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Genetics: Voyage of Discovery for Everyman

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Five speakers are participating in this symposium (1, 2); we have been instructed to review several "voyages to discovery" in science. These voyages each have a common theme: knowledge evolves incrementally with time and effort. As we develop our stories, it will become evident that discovery has repeatedly changed our views of the world and of ourselves. That is not very surprising. But we are living in impatient times. We might ask ourselves: could we have advanced in the relevant areas of science more wisely and faster? Could committees of wise men have designed better answers, sooner—assuming they knew which questions to ask? I think you know the answers because the questions are indeed rhetorical. Yet the policy makers and the politicians believe we could be more on target and could move faster. They are expressing a collective lack of faith in basic science—the science of mechanisms. Politicians want answers more quickly—even in an era where the applications of science gleaned from basic knowledge have many triumphs. On the other hand, citizens maintain a high level of faith and interest in science as it is; and in scientists as they are. The pollsters tell us that repeatedly (3). Perhaps the representatives of the people who hold office in our capitals in this bicentennial year of America do so without just representation of their constituents.

Let me begin to examine the dilemma of progress with our first voyage during which we will navigate some estuaries in our knowledge in genetics. It has been necessary in this transcript to omit most of the visual material I used to develop my themes during the spoken address. For those who wish to retrieve it at their leisure, I have tried to indicate the source of my material.

THE DILEMMA OF PROGRESS

You may recall that H.M.S. *Beagle* (4) began a voyage around the world, in 1831, which was completed 5 years later. On board was Charles Darwin (Fig. 1). What he saw and recorded led to a theory of biology which irrevocably changed our view of ourselves. You are more likely to remember that day in 1969 when the *Apollo 10* flight (5) began its journey to place man on the moon with considerably more sound and fury than accompanied the quiet departure of H.M.S. *Beagle* from Devonport. When the astronauts returned, our view of the world, and of ourselves, was again irrevocably altered.

As a young man, Darwin collected data on "the species problem" as he called it. He eventually composed his observations as a theory of evolution, about the *origin* of species. Darwin had come to understand the selective force of the environment on natural evolution. He understood the driving force; but he did not fully understand the vehicle. He did not know about genes. It was Gregor Mendel (6) who discovered the units of inheritance and their laws of segregation and assortment, and who later gave the necessary interpretation to Darwin's great theory.

Darwin worried about the discrepancy between his theory and the missing facts about the vehicle of evolution; perhaps it is this concern that is visible in photographs of Darwin in old age (Fig. 1). Even at the last printing of the final edition of *The Origin of Species*, Darwin was changing a sentence here, a word there to accommodate new knowledge and unresolved concerns. But, the elegant prose of his final sentence was never changed; it remained, stating:

> There is grandeur in this view of life with its several powers having been originally breathed by the Creator into a few forms or into one. And whilst this planet has gone cycling on, from so simple a beginning, endless forms, most wonderful have been and are being evolved (7).

It is a happy ending to a marvelous book.

The impact of Darwin's book on man's view of himself was not initially happy. This realization may have pained its author. Albert J. Guerard (8), writing about Thomas Hardy and his times, states that Darwin, unlike Hardy, disliked unhappy endings in novels, and wanted a law passed against them. In the real, as opposed to fictional life, Darwin had formulated his own dilemma, and he knew it; apparently, he did not want disappointment in the world of fantasy as well.

The Origins of Totalitarianism is a 20th century book whose title echoes Darwin's. In it Hannah Arendt reiterates the continuing dilemma for the Everyman of today. She states: "It holds that progress and doom are two sides of the same medal; that both are articles of superstition not faith" (9).

The legacy of Darwin's biology and of Mendel's genetics is molecular and human biology. For some of us, the new biology has resembled nothing as much as a state of chaos; but it indeed has a basic goal, described as follows by Sir Francis Crick.

> Which problems are likely to be solved by AD 2000 depends on whether they can be attacked by isolating a small part of the biological system or whether one is mainly concerned with its behavior as a whole. In the long run, problems involving complex interaction can hardly be avoided. Some of the most profound aspects of biology are of this character (10).

This statement, against oversimplification, and for the recognition of complexity, is an important point of departure for the themes that follow.

As we stand poised on the threshold of a biologic revolution, we might ask why it is that we play to our darkest fears; and why we push upon ourselves, clonal man and neo-Frankensteinism (without the leavening touch of a Mel Brooks). I suspect the reason is the fear of an unhappy ending. This recurring dilemma was nicely stated in the 16th century: "In this our time the minds of man are so diverse that some think it a great matter of conscience to depart

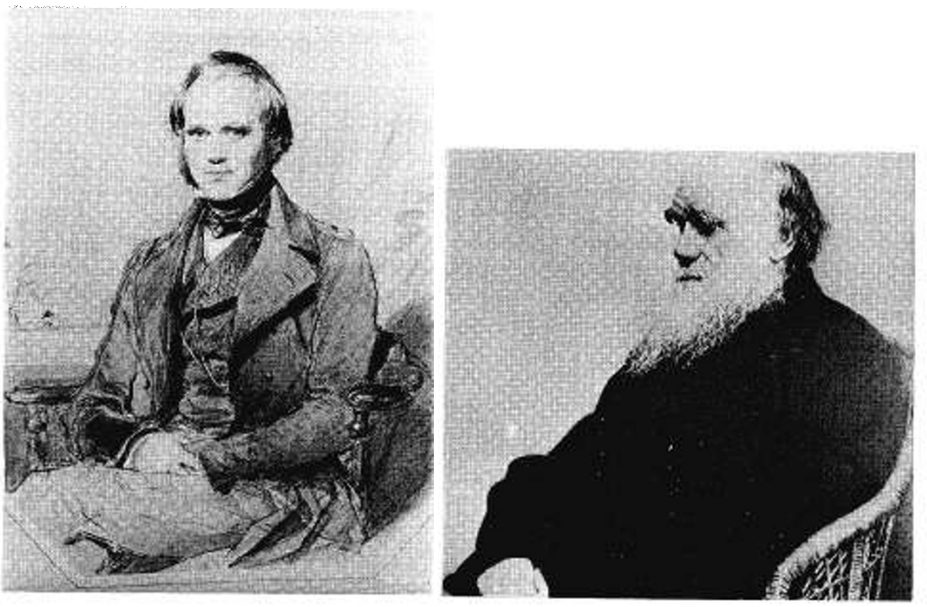

Fig. 1. The face of Charles Darwin in youth and age, before and after his view of life was announced to the world in 1859. (Portrait and photograph reproduced from Alan Moorehead, *Darwin and the Beagle*, Haimish Hamilton, London, 1969.)

