Acceptance of the Howland Award

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I am immensely gratified in receiving this award and I thank the American Pediatric Society for it. I am even more gratified by the thought that it is a sign of the Society's recognition of genetics in medical education, research, and practice.

Every schoolboy knows that Isaac Newton remarked that if he saw farther than others it was because he stood on the shoulders of giants. The aphorism did not originate with Newton, however, but has been traced by Robert Merton to Bernard of Chartres, a 12th century monk who observed with perhaps a tinge of irony that even pygmies could see farther than others when they stood on the shoulders of giants (1). It is in the nature of science today that we *all* stand on such shoulders, and it has been my good fortune to have experienced some special ones.

First, there was Dr. Edwards Park. No one has influenced my life more profoundly than he. It is clear that Shakespeare had him in mind when he put into Hamlet's mouth the words, "He was a man. Take him all in all, I shall not see his like again." And indeed we have not. Dr. Francis Schwentker was Dr. Park's successor. He helped me enthusiastically in working out a way to send me to England to study genetics, and did so at a time when the universal reaction to my plan was dropped jaws, raised eyebrows, and blank stares.

From Professors Lionel Penrose, J. B. S. Haldane, and Harry Harris at University College, London, I learned a great deal of genetics and of no less moment, I learned that nothing in biology makes any sense except in an evolutionary context.

Dr. Victor Najjar, at Hopkins, taught me the meaning of the word experiment. He also tried, unavailingly, to teach me how to behave in the laboratory.

And finally, Dr. Harry Gordon was exemplary to me, as he was to a generation of pediatricians of the virtues of charity, tolerance, and concern for human beings in distress. Of his like too, we shall not see another.

I now have 15 minutes, that flickering moment of fame to be experienced by us all, according to the late, great American philosopher Andy Warhol, and I prefer to use it saying something about how new and incisive insights into human nature are influencing how we think about disease; insights that bring into consonance the evolutionary history of the species, the life history of individuals and moment to moment adjustments of homeostatic systems.

I begin with an anecdote. A month or so ago, upon entering the hospital, I encountered a colleague, a cardiologist, a man I have known for 40 years. We greeted one another cautiously, each obviously groping for the other's name. I began, by saying, "What's new?" "Oh," he said, "It's so depressing, seeing all the dreadful things that happen to old people's hearts." "Well," I said, "At least we have escaped so far." "Yes," he said, "By hook or by crook." "No," I said, "It's by our genes." He looked at me with wild surmise, "You may very well be right," he said. "I hadn't thought of it that way." And he never will! This conversation, while hardly up to standards set by the great salons of the enlightenment, illustrates a very common present day mentality; a dim awareness that something, maybe something big, is hap-

pening, something that ought to change one's way of thinking, but somehow does not.

I think something big *is* happening. I think we are experiencing a sea change in medical thinking which may be leading us to some sort of coherent logic of disease, a change that will transcend disease classification and department boundaries to show that there is unity in diversity.

The mystery of disease has preoccupied philosophers since antiquity. Two polar concepts have prevailed (2, 3). In one, called essentialist, diseases have independent entity, existing apart from those they afflict. In the opposing conception, called nominalist, disease is a response to some aspect of living, the extreme position being that there are no diseases, only sick people, each of whom is sick in his own way.

The essentialist view has prevailed through much of history, receiving apparent confirmation in the 19th century in the discovery of bacterial and nutritional causes. Then, each disease was perceived as having its own single cause. And because each disease was separate and independent, no descriptive generalizations useful in understanding disease were necessary or even possible. This typological thinking, centering on the disease itself and variations expressed in patients risk being dismissed as noise. Genetic disease, as it has been generally perceived in medicine, fits neatly into this mode.

But such thinking, and it is widespread in today's medicine, can affect patient care. If the focus is on the disease not the individual patient, whether or not that particular patient enters the analysis at all depends upon the humanity of the particular doctor, it is not compelled by the context of thought within which the encounter takes place.

