the number of units transfused inappropriately.[8] Education, however, does not necessarily lead to a consistent change in clinical practice.[9] The use of fresh frozen plasma is controlled locally and determined largely by existing practice. Hospital transfusion committees should develop local guidelines based on a national protocol to promote the appropriate use of blood and blood components[7]; to achieve success representatives of all specialties using blood transfusion as well as haematologists must be involved.

A widespread practice in need of modification is the transfusion of 2 units of fresh frozen plasma to an adult in specific circumstances. Little, if any, scientific foundation exists for this practice and it is difficult to imagine what clinical benefit might be expected from a dose of fresh frozen plasma that is too small to increase the activity of any plasma factor yet sufficient to expose the recipient to its risks. Secondly, as with other blood components and in accordance with the Department of Health's circular on record keeping and stock control [10] and regulations on product liability,[11] the transfusion of fresh frozen plasma should be fully documented in patients' notes. This would become particularly important if a recipient were to acquire, say, HIV infection, when it would be necessary to identify the donor and provide written evidence to justify the use of the blood component implicated.

Thirdly, the introduction of further safety measures to the collection, screening, and treatment of plasma should be considered. The risk of infection with hepatitis B virus could probably be reduced if screening for antibody to hepatitis B core antigen was added to the current programme of testing of blood donations. Recently, pasteurisation of human plasma has been shown to allow recovery of more than 80% of the activities of clotting factors and protease inhibitors while ensuring that lipid enveloped and non-enveloped viruses are largely inactivated.[12] Such an approach is attractive, although it would reduce the already scarce supply of plasma. Some transfusion centres have introduced ways of collecting a larger volume of fresh frozen plasma (200 or 250 ml) than the average 180 ml from a single donation, thus lessening the number of donors who contribute to the volume that a single recipient receives. For this reason too, plasma collected by apheresis could be used when large volumes of plasma care required—such as in thrombotic thrombocytopenic purpura.

Finally, in this and related disorders, efforts should be directed to identifying the factor(s) in fresh frozen plasma that produce benefit as this could lead to the development of a plasma fractionation product.

HANNAH COHEN
Senior lecturer in haematology

St Mary's Hospital Medical School,
London W2 1PG

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The gene for Huntington's disease

History repeats itself

The gene causing Huntington's disease was localised to a specific chromosomal region soon after "reverse genetics" (now called positional cloning) was developed. In large families Huntington's disease was found to cosegregate with a variation in DNA sequence on the distal short arm of chromosome 4.[1] Any element of luck involved in mapping the gene for Huntington's disease quickly evaded researchers subsequently. It has taken intensive effort by countless investigators for 10 years to identify the gene mutation responsible for the disease.[2]

Why did it take so long? Progressing from genetic linkage to isolation of the mutant gene in any disease is a formidable task, as even close DNA markers are usually more than a million base pairs away from the disease gene. These difficulties were enhanced in Huntington's disease by the position of the gene, which made it difficult to identify flanking markers, an important step in positional cloning. In addition, data from critical families with important recombination events (crossovers) were initially misleading.[3]

Recent work focused on identifying genes within a 500 kilobase stretch of DNA and analysing them for mutations, and eventually one was identified with a sequence of tandemly repeated trinucleotides (CAG) at one end. This repeat sequence varies in length in normal subjects (between 9 and 34 trinucleotides) but is longer, occasionally containing as many as 100 trinucleotides, in virtually all patients with Huntington's disease.[2] Some patients may have a repeat length in the normal range, but the accuracy of diagnosis in these subjects has not yet been reassessed.[4]

The messenger RNA for the gene for Huntington's disease is 10·4 kilobases in length and is expressed in many tissues. Its predicted product has a molecular mass of 348 kilodaltons and bears no resemblance to any known protein.[2] It has been termed huntingtin, which does not trip easily off the tongue. Whether the trinucleotide repeat sequence is translated and forms part of the protein is not yet known. The next phase of unravelling the molecular pathogenesis of Huntington's disease—determining function and malfunction of huntingtin—is under way. There are many pressing questions, and the first of these relates to correlating genotype with phenotype. Analysing repeat length for such studies, and for clinical purposes, is easier now with protocols [5-7] that are technically easier than the original method.[2]