from a piece of their old customs. Again, on the other side, some be so new-fangled that they would innovate all things, and so despise the old—that nothing could please them that is new" (11). The words are those of Thomas Cranmer. He was dead, by burning, 3 years later because he could not solve the domestic and hereditary dilemmas of the sovereign family which was indeed diverse and torn between custom and innovation.

We can balance this perspective from the past with one of many possible choices from the present. Ortega y Gasset, the Spanish philosopher, wrote *Revolt of the Masses* in the early 1930's. Ortega's principle thesis about modern man's attitude to his own times can be paraphrased as follows: any set of values which departs from the norm of the mass, especially towards an esoteric direction is put down as arrogant in cultural terms and socially remiss (12). Does that not seem to reflect the political view of science today, and in particular, the popular view of genetics?

Are we suspicious of modern biology and of genetics simply because we have no real cultural perspective on science; and because its social potential is not yet accurately perceived?

I dwell on quotations from the past simply to emphasize that our modern fears and dilemmas are nothing new under the sun. Indeed, some of the genes in our neurones are probably coded for traditional anxieties and dilemmas; and they seem to have been nicely induced once again by living in the "Apollo revolution," the modern equivalent of Copernican, Gallilean, and Darwinian upheavals in our view of life.

THE PERSPECTIVE OF EVOLUTION

I suspect we have been changed for ever by the startling view of Earth rise, as seen from the moon (Fig. 2); partly because it is an overwhelming new perspective on our world; partly because a member of our own species was out there to take the picture. Shakespeare's couplet, with a little change in its wording, might be the legend for any photograph of Earth rise. "This happy breed of men, this little world/This precious stone set in the [sombre] sea" (13). Yet when the first excitement of the Apollo journey has worn off, we find a post-Apollo perspective nagging at us. Ortega y Gasset had already defined it for us: "The man of today feels that his life is more of a life than any past one. Or to put it the other way about, the entirety of past time seems small to actual humanity" (14). On the other hand, Tennyson, the poet, had a view contrary to Ortega's Everyman. Tennyson said in *Ulysses:* "I am part of all that I have met" (15).

That was the poet's instinctive recognition, in 1842, of the Darwinian view of human evolution yet to come. And so we have another theme for this voyage. Ortega tells us that as we evolve, we are myopic about our origins; Darwin and Tennyson tell us that we cannot know ourselves without knowing our past. It is time to consider evolution and how that reflection can illuminate our future actions.

Evolution on Earth has occurred in three phases (16): first, the nuclear, followed by the chemical, and then the biologic. However, we are participating in a fourth; the homologic phase, when man as a species can modulate his own evolution. It is an extraordinary opportunity which commands our attention and dominates our anxieties.

The initial periods accommodating nuclear and chemical evolution on earth required about 2.0 billion years to yield a transition from prebiotic, organogenic molecules to the formation of biomonomers. At some point, random collisions of biomonomers, with an input of energy from the earth's own heat, or from our solar system, permitted larger and more complex biopolymeric species to occur. Biologic evolution could then begin from the primitive repertoire of fuels and building blocks. The subsequent 4.0 billion years of biologic evolution have been partly recorded in the fossil records which Darwin and his colleagues observed and understood. Less than 3 million years were needed to cap the journey of early hominids with the emergence of *homo sapiens*.

Modern man appeared on Earth, not as we are told by one account, in the Garden of Eden, but more likely in ancient, temperate Africa (5). From archeologic records, we have gleaned how he roamed northward as a nomadic species precariously balanced between fertility and mortality. Indeed, survival was a delicate act for our small band.

One branch of our lineage colonized the land mass of the eastern Mediterranean (5) and we can imagine a Moses divining God's laws on one of the mountains of the Sinai peninsula.

Carbon dating techniques tell us that a sedentary and agricultural mode overtook the nomadic way of life in the late Pleistocene period when world population density was probably less than 5 million persons (17). Agricultural activity was initiated 9,000 years ago in Mesopotamia from where it spread steadily through Europe to become a way of life by 2000 B.C. even in barbarous Brit-

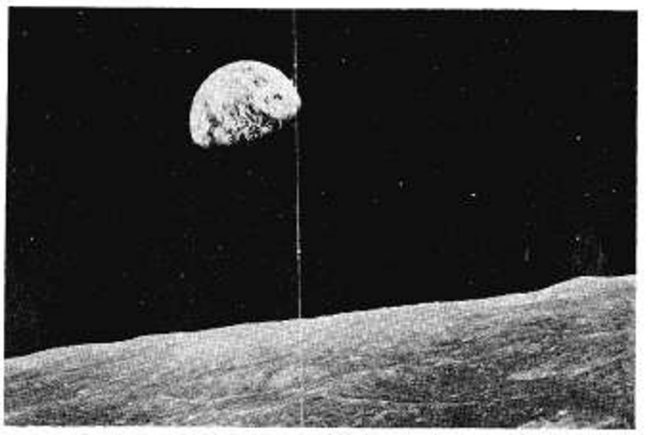

Fig. 2. Earth rise; the view seen during the *Apollo 8* mission that changed our view of life on earth (for source, see Reference 5).

ain and Scotland. These sedentary modes of life encouraged and permitted increased human fertility; and population densities in the Mediterranean regions increased 160-fold.

