Window Panes of Eternity.
Health, Disease, and Inherited Risk

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Personal health reflects harmony between individual and experience; it is optimal homeostasis. Disease is an outcome of incongruity leading to dishomeostasis. Relative to earlier times, disease in modern society has higher “heritability” (in the broad meaning of the term). Inherited risks are facts compatible with anticipation and prevention of disease. This viewpoint has major implications for medical practice, deployment of health services, themes of research, and education of health care personnel and citizens.

The Esselstyn Lecture for 1982 is given in the centennial year of Charles Darwin’s death. Darwin enlarged our understanding of life on Earth; life in all its diversity, life as the product of an evolutionary process. Nonetheless, Darwin’s ideas are not received knowledge for everyone living in America today. Some of us, being Fundamentalists, believe that we are here on Earth according to events ordained by God.

Fundamentalism has been a potent force in the making of America [1] and its continuing presence represents one way to deal with uncertainty in the modern world. Fundamentalism in modern America is a social movement rather different from its ancestral premillenialism of Puritan England [2]. The latter mobilized knowledge and science in preparation for a future. The former, particularly in its guise as scientific creationism, has no such ambition since saving ordained souls for a second coming is more important than reform that might deviate prophecy. Hence, should modern Fundamentalism suppress the teaching of genetics in American schools, it will encourage illiteracy in human biology at a time when such knowledge can be used to predict and prevent human disease. Such an outcome, to my way of thinking, would be contrary to the intent of this lectureship in the twentieth century, to the founding Puritan ethic of the seventeenth century in England, and even contrary to the ethic of this disputatious young nation in the eighteenth century (see below).

Charles Webster’s treatise [2] on science, medicine, and reform in Puritan England (1626–1660) and Marsden’s analysis [1] of the role of Fundamentalism in the shaping of American culture (1870–1925) are recommended to anyone interested in the place of science in society; our own or those from which we came.

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and [12]). Since prevention of disease is a principal theme of the 1982 Esselstyn Lecture, the dominant presence of a Fundamentalist ethic in society is a matter of abiding concern. But before I embark on the main theme we can afford to discover an ally of Darwin and the theory of evolution in an unlikely place in an unusual context.

DARWINISM AND EVOLVING KNOWLEDGE

The place is Moscow. The context is an article published on April 19, 1932, in the Soviet newspaper, For a Communist Education. The author is Osip Mandelstam, the poet. He is honoring Darwin on the fiftieth anniversary of his death. The title of the article is “On the Naturalists” [3]. Mandelstam is concerned with Darwin's literary style; his essay ends as follows:

The Naturalist's power of perception is as much an instrument of thought as is his literary style. Invigorating clarity, like a beautiful day during the temperate English summer, and a certain quality in the author which could be called good scientific weather, that is, a moderately elevated mood, work together in Darwin's writings to infect the reader with the same mood and to help him comprehend Darwin's theory.

No one can popularize Darwin's theory better than Darwin himself. It is essential that we study his scientific style, although it is futile to imitate it, for the historical milieu of which he was a part will never be repeated.

Mandelstam's notebooks [3] of 1931–32 contain these additional lines not used as such in the final essay.

It was no accident that the most erudite man of his age spoke directly to the broad reading public over the heads of the scholarly caste. It was important to him to relate directly to this public, and the public did understand Darwin far better than the scholar pedants. He brought his readers something actual, strikingly in tune with their sense of well-being; he answered a social demand.

These insights, originating in a Communist society of 50 years ago, concerning a man who worked in a bourgeois capitalist society a century ago, remain modern because they speak to issues in our own society. Mandelstam believed in the continuity of human culture and in the value of knowledge. He appreciated that Darwin's new paradigm of order in biological systems was linked to a historical perspective and reflected the needs of the culture from which it sprang.

Darwin worked in a post-Copernican, post-Vesalian culture and with a system of biological order whose characteristics reflected the overthrow of earlier paradigms. Ptolemy was replaced in the first context; Galen in the second. Both transitions reflected replacement of dogma by new knowledge. Darwin was born into and lived in the period of bourgeois revolutions when there was transition from static medieval societies to more fluid modern social structures [4]. It is no accident of history that the static Scala Naturae of Linnaeus gave way to a branched evolving view of life. One can argue that Darwin was merely a product of competitive

\[\text{b} \] The Spirit of Man is the title of an anthology of writings by philosophers and poets, compiled by Robert Bridges in 1915 in the darkness and stress of The Great War. It went through many printings over the next 25 years, clearly meeting a need of the reading public. Does anyone of us who delivers the Esselstyn Spirit of Man lectures ever draw on our namesake?
nineteenth-century English society to whom, along with his colleagues, Wells, Matthew, Blyth, Spencer, and Wallace, the idea of natural selection came easily [5]. But it was Darwin, and only Darwin, who made the evolutionary model so apparent, documented its process so brilliantly, proposed a mechanism for it, and made it seem so relevant.

What followed in the wake of Darwinian biology became modern scientific history. Mendelism resolved the principal difficulty of the Darwinian theory, by identifying the component of the life process upon which natural selection acted. Avery, Watson, and Crick characterized that component by discovering the chemical identity and structure of genes. This new view of life, from the vantage point of our knowledge about genes, is truly modern since it means that what is new this year is likely to be old in the next. Theories overturn rapidly; dialecticism is rampant. Yet, for all the turmoil, the new biology constitutes a system of reliable knowledge, because it serves as a basis for action and is relevant to choices of action that are important [7]. One dwells on these historical and cultural perspectives because they are ultimately relevant to prevention of disease in modern society.

THE PATIENT AS MICROCOSM OF EVOLUTION

In Darwinian terms, a successful individual prospers by passing on genes to the next generation. A successful species is composed of prospering individuals. Natural selection acting on the phenotype of individuals is the driving force of speciation. The Galtonian view recognizes that between species and within individuals there is measurable variation in one or another phenotypic characteristic; the limits of normative variation within species can be defined statistically. The prospering organism maintains the norm as a steady state in various biological functions. The cost of deviance from the norm is impaired function or disease (Fig. 1) which, in turn, can impair viability, longevity, development, or reproduction.

Human health represents congruity between the individual (nature) and his experience (nurture) [8–10]. When there is incongruity, adaptive resilience may be impaired and disease can emerge. To understand phenotype in terms of the nature:nurture paradigm is not new. But to use the paradigm to predict that heritability of human disease is increasing relative to what it was is both modern and controversial, and must therefore be explained as I will attempt to do in due course. Yet, to accept it offers an opportunity to apply reliable knowledge for the benefit of individuals at specific (vs. collective) risk to their own health.

