their illness, a reflection of the often unnoticed (and uncosted) burden borne by the families[6]. Not all affected individuals actually died from HC; later onset cases in particular not infrequently died of unrelated illnesses and we know of instances where HC was not diagnosed during life.

Table 1 also shows that we have found no proven example of mutation[7]; some isolated cases may be the result of mutation, but we cannot be certain, either because parents died relatively young, or because of uncertainty over paternity. One can safely say that new mutations represent a very small fraction of all cases of HC, and that if transmitted cases were to be prevented, the disorder would become exceedingly rare.

The rarity of mutation agrees well with another finding in our South Wales population[7]—the lack of an adverse effect of the disorder on fertility. In fact we found an increased mean family size, as have some (but not all) previous investigators[8]. This increase is for both males and females, with a relative increase over healthy sibs and an absolute one over the corresponding general population (Fig. 2), and has persisted over the entire period for which our records extend. We have studied in detail the pattern of family building in our population, but there is no evidence of a peak around or just preceding onset of the disorder, as might be expected if sub-clinical behavioural effects were involved.

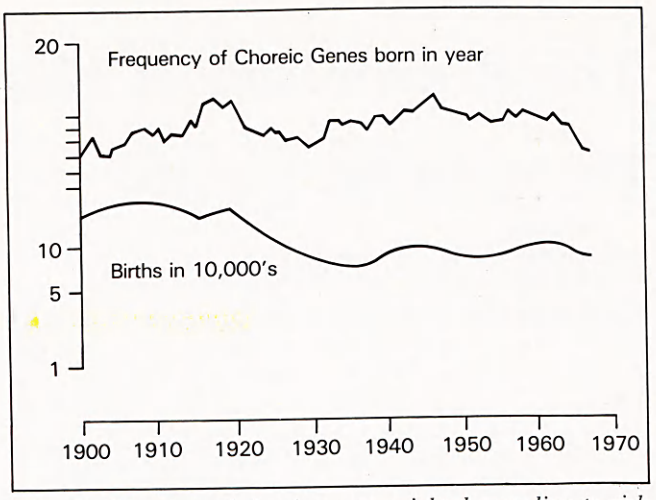


Fig. 2. *Frequency of choreic genes weighted according to risk compared with births in the related population of Glamorgan and Gwent, 1900–70, expressed on a log scale (five year moving averages used to smooth curves).*

Although we cannot fully explain the observed increase in fertility seen in HC, we can certainly document why there has been no decrease until the present time. Information was obtained by personal interview of a sample of 100 patients and their spouses, and a separate random sample of 100 first-degree relatives. Only one-third of the first group had had professional counselling, and thus had a clear understanding of the hereditary nature of the disorder, before their family was complete; the situation for the children at risk was somewhat better; two-thirds had some factual knowledge, but this lack of information clearly indicated the need for systematic genetic counselling for these families[9].

The same survey illustrated how difficult many families find it to tell their offspring about the genetic nature of the complaint, even if they recognise it themselves. Seventy per cent of parents stated that their children ought to be told before having their families; only 7 per cent were definitely against this course. Yet, of these same families, only 30 per cent had in fact told their grown-up children. We find that families frequently need professional help in this. Often initial information from the parents is followed-up by giving the children an opportunity to ask fuller questions; sometimes, when a parent finds the task too difficult or painful, the whole process is undertaken.

Genetic Counselling in Huntington's Chorea

In dealing with HC, the counsellor is faced by a unique combination of problems. The burden imposed by the severity of the disorder, the lack of effective therapy or prediction and the frequency of social and psychiatric problems arising directly or indirectly from the disorder all contribute to the difficulties of genetic counselling. Perhaps the largest factor, however, is the late and variable onset of the condition, illustrated in Fig. 3[10,11]. The two curves show the chance of someone with the HC gene showing the disorder at a particular