It is not surprising that population pressures and his inate curiosity coaxed man to begin his westward voyages of discovery from the cradle of the Mediterranean, sailing out through the Straits of Gibralter (5). He soon overran the Americas, still thinly populated with a mixture of nomadic and sedentary peoples bearing Mongolian genes, to which he imported Caucasian and Negroid genes. Thereafter, North American popuation densities under the influences of the agricultural and industrial revolutions, rose to be what they are today (18).

The dreams of Icarus have in part come true in the course of this extraordinary evolution of mankind. He now flies high, with wings equalling his ambition, and from somewhere nearer to the sun than we in this auditorium are at this moment, he photographs the St. Lawrence river valley, the route of so much immigration to my country. He sees a city called Montreal (Fig. 3), where today, man lives and works in a manner unlikely to have been anticipated by any of his ancestors of long ago. Every person, wherever he or she is in the world, shares in this remarkable modern perspective on our homes.

The excitement of evolution, and its lesson about our heritage, seems impossible to resist. And yet we do! We are a diverse species and among us there is the Flat Earth Society whose members insist the earth is flat. Earth they say, was photographed side-on, like a penny, and proof of its spherical nature is still lacking. We also have the Creation Research Society of California which, in 1972, won its case in the courts (19), thus forcing the State Board of Education to give equal time to Darwinism *and* to the Book of Genesis in the teaching of biology. With such examples from contemporary life, perhaps we should pause to review the exegesis of the word "evolution" (20), since our behavior towards the word, and the mechanisms of thought around it are, to some extent, dependent upon the genes we have inherited.

Evolution became a *word* in the Latin vocabulary where as noun and verb, it meant "scroll," and the unrolling of a scroll, respectively. Before that, Plato had referred to evolution as an idea of process.

The word lost its meaning and disappeared from the European languages of the Dark and Medieval Ages, when books replaced scrolls.

On the other hand, it remained a hidden psychologic factor in the Augustinian view of *Being* and *Becoming*. The Cambridge Neoplatonists, under More, restored both the word, and its meaning, to 17th century England, only to let it leave again to be taken over by the Natural Philosophers of 18th century Germany, to whom it meant again a doctrine of ideas; and by von Haller, to whom it meant an embryonic unfolding. Buffon, the great French

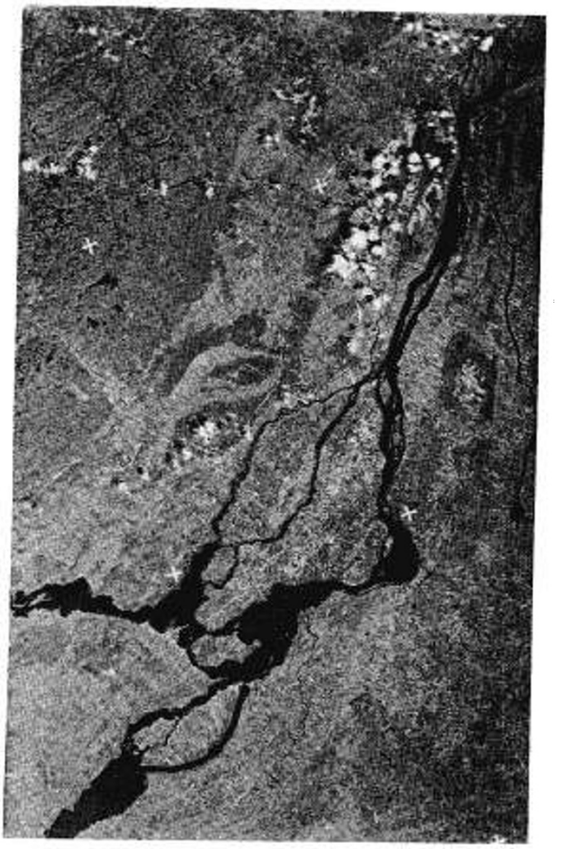

Fig. 3. Montreal. A satellite view of my home (5).

naturalist, also took up the word at this time, but he saw evolution merely as a degenerative process. It was Coleridge the poet who brought "evolution" back to the English language and since 1820 the word has held five coexistent meanings to scientists and philosophers. First, it came to encompass a major philosophical argument, Augustinian in origin, of Being vs. Becoming. Indeed, it is in the Augustinian corridors of our mind that our ambivalence over abortion appears to originate; in the absence of a scientific culture in which citizens can understand ontogeny, we confuse Being with Becoming. Second, it has retained its meaning for an unfolding of events. Third, it attained a special meaning for the embryonic unfolding of a completed being—or homunculus. Fourth, Erasmus Darwin used the term evolution to describe the development of an individual as a person. Lastly, Lamarck, Malthus, Lyell, Spencer, and Charles Darwin each perceived evolution as a *process* of organic change acting upon biologic species within a framework of time.

TEACHING OF BIOLOGY

From these perspectives, the Scopes Trial of 1925 is still revelant (21). The trial was about a modern heresy—the teaching of evolution. The case for Evolution was won in the forum of public opinion; but Fundamentalism won the decision in the classrooms of America for the next 40 years, a fact we would come to regret. After the trial, the biologists retreated, believing they had won the battle. It was in fact, the publishers of high school biology texts who won the war. They had to get their books past the school boards and because the American school book business is lucrative, they dropped words such as "evolution" and "Darwin" from the pages of their books; and these "expurgated" texts continued to sell. As a result, two generations of students heard little about how they came to be members of the human species. Only when *Sputnik* finally imposed upon us a sufficient cultural shock, could

we no longer resist making the transition from superstition and fantasy to evidence and perspective. But even the new biology texts which followed *Sputnik* have not solved everything; the Edelin trial of 1975 has told us a great deal about where we stand today on these public issues.

