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The Prevention and Avoidance of Genetic Disease: Summing Up

M. Bobrow

Phil. Trans. R. Soc. Lond. B 1988 **319**, 361-367
doi: 10.1098/rstb.1988.0057

Phil. Trans. R. Soc. Lond. B **319**, 361–367 (1988)
Printed in Great Britain

The prevention and avoidance of genetic disease: summing up

By M. Bobrow

Paediatric Research Unit, Prince Philip Research Laboratories, Guy's Tower, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, London Bridge, London SE1 9RT, U.K.

The preceding papers have dealt with major advances in understanding and detecting the mutational basis of human disease. If these advances are to be of practical benefit, systems of effective, efficient and acceptable delivery of the technology to the relevant population groups will need to be planned. In these delivery systems, the key figure is likely to be the clinical geneticist, still a somewhat shadowy figure, difficult to define: a doctor among scientists, and a scientist among doctors. The clinical geneticist, among other duties, acts as a user-friendly interface between the public (including the medical profession) and the conceptually quite difficult fields of modern genetics. Few people in this age of transition to computer literacy will underestimate the importance of a user-friendly interface, without which even the most powerful analytical machines are underused, error prone, or even incomprehensible.

Summary of proceedings

Mutation underlies all genetic disease, and virtually all disease has at least some genetic component. The impact of induced mutation can spread widely in space and time, to affect distant populations and future generations. Despite our currently poor understanding of the quantitative aspects of mutation induction in man, it therefore behoves us to minimize exposures to environmental mutagens (Edwards, this symposium).

Dramatic progress in the construction of a gene map has provided a framework for categorizing and dissecting human genes, and the evolution (if one can use 'evolution' of so rapid a process) of recombinant DNA technology has provided new tools for pursuing this goal. A quite appreciable proportion of the human gene repertory has already been at least crudely mapped (Robson, this symposium). Molecular techniques will clearly expand our understanding and definition of chromosomal disorders, and the borders between 'molecular' and 'cytogenetic' abnormalities are becoming increasingly blurred, with the delineation of microdeletions in diseases such as Duchenne and Becker muscular dystrophy (Monaco *et al.* 1985; Hart *et al.* 1986, 1987), slightly larger deletions on Xp21 causing disease 'clusters' involving adjacent genes (Francke *et al.* 1987), and cytologically invisible translocations (for example, those in XX males; see Andersson *et al.* (1986)) (Ferguson-Smith, this symposium).

Beautifully detailed demographic studies of the most prevalent serious genetic disease, Down's syndrome, provide a model for the control and monitoring of a common genetic disorder (Mikkelsen, this symposium). Although we now know quite a lot about what happens in this disorder, we still know regrettably little of how or why it happens. In multifactorial disorders, environmental manipulation still offers the best hope of disease reduction (Nevin, this symposium). It is frustrating that the ferment of molecular biology is coming most slowly to these areas, which have the greatest immediate potential for a public health impact.

In common single-gene disorders, in contrast, scientific and medical approaches have been radically altered in the past few years. The lessons first learned in the study of globin genes

have, unusually tidily, now been strongly reinforced in autosomal dominant (Huntington's disease; see Meissen & Berchek (1987)), autosomal recessive (cystic fibrosis (CF); see Farrall *et al.* (1986)) and X-linked recessive (Duchenne muscular dystrophy (DMD); see Hodgson *et al.* (1987)) disorders. Not only do these disorders have different modes of inheritance, but they also demonstrate the fundamental strategic differences that are likely to be required in dealing with disorders with radically different genetic characteristics, particularly in relation to the frequency with which new mutations arise. I shall return to this topic later.

The most elegant model for single-gene disorders is provided by the haemoglobinopathies, where detailed knowledge of gene structure is matched by very comprehensive physiological, demographic and social data (Antonarakis *et al.* 1985). Detailed knowledge of individual mutations has enabled reliable population screening and prenatal tests to be established. The error rate in prenatal tests using DNA-based techniques has been low, even during the early stages of evolving these test systems.