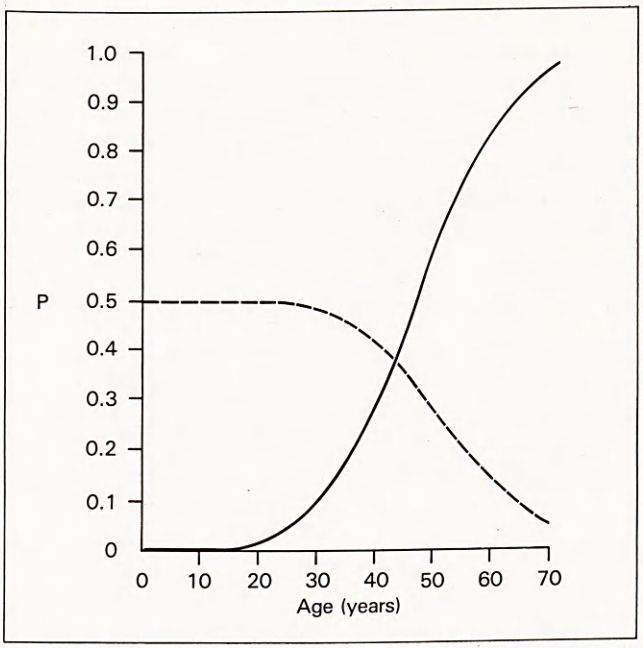


Fig. 3. *Age at onset and genetic prediction in Huntington's chorea, based on South Wales data*[10,11]. *Solid line—probability that an individual with the HC gene will show the disorder at a given age. Broken line—probability that a healthy individual with an affected parent has the HC gene at a given age.*

age, and the remaining risk for an individual with an affected parent. It can be seen that this risk is little short of 50 per cent during the reproductive period; for those whose parent is unaffected, the use of this curve in risk estimation may be very valuable since their risk will be close to half that of their parent; where the parent is relatively elderly, the risk for their child will be correspondingly small.

Our South Wales study was designed to be the foundation for systematic genetic counselling in our families with HC, a programme which has been going for about 10 years. This has involved a different approach to that required for a simple prevalence study, and, in particular, an effective recording system suitable for prospective use in a service setting was needed[12]. In setting up such a system we found it necessary to greatly simplify our original study record, and to evolve a register which allows both the follow-up of individuals through an easily completed form, with adjustment of risk estimate according to age and changes in the kindred, and the production of statistical data for monitoring trends in our population at risk. From the beginning we have avoided placing names, addresses or other identifying information on our computerised record, feeling that, however efficient the confidentiality of a system, we should not allow any unease to jeopardise our relationship with the families.

One group of particular importance, but often ignored, is those individuals whose risk has decreased to minimal levels, either as a result of their own or their parent's age. We do not attempt to follow actively those whose risk is less than 1 in 10, but we do try to ensure that they know the risk is low; a surprising number have an exaggerated idea of their risk, or fear that HC may occur in their children even if they themselves are spared.

A consistent line that our group has always taken is that genetic counselling should not be directive, though we try to provide as detailed as possible information about the nature of the disorder, the range of severity and age at onset, and possible future developments, and we now frequently suggest to younger individuals or couples that they delay plans for childbearing in view of the possibility of predictive tests. This non-directive approach is criticised by some, but we feel that in most instances it would be neither justified nor effective to advise those at risk not to have children; the facts must be weighed and decisions made by each couple in the light of their own situation.

Genetic counselling is particularly difficult in those cases where a person at risk has grown up unaware of the family disorder, commonly as a result of family break-up. It may be questioned whether it is desirable to trace and inform such individuals about their risk, but our experience of those who have not been informed and only learned of the situation in later life, leads us to the view that accurate information, sensitively given, is preferable to ignorance or to finding out later in a less suitable way.

The timing of genetic counselling is another difficult issue. Clearly, to be of any use it must be given before child-bearing, but how far beforehand is debatable. Again our own experience suggests that giving at least some information early, at around 15–16 years, may avoid causing greater distress, as can happen if first knowledge comes at the time of engagement or marriage. Such initial information need not be detailed, but it can form a foundation for later, more detailed genetic counselling. It is surprising how much quite young children often prove to know, and how a preliminary discussion may permit more open acceptance of a situation previously unmentionable within the family.