Preliminary data suggested that the length of the trinucleotide repeat and the age at disease onset were inversely correlated.[2] This has since been confirmed in a series of 440 patients.[4] One feature of Huntington's disease, which has long been recognised, is that patients whose disease has a very early onset nearly always have affected fathers. This has a molecular correlate. Paternally transmitted cases have a larger number of CAG repeats in the gene than those with affected

mothers. Paternal transmission also seems to be associated with expansion of the repeat, but whether or not this applies to maternal transmission is unclear.[4] This is interesting as similar findings have been reported in myotonic dystrophy. In this condition the gene also contains an unstable trinucleotide repeat, although the severe phenotype is transmitted by affected females.[8] These observations provide a molecular substrate for the previously controversial phenomenon of anticipation (the apparent tendency for autosomal dominant diseases to be more severe in younger than older generations of a family.)

The possibility of fresh mutation in Huntington's disease has, until now, been difficult to prove. Two such events were identified in patients with the features of Huntington's disease but who had unaffected parents.[2] It seems that the gene containing an expanded CAG repeat in these patients is derived from a parental one in which the repeat is at the upper limit of the normal range, indicating a premutational state.

How the expanded repeat, assuming it is translated, causes cellular dysfunction in Huntington's disease and why this applies to some parts of the brain but not others are just two unexplained issues. What is tantalising is that not only Huntington's disease and myotonic dystrophy but also three other neurological disorders (X linked bulbospinal neuronopathy and the fragile X syndrome, and one type of dominant ataxia) are associated with unstable trinucleotide repeats.[9,10] Other genes of known and unknown function containing such repeat sequences are expressed in the human brain.[11,12] There must be other neurological diseases that are caused by this curious type of mutation—a hypothesis that has not escaped the attention of the neurogenetic community at large.

A E HARDING
Professor of clinical neurology

Neurogenetics Section,
Department of Clinical Neurology,
Institute of Neurology,
London, WC1N 3BG

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Clinical consequences of isolating the gene for Huntington's disease

An accurate test brings a set of ethical problems

After 10 years of intensive international research the isolation of the gene for Huntington's disease is already having major scientific and clinical consequences.[1] The most immediate clinical consequences are genetic and arise from the specificity of the genetic change in relation to Huntington's disease as well as from the fact that almost all families so far studied show the same mutational basis.[2] A single molecular test on a sample of blood or other tissue now seems likely to predict or diagnose Huntington's disease with a high degree of accuracy. All clinicians and scientists concerned with patients and families affected by Huntington's disease need to recognise the implications of this advance.

Linked DNA markers have been available for presymptomatic testing for several years,[3,4] with over 1500 such tests completed worldwide.[5-8] But the need to test many family members, together with inaccuracy from possible recombination, has made testing difficult for most people and impossible for many. Mutation analysis now allows a test that should be accurate and specific, though both factors will need validating in larger, independent series. Moreover, privacy for the applicant will be enhanced because samples from many relatives are no longer needed (though confirmation of the mutation in at least one affected member will remain important). In the laboratory testing will be simpler, quicker, and possibly cheaper, though the method is technically demanding and will benefit from modification before being suitable for service use.[9]

Against these undoubted advantages must be weighed some potentially serious problems. The most serious is the possibility of testing without giving information, counselling, and support—especially worrying when economic pressure is being exerted to reduce health service costs and when some British laboratory services are being contracted out. Fortunately, patterns of practice have been established [10]; testing without counselling is generally agreed to be unethical and could have serious legal implications if problems were to arise. In Britain all centres performing presymptomatic testing for Huntington's disease have adopted a common protocol for counselling [11] and have formed a consortium to monitor testing and audit its practice.[12] This should form an important safeguard as well as providing a valuable example for genetic testing in other disorders.

Even with the best clinical practice other dilemmas may arise. Testing is sometimes sought by those at 25% prior risk, who have had an affected grandparent but whose parent is well though still at considerable risk. Testing in response to such a request might disclose that the parent of the person tested carried the gene for Huntington's disease and would thus develop the disorder, even though that person, unlike his or her offspring, did not wish to be tested. It remains to be seen how such potential conflicts of interest will be resolved.

The identification of a specific mutation for Huntington's disease will for the first time give a diagnostic test for the disorder, which can be used to confirm apparently isolated cases and in situations of clinical uncertainty. Such testing is unlikely to alter greatly the range of clinical phenotype resulting from the disease, as has happened with prion dementias,[13] but it will represent a further extension of molecular genetics into neurological practice. When such testing is carried out in people not known to have a pedigree of