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The Importance of Genetic Disease and the Need for Prevention [and Discussion]

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The importance of genetic disease and the need for prevention

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Until recently the effects of disease could only be reduced by prevention and treatment. It is now possible to interrupt development after fetal diagnosis. This prevents birth, but not the cause of the disease, and is usefully termed 'avoidance'.

Genetic disorders are the consequence of mutational events in the past, including the remote and the immediate past, and prevention, in its true sense, can only be applied to preventing further mutations. This requires a knowledge both of the mechanism of mutation and of the mutagens to which populations and individuals are exposed, and the maintenance of public health requires the collection of data relevant to mutational disease.

Introduction

Genetic disease, if defined rigorously, is the consequence of some derangement of the hereditary material in its transmission from one generation to the next. It is convenient to restrict it to conditions in which the derangement of the genome, a hybrid neologism covering both the chromosomes and their constituent genes, usually has a specific relation with some adverse consequence to the whole organism. All disorders are genetic in the sense that they are commoner in the relatives of affected individuals, but initially it is simpler to define genetic as a strong adjective relating to a minority of diseases, and accept that any estimates of mutational disease based on this minority of disorders will be substantial underestimates.

In the application of genetics to man we are dealing with problems of such depth and gravity, and with methods for their resolution of such complexity, that even those expert in neighbouring fields of study find communication difficult. In the main subjects of this meeting, the nature of genetic disorders of man and of the mouse, and the physical and chemical nature of the genes and their products, few, if any, of the speakers can claim a deep knowledge of more than one and a working knowledge of more than one another. False knowledge has been a graver problem than clean ignorance, and we have a duty, not merely to convey knowledge, but to define its present limits and the limits of its application.

It is now 60 years since Muller (1927) demonstrated that radiation would increase the mutation rate in the fruit fly and that these mutations led to similar consequences to those that arose naturally. Thirty years later, the World Health Organization (WHO), with the help of Muller and others, including J. B. S. Haldane and J. V. Neel, produced their report *Effect of radiation on human heredity* (WHO 1957). This definitive report, based on what was known of genetic disease in man and induced mutations in other organisms, was followed by the discovery by Lejeune and others of chromosomal disorders, adding an equally numerous group to that group of genetic disorders whose nature was inferred by the pattern of their inheritance. These were dominated by a few severe disorders involving an extra autosome or a missing sex-chromosome, a few milder disorders involving an extra sex chromosome, and a

large number of rare, but severe, disorders due to duplications, deficiencies and translocations. Further work on congenital malformations in man allowed the definition of many rare genetic forms but most of the commoner forms were found to have little claim to genetical status when adequately studied.

Nevertheless, the confusion of genetic, which means present at conception, and congenital, which means evident at birth, continued and still continues to dominate the literature on the consequences of mutational exposure. Although the reports of the National Research Council Committee on the Biological Effects of Ionizing Radiation (BEIR) (1972, 1980) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (1966, 1972, 1977, 1982, 1986) may be criticized for almost wholly neglecting the problems of recessive disease (Searle & Edwards 1986), this is largely balanced by their preoccupation with congenital disease. As the consequences of these two misunderstandings largely cancel out, both reports have been valuable in providing approximate guidelines for setting safety standards.

Some attempt to redress this confusion was made in a second WHO report (1986), which broadened its remit to include other sources of mutation and to discuss the opportunities for learning from accidental exposures of individuals and populations. This WHO meeting was held in Kiev in 1984 and published shortly after the Chernobyl disaster of April 1986.

The control of genetic disease

In medicine, in its traditional form, illness happened, and after it happened attempts were made to treat it. Although treatment can reduce the consequences of illness, it rarely reduces its frequency, and the reduction in incidence of many disorders, including the virtual eradication of some that were once major causes of death and disability, has only been achieved by modifying the environment. In infective disease it is merely necessary to break the chain of infection by cleaning up the environment, or by creating artificial immunity. Success was obvious because the effects of control measures involving water, air, diet and immunization were usually evident within a decade.

In genetic disorders we are faced with a problem of a different order of magnitude in which the results of preventive measures will be slight in the short term and the consequences of neglect may not be serious for centuries. However, the nature of genetic lesions and the scale and variability of the genetic material are such that we cannot assume that our remote descendants will have the competence to launder the genome to remove blemishes. If they have, they may not wish to live within the ethical and behavioural framework within which this was possible. Selection against multiple minor lesions would be so inefficient that it would involve either a minority of conceptions surviving induced abortion or the majority of conceptions being *in vitro*.

Until we are better informed of the scale of mutation, both natural and artificial, we must accept the need to reduce mutagenic exposure as much as possible. The biggest public health problem facing our species is the conveyance of our genetic material from one generation to the next with the minimum of damage. This is a formidable problem and it is a World problem. If the environment is damaged by smoke, fumes, noise, etc. the consequences are attenuated by distance, and very soon the concentration is below some threshold of effect: where damage is done it is done in the neighbourhood of the source, and will rarely act on those unborn. In mutational exposure the circumstances are very different. As the mutagenic material diffuses

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its concentration declines but the population exposed increases, and there is no threshold. The damage is not only likely to be distant from the source in space, but also in time. Most of the rare recessive disorders must be consequent on mutations many generations ago, and most mutations being induced now will only become manifest many generatons ahead. How far ahead does not affect the morality of inducing such mutations. It may be that the present levels of exposure are not substantially increased by human activity. They may even be reduced. All that is clear is that, so far, radiation from artificial sources has made a very slight addition to natural radiation. However, the profusion of novel chemicals now infiltrating our food chain, and even replacing some foodstuffs and some traditional methods of preservation, may impose a far graver potential threat than war, pestilence or famine.