Long-Term Prevention

Although the main role of genetic counselling in HC is, as with other genetic disorders, to help individuals in their decisions, the possibility of achieving a general reduction in future incidence of the disorder is an issue of the greatest importance. The combination of total ascertainment, systematic genetic counselling and prospective study has made it feasible to examine these aspects in South Wales to an extent that has not been possible elsewhere because we are dealing with data on a representative and almost complete population of families at risk, rather than a selected group that has sought genetic counselling[13].

Study of our families' attitudes to genetic counselling showed that the majority of young individuals at risk intended to limit their families in the light of information about the disorder[9]. Such intentions, however, may not be translated into action, and the only way of telling what is happening is to document the births in the population at risk[14, 15]. Fig. 4 shows that this has indeed occurred, and provides a striking contrast with the relatively constant rate in the past, as shown in Fig. 2. To what extent

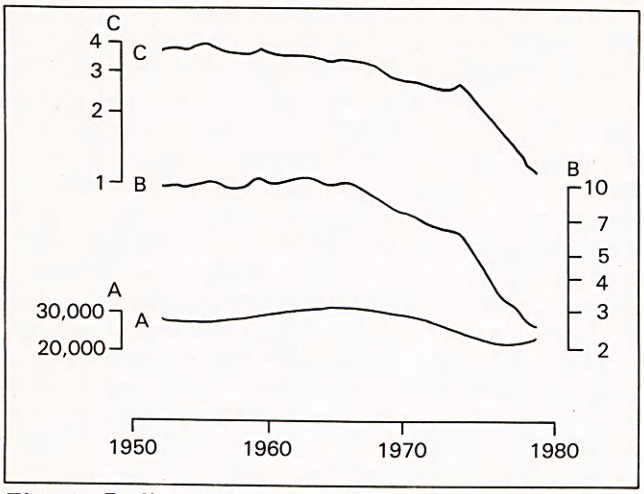


Fig. 4. *Decline of births at risk for HC in South Wales. A. Predicted new cases of HC per year. B. General population birth rate. C. Ratio of A to B.*

this change is related to the genetic counselling that most individuals at risk have received is uncertain, but the striking reduction in births over a relatively short period is of considerable significance, particularly in view of the lack of any form of predictive or prenatal detection for the disorder.

The trends shown in Fig. 4 are, for recent years, naturally based on predicted rather than actual cases, being derived from the number of births at risk in each year and the degree of risk of each birth based on the age-adjusted risk for the parent. Thirty years and more will be required before we can be sure whether these predicted cases of HC will actually develop the disorder, unless an accurate method is discovered for determining the presence of the gene. So far all the work described has been done in the absence of such a test. However, major developments in gene mapping are likely in the very near future to change our approach to prediction and prevention, and may well cause problems, as well as solving them, in genetic counselling.

Gene Mapping in Huntington's Chorea

The possibility of identifying the HC gene by means of genetic markers has been considered for a number of years. Several studies have used the classical polymorphic markers, principally blood groups, serum proteins and red blood cell enzymes, to investigate this; all, including an analysis of our South Wales families, were negative[16–18].

The limited number of available markers inhibited further work in this field until the recognition of DNA sequence polymorphisms, which provide an abundant source of genetic variation that can be studied using recombinant DNA techniques. Nonetheless, the identification of a closely linked DNA probe in the first series of randomly chosen markers came as a surprise, and has provided a major advance that logically was not expected for several years.