Today we are beginning to accept that causes are complex, multiple, and diverse, imposing a serious strain on the typological position. If the same disease has several causes, varying in number and kind from patient to patient, is it in all cases the same disease? Or are diseases just names, not entities? Further, since nearly all diseases appear to be familial, at least in minor degree, then, given this diversity of cause, we must assume that the *patient* participates in some way in the origin of the illness, in the form it takes, and when it has its onset. The disease, then, is perceived as a consequence of incongruence between the patient's particular homeostasis and the conditions of living, an incongruity between biology and biography. This position is nontypological, focuses on individual variation, on patients, each of whom has a developmental and cultural history, and it accommodates to the idea that *all* disease might be embraced in a single coherent logic. What could that logic be?

Fifty years ago, Cannon conceived of homeostasis as the ability to contain physiological functions within limits. Since then, biochemists and molecular biologists have defined many of the molecules engaged in these processes as well as the genes that specify them. And the amount of genetic variation in these molecules already known to exist, suggests a broad range of individuals vulnerable to particular experiences and a broad range of experiences to which particular people are vulnerable.

But where did all this diversity come from? The gene pool is a record of the evolution of the species, of how well we have adapted to all the environments encountered in human history, and the aliquot that is our individual heritage represents our unique participation in this flow of biological experience. So, in uncovering the genetic history of the species, molecular genetics will outline for the species our options and constraints, and in exposing individual genomes, it will supply for individuals lists of alternatives pointing to strengths and vulnerabilities. Species constraints and individual vulnerability represent the sources of human disease, and they must be the basis for its logic.

The mechanisms of mutation are a thing apart, random, offhand, and indifferent to the fates of the mutants' inheritors. Biological evolution requires genetic variation, and mutation is capable of producing variants that embrace a gradient of adaptive effect from the best to the worst. Cultural evolution has its imperatives too, which, although necessarily constrained by biology and intended to advance human welfare, often seem no less autonomous and indifferent to individual outcomes. Again, we may expect for each kind of experience a gradient of adaptive effect, expressed in intensity and duration and varying from best to worst. Obviously, it is the integration of these two kinds of variability in individuals that shapes the species, and it is how the experiences are incongruent with constraints common to all or characteristic only of individuals, that engenders disease. But the outcomes of these integrations and incongruities are modified by a third element: development. Development is historical in the sense that the past shapes the present, which in turn, informs the future. But it is also programmatic in the sense that genes propose alternatives and impose constraints for the directions through time an organism can take.

Elements of the interacting variables are listed in Table 1. Parental influences appear in the central column because they emerge for the individual as developmental variables.

One line of inquiry is, how are the variables integrated to lead to incongruence? A second is, are there predictable regularities in how they do so that can be codified into some general rules of disease? It is in giving answers to these questions that molecular genetics will bring us revelations. I prefer here the word revelations to, say, disclosures, because like that divulged in the Book of Revelation, some of what is discovered is likely to be too hot to handle.

The first of these questions is how are the variables integrated. In fact, although we know how to proceed with mendelizing traits, we have no model for analysis of complex phenotypes; it is in the process of evolving and must conform to something like the following. If there are continuums of effect for genes and experiences, then outcomes must depend upon which elements in each gradient is present in each individual and how they interact at each developmental stage. Such interactions may be rather straightforward; some genes are indifferent to the environment (Tay-Sachs, for example) and for some experiences we are all genetically undifferentiated (gun shot wounds, for example). But the position becomes complex where the effects of genes and experiences are each conditional upon the other, and both upon development. And further complications are introduced by reciprocal interactions; the phenotypes themselves affect the vari-

ables that induced them, setting up in turn further effects on the phenotypes, sometimes to intensify, sometimes to inhibit (4). Figure 1 is a diagram of such dynamic, dialectical processes. When the phenotype is, say, phenylketonuria, the dynamics are fairly simple. The phenylalanine hydroxylase mutant promotes hyperphenylalaninemia in the presence of dietary protein, and the hyperphenylalaninemia interferes with the development of the brain. But it does so only because human development is neotenuous; if the human newborn brain were as well developed as that of most other mammals, phenylketonuria might be, in some or in most cases, a harmless variant. So the developmental state affects the phenotype which in turn influences development. And when the disease is diagnosed, the environment is altered; the diet is changed and so are other routines at home. And finally, untreated patients seldom reproduce, affecting, thereby, the gene pool. But the relationships in such other diseases as diabetes, rheumatoid arthritis, or psychosis are a good deal more complex. In these disorders, life history, including aging, accounts for more individuality. Here there are more factors to reconcile, they are aggregated variously in individuals and the dialectical opportunities are maximized.