In most genetic disorders treatment, and specific preventive measures, have little to offer. In some, such as rhesus incompatibility, population methods of control may be feasible by breaking the immunological chain by immunological methods, virtually eliminating a major cause of fetal and neonatal death and a substantial cause of severe disability in a few years. However, most disorders are not of a nature allowing such approaches, and in many the damage is irreversible by birth, as in most cases of hereditary deafness, blindness and mental deficiency.

Prevention of such disorders is only possible by reducing the mutation rate and such prevention is limited to mutations that have not yet occurred. Many mutations, including all dominants that are mild, or expressed late in life, and all recessives, have a half-life of several, or many, generations and are well established in the genome of our species. In the haemoglobinopathies and cystic fibrosis a substantial proportion (1–10%) of loci in many populations contain the mutant allele. Most of the commoner mutations must have been maintained by some advantage in survival or transmission, but most of the rarer ones are merely the necessary scars of our survival. The genetic variation on which we depend both to advance our phenotype and to confound our potential parasites can only be acquired at a substantial casualty rate through the majority of mutants being detrimental. The mutational load already established in our species is sufficient to assure almost 1% of individuals will manifest some serious genetic shortcoming, excluding chromosomal disorders, and about half will be from recent mutations.

The nature of genetic disease

The term 'genetic disease', which has been the cause of so much unnecessary confusion, is usefully restricted to disorders that are the direct consequence of some disorder of the genetic material received at conception: all diseases to which the flesh is heir are influenced by the genetic background, and almost all disorders adequately studied have shown some tendency to be commoner in relatives than in the general population, the tendency varying greatly by disorder. However, disorders that are not consequent on a single genetic factor are necessarily related to the action of more than one genetic factor. Although such disorders are sometimes called multifactorial, or part genetic, an adjective that relates to some 99% of disorders is not a very powerful adjective, and can be implied by default. In practice, among the common disorders, those related to infection, because of genetic variation in the defence systems of the body, are among the most strongly familial, as well as the most preventable, whereas most common cancers show a weaker familial tendency. The common congenital malformations

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mainly show an intermediate tendency, but this is largely because of environmental similarities in successive births, and to a minority being due to rare Mendelian disorders.

I shall only consider genetic disorders, defined as being due either to a demonstrable lesion in the genetic material, or inferred as being due to such a lesion from the pattern of inheritance in families. Clearly, because most of the genetic information is not expressed directly as gene products, and because the body has hundreds of different cell types variously arranged into almost as many tissues, all with the same genetic contribution, the non-expressed parts of the genetic material must be of profound importance and must also be maintained by selection of greater, if more confused, ferocity. This problem can be handled either by attributing to various disorders arbitrary proportions of genetic determination, and using this as a multiplier, or by merely accepting that any estimate based on clearly defined genetic disorders must be an underestimate and if necessary multiplying the result by some arbitrary multiplier. The former approach, which is followed by the BEIR and UNSCEAR reports and by many others, takes the average of a series of arbitrarily allocated proportions weighted by estimates of incidence, which are usually far from accurate. In general, it seems preferable to guess one number, for which we have some very approximate upper limit, from the ratio of the total genetic material to the proportion expressed. The alternative involves guessing two numbers and basing major policy decisions on their product. Heritability is sometimes used as a basis for one of these estimates, but the absence of opportunity to standardize either the environment or the genome in man gives little justification for this approach.

If the term 'genetic disorder' is restricted to this distinct group, then these can be divided into those large enough to see as individual lesions, the chromosomal disorders (involving units of several megabases or more) and those amenable to study by extraction, concentration and purification of a million or so identical molecules, the genic disorders. Until recently, protein chemistry and analogy from viruses and bacteria limited this size range to coding sequences of a few kilobases. The methods of specific recognition, such as the Southern blot, enlarged this to a few tens of kilobases, with the option of studying overlapping sequences. Recently, the application of pulsed-field electrophoresis has extended this approach to a few megabases, so there is no longer any window of inaccessibility between what can be seen and what can be analysed.

As cytogenetic techniques improve there has been a steady promotion of genetic disorders from the genic to the chromosomal class. Retinoblastoma, the Prader–Willi syndrome and Wilms's tumour with aniridia usually reveal a deficiency on microscopy, and many other conditions, including most cases of α-thalassaemia and Duchenne muscular dystrophy as well as some cases of Christmas disease and haemophilia, are related to deficiencies beyond the resolution of the light microscope. The nomenclature is necessarily confusing because lesions of various sizes can all lead to the same severe consequences by disrupting continuity; even the technical distinction imposed by the microscopists' need to see, and the biochemists' need to concentrate, has now been bridged. However, these advances have not yet reached a stage sufficient to justify changing the useful distinction of chromosomal and genic, most of which are conveniently astride the round figure of one megabase. Because of the several excellent reviews on chromosomal variants and their incidence (see, for example, Hooke & Porter 1981) I will not consider these further.