The marker concerned (G8) is located on the short arm of chromosome 4 and a study in two large kindreds showed firm evidence of close genetic linkage[19]. Subsequent study of the probe in our South Wales families has confirmed this linkage. The G8 probe and subclones derived from it detect a variety of polymorphisms; the best documented is with the restriction enzyme Hind III (Fig. 5) and shows two variable sites which can be

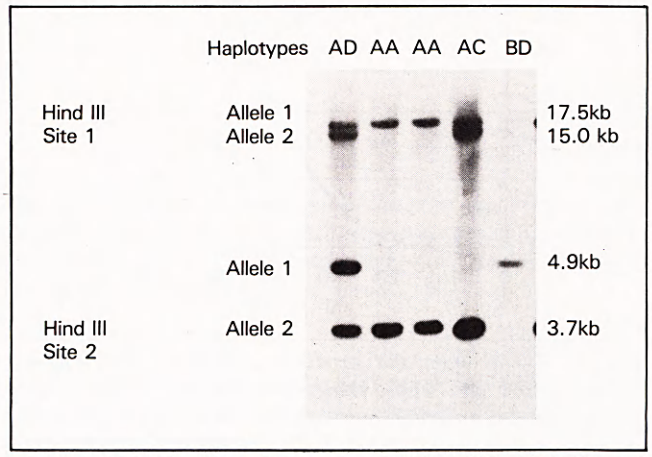


Fig. 5. *Hybridisation of the probe pk082 to Hind III digested human genomic DNA. After digestion of the DNA with the restriction enzyme Hind III, the DNA fragments were separated by electrophoresis on a 0.7 per cent agarose gel. Blotting of the DNA on to nitrocellulose filters was performed by Southern's method. The haplotypes observed in each individual were assigned previously. (Preparation by Miss Sandra Youngman.)*

combined to give four 'haplotypes' (A, B, C and D). A further polymorphism with the enzyme EcoR1 detects two variants at almost equal frequency, while less frequent polymorphisms are seen with other enzymes (Fig. 6). Taking these polymorphisms together, over 80 per cent of individuals are heterozygous at the G8 locus which means that, in principle at least, prediction in some form would be feasible for over 80 per cent of individuals if this marker were to be used.

Studies in our South Wales families[20, 21] suggest that the linkage is indeed close (around 2 per cent recombination between marker and disease); we have found no suggestion of heterogeneity involving more than one locus. However, the marker is not so close as to be in any way functionally related to HC, and while the linkage is close within families, there is nothing to suggest that in HC individuals overall any G8 type is more frequent than in the general population. In most families studied the disease is transmitted along with the commonest 'A' haplotype; where a rare marker type is transmitted with the disease, as seen in Fig. 7, a much clearer pattern can be seen of how the two are co-inherited.

The unexpected closeness of the linkage has raised the possibility of its application in prediction; families in which the HC gene is travelling with one of the rarer haplotypes, as in Fig. 7, show how this could be feasible.

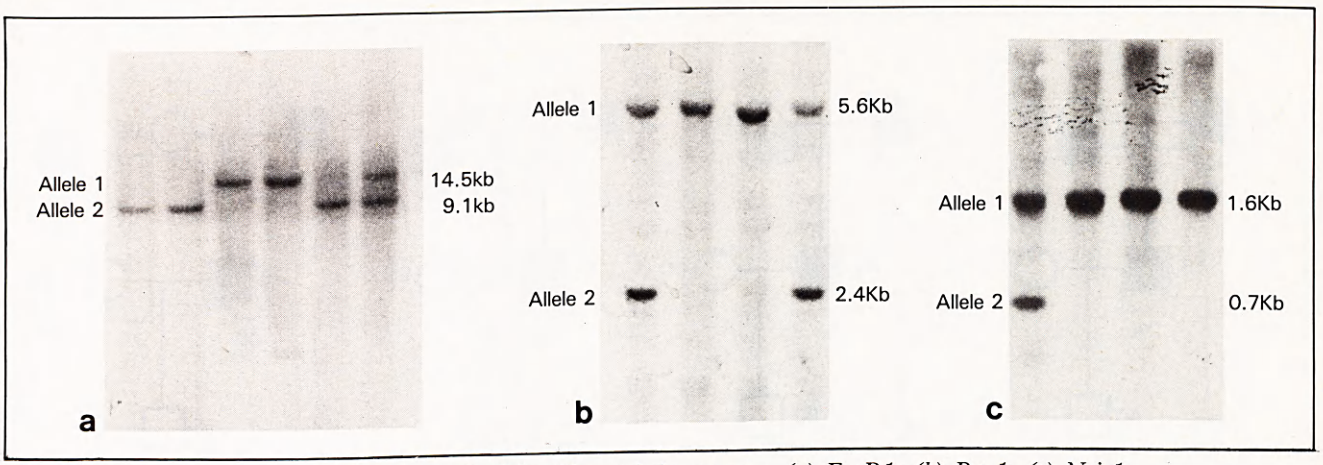


Fig. 6. *Polymorphisms shown by DNA probe G8 with restriction enzymes (a) EcoR1; (b) Pst 1; (c) Nci 1.*

