AMER. ZOOL., 26:835–844 (1986)

Science as a Way of Knowing: Human Genetics[1]

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SYNOPSIS. Genetics contributes to our way of knowing in two ways: 1) there is an analytical method that sorts out relationships between genes and phenotypes and 2) the genes transmit biological information, specify cellular structure, and mediate homeostasis and development. Human genetics can be used to clarify many aspects of human variation. The paper deals with three: 1) the meaning of individuality; 2) the nature of causes; and 3) possibilities and limits for goals in medicine.

The genes define individuals as unique representatives of many classes. They contribute variability to the qualities of each class. Phenotypes have two kinds of causes (Mayr, 1983): proximate causes lead to events consequent upon decoding of the DNA, while ultimate causes consist of the genetic and cultural events that shape the species and the individuals of which they are composed. Disease is a consequence of incongruence between a genetically conditioned homeostasis and experiences and events. The genes set limits for homeostatic response thereby limiting both the forms and expressions disease can take in various individuals and the extent to which the latter can be modified by treatments of various kinds.

Science as a way of knowing is a phrase with a degree of ambiguity. First, it suggests that science is a pathway to a desirable goal, perhaps that of knowing oneself, or of understanding electricity. But then, science is also a design for knowing, a matrix to give conherence to the strands of experience, one of the looms on which the fabric of knowledge is woven.

Genetics exemplifies both of these "ways." Its analytical method is a means to an end; it accounts for the variation observed in populations, traces the origins of phenotypes to genes, differentiates individuals, families and populations, and ferrets out homogeneous components from heterogeneous samples. It introduces order. And as for a design for knowing, the genes are the architects of biological structure, the mediators of development and homeostasis and the keepers and transmitters of biological information. It is clearly not possible to comprehend biology in any but a genetic context.

Human biology has not, until recently, had much of a genetic tradition, probably because human biology has focussed mainly on disease in which immediate causes, pathogenesis and treatment are paramount. But now technological advances have stimulated a keen interest in the genetic origins of human differences of all kinds.

There is little to distinguish human genetics from any other; the mechanisms are the same in principle, if not always in detail. So the question to be examined here is what are the uses to which we put our knowledge of human variation? How does genetics help us to know ourselves?

I would like to examine three ways. A knowledge of genetics is essential for a good grasp of a) the meaning of individuality, b) the nature of causes, and c) possibilities and limits for goals in medicine.

INDIVIDUALITY

Two kinds of individuality

As every biologist knows we express our individuality in two ways. First, we are each representative of numerous classes; for example, sex, religion, and national group, and we are also poker players, diabetics, or members of the American Society of Zoologists. In each class the individuals are distinguished only by the characteristics of the class. On the other hand, each of us is in a class of our own, representative only of ourselves by virtue of the uniqueness of our endowment and experiences. Genetics gives us some insights into both of these

[1] From the Symposium on *Science as a Way of Knowing—Genetics* presented at the Annual Meeting of the American Society of Zoologists, 27–30 December 1985, at Baltimore, Maryland.

kinds of individuality and helps to resolve controversies that arise out of confusing them. For example, when comparisons between groups reveal differences, there is a tendency to label the groups typologically, when, in fact, the differences within the groups may exceed those between. This is what Ernst Mayr (1961, 1983) calls typological thinking or essentialism. Its antithesis is population thinking. The latter takes into account the individuality expressed in populations and describes differences between them as a consequence of overlapping distributions rather than of typological distinctions. It was just such typological thinking that characterized the muddle that swirled around the supposed association of the XYY karyotype with antisocial behavior. Since the first cases were discovered in prisons, it was presumed in some quarters that men with an extra Y chromosome were doomed to a life of crime. The press even called the Y the "violence" chromosome, in plain disregard for the pacific character of most of its possessors. Later, population studies revealed that those with two Ys were somewhat more at risk for behavioral aberration than those with one; the former were about as variable as the latter (Witkin *et al.*, 1977).