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TABLE 1. INCIDENCE OF GENETIC DISEASE AT BIRTH (EXCLUDING CHROMOSOMAL DISORDERS) PER 1000 LIVE BIRTHS

	source, year and reference								
	Stevenson (1959)	UNSCEAR (1972)	BEIR (1972)	Edwards (1974)	Trimble & Doughty (1974)	UNSCEAR (1977)	BEIR (1980)	CMCF (1981)	UNSCEAR (1982)
dominant	33.2†	+++	10.0	0.6	0.8	10.0‡	10.0‡	1.85–2.62	10.0‡
recessive	2.1	+	1.5	2.5	1.1	1.1	1.1	2.23–2.54	2.5
X-linked	0.4	+	0.4	0.5	0.4	—‡	—‡	0.78–1.98	—
subtotal	35.7	10.0§	11.9	3.6	2.3	11.1	11.1	4.9–7.1	12.5
malformations	14.1	—	25.0	—	42.8	90.0	90.0	37.4–44.5	90.0
others	14.8	—	15.0	—	47.3			20.0–29.0	
subtotal	28.9	20.0	40.0	—	90.1	90.0	90.0	57.04–73.5	90.0
total	64.6	30.0	51.9	3.6	92.4	101.1	101.1	62.3–80.6	102.5

† Includes many conditions no longer regarded as dominant.
‡ X-linked included with the dominants.
§ Mostly dominant.
+ Defines relative frequency.

The incidence of genetic disease

Various attempts to define incidence have been made, but the observational problems are considerable, as disorders are not only easily missed and misdiagnosed, but some are not evident at birth although classified as congenital for sound administrative reasons. Table 1 gives the results of various sources. The latest, and most detailed, attempt is the report of what is often termed the 'Polani Committee': the Committee of Mutagenicity of Chemicals in Food, Consumer Products and the Environment (CMCF 1981). There is a reasonable consistency of overall incidence between the major subclasses, the differences being largely related to the inclusion or exclusion of congenital malformations.

The lowest estimate (Edwards 1974) used as a baseline the incidence of a few disorders that rarely escaped the notice of a comprehensive medical service, such as trisomy 21 and cystic fibrosis. Even if the error rates average a factor of four, the total estimate will probably be well within a factor of two, and in this is about as good as is possible for the enumeration of rare, or variously manifest, disease. One serious problem in such summaries is that interest is aroused by experience, as is the ability to make the diagnosis and, in consequence, referral of cases. In addition, areas of high incidence create centres of interest, of excellence and of published data. This is particularly true of recessive disorders in which figures on thalassaemia from Sardinia, or phenylketonuria from Britain, or cystic fibrosis from Anglo-Saxon groups, are obvious examples. In tuberose sclerosis, the first condition to be used for the estimation of dominant mutation rates in man (Gunther & Penrose 1935), the rate of diagnosis in the Oxford region (U.K.) has increased tenfold since the formation of a parent group and the special interest of a clinical geneticist (Lindenbaum & Hunt 1984). On the other hand, some much quoted incidence figures, such as neurofibromatosis based on Michigan, U.S.A. (Crow *et al.* 1956), seem too high by local standards by a factor of about two. It is not suggested that any greater credence is placed on the figures in table 1 than on any others: they are presented as an example of the difficulties. As the mutation rate is unlikely to vary more than this by area, disorders that are usually due to new mutations should be similar, whereas those due to old mutations will be greatly influenced by migration in recent centuries, or even millennia.

The prevention of genetic disease

Genetic disease is, by definition, the consequence of a mutational event, and prevention can only be achieved by the prevention of mutational events. The term 'prevention' has sometimes been extended to cover preventing manifestation by allowing death to precede birth, but this is hardly the correct use of a word with a clear meaning in medicine, and an unambiguous derivation. An appropriate term for avoiding the birth of affected children is 'avoidance' (Ferguson-Smith *et al.* 1978).

Even if all mutational events were to stop, the backlog of established mutations in the population would continue to emerge as genetic disorders, some abnormal alleles having a half-life of millennia and being sufficiently frequent to cause, eventually, the deaths and severe disabilities of a number of individuals comparable to the present population of the World. This lack of new variability might seem detrimental in relation to further evolution: however, this is hardly a major problem because of the immense natural variability of our species. Even in such obvious features as shape, size and colour we are more variable than any other free-ranging vertebrate, and lack of further variability is hardly a cause for anxiety. On the other

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hand, additional variability can only be acquired at a major cost in disability, because only very few mutations have any prospect of being beneficial.

Mutations lead not only to the individual problem of disability and suffering but, unless cleared at a rate commensurate with their formation, they will accumulate and may reach a level beyond the capacity of our present and future breeding structures to contain. The conveyance of our genetic endowment from one generation to the next is the major problem of public health, besides which the problems of most infections, of most cancers or of accidents are simple and stable, in the sense that they cannot be conveyed across generations.

In a stable situation the gain and loss of mutations must balance, but the balance is confused by the variable, and often long, latent period between the gain of the mutation and its eventual loss by death or by impaired health leading to reduced fertility. In infections, the interval between infection and disease may be measured in days, or even years, and in cancers in decades, but the effects of preventive measures are evident within the lifetime of observers, and the effects are usually localized in time and place to where and when the preventive action was initiated. Where populations are exposed to most forms of pollution, dilution with distance will usually limit the effects on health to within the same area as the source, and the responsibility to protect individuals will be national.

On the other hand, in mutational damage there is no safety in dilution. Although distance decreases the dose it increases the numbers exposed, and mutagens may themselves remain active for generations before causing a mutation. The constraints of space and time, and the failure of the damage caused to be limited to either the region or the generation releasing the mutagen makes prevention of mutations a problem of World health: indeed it is the problem of World health.