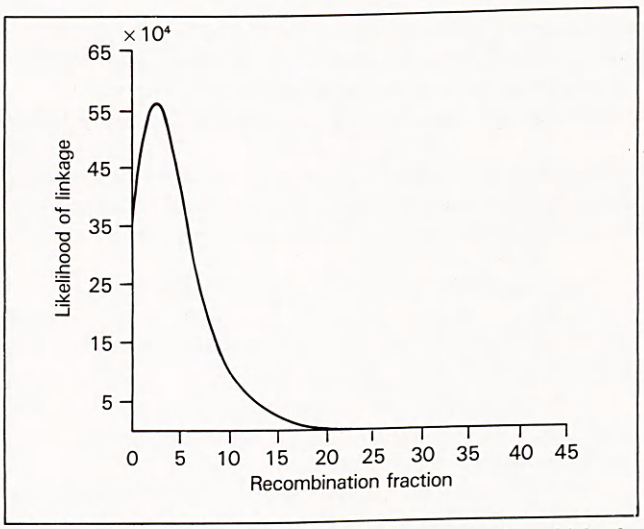


Fig. 7. *A family with Huntington's chorea in which the disease allele is segregating with the 'B' G8 haplotype.*

A person must be heterozygous at both the marker and disease loci if any prediction is to be possible for children; for an affected individual homozygous at the marker locus there is no means of distinguishing which haplotype is travelling with the HC gene.

The use of this approach in prediction will clearly depend on an accurate knowledge of the distance between marker and disease, as well as on complete proof that there is not more than one separate HC locus. Further polymorphisms at or around the G8 locus will also be needed to ensure that all individuals are heterozygous and thus informative; for greater accuracy 'flanking' markers on each side of the HC locus will be needed. All these aspects are being actively pursued at present[22], but they will not remove one major drawback for prediction: the necessity for typing a number of key family members in order to give a prediction for a particular individual.

The magnitude of this drawback is illustrated by the pedigrees shown in Fig. 8, and by the data from our South Wales families related to this (Table 2). Fig. 8 shows the family structures needed to give a prediction for an individual at 50 per cent risk. At least one grandparent must be living for this to be feasible, in order to tell whether the person at risk has inherited from the affected parent the gene that has come from the affected grandparent—or the one from the healthy grandparent. Table 2 shows that only a small proportion of young adults have the appropriate family structure; the two series show the situation for a consecutive series of 100 individuals (or their spouses) at risk who were pregnant, as well as for the larger body of individuals at high risk between the ages of 20 and 45[23].

It is thus clear that prediction of presence or absence of the gene will not be feasible for the great majority of people at risk, even if the available markers are developed to be fully informative and accurate. This situation is only likely to change when a test is developed that will identify a specific defect in the HC gene of a single individual, something that is still a long way off.

However, this apparently pessimistic situation changes if we look at the same family structures but ask a different question, i.e. is it possible to predict for the pregnancy of a person at risk, rather than for the person? Fig. 9 shows the various possibilities, and indicates that we can give useful information without the presence of the grandparental generation; the fetus now represents the third generation, and only a parent of the person at risk is needed. Our data in Table 2 show that this type of family structure is in fact present in around 90 per cent of cases, so that one is able to make a prediction for the pregnancies of most of those individuals where one can predict about themselves. Essentially it answers the question: has the fetus received a marker gene from its at-risk parent that came down from the healthy grandparent, in which case it should be unaffected (Fig. 9(ii)), or has the marker from the affected grandparent been transmitted, in which case the pregnancy is at the same 50 per cent risk as the parent (Fig. 9(i)).