Polymorphism

What is the extent of the genetic variation on which human individuality is based? Until 25–30 years ago it was generally assumed that human genotypes were largely homozygous; the relatively few mutants were assumed to be bad and to constitute a genetic "load" (Muller, 1950). Now we know that human beings are genetically highly polymorphic; that is, there are constellations of alleles for many gene loci in which two or more exist in frequencies of more than one percent (Harris, 1980). Electrophoretic differences in soluble enzymes, plasma constituents and other proteins suggest individual heterozygosity at 1–6% of loci, and since electrophoresis fails to discover all variants, this may be a considerable underestimate (McConkey *et al.*, 1979; Harris, 1980; Rosenblum *et al.*, 1983). And, of course, each of us has some rare familial variants and some new ones. Recombinant DNA methods have shown even more extensive polymorphism in introns and flanking regions, and these have proved useful as markers in mapping the chromosomes as well as in antenatal diagnosis (White, 1984). Surely all this variation, compounded by experiences, is more than enough to account for the immense range of apparent individuality which, as I shall point out later, has its counterpart in the various ways people get sick.

Most polymorphisms are found in all populations regardless of race; for example, the loci of the major histocompatibility complex have been found everywhere to be so variable as to cause nearly everyone to be heterozygous for each; but a few polymorphisms are geographically circumscribed; hemoglobin S in Mediterranean people and alpha-thalassemia in the Far East are examples.

We are accustomed to thinking about genes and their effects one by one, and as inherited independently. But, in making it possible to study chromosome structure, even to observe the details of DNA strands that sometimes include several loci transmitted together, modern techniques are giving us glimpses of new dimensions of individuality. For example, by examining the allelic composition, or haplotypes, of the several MHC loci, together with neighboring loci that specify elements of the complement cascade, it is possible to relate clinical differences in patients with immunological disorders to particular concatenations of genes (Ryder *et al.*, 1981; Alper *et al.*, 1982) (Table 1). Some of these allelic combinations are observed more often than chance would allow; they are in linkage disequilibrium (Bodmer and Bodmer, 1978). Presumably together they exert a stronger or different effect than that possible for each alone, thereby substantiating the axiom that selection acts not on genes but on phenotypes. Other interacting (or modifying) genes may exist at unrelated loci. Their discovery is likely to be among the benefits of chromosome mapping which should lead to the assembly of lists of genes accounting for variation within particular

TABLE 1. *Haplotypes associated with disease.*

Haplotype	Association
A3, BW47, DR7, BFF, C2C, C4AQO	21 OH'ase deficiency
AW30, B18, DR3, BFF1	Diabetes (IDD)
A1, B8, DR3	Several diseases

From Alper *et al.*, 1982.

phenotypes. And, of course, individuality is also strongly conditioned by development, experiences, the environment and particularly by learning. The latter has heritable features also, some of which resemble genetic inheritance (Cavalli-Sforza *et al.*, 1981, 1982).

These relationship of genes and experiences to individuality and to the distribution of phenotypes in populations represents population thinking. It is a way of knowing, and human affairs, both biological and social, are incomprehensible in any other setting. Essentialism, in contrast, in giving primacy to stereotypes, to the general rather than the particular, in embracing many under a rubric that describes only some, however useful or even necessary in classification and economical disposition of diverse classes, risks lending plausibility to ideology.

CAUSES

Ernst Mayr (1961, 1983) has pointed out that, until this century, biology was divided between medicine (including physiology) and natural history. Medicine and physiology, he goes on to say, deal with function; they are concerned with questions of how—how things are put together and how they work, and, we might add, how they go awry. The answers to these questions about function will reveal what Mayr calls proximate causes, which lead to everything that happens after the decoding of the genetic program. In contrast, students of natural history ask questions about why; of how things came to be what they are. These are questions about ultimate causes, about evolution; they are questions about the history of genetic programs, and of how they take shape and change. The mechanisms involved in the evolution of species give form and substance to individuals who become the testing grounds for new versions and new combinations of old genes. Obviously, no biological question can be said to be fully understood until both kinds of question have been answered. Human genetics contributes to our understanding of both kinds of cause.

Proximate causes will be elaborated more fully in the section devoted to medicine. Here I consider ultimate causes.

Effects of ultimate causes

If proximate causes of individuality are the outcomes of specific genetic programs, ultimate causes determine what kinds of programs are possible. They constrain, they set the limits to the forms the genotype is capable of specifying. Such constraints are expressed in the complex homeostatic systems required to maintain a steady state in the varied environments human beings encounter. It is our evolutionary history that makes us human, a history that is written in the nucleotide sequences of the DNA and in the amino acid sequences of the proteins. Such sequences show how the human genome evolved; for example the origins of the several globin loci are readily visualized in both DNA and amino acid sequences of the human and other hemoglobins (Orkin and Kazazian, 1984). A spectacular demonstration of the evolution of several families of genes engaged in immunological missions, written in DNA sequences has been provided by Hood and his colleagues (Hood *et al.*, 1985). And observations of DNA and amino acid arrangements of the proteins of organisms ranging from microorganisms to man not only validate phylogenetic trees based on morphological evidence, but show that changes occur with a regularity that suggests an evolutionary clock (Wilson, 1985). The inescapable conclusion is that we human beings, for all our intellectual power and technological prowess, are caught up in a biological network from which we shall not easily escape, despite all our boasts that we now control our own evolution.