Upon looking at my own children's high school texts, I find many of them to be impressive treatises on biology. Yet, only one devotes much space to human biology and the average content devoted to genetics is ever modest (Table 1). Yet genetics is to biology, as mathematics is to science. It is disappointing that in our teaching of biology to young citizens, human biology usually does not have first chair in the orchestra of life played by earth worms, butterflies, mosquitoes, frogs, and fish. Moreover, human biology is not only unnecessary for college entrance at my university—it appears it is not a requirement for intelligent living and personal behavior in any form whatsoever.

Table 1. *Human biology and genetics in high school biology texts*

Text and authors	Date	Pages	% of contents: Genetics	% of contents: Human biology
BSCS: Green	1973	725	6	3
Yellow	1968	756	9	8
Blue	1973	523+	19.5[1]	14.4[1]
Modern Biology (Otto and Towle)	1975	824	9.2	15.1
Biology: Introduction to Life (Nason and Goldstein)	1969	750	11	17
Biological Science (Gregory and Goldman)	1971	714	6	19
Foundations of Biology (McElroy *et al.*)	1968	724	11	22
Biology and Man (Swanson *et al.*)	1975	614	10.7	30.6
Human Physiology (Morrison *et al.*)	1972	470	6	82
Average		677	9.8	23.4

[1] Excludes laboratory curriculum.

How can we be a cultured people without an emphasis on the culture of ourselves as a remarkable biologic phenomenon. This deficit disturbs me as it did Childs in his presidential address to the American Society of Human Genetics (22). Does this discordance in our culture explain why we are obsessed with clonal man, for example, who is the very antithesis of evolution's greatest legacy, namely our superb genetic diversity? If we do not understand our genes, we are likely to remain obsessed with what harm they seem to contain. If we continue to ignore, or even to deny evolution in the formal structure of our learning, we will continue to be the mass man referred to in Ortega's philosophy. We *will* fall prey to our superstitions. In a darkened culture of science, where human biology and human genetics hold a rather dim candle, superstition about our genes will predominate. It will abate only with better education in biology, and with a better awareness of our genes and their relevance to human sociobiology.

GENETICS AND SOCIETY

I intend now to develop the theme that knowledge of genetics will change our *medical* lives both as patients and as practitioners. Moreover, I believe this to be an area where pediatricians can make a major impact on disease prevention in society at large. Genetics is a discipline which reveals the biologic basis of individuality among human beings. It informs us about faces in the crowd (Fig. 4) (23). It tells us about being an individual.

One way to make a simple statement about the individuality of human beings is to remind ourselves that identical twin births are not the usual way in which mankind reproduces itself. A haunting picture of twins (Fig. 4) appears on the cover of the posthumous portfolio of photographs by Diane Arbus (24). In the language of Arbus, twins were the unusual. Arbus is telling us that to be identical to someone else is a form of private trauma.

I suspect that Arbus never read any writings of Sir Archibald Garrod. Garrod collected, not photographic impressions, but chemical impressions of odd people; but like Arbus, he also honored the odd man out, the sport among us. From his chemical probings came the great theme of human chemical individuality (25).

Garrod developed his argument first in the famous paper on alcaptonuria, published in *Lancet* on December 13th 1902 (26). Because he is one of those geniuses whose fate it is to be often quoted, but seldom read, let me share with you the exact ideas, far

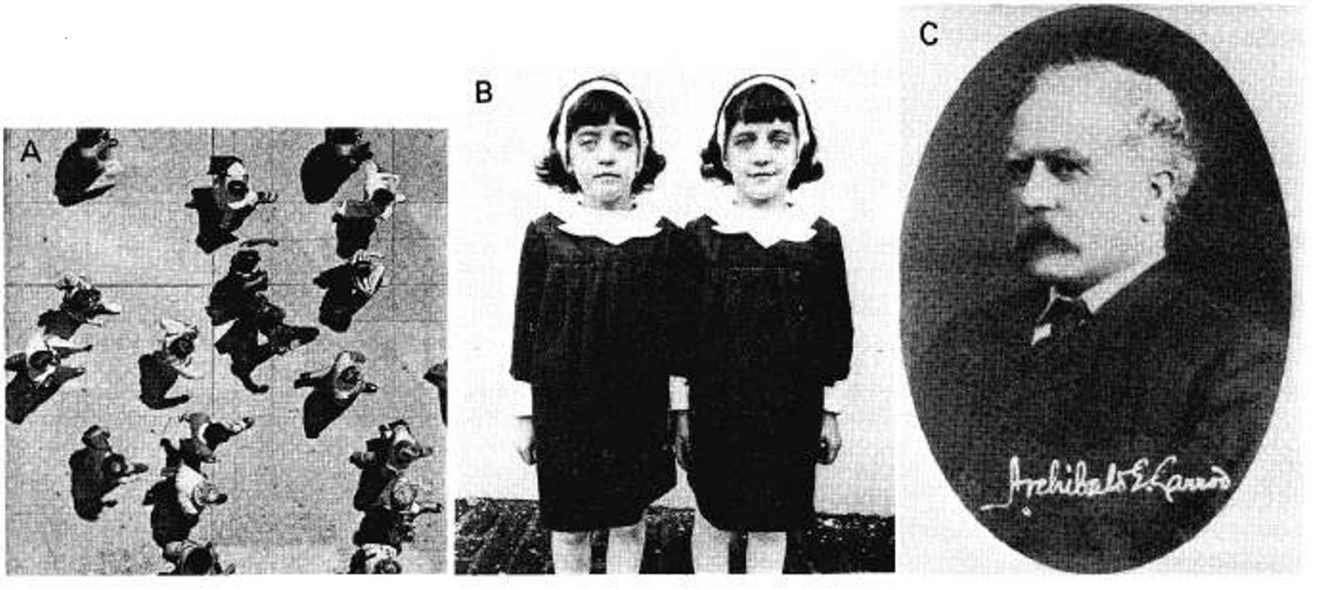

Fig. 4. Three views of mankind, (*A*) the "Schopenhauer" or crowd view (from Reference 23); (*B*) twins, the uncommon form of human individuality (24); (*C*) an individual, in this case Sir Archibald Garrod who first divined that interindividual chemical differences characterize the members of the human species.

in advance of their time, contained in the final paragraph of this extraordinary assay.