The origin of disease is the proper subject of medicine. To understand modern disease we need a historical view. John Graunt's Natural and Political observations upon the Bills of Mortality, published in 1662, demonstrated that the scientific method was applicable to human society as a whole and to the understanding of its apparently haphazard processes—in this case variation in longevity among individuals living in different parts of London [2]. Graunt observed high mortality in

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6Reference to Marshall Berman's recent analysis of Modernism and the experience of modernity [6]—under a title found in Karl Marx' Communist Manifesto—is not so out of place here as it may seem. Berman addresses themes relevant to the spirit of modern man, particularly the dialecticism between man and his modern environment. But more relevant still is this passage (p. 346) which, with slight modification [words added in brackets] is a refrain of the modern human phenotype and its origins in evolution: "The primacy of dialogue in the ongoing life of Modernism [medicine, genetics . . .] means that modernists [physicians, geneticists . . .] can never be done with the past [evolution, mutation . . .]; they must go on forever haunted by it, digging up its ghosts [phylogeny, ontogeny . . .] recreating it even as they remake their world and themselves [and our knowledge of it, of us . . .]."
infancy, a low mean age for the population, and short average lifespan with a low frequency of long-living citizens; he also recorded better life statistics in the suburbs relative to the city center. Graunt's analyses revealed that human disease in seventeenth-century London had its principal origins in environmental events. Improvement of the human condition would presumably improve individual and collective health. The advent of public health, more than the practice of medicine, over the next two and a half centuries remarkably improved human viability and longevity in our industrialized nations. Nonetheless disease did not disappear from society; it merely changed its face.

A given disease—call it a phenotype—has variance. Phenotype and its variance ($V_P$) is the result of two interacting sets of determinants each with their own variance. One set is intrinsic; the other is extrinsic. The first is genetic ($V_G$) with its origin in mutation; the second is experience with its origin in the environment ($V_E$). The reader will recognize nature and nurture under different names. The definition for heritability (of a phenotype) in the broad sense is the relationship between variance due to genetic determinants and total variance ($h^2 = V_G / (V_G + V_E)$). It follows that to diminish the extrinsic "cause(s)" of any particular disease, without eliminating the disease altogether, is to increase its heritability in the residual cases.

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*d* Heritability has two specific meanings for geneticists. Broad-sense heritability is that proportion of the variance of a particular phenotype attributable to genetic (vs. environmental) differences. Narrow-sense heritability is the proportion of variance transmitted directly from parents to children.
(viz. Fig. 1). To put it otherwise, the relative probability of a particular disease (phenotype) originating in mutation is higher today than it was in earlier times.

The argument for changing heritability of disease is nicely demonstrated in the example of rickets [11]. Rickets, a common pediatric condition (and described in Graunt's *Bills of Mortality*), was prevalent in northern nations during the pre-vitamin D era of medicine. Discovery and use of vitamin D (an example of reliable knowledge) reduced the frequency of rickets but did not eliminate the disease from industrialized society. The majority of rachitic children in modern nations have Mendelian disorders that affect homeostasis of calcium or phosphorus metabolism. They have a disease because they have experienced deviation from the normal metabolic steady state; the variance of their phenotype is largely accountable to mutation. Thus, the heritability of rickets, still a "common" disease, has increased in modern times. The transition from lower to higher heritability in the phenotype is the direct result of medical science (discovery) and public health (application). Rickets is a prototype that shows us how we might think about other human diseases in modern societies.

*Mortality and Life Expectancy as Measures of Progress*

For the past three centuries western nations have measured collective health in terms of mortality rates and life expectancy. The youthful state of Massachusetts proclaimed, at the founding of its new Medical Society in 1781, that health was "essentially necessary to the happiness of society" [12]. But even in the newly founded democratic nation, where health was measurably better than in the parent nations, there was still cause for concern by today's standard. Crude mortality rates were 8–28 deaths per 1,000 population and life expectancy at birth was 19–33 years in the New England communities (Fig. 2A). The early years of life were the dangerous years. If an adult survived to 30 years he (or she) was likely to live to 52–67 years and if he reached 70 he would probably outlive 80. By 1900 average life expectancy in the United States had risen to 47 years, and now it is 73 years. Improvement in longevity in this century, in comparison with the two previous centuries, reflects improvement in our passage through the dangerous years of life. As a consequence there has been a progressive rectangularization of the survival curve [13] (Fig. 2B).

Control of acute extrinsic-origin disease is the principal source of our enhanced longevity. Fries [13] argues that chronic disease is superseding acute disease in America; that mortality is being compressed into an ever shorter span of life before an inevitable occurrence of death at about 100 years. Such considerations led him to propose a "one-hoss-shay" view of life and death with an implicit hypothesis that "chronic illness may presumably be postponed by changes in lifestyle" [13]. On the other hand, if one believes that premature aging and death can reflect breakdown in DNA repair mechanism [14] or incongruity between genotype and experience involving critical functions, then we can visualize how heredity may have something to do with precocious aging and onset of degenerative disorders (e.g., atherosclerosis, hypertension, diabetes, cancer).

Human mortality in North America now has an interesting age-specific profile (Fig. 2C). Mortality is very high *in utero*, high in the prepubertal period of life, low in the reproductive period, rising exponentially from the fifth decade onward. These observations implicate a novel view of modern human mortality. In the past, diseases of infancy and childhood, largely attributable to causes of extrinsic origin, accounted for the high pre-reproductive mortality rates. Families compensated by having many children. Improved environmental conditions reduced mortality in the
FIG. 2. Average human life expectancy (left and middle panels) and mortality profiles for male and female sexes (right panel) related to age.  

A. Average life expectancy data for New England in 1781 and in U.S.A. in 1981 (from Estes, [12]).  

B. Change in life expectancy profile in U.S.A. in twentieth century (stippled area) and anticipated improvement (hatched area) with optimization of lifestyle and minimization of risks to health (from Fries, [13]).  

C. Mortality data (rate per 10^6 population by age) for Canada in 1971. Extension of left limb of graph to prenatal period coincides with known 20 percent (or higher) spontaneous abortion rate in man. The hump in death rate during fertile period reflects accidents, suicide, etc., composition of descending and ascending limbs discussed in text (derived from Statistics Canada data).
young; viability increased, fecundity could decline. Nonetheless age-specific mortality remains high in the early years of life relative to the reproductive years. Some early wastage of life is Mendelian in nature or the result of chromosomal dysgenesis and congenital malformation. The survivors, individuals that have been selected to reproduce, do so presumably with reduced mutational impact on their offspring. Those who develop degenerative illness or die prematurely in the post-reproductive period have multifactorial phenotypes that are significant for longevity but not for reproduction. Among all species on Earth, Homo sapiens is the only one with a long post-reproductive period of life [15]. Accordingly unhealthy longevity emerges as an important economic and social burden to modern human society [16].