At present there are around three thousand million individuals under the age of 20, and within 30 years they will have produced another cohort of similar size. The number of basic elements, the nucleotides per gamete, is also this number. That is some ten million, million, million base pairs which are transmitted to the next generation. Some failures in accurate transmission will have fatal consequences, and morally it is inconsequential whether they occur in the near or distant future, or in our own or other racial groups.

The present position, in very approximate numbers, is that each gamete which leads to a live birth conveys about one severe recessive allele. Far higher figures are often quoted, but are based on very indirect inferences (see Cavalli-Sforza & Bodmer 1971) and conflict with direct enumeration (Edwards 1974). In addition, each gamete has a greater than 1 in 1000 chance of having acquired a new and serious dominant mutation, and rather less of conveying either a new or old X-linked recessive disorder; probably at least as many new mutations will eventually be expressed as recessive disease. Most of the mutations are clearly old, but this is formally irrelevant to the need to limit damage from new mutations.

At present we have no way of knowing if the mutation rate has increased appreciably as a result of various environmental insults. In the case of radiation, the substantial background level, with an annual dose of the order of a thousandth of the dose necessary to double those mutations amenable to study, provides good evidence that radiation is a minor mutagen in nature and, so far, a minor mutagen even in populations exposed to nuclear accidents. Even after the Chernobyl disaster, the largest well-documented event, the exposure to individuals in most of the substantial population evacuated appears to have been well below a lifetime's natural exposure.

However, radiation is only one of a number of mutagens, and the only one with simple

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dosimetry and the baseline of a fairly standard world-wide background level. Until recently the detection of mutagens from population studies had to be dependent on counting mutant phenotypes and assumed the mutant phenotype conveyed all the information. This assumption of a 1:1 relation between a mutation and its consequence, originally propounded by Chetverikov (1926), is now known to be false, giving hope that the molecular elucidation of mutations may distinguish forms usually characteristic of various mutagens. This provides a feasible approach for population monitoring by the systematic study of mutations easily defined through clinical presentation. Examples include osteogenesis imperfecta, the haemophilias and Duchenne muscular dystrophy.

The mutation rate in man remains very badly documented, notwithstanding numerous summaries, many of which go well beyond the evidence. For a recent review see Vogel & Motulsky (1986). Estimates are either direct (Gunther & Penrose 1935), by the enumeration of new dominants to normal parents, or indirect, by assuming a balance between loss and gain. Direct estimates require high ascertainment and good diagnostic standards, and disorders in which mild forms are rare. Indirect estimates involve assumptions on fitness in the past. If recessives are used this also involves assumptions on ancestral breeding structure, and is rarely applicable. It is probably not possible to estimate the mutation rate within a factor of two on any but a very few disorders; these are themselves atypical, in both their nature and their mutation rate (Edwards 1974). The magnitude of this bias is considerable (Cavalli-Sforza & Bodmer 1971). Most Mendelian disorders have an incidence well below once per physician lifetime, and precise ascertainment and diagnosis can hardly be expected. Common ones, such as haemophilia, Duchenne muscular dystrophy and osteogenesis imperfecta can usually be diagnosed reliably, but even here mild forms cause confusion, a confusion not always mitigated by detailed investigation.

The main practical measures of prevention at present are the shielding of the gonads at diagnostic X-ray (diagnostic X-rays are still a major and unnecessary source of mutational exposure) and the restriction of any necessary substantial exposure to those above the usual reproductive age, as is now being done in the clean-up after the Chernobyl disaster. Prevention requires data, and data require both the development of new techniques and a procedure for applying them systematically for population screening.

In summary, there is no reason to anticipate that any recent environments to which whole populations are exposed have led to any substantial increase in mutation rate, but, in the absence of any systematic attempt to undertake such work as a priority in World health, such conjectures may merely carry empty reassurance. It is only in relation to radiation, the cause of the greatest public concern at present, that it is clear that, barring wars and accidents, anxieties at the population level are ill-founded.

The avoidance of genetic disease

'Avoidance' covers fetal diagnosis with a view to preventing viable birth, and was first used in relation to spina bifida, which is hardly a genetic disease (Ferguson-Smith *et al.* 1978). The potential of linkage for predicting the disease before it was manifest was advanced in the first paper on linkage in man, with special reference to carrier detection in Huntington's chorea (Bell & Haldane 1937). This approach was widely used for the diagnosis of heterozygosity to the D locus in rhesus disease from the early 1950s; later the feasibility of sampling amniotic

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fluid introduced the prospect of fetal diagnosis and selective termination (Edwards 1956). This is only relevant if the condition can be diagnosed with acceptable precision, if it is severe enough to justify such a procedure, and if the potential mother accepts it. Where there is experience of a severe disorder due to its being so common, as β-thalassaemia in the catholic population of Sardinia, or Duchenne muscular dystrophy in female relatives in the U.K., there is a majority of informed individuals at risk who create a demand for such procedures. The demand is, however, subject to strange anomalies, mainly because of the various ways the severity of the disease is perceived by relatives and by those involved in therapy. Phenylketonuria, for example, which most paediatricians would regard as a far more severe disorder than haemophilia were it to happen to their own children, is a disproportionately rarer cause of termination than haemophilia. Methods may be direct, and in principle accurate, or indirect, and liable to various errors from either mutation or recombination.