> If it be indeed the case that in alkaptonuria . . . we are dealing with (an) individuality of metabolism . . . the thought naturally presents itself that (it is) a merely extreme example of variation of chemical behaviour . . . elsewhere present in minor degrees, and that . . . just as no two individuals . . . are absolutely identical in bodily structure, neither are their chemical processes carried out on exactly the same lines . . . Again in their behaviour to different drugs and infecting organisms the members of the various genera and species manifest peculiarities which presumably have a chemical basis . . . (26).

More than half a century was to elapse before these ideas entered our collective medical consciousness. We need now to keep them vigorously in focus as long as political and societal processes steadfastly seem to reject the biologic basis of individuality among citizens. In a moment, I will explain why I believe a danger of rejection is, in fact, the case, and why there may be a danger that national health practices, as needed as they are, could treat all citizens as though they were *not* biologic individuals.

The constant dilemma which faces the citizen is wittily stated in a poster published by the Swiss artist Folon (Fig. 5). The poster depicts 50 men in hats, 46 of whom are identical to each other and wear blue hats. Only one dares to be different; he is near the center and he is wearing a red hat. Three of his neighbors dare to be a little different; they are looking at the man in the red hat. This poster is to be found in the area of our laboratory devoted to genetic screening, where we feel it makes a symbolic statement about our screening programs whose objective is to identify individuals in whom particular alleles place them or their offspring at risks for disease which are different from those of their neighbors and relatives. In the poster, the artist has symbolized the tensions which exist between society and individuals—tensions which need to be resolved in some of our approaches to disease prevention.

The theme of genetic individuality can be symbolized in another fashion (Fig. 6). I have used squares, instead of men in hats, to symbolize citizens in a society. The left side of the diagram represents 16 citizens as they are perceived by, let us say, a Health Commissioner. They are seen as being similar in their susceptibility to some illness, let us say, early onset coronary heart disease; and all are presumed to be malleable to a common process of prevention indicated as activity (*A*), to be initiated by the Commissioner, at a presumed cost-effectiveness to society. The Commissioner's approach de-emphasizes the biologic diversity among the citizens and produces, as it were, a sociopolitical entropy. On the right side of this diagram, I have represented the same 16 persons as they might see themselves, each with his own identity and dignity. They seek individuality in the sociopolitical structure. They invest the system with an energy which yields diversity. However, such diversity and the expression of personal dignity may be inimicable to the activity initiated by the central agency; and tensions may arise in the system as symbolized by the arrows pointing in opposite directions in the diagram. How can a knowledge of genetics resolve these conflicts between society and the individual; and can it enhance the efficiency of any disease prevention activity?

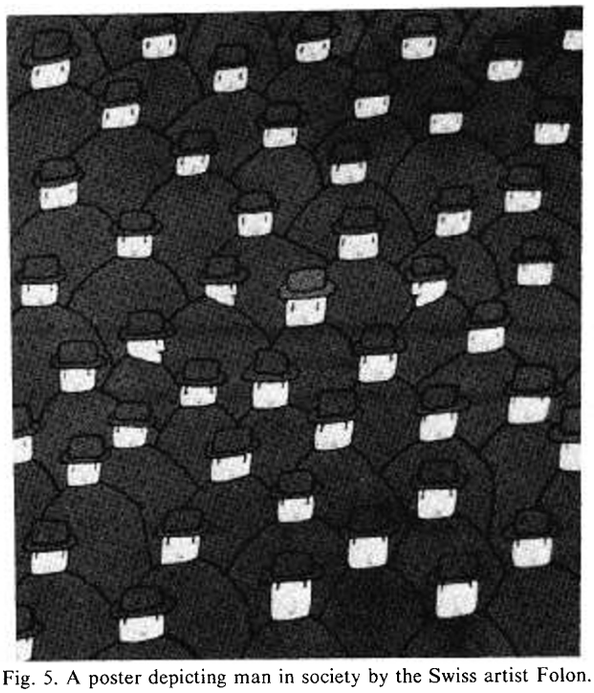

Fig. 5. A poster depicting man in society by the Swiss artist Folon.

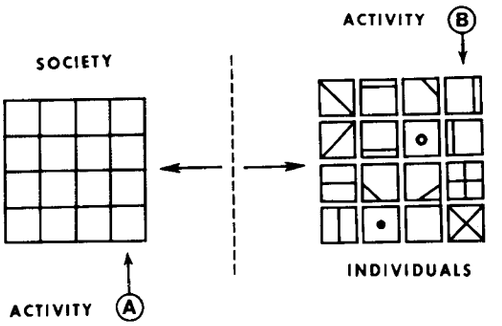

Fig. 6. A symbolic view of a disease prevention activity in society. The activity is promoted either uniformly by a central agency as if all citizens were at equal risk (*activity A*); or selectively in recognition of the genetic individuality of citizens, only some of whom are at specific risk (*activity B*).

Genetics can do so by recognizing the biologic individuality of citizens. We can initiate an activity, designated (*B*) on this slide, which permits us to identify particular individuals who may be at a specific high risk for developing the disease of concern to the Commissioner. The average risk in the population for a given disease is, after all, derived from those at higher risks and those at lower risks. Preventive measures can then be directed at those persons at specific high risk. Compliance with the preventive measure, be it taking a drug, following a diet, or giving up a habit, is likely to be better if one finds he or she is at specific risk than if the health message had been directed uniformly at all citizens, none of whom would necessarily feel he or she was particularly vulnerable (27).