It should be emphasised that such a prediction does not influence the risk situation for the parent; this may well be an important factor in the decisions of couples in future application of predictive tests. Equally, a predic-

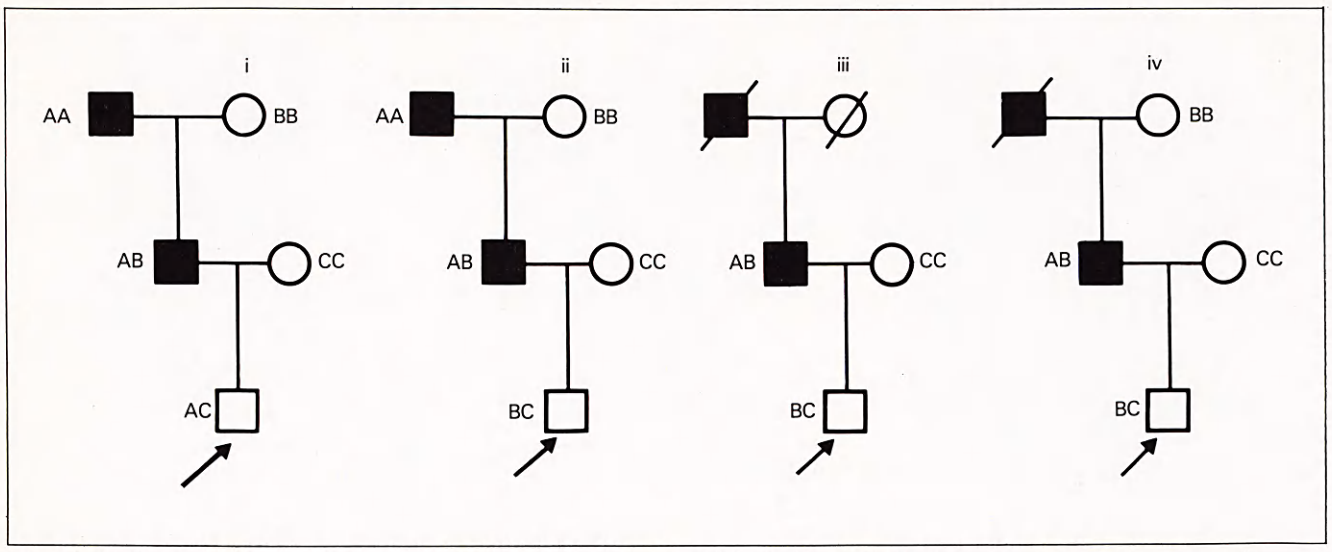


Fig. 8. *Pedigree structures required in prediction for individuals at risk of HC (individual requesting prediction arrowed).*
(i) Both grandparents are living. The affected parent has received HC along with the 'A' marker type from the grandparent; since the child has also inherited the 'A' marker, he would be predicted as affected, in the absence of recombination.
(ii) Here the offspring has inherited the 'B' marker type from his affected parent. This has come from the unaffected grandparent, so a prediction of normality would be made.
(iii) Neither grandparent is living. Prediction is impossible, since although the individual at risk has received the 'B' marker type from the affected parent, it is not known whether this came with the HC gene or from the unaffected grandparent.
(iv) The affected grandparent is dead but must have carried the 'A' marker and transmitted it with HC to his affected son. Thus a normal prediction is possible for the individual at risk.

Table 2. Frequency of pedigree structure in South Wales families at risk for HC. A—Adults at greater than 10 per cent genetic risk, age 16–45. B—Consecutive series of pregnancies of individuals at greater than 10 per cent risk.