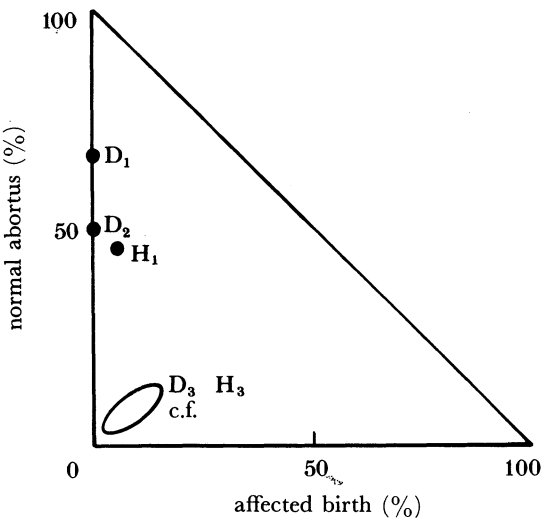

FIGURE 1. Errors in fetal diagnosis with present techniques. D_1, Duchenne muscular dystrophy: sons of mothers of an affected boy; D_2, Duchenne muscular dystrophy: sons of known carriers; D_3, Duchenne muscular dystrophy: sons of known carriers with DNA phenotype of affected brother; H_1, Huntington's chorea: exclusion tests for grandchildren; H_3, Huntington's chorea: children of known carrier with typing of parents and at least one grandparent. c.f.: cystic fibrosis: non-identical DNA markers with affected sibs. The vague oval covers the likely risks, which vary with the degree of parental heterozygosity.

Figure 1 shows the status of fetal diagnosis in various defined conditions. Figure 2 has lines added and it is my interpretation of the median line for those at risk. Such procedures can greatly ease the burdens (including the burden of childlessness) for those at risk, but can make a very limited impact on the population incidence unless screening is possible, as in thalassaemia. The terminology used in fetal disease is confusing. Action must be preceded by diagnosis, which may be direct, as by using ultrasound, or based on examination of fetal fluid, cells or tissues that can be acquired without excessive risk or discomfort. At present, the main source of fetal material is by chorionic biopsy at 9 weeks (this provides both dividing cells and high-quality DNA) and amniocentesis at 16 weeks, after which 2–3 weeks are usually needed to culture cells as the cells available directly contain many dead cells with degraded DNA. The former method is necessarily more hazardous to the fetus because solid tissue is removed, but

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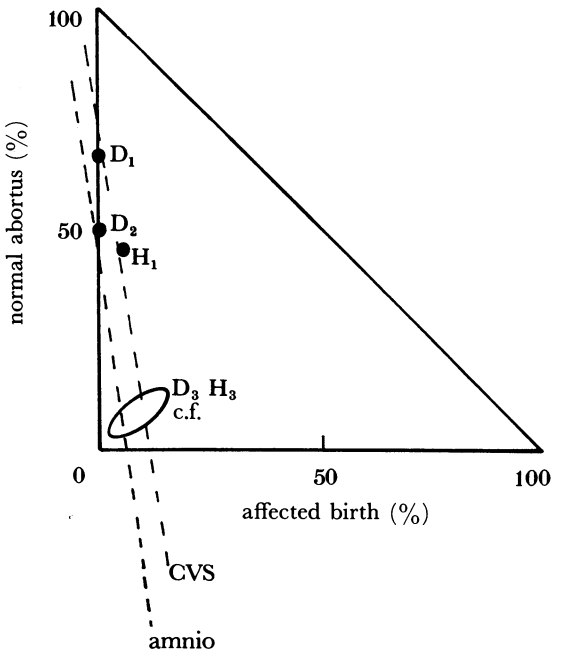

FIGURE 2. As figure 1 but with lines added to represent possible median tolerance of such techniques. It is suggested that about 50% of women with a 50% risk of a son having Duchenne muscular dystrophy will regard amniocentesis and a 20 week abortion as acceptable, and considerably more will accept a 9 week abortion after chorionic biopsy.

if termination is indicated it is far less distressing. The risks are probably of the order of 3% and 1% respectively in good centres, but are very difficult to quantify, and are declining. Direct placental biopsy has the advantage of a lower risk of maternal infection and of being practical from 9 weeks onwards, and of providing both dividing cells and fresh DNA. Basically, the procedure is of fetal diagnosis, usually to impair rather than improve fetal health; such terms as genetic amniocentesis only confuse the issue, for the nature of the disease is not critical to either the technical or the moral issues.

Diagnosis based on cells and tissues can be direct, by studying enzymes, most of which are not expressed in the tissues or cells available, or by studying the lesion in DNA; or it can be indirect, by studying neighbouring loci on the assumption that they would travel together with the offending allele. DNA has the advantage that any tissue provides information on any other tissue. Direct DNA analysis is now possible in some of the haemoglobinopathies, but in most other cases analysis is usually done by tracking the abnormal segment of DNA by defining nearby variants. Where these variants have been defined by molecular methods centred on the offending segment, they are so close that there is no realistic chance of a crossover, and in recessive disorders no realistic chance of a new mutation, and high diagnostic precision is possible. Where the phenotype of the fetus must be inferred by tracking nearby loci whose linkage relation has been inferred by family studies, or where the mutation is likely to be recent, the precision is limited.