I have attributed a significant mortality in the early years of life (including the prenatal period) to Mendelian or gene-influenced disease, chromosomal disorder, and congenital malformation. A similar profile for morbidity is anticipated. Three sets of observations support this proposition. First, congenital disease is abundant in pediatrics; up to 50 percent of admissions to North American pediatric referral hospitals belong in this category [17]; the percentage is smaller in less developed countries [18]. Second, over 75 percent of the disadaptive Mendelian disorders listed in the McKusick Catalogues [19] are expressed phenotypically by five years of age (Fig. 3). Third, autopsy studies indicate a high prevalence of gene-influenced and chromosomal-associated disorders and congenital malformations in pediatric patients [20], and in spontaneously aborted fetuses [21].

The nature of mortality in the post-reproductive life period is less clearly characterized. It is fashionable to refer to failure of health maintenance in this period of life as the product of an unfavorable lifestyle [13]. The term “disease of lifestyle” implies that wiser living will help us to live longer. A further implication is that the enemy to health is extrinsic, and related to diet, habits, and experience [22]. According to this view, those who are unhealthy are less moral (in health parlance) than those who are healthy and long-lived.

However, we do not ask why it is that only some and not all of those who smoke, drink, or eat profligately develop precocious degenerative disease. We envisage uniform risk (to the population) in particular experience whereas we could be considering particular risk (to the individual) in universal experience. We are not accustomed to think in genetic terms; we do not accept the biological axiom that in-

![Age at Expression of Mendelian Phenotypes](image)

**FIG. 3.** Relation between percent of total and age at which clinical phenotype of Mendelian disease is established. Data represent 34 X-linked, 73 autosomal dominant, and 85 autosomal recessive phenotypes described in McKusick Catalogues [19]; every third entry describing disadaptive phenotypes was selected. Data reflect work in progress [Costa T, Scriver CR, Childs B: unpublished data, 1982].
individual citizens are genetically unique (unless they are a monozygotic twin), each with a relative state of health within the collective, each potentially at particular risk for a specific disease depending on genotype.

**GENETIC SCREENING: A FORM OF PUBLIC HEALTH**

Screening has the potential to identify individuals at risk. A successful screening test will discriminate apparently well persons in a population who probably have incipient disease from those who probably do not [23].

Genetic screening, to identify phenotype originating in mutation, is a comparatively recent development relative to screening for disease in general. Genetic screening is a search for persons within a population who, because of their genotype, may be at risk for disease in themselves or their descendants, in the universal or a particular environment. Genetic screening recognizes three broad objectives [24]: first, to identify persons at risk for their own health and for whom medical intervention could neutralize the harmful effects of gene expression; second, to identify persons at risk for passing a potentially harmful gene to their offspring and who could benefit from counselling about reproductive options; third, to enumerate frequencies of genetic variants in the population, measure the biological consequences of such variation, and study its epidemiological significance.

The extent of Mendelian variation in the human diploid genome is gradually being appraised. Genetic polymorphism (meaning heterozygosity with frequency of the variant allele q > 0.01) expressed as electrophoretic variants among soluble proteins of blood, is about 7 percent per structural locus per person [25]. The frequency of variants among the abundant structural proteins of cultured fibroblasts is rather lower—on the order of a tenth that observed in blood proteins [26]. These are minimal estimates of polymorphism in different sets of gene products. Protein polymorphisms are without apparent effect on health in the "normal" environment, but could be disadaptive in unique environments.

Another measure of human single gene diversity is found in variant Mendelian phenotypes. McKusick listed over 1,300 human variant phenotypes of proven inheritance in the fifth edition of the Catalogues [19] with an additional 1,400 or more of presumed Mendelian inheritance. The aggregate number in the forthcoming sixth edition will exceed 3,300 [McKusick, personal communication, 1982]. The majority of the "McKusick" phenotypes impair, to some degree, one or other of viability, development, reproduction, or longevity [Costa, Scrivcr, Childs: unpublished data, 1982].

If the majority of the Mendelian clinical phenotypes are disadaptive under universal conditions, and if protein polymorphism can sometimes have a harmful expression in a specific environment (e.g., G6PD deficiency), it follows that to identify genotype by screening can anticipate disease. Knowledge of genotype under these circumstances becomes reliable knowledge, as defined by Ziman [7], since it serves as a basis for action in the medical context, and is relevant for choices of action that are important both to individuals and to society.

**Screening for Medical Intervention**

Screening of the newborn for inborn errors of metabolism emerged as a new form of screening for disease about two decades ago. As an innovation in public health, it was originally intended to prevent certain types of mental retardation. While the new initiative recognized that mutation could be a necessary condition for certain types of mental retardation, most of the early projects paid only token attention to
the hereditary basis of the phenotype and equally little attention to other components essential to a successful program. Phenylketonuria [27] represents the prototype experience with newborn screening for a "genetic" disease. Screening for congenital hypothyroidism is a recent extension of that experience [28].

Laws were passed in the early days of newborn screening to compel participation, yet little or no support was provided for diagnosis, follow up, and treatment of patients identified by screening. The very existence of such an anomaly reveals an inappropriate view of the goals of screening. One cannot imagine screening for tuberculosis without the ancillary components of a prevention program. Screening itself is but one component of a larger program serving the common goal [9]. The infant with a positive screening test must be located; the test must be confirmed, and an appropriate diagnosis assigned. If the subject has incipient disease, counselling must be given and treatment begun; progress and outcome must be evaluated. Since genotype is permanent, commitment to the proband is continuous and long-term. Some health care systems foster the development of integrated programs for prevention of hereditary disease identifiable by newborn screening; others have yet to meet the challenge [9,24]. The American Academy of Pediatrics [28] recently found it necessary to reiterate the importance of integrated newborn screening programs, to accommodate new developments in our knowledge of phenylketonuria and the prevention of congenital hypothyroidism [28].

Screening for Reproductive Counselling

Screening of Tay-Sachs heterozygotes is the prototype for counselling about reproductive options [29]. Tay-Sachs disease is untreatable; its impact on patient and family is great. Prenatal diagnosis is possible and pregnancy termination, when the fetus is affected, is acceptable to the majority of concerned parents. Screening of populations, in which the mutant allele is prevalent, has become an effective form of Tay-Sachs disease prevention, provided follow-up counselling and prenatal diagnosis are integral components of the program.

Further Applications of Genetic Screening

The prototypes illustrate how population screening for genetic disease can reduce impact of mutant alleles on individuals and populations (Fig. 4). These early developments have been cost-effective [30]. They suggest that identification of persons at specific risk would be practical for many other Mendelian or multifactorial disorders during the incipient stages. But whether society is ready for a larger initiative in this direction is another matter. If surveys on attitudes of participants are barometers of opinions [9,31-33] some citizens are ready for more genetic screening and services, even if their physicians are not.