MEDICINE

If genetics provides a way of knowing individuality, it should be central to the

study of medicine and yet it is given a subsidiary place in the medical curriculum, if any at all (Childs *et al.*, 1981). It is true that all teaching hospitals have medical genetics clinics for the care of patients with "genetic" diseases, including inborn errors, chromosome abnormalities and anomalies of development. But this is evidence that genetic disease has been classified typologically. Other kinds of disease classified as, say, endocrine, immunological, pulmonary or renal, even though plainly influenced by the genes, are not attended by medical geneticists, and there is a significant risk that their familial aspects will be ignored. Why should this be?

Limitations of the past

A minor reason is that genetics has no tradition in medical education and practice. Unlike biochemistry, physiology, and molecular biology which flourished in medical schools from the start, genetics was introduced more often than not by zoologists and botanists who, because they knew Mendelian genetics, were able to counsel families about reproductive risks.

A more compelling reason is that medical people just do not think genetically; medicine is still largely essentialist; population thinking has yet to achieve any widespread appeal (Childs, 1982). Perhaps this is not surprising, is even to be expected. The last 20 or 30 years are characterized by an immense expansion of knowledge of biological structure and function. Biochemists and molecular biologists have been elaborating the fundamental rules of homeostasis as they apply to (among many organisms) *Homo sapiens*, while medical investigators have been applying the newly acquired information to the elucidation of the pathogenesis of disease. Both groups focus piercingly but narrowly on proximate causes. In all this, variability would be a nuisance. So, individuality has been shunted aside in the interest of working out prototypes. But, unfortunately, prototypic teaching does not cultivate curiosity about the variability that inevitably modifies the prototype. Neither does it arouse much curiosity about the origins of variability nor about its limits or the constraints those limits put on types of disease and their signs, symptoms and susceptibility to treatment. It overlooks ultimate causes.

A third reason is the exigence of disease. It is the effects of proximate causes that are treatable; for example, ultimate causes are peripheral to events in a coronary care unit. It is the *fact* of a disease, its symptoms of discomfort and disability, its signs of homeostatic stress, its mere existence, that pose the problems with which investigators struggle. So the ways medical information is generated and the ways the conventional missions of medicine are pursued conspire against an emphasis on variability, and rather than liberating medical thought, genetics has been subordinated to serve a traditional and typological role in the classification of disease and the organization of medical care.

SIGNS OF CHANGE

Genetic heterogeneity

But, as everyone knows, there are signs of change. For years, human geneticists have been pursuing the Holy Grail of heterogeneity, one of the many aliases behind which individuality hides. Heterogeneity simply means the manifold genetic origins of like phenotypes, and it can underlie differences in age at onset, severity, clinical expression, even mode of inheritance of disease or other phenotypes. This quest has been much advanced by the advent of recombinant DNA methods. Observation of base sequences has turned up many kinds of mutations in human DNA (Table 2). All of those listed have been observed in hemoglobin variants, most in beta thalassemia. And for each type of mutation there are numerous possible variations, many already described, others awaiting discovery. Obviously, the elucidation of heterogeneity has implications not only for the dissection of the human genome and the measure of its range of variation, but also for the design of treatments specific for genetic cause. Now the whole of the human genome is a hunting ground for the detection of restriction fragment length polymorphisms, deletions and other quarry