In dominant disorders the procedure is limited to conditions mild enough, or unusual enough, to allow adequate family data, and yet severe enough to justify termination. As severe disorders (with a few exceptions, including Huntington's chorea) will be highly mutable, fetal

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diagnosis must depend on defining cases after the first affected case, and most cases will be the first affected. The routine dissection of the genetic lesion in all cases of the commoner dominants, as soon as the locus is defined, is at least possible and may well be the cheapest way of population monitoring, when the benefits to the family of the affected individual would be a bonus. At present individual families can benefit from even limited predictions, but avoidance methods cannot avoid the births of more than a small minority of severe dominant disorders, even assuming a complete consumer demand for affected individuals to die before birth.

In X-linked disorders, most of which are effectively dominant in the male and recessive in the female, the problems generated by a high mutation rate are similar: individual families can benefit but the population incidence is resistant to any major reduction until screening methods, which will depend on defining expression in heterozygotes, is available. The implications are easier to follow in a lethal disorder, such as Duchenne muscular dystrophy, and are summarized in figure 3 (Edwards 1986).

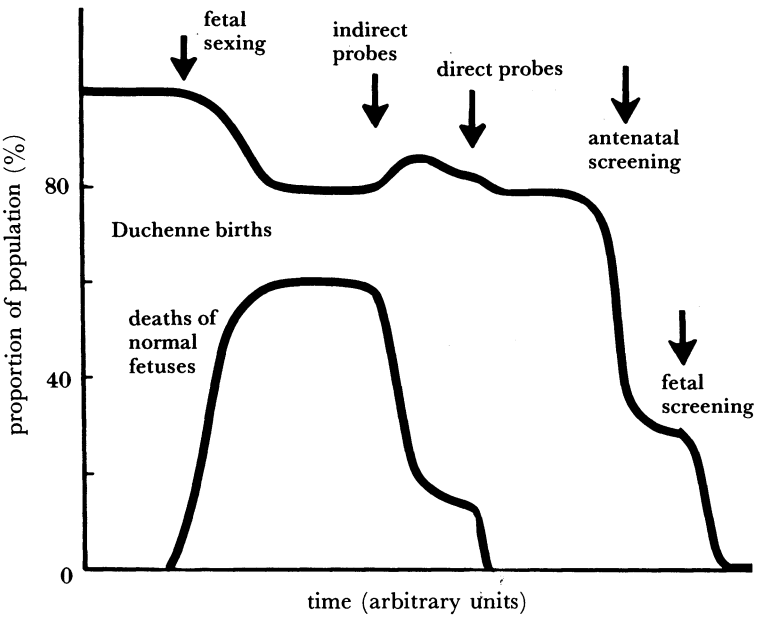

FIGURE 3. Consequences of complete ascertainment and fetal diagnosis with termination in Duchenne muscular dystrophy. Vertical axis gives percentages, or approximate annual numbers in the U.K. (Edwards 1986). Fetal sexing on an appreciable scale started in the late 1970s. Use of direct probes was possible in 1985 (Worton, this symposium).

A correct diagnosis in a recessive means that a previous child must be affected and tested, and the fetus at risk considered affected on the basis of the same neighbouring and variant loci. This involves an identity of four meiotic events, so the error rate is about four times the recombination rate, and, for various reasons involving the asymmetry of the likelihood distribution of linkage estimates, the error rate can hardly be less than $4t+1/n$ where t is the recombination fraction and n is the number of concordant pairs of affected sibs on which the data have been acquired. In addition, because a previously affected sib is needed, and almost 90% of recessive disorders will be the first-known case in the family with the distribution of sibship sizes in the U.K., linkage has a limited prospect of influencing population frequency.

In summary, avoidance by fetal diagnosis and termination has lead to benefits for many families, and the birth of many children who would not otherwise have been conceived, but such methods have little prospect of reducing the burden of genetic disease at the population level (table 2).

If genetic disorders could be treated satisfactorily then the problems of prevention and avoidance would be less pressing, although the consequences would be a slow but inexorable increase in incidence. Direct treatment, by replacing the abnormal DNA segment by a normal segment, may be feasible in the cells of the blood through treating stem cells, but where there is a risk of insertion into the germ cells this would impose quite unacceptable future problems and, as a form of racialism in time, could hardly receive informed ethical approval.

At present, therapy is restricted to replacing what is missing or withholding what cannot be metabolized normally. This is only possible if replacement can get into the right place, as in putting factor VIII into the blood of haemophiliacs, a procedure likely to be revolutionized in safety and cost when the immunologically reactive, the auto-destructive and the active parts of the molecule are defined and organisms or cells modified to produce the active part. This could well be relatively small and stable, and might even survive being taken by mouth. In cystic fibrosis the main cause of death is limited to the lining of the lungs, which are readily accessible to medication from sprays and powders, so that therapy is in principle feasible within a decade, a fact that gives hope to those affected and greatly confuses the choice of action now that fetal diagnosis is becoming reliable. Heart–lung transplantation offers the possibility of cure of the main cause of disability, but imposes serious problems of resources both in finance and organ availability. In disorders that affect solid tissues, such as muscle, brain and the sense organs, it is difficult to see how any large missing molecule could gain access. In many disorders there is evidence before birth.

Phenylketonuria, the commonest recessive disorder in caucasians, is amenable to treatment by dietary restriction, which greatly improves development. However, notwithstanding some exceptional cases, the intellect is usually dulled compared with the parental IQ, and there is a major burden in the children of affected girls who are at risk for severe microcephaly, although this risk can be reduced by returning to the rigours of the childhood diet. The disorder remains a serious one outside the several centres of excellence that divert major resources to this one disorder. Specific treatments are available for many disorders, and some may be both simple and effective, as in congenital adrenal hypertrophy, where the major problems are usually related to late diagnosis, which is not a problem with the second child: nor is fetal diagnosis and termination.