Physicians are less well trained for prevention than for diagnosis and treatment of established disease and medical education places little emphasis on prevention in medicine and almost none on genetics [34]. Citizens are also poorly informed about their own genetic individuality [35,36] and the potential impact of genetic variation on health maintenance. Furthermore, policies of current government, and some collective attitudes, tend to discourage the development of any initiative in public services and education that pertains to genetics. Believing such problems are rare to begin with, and intractable when found, many would prefer to do nothing, or as little as possible. Some have even recommended taking the word "genetic" out of the term "genetic disease" to avert its presumably pessimistic implication [37].

However, inherited disease has both necessary and sufficient conditions [37,38]: a
FIG. 4. Symbolic diagrams depicting phenotypic impact (cost) of disease (shaded area) on development, survival or longevity, and well-being of patient in three prototypes: \textit{left panel}, Tay-Sachs disease; \textit{middle panel}, phenylketonuria; \textit{right panel}, monogenic hypercholesterolemia, heterozygous genotype. Reduction of impact on proband, family, and society indicated by interrupted line ($\bigcirc - - - \bigcirc$) can be achieved with screening (solid circle), follow-up, counselling, and treatment (in PKU), or prenatal diagnosis (in Tay-Sachs disease). Improved outcome for hypercholesterolemia is anticipated when screening and early treatment are both available and implemented. Some cost is attached to procedures that offset mutant gene expression, hence "relaxed" cost is not zero.

component of nature (mutation), a component of nurture (the environmental event interacting with the gene product). It matters little which condition is sufficient or which is necessary since both are required for expression of the phenotype; that is to say, many "genetic diseases" are at the same instance "environmental diseases" [8,38]. Because this is in fact the case, it is possible to treat certain "genetic diseases" by modifying the environment: phenylketonuria is the prototype [27]. Without this example, and others [38], perhaps we would find only "stagnation of research and treatment" of genetic problems [37], but the opposite is true.

\textbf{BROADENING THE CONCEPT OF DISEASE PREVENTION:
OLD TERRAIN, NEW MAPS}

\textit{Neo-Vesalian Anatomy}

Vesalius published his revolutionary anatomical plates in 1543 [39]. Dogma was put aside; the tools of Baconian science applied to medicine gave it new knowledge and new importance. Four and one-half centuries later, another revolution in anatomy is occurring; it is chromosomal and genetic cartography achieved by mapping of genes to specific chromosomes and bands on chromosomes [19,40] and the delineation of nucleotide sequences in specific genes, respectively [41]. We are beginning to possess chromosomal addresses for Mendelian disease (Fig. 5) and we can read genotypes in the DNA script.

\textit{Chromosomal Band Deletions} The establishment, in 1956, of the normal diploid human chromosome number of 46 and the subsequent delineation of banding patterns made it possible to develop karyotype nomenclature and delineate disorders of chromosomal number or structure associated with disease [42]. High-resolution chromosomal banding of prometaphase karyotypes in synchronized peripheral blood lymphocytes represents a more recent technology clearly capable of further refining the morbid anatomy of human disease. Specific deletions of chromosomal
FIG. 5. Chromosomal cartography of morbid anatomy originating in mutation of structural genes [McKusick VA: personal communication, April 1982].
segments can be associated with specific Mendelian phenotypes, for example: deletion in the region of band 13 on the short arm of chromosome 11 (del 11p13) occurs with the aniridia-Wilm's tumor association [43]; del 13q14 occurs with retinoblastoma [44]; del 15q11–13 with the Prader-Willi syndrome [45]. Not all patients with the eponymous syndrome have the chromosomal phenotype. However, genes for specific enzymes are closely syntenic with the chromosomal regions in question (catalase on chromosome 11, esterase D on 13, α-mannosidase (perhaps) on 15). Careful study of these and other syndromes will determine whether enzyme phenotypes can be used systematically to diagnose the chromosomal phenotype prospectively. This represents an interesting development in genetic counselling and a novel application of gene mapping and cytogenetics.

Heritable Fragile Sites Another example illustrates how neo-Vesalian anatomy can be put to use. Mental retardation occurs in 5 percent of human beings. It is the most common disadaptive handicap in our society and it has hundreds of causes. Down syndrome (trisomy 21), among the most prevalent forms of “syndromic” mental retardation, is now the prototypic chromosomal disorder eligible for systematic genetic counselling in the prevention of mental retardation in at-risk population. Another common syndromic form of mental retardation associated with an abnormal karyotype [46] has recently been found. Males outnumber females in institutions for the retarded, and X-linked mental retardation is more common than Down syndrome in the male; the former may account for about a quarter of retarded males. X-linked mental retardation is a heterogeneous phenotype [51] but about half of its patients have a heritable, folic-acid-sensitive fragile site on the X chromosome (fra(X)(q28) phenotype). Assuming that this marker phenotype can be systematically demonstrated in skin fibroblasts and its biochemical basis delineated, it should be possible to counsel pedigrees at risk for recurrence. An appropriate advance in technology might even permit screening of mid-term pregnancies for X-linked and autosomal [47] fragile sites. This would be another development with considerable practical (and social) consequences for disease prevention. Gerald [48] goes so far as to say it is a development with which “every pediatrician must become familiar.”

DNA Polymorphisms A recent fortuitous discovery offers yet another method of forecasting intrinsic risk for disease, in this case by “reading” DNA sequences at specific chromosomal loci. Kan and colleagues [49] observed a polymorphic site in a non-coding sequence of DNA adjacent to the 3' end of the β-globin locus on-chromosome 11p. The site was identified with the Hpa I restriction enzyme and a probe covering the β-globin locus and the restriction site. It was further noted that a high proportion of persons with the sickle-cell mutation in the sixth codon of the first exon in the β-globin locus were mutant at the Hpa I cleavage site. Since DNA restriction fragments can be identified relatively easily by the blot-hybridization-transfer technique of Southern, identification of restriction fragment polymorphism length (RFLP) is a simple way to identify individuals with mutation in the coding region adjacent to the restriction site, if the two mutations are in linkage disequilibrium. This approach to proband classification is valid only when population studies have shown that the RFLP is present at sufficient frequency and pedigree studies identify its coupling state with the structural mutation gene of clinical interest [50].

Mutation in the coding sequence of an exon of a structural gene can sometimes be identified directly by a restriction enzyme. The sickle β-globin mutation in codon 6 is detected by the restriction enzymes Dde I and Mst II; for practical reasons, the latter is easier to use. Two groups recently reported use of Mst II for reliable diagnosis of sickle disease (see editorial by Kronenberg HM: New Eng J Med 307:50, 1982).
Botstein and colleagues [51] have argued that about 150 carefully selected cleavage sites containing DNA polymorphisms in the human genome could serve as markers for most of the structural gene loci and their mutant variants recorded in the McKusick Catalogues. One new RFLP marker has recently been found in the proposed “search and define” program [52].