(White, 1984). For example, at a meeting last summer it was reported that over 800 genes have been mapped, while regionally localized DNA segments not known to represent specific genes, but of use in mapping, number in excess of 500. The X-chromosome is the best known, with 214 mapped sites (Chapelle, 1985). All of these numbers are immediately overtaken by events and the tempo of discovery is such as to suggest that the means are at hand to define the whole map. Further, since genes can be discovered in the absence of knowledge of their product or its role in homeostasis, it may become possible to practice a kind of upside-down genetics in which phenotypes are traced from the gene, rather than the other way around. An important outcome of this mapping of genes will be the characterization and enumeration of the molecular variability of cellular structure and homeostatic mechanisms; the pathways, cascades, mosaics and networks of interlocking and communicating systems. In turn, these details will be used in explaining the processes of disease and the design of new treatments. And in bringing together mechanism and individual variation, genetics is likely to move into the mainstream of medical thought and practice, by going beyond inborn errors, anomalies and chromosome aberrations to define the genetic contributions to the common diseases of adult life. The former are numerous, rare, burdensome, resistant to treatment and largely confined to prepubertal life. The latter, mainly representing postpubertal disease, are less numerous, more frequent, less burdensome as to mortality, and more likely to respond to ameliorative treatment. They are believed to be multifactorial in origin; genetic susceptibility is suggested by familial aggregation of cases and partial concordance of monozygotic twins, and special provocative and precipitating experiences are postulated.

A continuum of disease

This is a typological description of what appear to be two kinds of disorder. But the differences may be largely illusory. If disease is defined as incongruence between homeostasis and experience, then it can be shown that there is a continuum of disease to which the genetic contribution declines from conception to old age. First, intrauterine selection is intense; up to three-fourths of conceptuses do not make it to term and the evidence suggests that many of the losses are genetic (Roberts and Lowe, 1975; Edmonds *et al.*, 1982). Second, much of the mortality of the first year of life is also genetic, and in general, onsets of monogenic diseases decline rapidly with age; more than 90% of such disorders have declared themselves by puberty, only about 1% after 40 (Costa *et al.*, 1985). Third, in postpubertal diseases the cases of early onset are more likely than those of later onset to be severe, more life-threatening, more resistant to treatment, and more likely to to have affected relatives (Childs and Scriver, 1986). That the latter represents concentrations of genes in the cases of early onset is suggested by the aggregation in the younger cases of several autoimmune diseases of certain immunologically significant polymorphic alleles (Childs and Scriver, 1986). And fourth, advancing age is accompanied by a narrowing list of diseases; people with genes predisposing to disease are likely to come down with them before old age (Kohn, 1982). Taken altogether this evidence suggests a gradient of genetic effect that wanes throughout life. The most selectively disadaptive genes exert their effects with minimal reference to the rest of the genotype or the environment, and they tend to do so early in life.

TABLE 2. *Kinds of mutation found in human DNA.*

Missense
Deletions
Nonfunctional mRNA
Nonsense mutations
Frameshifts
RNA processing mutants
Splice junction
Consensus changes
Occult sites
Promoter region mutants
RNA cleavage mutants
Position effect mutants

After Kazazian, 1985.

Others specify a Mendelian phenotype, but one that is modifiable by other genes and by experiences. Still others merely predispose to disease; they are disadaptive only in the presence of certain other genes and of special circumstances and experiences, and they are likely to have onset in adult life. So there are monogenic disorders and multifactorial disorders and some diseases have versions of both; diabetes and gout are examples (Childs and Scriver, 1986). Some cases, usually of early onset and often the most severe, segregate as Mendelian phenotypes, while others, usually of later onset and of milder expression, are irregularly familial, suggesting multifactorial origin. And those of latest onset, the least affected by genetic variation, are most obviously associated with special experiences. That is, monogenic and multifactorial disorders are not typologically distinct either in expression or cause, but differ only in the degree of selective disadvantage imparted by the genes involved. The typological distinction is based on the artifact of Mendelian segregation of the monogenic phenotypes—I say artifact because the genes of the multifactorial conditions are no less Mendelizing; it is just that their effects are individually less salient. The typological distinction is also less than compelling when we consider ultimate causes. The genes that promote disease are a product of the processes that engender the variation necessary for evolution. Those processes are indifferent to outcome; mutation, recombination and segregation of chromosomes merely generate the variation that is tested in living. Most is the stuff whereby the species prospers, but some is incompatible with any life, some is disadaptive when in conjunction with special experiences. That which is incompatible with life is most likely to be a consequence of mutation at one locus or a major chromosomal aberration; individual susceptibility is more likely to be associated with several or many genes. But only likely; we know of single gene differences and chromosomal aberrations compatible with good health and there are multigenic developmental disasters. So we do best to see disease as a continuum with emphasis on disadaptive genes in early life and adverse experiences later on. A cohort of human beings is at its most variable genetically at conception and at its least in old age. Conversely, variability due to experience increases with age.