Although a few disorders may be amenable to treatment, and most benefit from medical supervision, the prospect for therapy making any major impact on the suffering from most genetic disorders seems limited, and, in the long term, successful treatment of genetic disorders must increase their incidence. The preoccupation of the financial aspects of costs, which can be costed, and benefits, which cannot, is already leading to policies in which the availability of expensive treatment is an indication for funding diagnostic procedures allowing death before birth. It is easier to expand fetal diagnostic procedures than to limit therapy, a position now confused by the development of fetal surgery.

Table 3 attempts to portray the status of various disorders and the prospects of fetal diagnosis in a population of 2.5×10^6 with 30000 births a year, which is about the average for the regions into which the National Health Service in the U.K. is divided.

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TABLE 2. EFFECT OF FETAL DIAGNOSIS USING NEIGHBOURING MARKERS ON THE INCIDENCE IN THE POPULATION AND THE RELATIVES OF AFFECTED INDIVIDUALS

disorder	population incidence	familial incidence	proportion of false positives
dominants			
lethal	none	none	—
severe	slight	some	most
moderate	some	most	some
mild	most	most	few
X-linked			
lethal	slight	most	some
moderate	some	most	some
recessive	slight	most	few

FUTURE PROSPECTS

Because prevention can do nothing about the serious mutations already established in the population, which are almost as numerous as the population itself and which, given time, will lead to the birth of individuals with serious genetic disorders whose numbers would be comparable to the present world population, any success in reducing the rate of mutations will hardly modify the need for treatment if possible and avoidance if not.

Although the slight effects of mutations that are not consistently related to clearly defined phenotypes are clearly more important than those due to Mendelian disorders, because the non-coding segments are far more extensive than the coding segments, it is at present only possible to consider the approximate load from clear-cut genetic disorders. We must accept that these are the mere tip of an iceberg, with perhaps the hidden and more hazardous part of around tenfold the volume of the visible part. If, as with parasites and predators, genetic disorders were dominated by a few species that could be eliminated by specific methods, aided by general advances in the availability of adequate and safe sources of food, air, fire and water, then we could anticipate effective policies of prevention.

Muller (1950) pointed out the paradox that because severity is inversely proportional to longevity, all dominant mutations are equally detrimental, whether they impose a small risk over many generations, or are fatal before reproduction in the first generation. The same applies to alleles predisposing to disease. Although the so-called multifactorial disorders which are diagnosed before irreversible changes have occurred are in principle amenable to therapy, they are not amenable to artificial selection.

However, with a few exceptions, of which Rhesus disease is the most important, the successes possible with infective and nutritional disorders are not possible in genetic disorders. The mutations are integrated into the genome and can only be removed by preventing their transmission before conception, including *in vitro* conception, or arranging death before birth.

Where a specific lesion can be anticipated it can in principle be defined, and its transmission prevented or aborted; this is now possible in the chromosomal disorders and the increasing number of genic disorders that can be defined by enzyme analysis or defined or predicted by DNA studies. However, the detection of unexpected variants, which, by definition, are new

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TABLE 3. APPROXIMATE ANNUAL LOAD OF NEW CASES OF GENIC DISEASE IN THE OXFORD REGION, U.K.
(POPULATION SIZE 2.5×10^6, SURVEY OF 30000 BIRTHS)

	annual number	antenatal screening	fetal	birth	neonate	parent	probes available	severity	status
dominant									
Huntington's chorea	5	–	DNA	–	–	late onset	N	+++	possibly unique
polycystic kidneys	30?	–	DNA	–	–	+	N	variable	mainly old
neurofibromatosis	5	–	–	–	20%	+	?	variable	often new (30%)
tuberose sclerosis	3	–	DNA	–	20%	+	N	variable	usually new (70%)
myotonic dystrophy	5	–	–	–	20%	+	N	variable	rarely new
recessive									
haemoglobinopathies	10?	Pr	DNA	+	+	Pr	D	+++	old, many forms
cystic fibrosis	15	–	DNA; Pr	+	+	–	N, ?B	+++	old
phenylketonuria	2	–	DNA	–	+	(+)	D	++	old
adrenogenital	5	–	DNA	+	+	(+)	D	+	old
α anti-trypsin	5?	Pr	DNA	+	+	Pr	D	+	old, several forms
Tay Sachs	<1	Pr	Pr	+	+	Pr	–	+++	old
X linked									
Duchenne muscular dystrophy	5	–	DNA	+	+	(+)	D, F, B	+++	recent 80% new mutants
haemophilia	3	–	Pr, DNA	+	+	(+)	D, F, N	+	recent 30% new mutants
retinitis pigmentosa	2	–	DNA	–	–	(+)	N	++	recent 10% new mutants
christmas disease	<1	–	Pr, DNA	+	+	(+)	D, F	+	recent 30% new mutants
fragile-site (? genic)	5	–	Chr	+	+	(+)	–	+++	some very large families

D, Direct.
N, Neighbouring.
Pr, Protein or enzyme methods.
F, Flanking variants (within kilobases).
B, Bracketing variants (within megabases).
Chr, Chromosomal (fetal blood).