	No.	Affected or at risk parent living No. (%)	At least one parent living No. (%)	Affected grandparents living No. (%)	At least one grandparent living No. (%)	Affected sibs living No. (%)
A. Adults at risk:						
Affected parent	344	152(44.2)	265(77.0)	7(2.0)	40(11.6)	66(19.2)
Affected grandparent	293	263(81.8)	282(96.3)	25(8.5)	57(19.5)	1(0.34)
Total	637	423(66.4)	559(87.8)	32(5.0)	99(15.5)	67(10.5)
B. Pregnancies at risk:						
Affected parent*	67	38(56.7)	61(91.0)	2(3.0)	12(17.9)	3(4.5)
Affected grandparent*	33	28(84.8)	28(84.8)	0(0)	7(21.2)	0(0)
Total	100	66(66.0)	89(89.0)	2(2.0)	19(19.0)	3(3.0)

*Relationship to pregnant individual (or spouse) not to fetus

tion of this type is incomplete in that 'abnormal' prediction indicates no more than a 50 per cent risk.

How far are these possibilities for prediction likely to become part of clinical practice and genetic counselling? So far, those groups studying the G8 probe in families have not applied it in prediction, taking the view that it is essential first to document the potential error rate, to exclude heterogeneity, and to discuss widely with families and clinicians the ethical and practical aspects of its possible use in prediction. Once these issues are resolved, there seems little doubt that there will be requests from family members for prediction, and that this will face all involved with difficult problems.

Previous surveys of relatives have shown that a majority would wish to have a predictive test (58 per cent in our own randomly chosen sample[9], higher in some surveys of more selected groups). Surveys carried out since the discovery of the linked marker are broadly similar, but it would not be surprising if some of those responding positively when they knew a test did not actually exist were to change their minds when confronted with a test actually available.

So far, discussion of prediction has centred on the problems of telling an apparently healthy person that he will almost certainly develop a serious and untreatable disorder at some future time. However, as this is not likely to be practicable for more than a small proportion of such individuals because of pedigree structure, I think

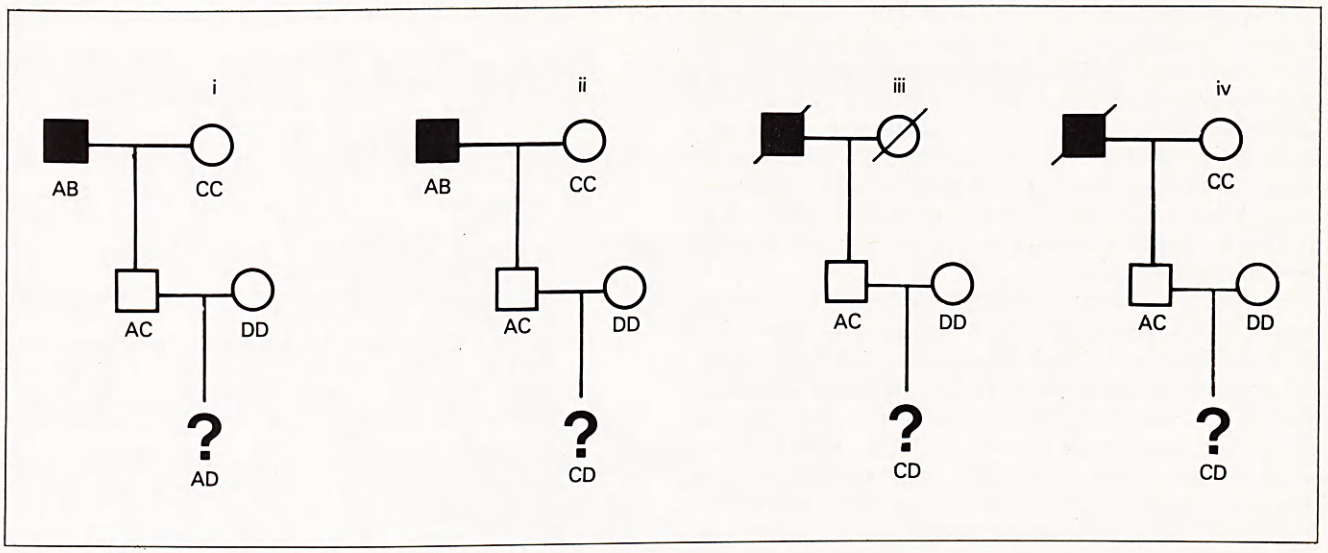


Fig. 9. *Pedigree structures for prediction in a pregnancy at risk.*
(i) Although no prediction can be made for the parent at risk, the fetus has inherited the 'A' marker type from the affected grandparent and is thus at the same 50 per cent risk as is the parent.
(ii) The fetus has here inherited the 'C' marker type from the healthy grandparent; HC can thus be excluded, in the absence of recombination.
(iii) No prediction can be made for the fetus since both grandparents are dead.
(iv) HC can be excluded in the fetus, since it has inherited the 'C' marker from the healthy grandparent, as in example B.