The second line of inquiry is, are there rules and regularities. These rules may be seen to take shape when observing the fates in life of a cohort of conceptuses. Evolutionary pressures will bear differentially upon the life histories of the members of the cohort according to mutational effects on the properties of homeostasis.

To begin, because so much of new mutation is bad, the conceptuses and embryos are inevitably the objects of what evolutionary biologists call "purifying" selection; *i.e.* nearly all of the very extensive intrauterine losses are likely to be due to genetic defect. Later, in infancy, further such "purification" is observed in a peak incidence of often lethal monogenic disorders that declines rapidly so that there are few mendelian diseases with onset late in life (5). There is also a reciprocal increase across much of the life span of onset of nonsegregating but familial diseases, but in these too, the genetic component declines with age at onset. So, in general, the genetic contribution to disease diminishes with age at onset, *i.e.* the heritability declines (6, 7). Another way of putting it is that the cohort is at its most variable genetically at conception and at its least in old age, and reciprocally it is at its least variable in regard to experience at conception and at its most in old age. These relationships are shown schematically in Figure 2.

Several other progressions flow from these inverse trends (7). First, there is a fall off in the number of different diseases from early to late life. Second, there is a rise in the frequency of the genes involved in disease and of the disorders they cause. Rare harmful mutants; chromosomal abnormality and dominant le-

Table 1. *Some elements of individuality*

Genes	Constitutional factors	Environment
Major genes	Age	Time
Modifiers	Sex	Geography
	Developmental stage	Climate
	Parental factors	S.E.S.
		Occupation
		Education
		Diet

Fig. 1. Interactions among genes, experiences, and development are dynamic.

thals, followed by recessives, are selected out early. Genes of later disorders, usually dominants, are often of polymorphic frequency and only conditionally bad. Third, there is a seamless progression of complexity of cause from monogenic to multifactorial disease and from early to late onset, and the progression from early to late onset is accompanied by a decline in the number of affected relatives. Fourth, early onset disorders are likely to carry the heaviest burdens as measured in loss of life, curtailment of reproduction, and residual handicap (5). Fifth, success in treatment and prevention are likely to be inversely related to the salience of the gene effect (7, 8); this and other progressions are shown in Table 2. Sixth, these same characteristics are observed within as well as between diseases. Gout is an example (9). The youngest cases are likely to be the most severely affected and to have the most relatives with gout, qualities that diminish in frequency with increasing age at onset. Most patients with gout have an inborn error of metabolism marked by overproduction of uric acid, but patients more than 60 y of age who have the least severe disease and the least affected relatives, are often people who are being treated for hypertension with diuretics. Although genetically vulnerable, it is the effect of the diuretic that provokes the gout.

But the ebb in heritability is not smooth. It drops sharply at the end of each developmental phase rising again early in the next. For example, early losses in gestation are mutational, while the end is marked by such genetically undifferentiated disorders as prematurity and birth injury. This is followed by a rise in heritability in infancy and early childhood expressed in the mendelizing inborn errors as well as such strongly familial but nonsegregating disorders as allergies, type I diabetes, and the familial cancers, while late childhood, teenage, and early adult life are characterized by auto accidents, drugs, and mayhem. Later, in mid-adult life, there is a new spurt of heritability marked by premature heart attacks, autoimmune disease, more familial cancers and the like, while very old age, the genetic storm long since spent, is marked by the scars of living, by what Alexander Pope described as "this long disease, my life."

But how about infections and later cancers? Aren't these

Fig. 2. Reciprocal contributions to disease of experience and genes according to age at onset.

Table 2. *Some differences in qualities of disease with different ages at onset*

	Type I GMI gangliosidosis	Rheumatoid arthritis	Type II diabetes
Prevalence	0.00001	0.01	0.01-0.05
Modal onset	Newborn	4th decade	6th decade
Genes known	++++	++	+
Severity, disability	++++	++	+
Treatment	None	+	+++
Y of life lost	70	3-18	3-10

environmental diseases? I suggest that they follow the same general pattern, although in their own ways.