A systematic restriction fragment length polymorphism (RFLP) screening programme in several laboratories has now produced clones very close to the locus for cystic fibrosis (Beaudet *et al.* 1986). The most impressive feature of this approach is that it was almost bound to be successful. There is now a substantial and useful battery of linked probes, including one that is in very strong linkage disequilibrium with CF, and expressed in a very suggestive range of tissues (Estivill *et al.* 1987). A comprehensive set of gene markers for chromosome 7 is an important long-term by-product of the work on CF (Tsui, this symposium).

The most unusual of the loci in the current limelight must be the Duchenne muscular dystrophy (DMD) locus: very large and very highly mutable. Cloning of intragenic fragments, and now of copy DNA (cDNA) fragments (Monaco *et al.* 1986), from this are the result of very elegant and imaginative molecular genetic experiments (Worton, this symposium). Deletion mutants play a particular role in this disease. For example, my laboratory has screened DNA from 253 patients with Duchenne or Becker muscular dystrophy, with 17.8% showing deletion of one or more probe sites. Observations from G. J. B. van Ommen and co-workers suggest that the use of FIGE may demonstrate up to 50% structural rearrangements (den Dunnen *et al.* 1987). It seems probable that more than half of DMD cases will be due to deletion mutants, and the true proportion could be very large.

The successful discovery and evaluation of a probe linked to Huntington's disease (Gusella *et al.* 1983) has raised manifold personal and ethical problems (Lamport 1987; Shaw 1987; Smurl & Weaver 1987). It is now most urgent to consider the sort of population-based programmes required to facilitate the use of these probes for disease prevention (Harper, this symposium).

Powerful and successful as current techniques have been, as evidenced by the progress in defining the genetic basis of these (and other) diseases, newer procedures are greatly improving the speed, range and precision of genomic analysis. Genomic maps, with a resolution of the order of 100 kilobases, which will provide an excellent base for detailed analysis, are likely to become available for substantial parts of the genome (Southern, this symposium).

The final group of papers (Lyon, Evans and Caskey, this symposium) emphasize what is too easily forgotten: that genetic disease stems from mutation, and a direct numerical relation must, somewhere, exist between these two processes. The response to mutagens is highly complex, depending on cell type and stage, the type of mutation being assayed, and other factors. The phenotypic response of different species to apparently similar mutations may be quite different, further complicating the interpretation of experiments.

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The organizers have emphasized an important distinction between avoidance and prevention. Several different strategies will combine to lessen the socio-medical impact of genetic disease but (with some important individual exceptions) they will only be stemming the tide, as long as recurrent mutation replenishes the stock of harmful genes. We have, as yet, virtually no insight as to whether a significant proportion of human mutation is potentially controllable: or at what price, in evolutionary as well as more immediate terms, such control might be gained.

Despite the many fascinating and unanswered questions, it is clear that molecular genetics is already providing powerful tools for the diagnosis of genetic disease. What progress has this infant subject made so far? The major genetic contributions to ill health are probably in the complex areas of congenital malformation and multifactorial disease. Progress is appearing in dissecting out genetic components of psychiatric disorders (particularly manic-depressive psychosis; see Egeland *et al.* (1987)), coronary artery disease (Bock & Collins 1988), and even some malformations (Moore *et al.* 1987). However, the storyline is undoubtedly clearer in relation to single-gene disorders. There are thousands of these, and even to map them all is a daunting task, more because of their individual rarity, rather than their sheer numbers.