mutants, is impractical both through the sheer number of possible sites of mutation and the background of variability against which any new variant must be defined. Even if methods were available for completely sequencing DNA from cells sampled from a human embryo, or for defining all differences from the parental genomes, the interpretation would be limited to the exclusion of mutations known to have been detrimental in the past, and recurrent mutations at the nucleotide level are unlikely. Estimates of the expected number of such variants are vague because of lack of data but indirect estimates on the inappropriate assumption of neutrality are consistent with 10–100 per generation (Kimura 1982), and strongly detrimental mutations would be far less. Once such variants were found prediction of phenotype would be largely dependent on precedents from expressed disease in the past. Because of the similar number of base pairs and of the human population some millennia would be needed for the enumeration and documentation of even half these variants. Those related to coding sequences of essential proteins could be defined by predictions based on structure, but the bulk of the DNA does not code and, as very few detrimental mutations have been defined in non-coding regions, they cannot usually be expressed as Mendelian disorders and consequently do not allow clean predictions. Many may be expected to be of a strongly interactive nature involving other loci and the environment. Vague predictions, which are possible from empirical data on so-called multifactorial disorders in relatives of those with manifest disease, are rarely large enough to justify termination, and predictions based on the detection of determinants are unlikely to exceed predictions based on manifest expression.

The use of a complete genetic map

The understanding of human disease is dependent on the metabolic pathways, which can be represented by maps. Basically these document the actions and interactions of metabolites, mainly within the cytoplasm. Because cellular differentiation is the basis for our biochemical versatility, and even within cells many activities are segregated within organelles, the unravelling of these pathways is very difficult. The broad outlines are now well documented as metabolic maps, which are basically cytoplasmic maps. The proteins that make up the bulk of these maps and that control the formation, modification and degradation of themselves and of other metabolites, are derived directly from the coding regions, which are linearly arrayed. These can be mapped to give the genetic or nuclear map, a map rapidly evolving through several techniques, and now within range of direct attack by total enumeration.

Sequencing the genome has attractions as a challenge to technical ingenuity both because it resolves something unknown about ourselves and because it provides a challenge which can only be met by developing new instrumentation and data-processing methods. These involve resources similar to those expended on surveying the back of the Moon, and have strong justification on the aesthetic grounds of the ugliness of ignorance, as well as the feasibility of being politically attractive as a relatively harmless venture into advanced technology.

Although such a core of data will provide the basis for a new biology, with profound implications for evolution, and for the nature and frequency of natural mutations, it is less clear if such maps would be of substantial value to the control of genetic disease. The pioneers in genetics clearly expected the genetic or nuclear map to have a close connection with the metabolic or cytoplasmic map, so that sequences of several genes would be related to serial metabolic activities, or to the coherent development of parts of the embryo. Although such

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integrated segments are known, they are relatively rare in the genomes of higher organisms. The large families of proteins that have clearly evolved from a single source, such as the three loci in the myoglobin, haemoglobin series or the three in the heavy and light chains of the immunoglobulins, or the many members of the serine protease family, are widely scattered over the genome. The various mammals differ widely in the number and proportion of their chromosomes, although not in their total DNA. Between mouse and man there has been a widespread disruption and reorganization, involving at least 100 cuts and joins, but there is no reason to relate the difference in the order of the loci to the differences in phenotype (Searle *et al.* 1988).

Comings (1979) advanced the term the 'New Genetics' to cover the application of knowledge of genetic maps without reference to the metabolic map for phenotypc prediction. This term has been widely used in the distinct sense of 'recent methods in DNA research', but it is a useful term, and is important in providing a procedure for predicting fetal disease, with necessarily limited accuracy, while awaiting methods allowing either accurate diagnosis or effective treatment. In thalassaemia it has never been needed, because the DNA was defined by direct methods, but it is the only procedure available for prediction in Huntington's chorea and, at present (mid-1987) for cystic fibrosis, and still has a declining place in the fetal diagnosis of Duchenne muscular dystrophy. By definition, as a method of control of genetic disease it is limited to prediction and termination, by methods which, because they by-pass the cytoplasm, offer little prospect of an improved understanding of the disease process. In Comings's words 'We now have the ironic situation of being able to jump right to the bottom line without reading the rest of the page, that is, without needing to identify the primary gene product or the basic biochemical mechanism of the disease. The technical capability of doing this is now available. Since the degree of departure from our previous approaches and the potential of this procedure are so great, one will not be guilty of hyperbole in calling it the "New Genetics"'.

It now seems reasonable to infer that the genomic organization involves short range interactions, related largely to physical contact and involving sites within a few kilobases, and long range actions involving diffusion. Middle range actions, on which the meaningfulness of gene order on function would depend, appear to be rare, and to lack any simple mechanism. Consequently, the central feature of the genetic map, the order of the functional segments, would seem of limited value. The sequencing of this set of sequences, without a knowledge of order, is a far simpler procedure technically, and will provide the information on the individual loci necessary for exact diagnosis and the development, or the abandoning, of therapy.

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Discussion

H. Sharma (71 *Barrack Road, Hounslow, U.K.*). Genetic disease varies in significance. For instance, phenylketonuria can be easily corrected by diet in childhood. On the other hand, there are inherited diseases for which abortion can be available, if parents choose. Is there a list organized by government, or a voluntary code of practice, for diseases in which abortion may or may not be available?

J. H. Edwards. No. The matter is unsuitable for such a list. Even in a society allowing, or encouraging, abortion on demand, there are women unconditionally opposed to abortion for any reason, and others to whom any pregnancy justifies termination.

In addition, almost all diseases vary from very mild to very severe, and new diagnostic techniques are finding milder and milder forms.

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