Diseases of Aging

Unhealthy longevity is a macroeconomic burden on industrialized societies [16]. Increasing longevity has impact on pension plans, and chronic illness or premature death in the post-reproductive adult has profound impact on health insurance systems. Despite steeply rising disease care costs and slowly increasing longevity in the past four decades, there has been little initiative to prevent the impact of unhealthy longevity (Fig. 6). Medical genetics could make a contribution to health maintenance in the aging population because it has the capacity to anticipate some, perhaps many, of those at risk for premature onset of degenerative disease.

The biological basis of aging is an enduring but relatively neglected enigma for which various explanations have been offered (viz. [14] for overview). Weismann proposed that aging was an adaptive characteristic which allowed natural selection to operate, so that post-reproductive individuals were removed from the population, thereby reducing competition with fertile individuals for food and space. Selection operated, Weismann conjectured, on a programmed limit to mitotic divisions occurring in somatic cells—a hypothesis that anticipated Hayflick by 70 years.

Weismann’s hypothesis originated in the context of nineteenth-century thought. Of course, it was inimical to liberal democratic twentieth-century scientists and naturally it has been replaced by a new concept—obligate aging. This hypothesis implicates germ-cell mutation as the source of aging. Since the mutations are expressed in post-reproductive life in the human species, they must escape selection. Accordingly, that they become fixed by random drift is a necessary component of the theory.

In its turn, the theory of obligate aging has evoked a counter hypothesis [14]—the longevity assurance theory—which states that longevity in mammalian species is proportional to the ability of the organism to repair its DNA. The repair apparatus is inherited in Mendelian fashion. The hypothesis is supported by considerable evidence, and specific Mendelian failures of DNA repair are an occasional source of premature senescence in man [14,19].

Our principal concern here is to find a universal explanation that accommodates

FIG. 6. Trends in life expectancy (dotted line), national health expenditures, and prevention expenditures, since 1940, in U.S.A. Costs are calculated in constant 1967 dollars (taken from Gori and Richter, [16]).
not only the process of normal aging but also the heterogeneous pattern of precipi-
tant diseases of aging. It seems improbable that atherosclerosis, coronary heart
disease, chronic pulmonary disease, stroke, cancer, diabetes mellitus, and
Alzheimer’s disease, to mention only a few phenotypes, can all be attributed to
failures in DNA repair originating in mutation at the few loci responsible for the
repair apparatus. On the other hand, we have clear evidence that Mendelian in-
heritance at many loci is associated with precocious aging; and, more importantly,
this information can be used for preventive measures.

Aging, in many instances, reflects the consequences of metabolic dishomeostasis.
Intrinsic events interacting with the “normal” environment (Fig. 1) initiate disho-
meostasis, setting in motion a train of chronic events that leads to pathological
aging. Knowledge of receptor-mediated endocytosis at the plasma membrane of
somatic cells [53,54] reveals how a Mendelian event can alter cellular and metabolic
homeostasis and shorten longevity in the vulnerable individual (Fig. 7).

Cholesterol dishomeostasis is one of the causes of atherosclerosis [55]. Impair-
ment of receptor-mediated endocytosis of LDL-cholesterol in the phenotype known
as type II familial hypercholesterolemia increases the endogenous burden of
cholesterol [56]. The steady-state serum cholesterol level is increased two- to three-
fold in heterozygotes who bear any of the dominantly inherited alleles that disturb
cholesterol endocytosis. The frequency of such heterozygotes is 1 in 500 in the
population at birth. Because their genotype places them at elevated risk for
atherosclerosis, heterozygotes appear at elevated frequency among those who
develop coronary heart disease before the age of 60. Such persons are said to be 3
percent of surviving patients in coronary care units [57].

If we adopt a fatalistic attitude to monogenic hypercholesterolemia, believing it is
untreatable because it is genetic, or that it is a form of obligate aging, we will com-
mit such persons to premature unhealthy longevity; their family history will be a
curse. Superstition will prevent action. In desperation we might recommend a strin-
gent (moral) lifestyle designed to reduce the cholesterol burden. Unfortunately, that
course of action will have little effect because the steady-state synthesis and degrada-
tion of cholesterol in the mutant state is set to compensate for any extrinsic adjust-
ment. Accordingly, treatment will fail, fulfilling the prophecy that nothing can be
done for genetic disease.

On the other hand, because we are informed about the mechanism of cholesterol
dishomeostasis in type II familial hypercholesterolemia, it is possible to design
therapy that bypasses the defective receptor and down regulate cholesterol biosyn-
thesis to the normal level; fractional clearance of cholesterol can also be increased by
pharmaceutical tricks [58]. Such therapy shows preliminary evidence of success
[59]. The next step toward preventing premature coronary heart disease in this
monogenic phenotype will be to develop a test for defective receptor function in
heterozygotes. The final step will be long-term studies of prospectively treated
heterozygotes to determine whether the mutant phenotype can be completely
neutralized, accelerated atherosclerosis prevented, and the threat of precocious,
unhealthy longevity lifted. Here then is a dramatic illustration of a high-burden,
common disease of aging that is potentially eligible for prediction and prevention. It
illustrates the axiom that disease reflects specific (individual) risk in the universal en-
vironment.
FIG. 7. A profile of mortality due to heart disease. Coronary (ischemic) heart disease (fully shaded sector, panel A) accounts for over 40 percent of premature mortality in North America. Atherosclerosis (panel B), the major pathogenetic mechanism of ischemic heart disease, is heterogeneous in origin [57,70]. About half surviving patients with premature myocardial infarction are hyperlipidemic. Monogenic hypercholesterolemia is one cause of hyperlipidemia. Type II familial hypercholesterolemia heterozygotes have disordered absorptive endocytosis of LDL-cholesterol (panel C); various alleles at one or more loci account for various mechanisms of aberrant receptor-ligand interaction. R gene (for receptor) has three function domains; ligand component, banding B; transmembrane core, C; cytoplasmic locator, L. RL Gene (for receptor locator) is presumable at independent locus. Phenotypes shown are: zero, * or deficient, –; symbols: b, binding; i, internalization (see [56] for details).
MOVING FROM CHANCE TO PURPOSE: RECOGNITION OF INHERITED RISK

Age-specific mortality and morbidity due to stroke and coronary heart disease have, in fact, improved in the past two decades [60–62]. Mortality in the newborn nursery has also declined and more low-birth-weight infants are surviving [63]. These achievements could be construed as victories for the environmentalists. One can also see them as worthwhile achievements that inevitably increase the heritability of disease in the survivors at both poles of the human life span. Moreover, if disease is a combinatorial product of interactions between genotype and experience it follows that to optimize the environment to suit a universal population can only eliminate that fraction of disease originating in universal experience. In other words, maximizing experience to minimize disease (the public health paradigm) must have diminishing returns; the irreducible disease burden that persists after we have harmonized the world will ultimately reflect individualized dishomeostasis of intrinsic origin.