it may prove more helpful to take a different view of prediction. The aim would be not so much to predict the presence or absence of the gene in the person at risk, but rather to give the option to such a person of having children likely to be free from a risk of the disorder. It is quite possible that a proportion of those who would not wish to have any prediction for themselves might wish to have prediction in pregnancy, particularly if they knew that such prediction would not have implications for themselves.

It is too early to know what attitudes will be encountered, indeed, it is likely that these attitudes may change quite rapidly as family members become aware of, and adjust to, the new possibilities. One factor that will be highly relevant is the development of first trimester prenatal diagnosis using chorion biopsy[24], which allows a decision to be made regarding termination of an affected or at-risk pregnancy before 12 weeks' gestation, in contrast to amniocentesis, where a diagnosis is often not possible until 18 weeks. Preliminary experience from families at risk for Duchenne muscular dystrophy, where similar decisions have to be made concerning male pregnancies at 50 per cent risk, suggests that for some couples the early timing of decisions is a critical factor in determining acceptability. We have studied the G8 probe in chorion biopsy samples and shown that, using this technique, typing of the polymorphisms is indeed feasible[25]. The proportion of couples taking this approach remains to be seen. Therefore, in my view it is important that the families are made aware of the full range of options, and that they can choose whichever they consider best for themselves, including the option of having no tests at all.

Future Developments

So far the localisation of the HC gene has been viewed in terms of prediction and prevention, but it also provides hope for isolation of the HC gene itself, and for studying the mutational abnormalities that occur in the gene to produce the disease. This would also open the way to identifying the specific gene product of the HC locus, something that conventional biochemical and neurochemical research has not yet achieved. In fact, such work need not await the isolation of the HC gene, though various techniques of analysing the G8 region of the genome are currently being applied. It is already possible to test 'candidate genes' by means of their localisation. Thus an increasing number of gene probes involving important neurotransmitter functions are already known, while many others studied in experimental species are thought to be highly conserved throughout evolution; if such genes are not localised in the same region as G8, they are unlikely to be causally involved with HC; if they are, they will at least deserve further study.

The expression of DNA sequences from the G8 region can also be studied by the construction of 'libraries' of cDNA derived from messenger RNA in tissue likely to express the HC gene. Thus any sequences that prove both to have the appropriate chromosomal location and are expressed in basal ganglia would merit close attention.

Localisation of the HC gene should provide the key to fuller understanding of the disorder; this in turn may provide a rational basis for therapy and, possibly, for measures that might postpone or modify the course of the disease in those gene carriers as yet unaffected. Once this becomes feasible, the outlook for prevention would be

entirely different. There would be a direct advantage for those genetically affected to know in advance, and the potential ethical conflict between knowledge helpful for genetic counselling but traumatic for the person concerned would be resolved. All of us involved in genetic counselling for HC hope that such therapeutic developments will follow closely on the availability of predictive tests though, realistically, it seems likely that there will be an interim period during which prediction will be feasible, but therapy ineffective.

How far then have we come along the road to prevention of Huntington's chorea? A little way certainly, but there is still far to go. We have seen that a striking change in births at risk can occur in the complete absence of any tests of prediction or any measure other than genetic counselling, and we now have a DNA marker which, while far from perfect, is a first step towards accurate prediction and the isolation of the HC gene itself.

As new molecular developments occur during the coming years, it will be essential to place them in the context of careful clinical and epidemiological research, so that we can accurately assess their impact on patients and families and can ensure that they are applied wisely.

Acknowledgements

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