An absurd example can be used to illustrate this theme further. We could prevent all mental retardation from thyroid hormone deficiency by putting all infants on thyroid hormone medication at birth. However, the effort would be wasteful and perhaps even harmful in order to save one infant from the effects of congenital cretinism among the 6 or 7,000 births not at risk for this illness. Fortunately, we do not follow this irrational approach; instead, for example, all newborn infants in my province are now screened under the authority of the Quebec Network of Genetic Medicine (27) to find the specific child who needs thyroid hormone replacement (28) before he develops symptoms or is brought to medical attention too late to prevent mental retardation.

The screening approach sounds so logical that we ought to apply it in many other situations. And yet, here we are in America flirting with the idea that dietary control for the *whole* population could reduce the incidence of early onset coronary heart disease in a *fraction* of the population. However, before we look at this particular example in more detail, we should examine the spectrum of disease in man to see how frequently there is a genetic component that would merit the genetic approach emphasizing the role of biologic individuality in disease prevention.

In Figure 7, I have arranged representative examples of disease

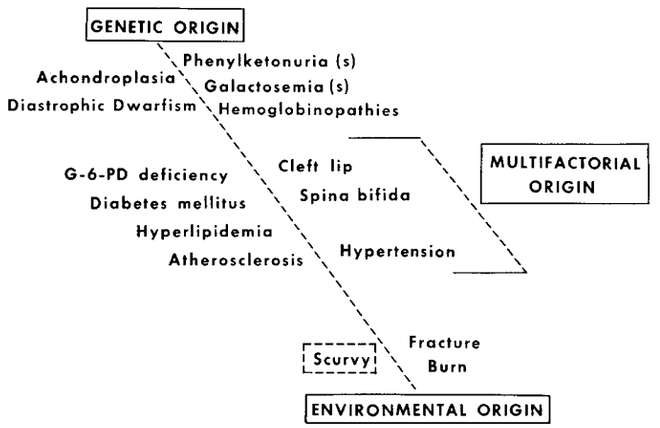

Fig. 7. A spectrum depicting origins of disease extending from: (*top*) predominantly monogenic and chromosomal; (*middle*) multifactorial (genetic and environmental combined); to (*bottom*) environmental.

along an axis joining several examples with clear-cut monogenic origin (at the *top left*) with two of unquestioned environmental predominance (at the *bottom right*). In the middle of the spectrum, environmental and genetic components coexist to cause disease. The position on the spectrum for a multifactorial condition is movable according to the interaction of various events. For example, individuals who inherit broad face shapes are at higher risk for expression of the cleft-lip allele, whereas those with narrow-shaped faces are at lower risk (29). The well known predisposition of individuals with X-linked glucose-6-phosphate dehydrogenase deficiency to develop hemolytic anemia is not usually expressed unless the individual is exposed to certain oxidant drugs or foods. Even fractures, which we consider to be largely environmental in origin, occur with much greater frequency in subjects with the genetic disease osteogenesis imperfecta.

The studies of Trimble and Doughty (30) and others before them indicate that at least 180 individuals per 100,000 live births are *born* with diseases of single-gene causation; that at least another 160 have chromosomal anomalies; and that 3,580 individuals have congenital malformations of multifactorial origin, while another 1,580 will have diseases with some genetic content which will emerge during a lifetime. The adjusted data suggest that as many as 1 in 10 humans is born with some degree of genetic or congenital handicap.

The fallout of these births into a demand for medical care is equally impressive. Several studies (31) indicate that up to 30% of pediatric hospital admissions are accounted for by patients with diseases which have a gene-dependent component. The corresponding figure for admission to adult-age hospitals is at least 11%.

If we turn to another perspective, namely the classification of genetic disease as pioneered by McKusick, we learn that the single-gene diseases in the 4th edition of the *Catalogues of Mendelian Inheritance in Man* (32) now number 2,336, of which 1,142 are quite secure in their assigned inheritance pattern; whereas 1,194 are presumptive but highly probable in their assignment. The diseases listed in the McKusick catalogues would flood the upper left portion of the diagram (Fig. 7); I have indicated only three classical examples.

It is the multifactorial diseases in the middle of the spectrum that I now wish to consider further. You will notice that they comprise some common problems. We recognize important environmental components in each but genetic predispositions also exist. Moreover, diseases such as hyperlipidemia and atherosclerosis have many causes, with many genes and many external provocations being involved in the appearances of the particular disease in the population.

The various themes up to now lead me to this synthesis. With rare exception, each citizen is born with a unique set of genes. Our genes, expressed through a lifetime in various environments, place us each at different levels of risk for any given condition or disease which has any genetic content whatsoever. Therefore, to expose all citizens to the same preventive medical program for one of modern societies' high burden, common, multifactorial diseases is not the optimal approach. We could benefit from genetic screening, to find out who is at particular risk. Yet, there has been some indication, in my country at least, that health care planners believe that the diseases of life style such as lung cancer and coronary heart disease could be reduced in prevalence among middle-aged citizens by initiating a change in the lifestyle of all younger citizens. A good idea in theory we might agree; but in practice, reminiscent of treating all infants with thyroid to prevent cretinism in childhood. It would seem better to find the persons carrying the genes which place them at special risk in the environment of our society, and to recommend a change in their particular lifestyle. The rest of us could get on with our natural, happy profligate lives to succumb eventually to some other weakness of the flesh. But these are idealized goals and there are many problems which beset their fulfillment. The example of early onset coronary heart disease will illustrate some of the issues.

Mortality statistics for Canada are representative of modern society. Myocardial infarction is now a major cause of death in males between the ages of 45 and 60 years. Osler was among the first to comment on the importance of genetic factors in heart disease. It was much later that hypercholesterolemia and hypertriglyceridemia were recognized as significant predisposing factors for coronary heart disease. However, until very recently it was not known whether hyperlipidemia, predisposing to early myocardial infarction, is caused by any monogenic factors at all, or whether it is a reflection only of more complex multifactorial events, including lifestyle.