However, I have abstracted (see table 1) the 'top 20' single-gene disorders, in order of gene frequency, in the U.K. These account for a total disease frequency of about 8 per thousand

TABLE 1. 'TOP 20' SINGLE-GENE DISORDERS, SHOWING THEIR FREQUENCY PER THOUSAND BIRTHS

(Modified from Weatherall (1985), tables 2, 3 and 4.)

dominant	
† Huntington's chorea	0.50
† polycystic disease of the kidneys	0.80
diaphyseal aclasia	0.50
† hypercholesterolaemia	2.00
otosclerosis	1.00
neurofibromatosis	0.40
† myotonic dystrophy	0.20
† spherocytosis	0.20
polyposis coli	0.10
dominant blindness	0.10
† α-1 antitrypsin deficiency	0.50
recessive	
† cystic fibrosis	0.50
† phenylketonuria	0.10
congenital deafness	0.30
congenital blindness	0.10
† adrenal hyperplasia	0.10
† haemoglobinopathy	0.15
X-linked	
† Duchenne muscular dystrophy	0.20
† haemophilia	0.10
† ichthyosis	0.10
† fragile X mental retardation	0.10
total of 'top 20' diseases	8 per 1000
(total marked†	5.4 per 1000)

Total of all diseases in three source tables = 9.04.
Estimated range of total frequency of all single-gene disorders = 4.5–14 per 1000.

† Reasonable gene mapping or gene probe information available.

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births, possibly representing up to 80% of all disease due to single genes. Of these, conditions for which some gene mapping information is available represent 5.4 per thousand births, possibly as much as one half of single-gene pathology, and strong rumour suggests that two or three further common disorders are likely to join this group soon. The genetic tools are thus virtually to hand for tackling the major single-gene disorders.

The future

These genetic techniques for carrier detection, or for prenatal testing, must be combined with developments in medical practice if substantial avoidance of genetic disease is to be achieved.

Genetic counselling in itself modifies reproductive behaviour, is increasingly available, and increasingly useful, as it is based on more accurate genetic diagnoses. Prenatal diagnosis, and the tools of fetal medicine, are in themselves in a phase of very rapid growth: obstetric ultrasound is astonishingly effective at detection of morphological anomalies, and under ultrasound control the sampling of fetal tissues (chorionic villi, amniotic fluid or fetal blood) is accomplished with reasonable safety on a routine basis, to allow its general use at least in high-risk pregnancies (Rodeck & Nicolaides 1984).

In vitro fertilization (IVF) may be used in future in two contexts: as with artificial insemination by donor (AID) to allow parenthood to be uncoupled from gene transmission; and as a means to very early prenatal diagnosis. On the very reasonable supposition that pregnancy selection is less traumatic the earlier it is done, the concept of diagnosing genetic abnormality before re-implantation of an early zygote is appealing. The major technical problems to be overcome are the minute amount of material available from embryo biopsy, and the need to maintain the viability of the rest of the embryo while awaiting the outcome of diagnostic tests. With continued development of methods for rapid *in vitro* amplification (Saiki *et al.* 1985) of gene sequences as well as technology relating to freezing embryos, there is no reason to doubt that these technical problems will be soluble. Whether this option would prove popular with patients remains to be seen, and will depend critically on improving the success rate of IVF, and perhaps on the 'presentability' of the technique in terms of the very considerable extent to which it interferes with the privacy of reproduction. It is also in early embryos that some forms of gene therapy may be considered. I personally find it hard to imagine any substantial number of couples opting to 'treat' an eight-cell embryo diagnosed as carrying a serious abnormality. It may, however, conceivably turn out to be easier to treat a batch of embryos than to diagnose which among them is abnormal.

The application of these techniques will depend upon the infrastructure of the well-found clinical genetics group: accurate diagnoses, genetic registers, efficient coordination of geneticist, obstetrician and laboratory, and detailed knowledge of the population being served.

Different disorders will present somewhat different problems. The most important strategic distinction is perhaps between disorders whose frequency is to a significant extent driven by recurrent mutation, and those in which new mutation is an uncommon event. It is axiomatic that this distinction will reflect the mode of inheritance of the disorder, the degree to which the disorder causes reproductive impairment with loss of the mutant from the gene pool, and the intrinsic mutation rate of the gene locus concerned, which is likely to vary widely.