The dilemma of persisting disease in a better world—of precocious, unhealthy longevity and a rising proportion of birth defects in the total disease burden—remains a challenge waiting to be recognized and met. Some have pondered it. Among them Wynder, then President of the American Health Foundation, opined that “in public health, the best question is one that can be answered and whose answer can be applied to the reduction of disease. The greater the impact on health, the better the question” [64] [my italics]. Wynder was not, to my knowledge, thinking about genetic medicine as an answer to his call. In a similar vein, Comar, discussing risk acceptance and the move from the world of facts to the world of values, stated: “we can predict statistical effects on populations [but] there is no way to predict effects on individuals” [65]. If we take these statements at face value we might deny further progress in, for example, genetic screening programs, or in the possibility of preventing premature ischemic heart disease in specific individuals. Environmentalists and critics of the genetic viewpoint would consider my examples esoteric, relevant to but a few patients at any one time—just not in the mainstream. To counter that objection, I propose a small list of “common” and “important” diseases (Table 1). Each is a phenotype heterogenous in origin. Some patients—the majority perhaps in some phenotypes—have the disease because of their genotype. Such persons are at particular risk and develop their particular disease in the universal environment. We are reminded that prevention of disease in probands, or of recurrence in relatives, might be possible if the risk attached to genotype is identified at the incipient stage and the life experience modified to fit the constraints to health imposed by genotype.

Sudden Infant Death Syndrome (SIDS) This condition is the most-common cause of death in infancy after the first month of life. It affects two or three infants per 1,000 and exhibits noteworthy racial and regional variation. It is considered a multifactorial event [66]. There is no evidence of Mendelian inheritance in the majority of cases, but in some infants with near-SIDS, there are identifiable abnormal phenotypes in ventilatory and respiratory function; these abnormalities may also be present in one or both parents in some families [67]. In such families subsequent sibs would be prime candidates for theophylline therapy or electronic monitoring, particularly if they exhibit the high-risk phenotype. This is not a global prescription for SIDS; it merely recognizes heterogeneity in the syndrome. It could be considered a rational form of intervention and support at acceptable cost for a devastating problem in some families.
**Cerebral Dysfunction** Cerebral dysfunction associated with X-linked and autosomal fragile chromosomal sites was mentioned earlier. Other forms of impaired CNS development are associated with heterozygosity. Females heterozygous for X-linked deficiency of ornithine transcarbamylase are at elevated risk for modest intellectual deficits, perhaps as a consequence of episodic hyperammonemia [68]. Identification of carriers of the gene in pedigrees in which the gene is segregating constitutes prediction of persons at risk. Modification of protein intake to fit the tolerance of these subjects, which can be monitored by urinary excretion of orotic acid, could prevent disadaptive development.

Heterozygotes for various lipidosis are also said to have modest neuropsychological consequences of their phenotype [69]. Whereas these findings are the result of a pilot study, they illustrate the theme that heterozygosity can be a risk factor. In this case, no feasible form of preventive medical treatment seems available but accurate prenatal identification of heterozygotes might represent reliable knowledge for some families, and postnatal identification might lead to special educational measures whose outcome could at least be studied prospectively.

**Atherosclerosis** Among the universally recognized typological classifications of disease, atherosclerosis is a pathological process of immense complexity [70]. It is the most common lethal disease in the adult population; it has no single cause. Hypertension, cigarette smoking, hyperlipidemia, gender, and alcohol all contribute to expression of the atherosclerosis phenotype. In the genetic paradigm of disease, atherosclerosis is the outcome of events emanating both in the environment and in the organism. Those that provoke dishomeostasis of lipid metabolism lead to atherosclerosis. There is, for example, a spectrum in the distribution of predominant causes in the cholesterol-dependent forms of atherosclerosis (Figs. 7 and 8). Exorbitant chronic intakes of cholesterol are atherogenic to persons with apparently normal genotype, and monogenic events impairing receptor-mediated uptake of LDL-cholesterol are also atherogenic in the presence of normal cholesterol intake. It is now apparent that other single gene mutations influence cholesterol homeostasis.
lesterololemia (receptor deficient form or familial hypercholesterolemia Type II); 4 + Chol indicates profligate dietary burden of cholesterol. Most subjects are FH heterozygotes (FH/ +), multifactorial (FH/+,X), or polygenic X + Y + Z in origin of phenotype.

[71,72] and that different monogenic events can interact to cause polygenic atherosclerosis.

The message in atherosclerosis is universal, not necessarily specific: recognition of genotype is a form of taxonomy. Classification by itself, however, is insufficient; it merely explains why this person has this or that "disease." The power in recognition of genotype is the predictive component; it anticipates disease. Since the disadaptive gene must express itself in an environment, to identify genotype is the first step to prevention—by modifying the macroenvironment of the person or the microenvironment of cellular homeostasis [73].

*Psychoses* Behavioral genetics is an area of major importance, inadequate still in theoretical constructs yet immense in implications. The major psychoses are transcultural disorders that affect large numbers of citizens in all societies. Schizophrenia and the affective disorders are undoubtedly both heterogeneous, both typologies probably embracing several specific diseases. Heritability of the psychoses is high, concordance being higher in monozygotic twins, whether reared apart or together, relative to dizygotic twins [42]. This finding indicates that the major psychoses, non-Mendelian in the aggregate, may yet yield to genetic analysis in their components. In fact, the depressive psychoses, when classified into bipolar and polar forms, seem to have different degrees of heritability and expression in relatives [42], and schizophrenia has at least one minor but clearly Mendelian form that is apparently both detectable and preventable [74].

Phenotypic subclassification will be as relevant and important in the major psychoses as it is now in atherosclerosis; when Mendelian forms are recognized, abnormal gene products are more likely to be discovered; with a biochemical marker identified, the opportunity for specific therapy is offered; detection of persons at risk and prevention of disease are potential realities. In this hypothetical context, the recent finding of a possible association between HLA haplotype and susceptibility to depressive psychosis tentatively suggests that a locus on chromosome 6 is involved in

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**FIG. 8.** Hypothetical distribution of individuals with the atherosclerosis phenotype leading to precocious coronary heart disease (CHD). When genotype is the predominant "causal" event, individuals are placed at the "genetic" end of the spectrum; when environment predominates, they are placed at the other pole. Subpopulations A-D represent individuals whose phenotypes reflect combinations of "causes" in the relationship \( P = G + E \) (phenotype = genetic + environment). Individuals at the upper end of spectrum have high heritability of phenotype \( h^2 = V_C/V_P \), where \( V = \variance \); those at opposite end have low heritability. FH/FH indicates homozygous monogenic hypercholesterolemia (receptor deficient form or familial hypercholesterolemia Type II); 4 + Chol indicates profligate dietary burden of cholesterol. Most subjects are FH heterozygotes (FH/ +), multifactorial (FH/+,X), or polygenic X + Y + Z in origin of phenotype.
the pathogenesis of affective illness [75]. If the association of haplotype with behavioral phenotype is not one of cause and effect, it might still prove useful in identifying persons at risk.