Goldstein, Motulsky, and their colleagues (33) in the Seattle study discovered that monogenic causes of coronary heart disease appear in 54% of the *hyperlipidemic* survivors of early myocardial infarction; among 20% of all survivors (hyperlipidemic and nonhyperlipidemic) under 60 years of age; and in 7% of patients over 60. Moreover, males with the monogenic hyperlipidemic traits had their myocardial infarction 11 years earlier than coronary heart disease patients without hyperlipidemia. In other words, to inherit one of the alleles for hyperlipidemia elicits an increased risk for early onset coronary heart disease (34). It was estimated that between 0.6% and 1% of the general population carry three genes causing hyperlipidemia; it is these persons who come to be half of the ischemic heart disease population with hyperlipidemic myocardial infarctions.

The evidence for monogenic forms of hyperlipidemia in the general population was obtained by examining the (hyperlipidemic) survivors of myocardial infarctions and their relatives. The hyperlipidemias were segregated into three traits: isolated hypercholesterolemia; isolated hypertriglyceridemia; and a still controversial condition called combined hyperlipidemia. The forms of hyperlipidemia which involve triglycerides are 3 times as common as isolated hypercholesterolemia, suggesting that hypertriglyceridemia may be the more important risk factor for coronary atherosclerosis. The survey revealed three independent alleles each inherited in autosomal dominant fashion. One allele is responsible for familial hypercholesterolemia; it is carried by 0.1–0.2% of the general population, by 4.1% of the survivors of myocardial infarction under the age 60, and by 0.7% of the survivors over age 60. A second allele is responsible for familial hypertriglyceridemia which is present in 0.2–0.3% of the general population, in 5.2% of coronary heart disease survivors under age 60, and in 2.7% of survivors over age 60. A newly discovered third allele is responsible for familial combined hyperlipidemia in 0.3–0.5% of the general population, in 11.3% of myocardial infarct survivors below age 60, and in 4.1% of the survivors over age 60.

The fact that these combined genes occur in about 1% of the general population poses an important public health challenge since early recognition of such persons *might* offer a valuable opportunity to direct preventive measures to individuals at high risk for coronary heart disease. An anticipatory change in lifestyle,

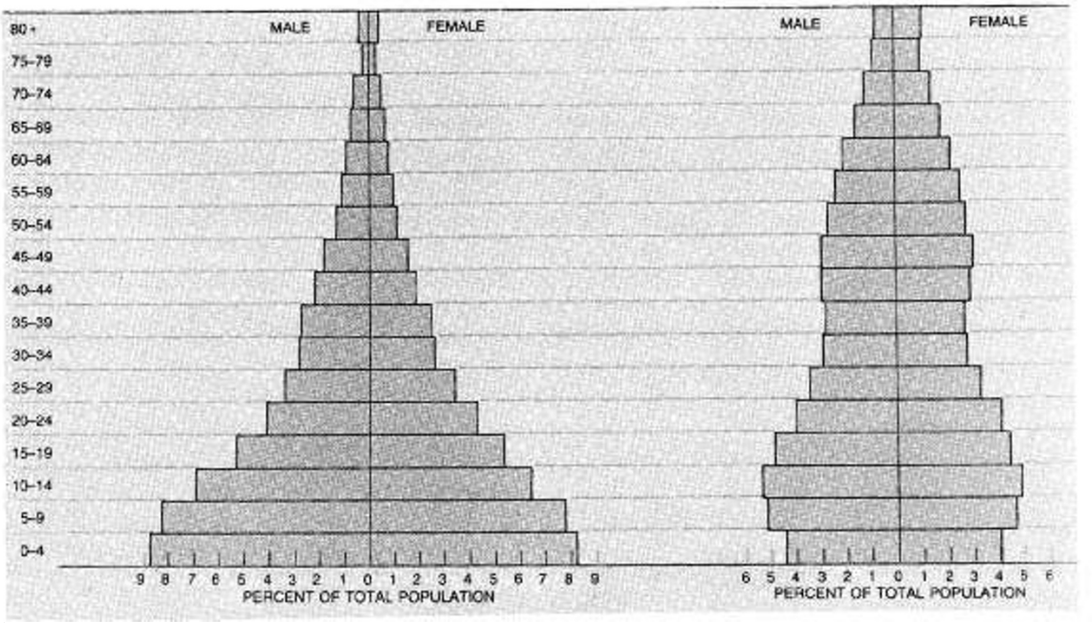

Fig. 8. Census profiles for a developing country (*left*) and for a developed nation (*right*) (37). Genetic disease has particular relevance in the latter.

which prevents early myocardial infarction, could be highly beneficial to these individuals; whereas to initiate diet and drug treatment in hyperlipidemic survivors after the first infarction may not alter significantly the poor subsequent prognosis. Whereas it has yet to be proven that early treatment will reduce the risk of coronary heart disease in those at specific risk, it is quite evident that a genetic approach to the problem will avoid conscription of all persons into the research protocol. Furthermore, the genetic approach rationalizes the empiric evidence that different types of hyperlipidemia need different forms of treatment (35).

Unfortunately, in the absence of pedigree studies, we have no useful markers at present which would permit pediatricians to identify persons early in life who are at specific monogenic risk for early onset, hyperlipidemic heart disease (36). Continuing research to identify a marker for simple recognition of the monogenic forms of hyperlipidemia will be needed in order to initiate the genetic approach to the prevention of coronary heart disease in those at increased risk for this illness. In the meantime, we must face the dilemma of whether to attempt reduction of this disease burden in our society by adopting universal nongenetic measures, with the danger of alienating many who do not need nutritional and drug therapy; or whether we should move cautiously toward a definition of specific risks for individuals at the price of a continuing high rate of coronary heart disease in those who did not receive potentially effective early treatment. The pediatrician-scientist cannot avoid being part of this problem and its resolution.