On the list of currently 'testable' diseases are at least two dominants in which new mutation

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is thought to be rare: Huntington's disease (Shaw & Caro 1982) and myotonic dystrophy (Harper 1985; Shaw *et al.* 1986). If accurate testing, and limitation of affected pregnancies by one means or another, were widely available and enthusiastically received by all affected families (an unlikely situation), these diseases could, in principle, be virtually eliminated from the population: 'avoidance' would lead to 'prevention'.

Several important recessive diseases may have low mutation rates, as has been documented, for example, for sickle-cell disease. It seems likely that Tay-Sachs disease and cystic fibrosis will fall into this same category, the main reason for this guess being the clear difference in disease frequency in different populations. It is hard, at the moment, to think of a good reason for spontaneous rates of mutation at a particular locus varying much between the various major human population groups.

An autosomal recessive with a low mutation rate invites population screening for carriers, leading to counselling and prenatal diagnosis, as has been so successfully applied for thalassaemia in some populations (Cao *et al.* 1984). If few individual mutational events have occurred, most disease carriers will have the same mutation sequence, and population screening is technically simplified. The clinical disorder will be 'avoided' in direct proportion to the efficiency with which the screening and prenatal diagnosis programme is delivered. The gene frequency, however, will be little affected: for these serious diseases, it is genetically irrelevant whether the homozygote dies in early adulthood or in fetal life. Any significant effect on gene frequencies would involve selection against heterozygotes, a eugenic route that many (including myself) would be reluctant to follow. The prevalence of these disorders can thus be significantly reduced by screening of whole populations to detect genetic carriers; but true prevention is not easily envisaged. Indeed, because avoidance by prenatal testing is likely to result in reproductive compensation (Modell *et al.* 1984), these programmes are likely to be somewhat dysgenic.

Disorders relatively frequently caused by new mutations include all the severely deleterious X-linked recessives, such as DMD; many dominants such as achondroplasia, osteogenesis imperfecta and neurofibromatosis; and the common chromosomal disorders such as Down's syndrome. For the single-gene disorders, many different individual mutations will be involved, rendering the technicalities of setting up large scale screening programmes more complicated. It is possible that screening tests based on gene products will be more applicable than direct analysis of gene structure. Screening of the general population to detect mutation carriers before reproduction will only be effective for that proportion of the disease prevalence which is not immediately due to new mutation. This would be only 1–2% for Down's syndrome, perhaps 20% for achondroplasia and *ca.* 67% for DMD (although this last figure is not uncontroversial, some people believing that virtually all DMD mutations arise in male gametogenesis, so that virtually all affected boys arise from carrier mothers) (Lane *et al.* 1983). Although the reduction of DMD by two thirds would be very well worth achieving, even excellent carrier detection, counselling and prenatal diagnosis in this situation would therefore leave appreciable disease prevalence.

Further inroads into the prevalence of these diseases would have to depend on either developing acceptable techniques for screening very large numbers of low-risk pregnancies or, even less credibly, the development of some means of modifying spontaneous mutation rates. A partial step towards the first alternative is to define sub-populations at somewhat elevated risk, for pregnancy screening, as with maternal age and Down's syndrome. If, for example, DMD

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mutations were to be found to occur preferentially on specific chromosomes whose altered structure renders them mutation-prone, similar strategies may become feasible. Although this is an unsupportable speculation at present, the possibility that the high mutation rate in DMD may not be entirely an intrinsic property of the coding sequence and its size is supported by suggestions that the mouse gene transcript is not grossly different from the human, including its size, although generations of mouse geneticists have the impression that spontaneous mutation to DMD is not a common event in that species.

Technical advances in molecular genetics have revived the relevance of basic genetic and population genetic principles, and interaction between the disciplines (clinical genetics, obstetrics and community medicine) is needed in developing strategies for the delivery of health care systems tailored to the specific problems of individual diseases. I believe medical geneticists can look forward to a very satisfying and fruitful period over the next 5–10 years.

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