**Alcoholism** Epidemiological studies in three countries (Sweden, Denmark, and the United States) indicate that genetic factors and environmental influences are both involved in the pathogenesis of alcoholism (viz. [76,77] for details). One author calls alcoholism a “pharmacogenetic disorder” [77]. Genes influence the metabolism of ethanol itself and also the response of specific cellular events (e.g., in liver or brain) in the alcoholic. Genetic components of alcoholism, in the opinion of some, offer special opportunities to intervene beneficially in high-risk situations. For example, blood acetaldehyde concentrations are higher after an ethanol load in young non-alcoholic men with an alcoholic parent or sib, compared to matched controls without an alcoholic relative [78,79]; transketolase binding of thiamine pyrophosphate is attenuated in cultured skin fibroblasts and erythrocytes in vivo in patients with the Wernicke-Korsakoff syndrome relative to controls without the syndrome [80]. The first finding [78] was statistical in nature; it was not stated whether individuals in the experimental group segregated into those with an abnormal response and those without, suggesting a bimodal (Mendelian) phenotype; should that eventually prove to be the case, it might then be possible to anticipate family members at high risk for alcoholism and to counsel avoidance measures. In the second example [80] it is implied that a constitutional phenotype predisposes to development of the Wernicke-Korsakoff syndrome in chronic alcoholics; the appropriate pedigree studies have not yet been done to determine whether the biochemical phenotype segregates in Mendelian fashion and is expressed in non-alcoholic relatives. In the meantime, the finding implies that specific thiamine therapy might prevent development of psychoses in established alcoholics who have the thiamine-dependent phenotype; this constitutes specific preventive therapy and it is the approach which is radically different from a proposal to fortify all alcoholic beverages with thiamine [81]. The latter assumes uniform risk in the universal population whereas the former infers specific risk in particular persons. One is a conventional public health approach to prevention of Wernicke-Korsakoff psychosis in the population; the other applies the principles of genetic medicine.

**Hemachromatosis/Iron Overload** I was taught, in my undergraduate medical studies, that hemachromatosis is a rare disease of minor clinical importance; its interest lay in a display of classical elements of pathology. No one told me the disease was inherited; no one mentioned the risk of iron overload in heterozygotes. That was long ago; the view of hemachromatosis has changed [82]. Students of the disease now believe it is the expression of (a) mutant allele(s), inherited in autosomal recessive fashion, at a locus tightly linked to the HLA region on chromosome 6 (that locus again!); linkage studies confirm that the susceptibility allele is in disequilibrium with the HLA-A3 haplotype [83]. The phenotypic expression of the “hemachromatosis gene” involves excessive intestinal absorption of dietary iron, but the mutant gene product is unknown at present. HLA typing can identify homozygotes at high risk for disease in adult life; it is uncertain whether a test for heterozygosity is possible but further research on this problem is warranted. Whereas homozygosity is rare, Hardy Weinberg equilibrium and population studies suggest that 10.4 percent of Utah Mormons, 9.5 percent of Breton French, and 8.4 percent of Scots are heterozygous for the hemachromatosis allele [84]. If such persons are susceptible to modestly enhanced iron absorption and the pathological consequences thereof, it follows that male heterozygotes in particular could experience iron overload. Iron
medication, high consumption of wine, even iron fortification in bread [84] could be disadvantageous to heterozygotes. The polymorphic status of the hemochromatosis gene implies selective advantage for the allele itself (particularly in females), "hitchhiking" of the gene with tightly coupled advantageous HLA haplotype in human evolution [84], or even a founding effect in Celtic and Mormon populations. That was long ago. The allele is an intrinsic risk factor of clinical significance in the modern world.

Osteoporosis Osteoporosis is the most prevalent form of metabolic bone disease in man, yet it remains an enigmatic, expensive, and disabling condition. The disease is undoubtedly heterogeneous in origin. A recent study [85] of post-menopausal idiopathic osteoporosis indicates how intrinsic factors may increase risk for the disease. Intestinal lactase deficiency is more prevalent in the post-menopausal disease than in control subjects. Lactase activity, in some way, enhances calcium absorption. Lactase-negative individuals are presumed to have altered calcium absorption and thus may be predisposed to osteoporosis. The lactase phenotype (positive or negative) is polymorphic in the human species. Populations indigenous to temperate geographic regions are predominantly lactase-positive. Individuals in these populations who are lactase-negative may be at risk for osteoporosis. The observations merit further study and the availability of a simple test for lactase deficiency provides a simple method to do so and perhaps, eventually, to predict persons at risk for osteoporosis. Studies in populations indigenous to tropical regions are also indicated to discern whether adaptive mechanisms for calcium homeostasis, that are not lactase-dependent, protect such persons from osteoporosis. Thus we see that a major polymorphism, with apparent adaptive significance for man [86] might become relevant to the interpretation of a common disease.

DARWINIAN HUMAN BIOLOGY: MEDICINE TRANSFORMED

The temporal parameters of human life are different from those of other mammals and primates [15]. Humans have a relatively long intragestational period of fetal development that produces single or occasional multiple precocial offspring. Postnatal, pre-fertile development is also long. The reproductive period itself is only a portion of total lifespan; post-fertile life is again long—for a few in earlier times, for many in modern societies. Our extreme precocial development is compatible with attainment of a large brain [87] but only if our evolution as a species (i.e., through development of individuals) can occur under very stable environmental conditions. Maternal metabolism and the conditions of early postnatal life assure that this is so [87]. Our large diploid genome, shuffled continuously by sexual reproduction, and its capacity for repair [14], are compatible with large interindividual variation and yet relative stability of intrinsic determinants. Upon this biological system selection by consequences is at work perhaps in a three-tiered mechanism [88]: Darwinian selection, acting on individuals, unquestionably shapes our biological nature; selection by operant conditioning may influence our behavior; selection through learning, verbal or written expression, appears to influence evolution of culture, both in animals [89] and in man [90].

Since mutation is the fuel of diversity, whereas homeostasis is the engine of survival, we are, perforce, interested in the impact of mutation. Mutation load—a population statistic—has appeal because of its simplicity. But it has limited use in medical genetics because the only measure of its impact is on survival and fertility; it is measured only in Darwinian fitness and does not measure impact on human welfare. Mutation component—a new term defined by Crow [91,92]—considers
more than biological fitness. It refers to the proportion of the incidence of disadaptive disease accounted for by recurrent mutation; it considers the origin of phenotypes with normal distributions for which the optimum value is intermediate between extremes. In other words, it can address the origins of deviance in homeostasis by considering heritability of phenotype in broad and narrow senses. If narrow-sense (Mendelian) heritability for the particular phenotype is high the mutation component is high and increase in mutation rate, by whatever means, produces a rapid response in mutation impact (meaning deleterious effect on human welfare); the milder the effect, the more the impact is spread over time. If narrow-sense heritability is low the response to increased mutation rate is small and slow [91].