Management of disease

Is this simply an interesting observation or can it help in practical ways in our struggle with disease? It may help most in emphasizing the genetic contribution to susceptibility to disease and in defining limits to success in treatment and prevention.

Presumably gene mapping will proceed until we know most of the disadaptive genes that cause the monogenic disorders, as well as the special combinations most frequently associated with the more common multifactorial diseases. These observations should be helpful in the discovery of proximate causes, and in defining the three elements that are required for the design of treatment and prevention. They are: a) the gene products and the part they play in homeostatic systems; b) the experiences that stress such systems; and c) the consequences of such incompatibilities, that is, pathogenesis. When all are known, we may be able to envision how to nullify some critical step in pathogenesis, or to minimize or eliminate the environmental stressor.

Treatment

Treatment is most successful when the precipitating factors and pathogenesis are known and all genotypes are equally susceptible (Table 3). In such cases—infections and nutritional diseases are examples—an actual cure is effected by removing the offending agent or by supplying the deficiency. It is next best when something is known of both provoking experiences and pathogenesis, and when individual susceptibility is observed to be a product of several genes. Some of these diseases, although incurable, are kept in abeyance by environmental manipulation. For example, insulin-dependent diabetes is treated with insulin and non-insulin dependent diabetes is controlled by diet and weight loss. Treatments are sometimes moderately successful in monogenic disorders when the provocation is known,

TABLE 3. *Success of treatment and prevention depending upon knowledge of genes, provocations and pathogenesis.*

Genes	Experiences	Pathogenesis	Treatment	Prevention
1. None	Known	Known	+++	++++
2. Multiple	Known	Known	++	+++
3. Multiple	Unknown	Known	++	−−
4. Mono	Known	Known	++	±
5. Mono	Unknown	Known	+	−−
6. Mono	None	Known	−−	−−
7. Mono	None	Unknown	−−	−−

although often lifelong and sometimes difficult to maintain. Phenylketonuria, galactosemia, and the adrenogenital syndrome are examples of such success. Treatment is least successful in monogenic disorders in which the gene effect prevails over all environments, regardless of whether or not the details of pathogenesis are known. None of these monogenic disorders can be said to be cured.

Here we are seeing the effects of ultimate causes; that is there is an inverse relationship between success in treatment and the intensity of selection against the gene effects. The more profound the transgression of adaptation, the less likely is even a plausible treatment to work. Where there is no experience or condition of the environment that contributes to the cause, our interventions are usually unavailing; except perhaps where the disadaptive effect is pretty mild anyway, or occasionally, when there is a definitive surgical solution (Hayes *et al.*, 1985).

Prevention

Prevention is most successful when the precipitating experiences are known and can be manipulated (Table 3). And because pathogenic changes are likely to leave some scars, however inapparent, prevention is likely to be more in the patient's interest than any treatment, even though the latter may represent a cure. As with treatment there is a progression of lessening success with increase in the disadaptive qualities of the genes. The position is least ambiguous when the provocation acts equally over all genotypes. Such disorders—lead intoxication and nutritional diseases are examples—might be called diseases of society rather than of individuals, since they occur most frequently among those denied the benefits of social organization. The greatest ambiguity is met in monogenic disorders expressed only in the presence of a precipitant. When the latter is a dietary necessity such as milk, even when the manifestations can be controlled by appropriate adjustment as in phenylketonuria and galactosemia, the disease cannot be said to have been prevented. But when the provocation is a drug, as in glucose 6-phosphate dehydrogenase deficiency, the expression can be prevented altogether by withholding it.

Antenatal diagnosis

So here again are seen the subtle constraints of ultimate causes. Prevention is no more successful than treatment when the mutant exerts its effects over all environments. But if those constraints will not be denied, one way out is to anticipate them. When a diagnosis of an untreatable disease can be made early in gestation it is possible, paradoxically, to prevent the disease by preventing the birth of affected fetuses. This is a definitive, and for many physicians and families acceptable, solution for severe disease, and it is now possible to make an antenatal diagnosis of more than 150 such disorders (Epstein *et al.*, 1983). Here again the limits are set entirely by the techniques available and the energy with which they are applied. Uncertainty enters in when the disorder is more or less treatable or has a delayed onset. And, of course, the method is useful, except in a limited number of cases, only in families concerned about recurrence; widespread discovery of heterozygotes is not yet possible. But it is a solution of wide appeal and one that is in tune with nature; most diseases

for which the method is appropriate are under heavy adverse selection. And it is one that will be greatly expanded as a result of the "new genetics."