Infections are a consequence of how some microorganisms have evolved to breach our complex defenses, and it is natural that they do so in relation to the prevailing molecular versions of the entry points they choose. So there may well be some organisms of universal, or nearly universal, virulence. But new genetic vulnerabilities are turning up all the time. There are many monogenic inborn errors of the immune system, each rare, and, of course, of early onset, but if there is a gradient of mutant effect for many of the genes of the immune system, there must be more frequent alleles expressed not in disastrous, complete deficiency, but perhaps in rather more infections than normally expected or in an unexpected susceptibility to particular organisms, and not necessarily expressed very early in life. For example, in a study of adopted subjects in Denmark, Sorensen showed that when a biological parent died of infection at less than 50 y of age, the rate of early mortality from infections for their adopted offspring rose nearly six times (10). And we are learning the molecular details of these interactions. The relationship of the P and Lewis blood group substances to adherence of genetically distinctive strains of *Escherichia coli* in women susceptible to urinary tract infections is exemplary (11, 12).

As for cancer, although no longer a "riddle wrapped in mystery inside an enigma" (13), we are still uncertain as to its manifold causes. But in the context of the argument being developed here, the genetic causes are a mirror image in the somatic line of the germline mutants of embryonic losses and inborn errors (14, 15). Familial early onset cancers are usually associated with recessive, germline mutants of suppressor genes, protected from selection until the advent of a somatic second hit. Late onset types are more often associated with several and perhaps many, dominant acting mutations in oncogenes, mutants that must be somatic avatars of germline dominant lethals of embryonic life; imagine what a germline oncogene would do to an embryo. These somatic mutations are promoted by mutagens with effects enhanced perhaps by aging of the DNA repair system. So are we all equally susceptible to some form of cancer? The age-specific incidence for some cancers continues to rise into very old age suggesting that for them we are. So, to the degree that somatic mutation is the cause, the answer is yes. But if the number and complexity of steps required also increases with age, to the degree that we are genetically differentiated in the attainment of those steps, the answer is no. But that such influences may be for many only modest modulators is attested by Sorenson's demonstration of a 5-fold increased risk of cancer in adopted offspring of foster parents who died of cancer, as opposed to no increased risks when biologic parents had died of the same disease; heritability is at a minimum (10).

No doubt there are exceptions to this argument. Nature, the tinkerer, is also a great compromiser. But my purpose, in 15 minutes, is not so much to present a detailed argument, for which I have, in any case, no time to present substantial evidence. Rather, I wish to sketch a way of thinking about disease which, even while embracing the reductionist accomplishments, tries to accommodate some of the regularities and constraints to which they seem to point.

In concluding I return to my cardiologist friend? Suppose I had asked him, "What have type I diabetes, atherosclerosis, and manic depressive disease in common?" I doubt he would have known that in certain families these heterogeneous disorders are associated with specific genes of known chromosomal location, or perceived that the investigators studying their genetic basis all work within the same intellectual context, use the same methodological framework and the same laboratory techniques. It is the special triumph of reductionism here to unify, to expose rules that show relationships where none seemed to exist. And these rules have special meaning to pediatricians who face at once the devastation of purifying selection (a usage laden for us with an especially poignant irony) and the earliest encounters of vulner-

able genotypes with experiences that can lead in later life to no less unhappy conclusions, but which may by judicious intervention be averted. But here we face a further uncertainty. We shall have to look for further rules to help us in distinguishing judicious intervention from officious meddling (16). But the point is clear enough; the logic of disease leads inevitably to a logic of prevention, and given all that has just been said, it demands attention early in life. So it is a burden imposed principally upon pediatrics. But it is not a burden we have a choice to take up or leave; it is a burden imposed by nature. It is no doubt less glamorous and less exigent than the imperative to find a treatment, but it is likely to be less invasive, perhaps less expensive, and certainly less wear and tear for the patient.

Again I thank the American Pediatric Society for this award, and especially for affording me this bully pulpit.

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