By now I hope that I have convinced you that knowledge of our genes is the concern of everyone; that there are probably few states of health or disease without a genetic component; and that our awareness of these very problems is to some extent a function of our own genes expressing homologic evolution.

I believe this view of life is relevant for developed and developing country alike. Imagine two age-specific census profiles (Fig. 8); the one on the *left* is for a country with a high birth rate and also with high childhood mortality, typical of developing countries with an agricultural demography and where nutritional and infectious disease still dominate the scene; the graph on the *right* is for a developed country largely free of these scourges. It is simple enough to see the high birth rate in the former country as a Darwinian solution to maintain a pool of survivors so as to pass on our genes. But let us suppose that in one generation, the birth rate and childhood mortality both drop abruptly. The demographic profile will then shift to that characteristic of the developed

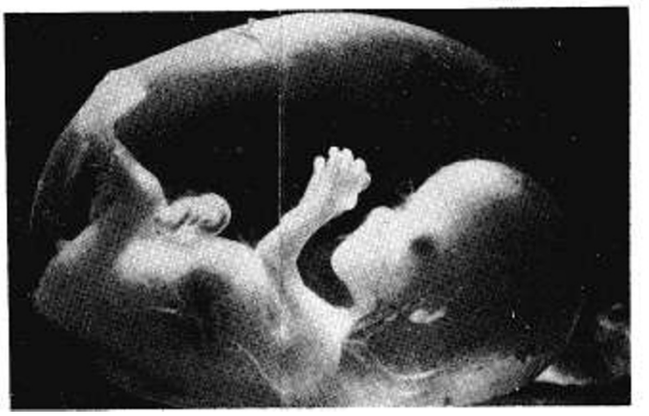

Fig. 9. Midtrimester human embryo (18 weeks) (from Reference 38).

postindustrial community. There will then emerge, on the plane left by the receding flood of acquired diseases, the mountainous topography of genetic problems, the genetic handicaps that affect up to 30% of admissions to pediatric hospitals in developed countries today. That is why I feel it is not too early for pediatricians to be concerned about human genes and their effects wherever we are in the world.

Perhaps this audience doesn't need to hear any of these messages. But wait until any one of us tries to counsel someone else recently identified as a carrier of a mutation, for example the Tay-Sachs or sickle hemoglobin gene, and we will soon find that the theme of genetic diversity is little known even in our own culture; to come face to face with it may bring fear to the subject, instead of comfort.

CONCLUSION

My brief voyage in this symposium is now ending. The journey of Earth began long ago and it is continuing. It has yielded mankind through the forces of evolution, a process first recognized on distant shores, by a young man on board H.M.S. *Beagle*. Homologic evolution has given to man through his extraordinary *Apollo* journeys the beginning of a new view of Earth and compelled us to recognize what our fragile environment means to us.

The future of man rests in our own hands and it is not surprizing that during the voyage we battle over the rights of the helpless embryonic human passenger who sets out on a perilous voyage generation after generation (Fig. 9). I am hopeful that better knowledge and teaching of our own biology will help us to make wise decisions about our future journeys. Hopefully the second century of Darwinism and Mendelism will bring new knowledge about our genes to benefit our own fitness. I hope the second century will also bring with it a new respect for our personal genes and those of our neighbors.

In a letter to a friend written in the 1880's, Thomas Hardy said (39): "What we gain by science is, after all, sadness. . . . The more we know of the laws and nature of the Universe, the more ghastly a business one perceives it all to be." Hardy was puzzling out the place of man in the changing, disruptive Victorian universe, much like Everyman today.

Thirty years later, shortly after Mendel's work had been translated into English, Hardy created this moving poem, entitled "Heredity" (40).

I am the family face
Flesh perishes, I live on.
Projecting trait and trace
Through time to times anon,
And leaping from place to place
Over oblivion

Hardy describes a voyage that is unending, in which we are both passenger and vehicle. If we use the science of genetics wisely I believe we can help individuals to face their ghastly universe with dignity; and in so doing, some of the sadness that accompanies progress will be ameliorated.

ACKNOWLEDGMENT

I am a part of all that I have met. My esteemed colleagues, teachers, friends, and family will recognize themselves in this address. Thanks to them; and to my university which believes it is as important to reflect as to act.

NOTES AND REFERENCES

1. The honor of being President of the Society for Pediatric Research offers the opportunity to make innovations in the program of the annual meeting. We elected to hold a symposium entitled Voyages to Discovery. It was sponsored jointly by the Society and the Journal of Pediatrics Educational Program. The objective of the symposium (and of the Presidential Address as its first part) is to invite reflection on the role of basic and clinical research in the prevention of disease in children; and to examine the nature of scientific progress in five "classic" areas of pediatrics (genetics, rickets, respiratory distress, diabetes, and infant feeding).
2. This Presidential Address to the Society for Pediatric Research evolved from three previous talks given at The Centennial Symposium. Dilemmas of Modern Man, Winnipeg, October 1974; the Blackfan Lecture, Harvard University, May 1975; and the Centennial Symposium on Genetics, Johns Hopkins University, October 1975.
3. Recently published polls have affirmed citizen interest in science; *see:* Science, *191:* 1032 (1976); and Media Impact, Vol. 2. A Research Study on Science Communication by Dubos, O., and Martel, L. (Chapter 3) published by the Ministry of State for Science and Technology, Government of Canada, Ottawa, June (1975).
4. The illustration of H.M.S. *Beagle* used in the spoken presentation was taken from Conrad Martens' watercolor reproduced in: Alan Moorehead, *Darwin and the Beagle* (Haimish Hamilton, London, 1969). H.M.S. *Beagle* is also the subject of recent detailed report. Thomson, K. S.: H.M.S. *Beagle* 1820–1870. Amer. Sci., *63:* 664 (1975).
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37. Illustration of population profiles taken from Freedman, R., and Berelson, B.: The human population. Sci. Amer., *231:* 31 (1974).
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