It has been a recurring theme in this lecture that, within the overall distribution of a "disease" phenotype in the population (e.g., atherosclerosis), broad-sense heritability has increased in modern times; yet, within the collective phenotype we can identify subjects of phenotype with high narrow-sense heritability (e.g., monogenic hypercholesterolemic atherosclerosis). This view suggests a greater need for genetic epidemiology in the study of modern diseases. Accordingly, we need data on prevalence, incidence, and social cost of disease. We also need record linkage to study correlates between relatives for disadaptive disease.

The perceptive reader will see that this approach can monitor new mutations in an era whose environment is in danger of increasing mutagenic pollutants. But a byproduct of record keeping is simple enumeration of gene-influenced disease. It is being done now in some populations [93, 94] with the startling discovery that the frequency of non-chromosomal hereditary disease is between 5 percent and 10 percent of live births. The World Health Organization [95] is evaluating ubiquity and burden of genetic disease and considers it a problem that warrants measures for control and prevention as well as services for management of genetic disabilities. A call to action from the WHO is a far cry from recourse to prayer (which Galton showed to be singularly ineffective in altering phenotype [96]) or pessimism [37]. It is the new epidemiology.

PREDICTIONS

It is ironic, and yet appropriately modern, I suppose, that there is any gap whatsoever between what we need and what we have in genetic medicine. There are clear and present needs but their attainment will probably be delayed more than is desirable unless we drive a troika of research, services, and education.

Research The fructifying influence of research on medicine is well-documented [97, 98]. In the aggregate, medical science is reliable knowledge. One requires only modest clairvoyance to predict how research in human genetics should benefit medicine in the next generation—the beginning of the second Darwinian century.

i. All—or nearly all—human genes will find their places on the chromosome map, the nucleotide sequences of many will be described, and regulation of their expression delineated much more precisely than is the case now.

ii. The mechanisms of ontogeny will be better understood; accordingly, the origins of certain congenital malformations will be surmised.

iii. DNA polymorphisms in non-coding regions will be delineated to permit mapping of predictors of disadaptive clinical phenotypes associated with adjacent structural loci.

iv. Treatment for disadaptive phenotypes will improve because the tailoring of nurture to fit particular natures will be refined. Nutrition and pharmacy will attain new dimensions.
v. Gene therapy will not be ignored: present novelties such as the potential for design and use of suppressor genes [99] and the cloning and insertion, by transgenic methods [100], of normal genes into mutant germ cells, will be attempted in man. *In vitro* fertilization techniques will be essential for such developments. People will initially fear these developments as much as they did pasteurization, vaccination, fortification of natural foods, and use of drugs and antibiotics; but reason supported by evidence will prevail.

**Resources and Services** Knowledge without application can be beautiful but sterile. Services to utilize knowledge constitute societal resources. Despite evidence that genetics services help citizens [9,24], development on this front has been slow. I predict that genetic screening, suitably integrated into programs, will become a greater systematic resource in public health and private medicine.¹ Screening and diagnosis allow individuals to convert uncertainty (probability) to prediction (binary statements about presence or absence of intrinsic risk). Nonetheless moral persuasions and fiscal fervor are, at this moment in America, imposing values held by some on others who care to know—and need to know—how to make choices that matter for their personal lives. Services that are needed (e.g., prenatal diagnosis) are being denied or withdrawn because there is controversy over values. When the fact of genetic diversity and specific need is ignored, citizens will suffer. We need wisdom to steer a better course. Assuming wisdom will prevail over fundamentalism and parsimony, we can anticipate expansion of genetic services [9], registers [101], and record linkage [94]. Formal economic analysis [30] will adequately defend these developments by demonstrating cost effectiveness.

**Education** Bromley [102] considers education another frontier of science: “Public scientific literacy is a necessary—if far from sufficient—condition for development of the new constituency for science and technology.”

Recruitment of geneticists, who will do research and apply knowledge, begins in the formative years—spent in school. Citizens, who will benefit from genetic knowledge, have a universally shared opportunity to learn something about their own biology—in school [35,36]. How ironic that the teaching of genetics is, once again [103], being turned off in the classrooms while textbooks are being expurgated of their material on human genetics and evolution.

Nor can we hope that physicians will be more literate and therefore act as more informed arbiters of knowledge and application. Our medical curriculum is barren of much exposure to medical genetics [34]; its web of genetics teaching has a gossamer quality. Accordingly, if the blind are leading the blind we are in dire need of enlightenment. Curriculum revision, more post-graduate residencies in medical genetics, a larger number of traineeships and fellowships (funded by government agencies and private sources—perhaps even by health insurance carriers) would brighten the path.

**CONCLUSION**

*Homo sapiens* possesses a “nested set of characteristics” [104]: we share with all mammals three middle-ear ossicles; with all vertebrates, a backbone; with all

¹A Subcommittee on Investigation and Oversight of the Committee on Science and Technology U.S. House of Representatives (97th Congress, Hon. Albert Gore Jr., Chairman) recently held hearings on Genetic Screening and the Handling of High-Risk Groups in the Workplace (October 14, 15, 1981; Proceedings published by U.S. Government Printing Office, Washington, DC, 1982). Here is a bread-and-butter issue; not genetics and life or genetics and family planning but genetics and jobs. Issues, practices, and misadventures are aired. The Proceedings are interesting reading.
eukaryotes, nucleated cells; with all living organisms, cellular RNA and a plasma membrane. Our journey of descent with modification implies that life on Earth possesses a biological memory, relatively stable yet capable of modification and amplification. Genes are the map of our journey. Human genetics is a voyage of discovery.

Disease reflects the evolutionary process. Health is diversity with harmony; disease is disadaptive dissonance—incongruity between genotype and experience—dishomeostasis. In increasing proportion, relative to earlier times, disease in modern society reflects our mutations. Disadaptive phenotype is expressed maximally in utero and in early life, but also later in life as we age. Selection and adaptation are measured in biological, behavioral, and cultural terms. We are the product of collective and personal events. In living out our term we contribute to and become part of biological history.

Mandelstam, who understood so well the importance of Darwin, felt deeply the meaning of human life and culture. Let the words of poem number 8 in his opus [105], written in 1909 when he was eighteen, be the last addressed here to the Spirit of Man in a troubled world.

What shall I do with the body I’ve been given,  
So much at one with me, so much my own?

For the calm happiness of breathing, being able  
to be alive, tell me where I should be grateful?

I am gardener, flower too, and unalone  
In this vast dungeon

My breath, my glow, you can already see  
On the window panes of eternity

A pattern is imprinted here  
Unknown till now.

Let this muddle die down, this sediment flow out.  
The lovely pattern cannot be crossed out.

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