The future

We are all wondering just now what other impacts the "new genetics" will have on diagnosis, treatment, and prevention. Will it transform medicine and, together with other technological advances, lead to a society free of disease in which human beings, after serene untroubled lives, die of programmed senescence at around 85? The idea can be dismissed as nonbiological; it denies the constraints of ultimate causes. At a minimum, even if all precipitating provocative experiences were known and could be nullified, there would remain those genes that exert their bad effects without any such provocations. But since man is adapted to the conditions of the past, not the future, and since the creation of new environments and experiences uniquely characterizes human beings, no environment non-threatening to a genetically diverse population is likely ever to prevail, even if society wished it, which it most manifestly does not. So the question is not the recreation of the garden of Eden, but of *how much* we can reduce the nongenetic contribution to disease.

Genes and susceptibility

Gene mapping promises to be helpful in discovering markers associated with disease. Here, immediate utility will be directly proportional to the strength of the adverse selection. When a single mutant can be exposed as a cause there is hope for some kind of definitive disposition because of the reciprocal relationship between success in treatment and the appositeness of antenatal diagnosis and abortion; for genes of strongly adverse effect the latter may be preferred, for milder cases the former.

But ambiguity will increase as the map density increases. Some genes will be shown to be strongly associated with disease and may be inferred to be a part of cause, and as such they will be useful in unravelling pathogenesis. But not all will carry equal weight. For example, if alleles representative of several loci are found in a majority of the cases of a disease, we will wish to explore which loci furnish the genes most directly related to the pathogenesis. Perhaps two or three will be seen to supply the main culprits with others as modifiers, perhaps to heighten severity or make for earlier onset. Other genes, shown to be merely linked to those implicated in cause, may have use as markers, or as indicators for further exploration in search of genes involved in cause.

But most of these genes are likely to have limited utility as diagnostic indicators. Since most multifactorial diseases are common, the genes are likely to be polymorphic, so many more people will have them without disease than with. Even so, relative risks can be calculated and occasionally the genes may have some utility as evidences of susceptibility. Some, like the now celebrated low density lipoprotein receptor mutants, may represent a risk of such moment as to require drugs or special diets (Goldstein and Brown, 1985), others may be a mixed blessing. That is, although the relative risk may be, say, 5–10-fold, the probability of getting the disease may still be low. Further, relative risks are based on populations and so are not equally applicable to each member thereof. So, the knowledge that one has one or more genes commonly associated with particular diseases may represent data of uncertain meaning but which may carry a potential psychological impact grossly out of proportion to the biological risk. There is also the fear of early discovery in individuals of genes that produce disabling and untreatable diseases with onsets in middle life, again with a psychological impact, this time perhaps not so disproportionate (Wexler, 1985). So, these genes will have uses in understanding the nature and variability of diseases, but we may have to wait for a more thorough knowledge of their functional significance, singly and in combination and in relation to specific experiences, before we can use them wisely in diagnosis or prevention.

Gene therapy

There are other applications of the new genetics known in medicine as gene ther-

apy. Given the less than spectacular record of treatment of monogenic diseases, it is no surprise that investigators should wish to substitute good genes for bad (Friedmann, 1983). It is intellectually strongly appealing since in theory it overcomes the evolutionary constraints that inhibit conventional treatment. It circumvents homeostasis altogether, simply correcting the defect in the gene that is reflected in homeostatic breakdown. Such gene substitutions have been accomplished in animals so plans are afoot to try it in human beings, perhaps to begin by transforming cells of the bone marrow in cases of an invariably fatal immunodeficiency. After surmounting inevitable problems it may well succeed and other conditions will be tried. But for all the hundreds of monogenic diseases listed in McKusick's catalogue or for the thousands yet undescribed, quite apart from the numerous technological problems yet to be faced, or perhaps yet even to be imagined, no one can predict the outcome. Perhaps the constraints, so easily thrust aside in theory, may in practice limit the number of conditions tractable to gene therapy. Or it may turn out that the ultimate constraint will be financial.

CONCLUSION

In conclusion, genetics helps us to know ourselves, both as a species and as individuals, and to know how we came to be what we are. It also shows us that some disease is an inevitable by-product of the mechanisms for supplying the variability essential for a successful species. Curiously, it has not had much impact on medical thinking, but it is likely that the methods of the new genetics will remedy that deficiency by establishing the idea of genetic variation as essential to the study of human biology and medicine.

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