



---

## **Medicine Through a Genetic Lens**

**Barton Childs, M.D.**  
**Professor of Pediatrics**  
**The Johns Hopkins University**  
**School of Medicine**

It is the wisdom of medical educators that medical students be given a substrate of information and experience upon which to depend in entering a medical career. In this, the school assumes an obligation to adapt the curriculum to changing ideas and techniques. That is, from time to time discoveries lead to new ways of coping with old problems and medical education is renewed. For example, expanding knowledge of biochemistry and molecular biology led first to a diminishing reliance on morbid anatomy to validate pathogenesis, and then to molecular versions that could be established in the living patient. The latter is much enhanced by the development of a variety of visual techniques. These advances in medicine have had consequences; for example, today's students display less ardor for high skill in the physical examination. Other changes in teaching occurred. Grand rounds, a cardinal teaching exercise, has changed out of recognition, while the clinical pathological conference has all but disappeared. The story of the changes in these two teaching exercises is illuminating.

### **Grand Rounds**

Designed as a device for demonstrating the discernment and skill of a superior clinician in a diagnostic approach to patients one at a time, the content of grand rounds changed gradually from emphasis on how one outstanding doctor deals with one patient, to lectures on optimal approaches to all patients with some specific disease. The appeal is now to authority, no longer to experience. In the course of this evolution, something disappeared: the individuality of the patient. An important feature of the original exercise was the

colloquy between the physician and the patient. The doctor spoke directly to the patient, calling him or her by name, and, after asking pertinent and personal questions, went on to the physical examination, ending the session with a reassuring word. The discussion about the case, away from the bedside, then revolved around that specific patient, with allusion to generalities about other cases as aids to formulating a course of action for a single specific person.

What is reflected in this evolution of grand rounds is this. The problem of the individual patient gave way to the generalities of pathogenesis. It is the literature that dominates, not the insights of virtuoso physicians who relied on experience, skill and intuition to come to a diagnosis and then to design a course of management for a single patient. The appeal is to authority and the thinking is typological. Today the accolade goes to those who are artful in the use of mechanical and laboratory aids and ingenious in interpretation of the abundant data they yield. Reports of results of tests vie with the patient for the doctor's notice.

### **The Clinical Pathological Conference**

The purpose of the CPC was to test the validity of a diagnosis made in life against the reality exemplified in morbid anatomy. Again there was a show, this time a contest between the clinician and the pathologist. The former recounted in detail the process whereby the specificities of historical, physical and laboratory information had drawn him to a diagnosis. Then the pathologist had the last word. Observers learned not only the pathology of the case, but how a skillful physician was led, or misled, to a diagnosis. But modern methods have made morbid anatomy and the CPC unnecessary because they allow pathogenesis to be traced to molecular mechanisms of homeostatic dysfunction, which, with few exceptions, can be traced to one or more variants among the proteins that constitute the unit steps of homeostasis, and it is increasingly possible to find and to characterize the genes that specified them. In astonishing feats of reductive science, diseases are shown to originate in homeostatic perturbations due to variant proteins, themselves the products of variant alleles, and the diagnosis is based, not on morbid anatomy or biochemical or even molecular variation alone but on the individuality of the gene product. But again, something has been lost. The point of the CPC was to learn not only whether or not the diagnosis was made in life, but to observe correlations between individual expressions in the history, symptomatology and course

---

of the disease with the morbid anatomy of each case. The appeal was to the diversity of cases. In the CPC, the clinician called upon a broader range of knowledge of the patient than that which leads to a molecular or genetic test today. And that made of the case a specific person. Molecules yes. But humanity too.

The causes of this fundamental shift in medical teaching are not easily fathomable. How did the molecular definition of pathogenesis displace the patient as the central focus? How did analysis displace synthesis? Certainly government support of medical and basic science research, the efflorescence of molecular biology, the adaptation of fibre optics to medicine and new approaches in radiology were all prominent. And medicine has not escaped the influences of the quickening pace of social change. But, whatever the causes, today's medicine is readily embraced within the metaphor of the body as a machine that has for so long exerted a strong attraction for the medical mind. Devices that see into the innermost recesses of the body, a new anatomy expressed in the molecular detail of every kind of cell, and a biochemistry and physiology that characterize the actions of cellular homeostasis, all contribute to the concept of a machine, and in our mechanized society we expect all examples of a particular machine to conform to the same plan. This metaphor has been very useful and will continue to be; the human body is a machine. But human beings are manifestly not all the same and it is in imposing diversity on the metaphor of the machine that genetics adds significantly to how we think about disease. Why has it not done so already? Perhaps because change in the conceptual basis of a profession is always deliberate. But the wherewithal for such a shift is already here and it has begun to influence our thinking about all disease. So it is time for formal action to incorporate into medical education the new ideas generated by a penetrating understanding not only of the structure of genes, but of their origin in evolution and the function of their products in human homeostasis and disease.

### **Genetic and Medical Thinking: A Synthesis**

How does genetics add significantly? There are two ways. First, genetics can be adapted to help in the fulfillment of the conventional aims of medicine: diagnosis, treatment, prevention; and that is more or less what medical genetics has done so successfully. But genetics can contribute more fundamentally by modifying medical thinking to accommodate a view of disease as originating in the

imperatives of evolution and natural selection.

“Modify medical thinking”. What does that mean? It means observing the human machine and its diseases through a genetic lens. It means a synthesis of medical and genetic thinking. Such syntheses are not new. An example is that of genetics and evolutionary biology which emerged in the 1930s and 40s as neodarwinism, to the profit of all of biology.

What does it mean to observe medicine through a genetic lens? How different is the product from conventional medical thought? One way of putting it is to say that the machine mentality limits its scope to what can be seen, sensed, related by the patient or revealed by the laboratory which reports on present conditions, while the genetic lens adds the phylogenetic past, the freedoms and constraints imposed by development, maturation and aging, the uniqueness of the individual and the specificity of his experiences of the environment. One way to bring out contrasts between ways of thinking is to compare polar positions. Here these are expressed in contrasting questions that are exemplary on one hand of those of conventional medicine, and on the other, of those asked after genetic modification.

The medical questions are a) “What disease does this patient have and how do I treat it?”; and b) “How can I prevent this disease?” In each question the emphasis is on the disease, its pathogenesis, and its treatment or prevention, not on the patient. The latter who constitutes the arena wherein the struggle against disease is to be waged, could be anyone. The appeal is to authority, the thinking typological.

The questions asked when medicine is viewed through a genetic lens are a) “Why do we have disease at all and how do we define it?”; b) “Why does this person have this disease at this moment in his/her lifetime?”; c) What can we do to restore this person to his/her unique steady state?; and d) “How can we employ knowledge of an individual’s special qualities to prevent disease and maintain health?” These questions are added to, not substituted for, the questions above, and their answers expand greatly the conceptual grounds upon which a patient’s problem is considered, even while adding nothing to the burdens of diagnosis and treatment or their cost. The answers comprise a conceptual basis for medical education, a set of explanatory principles within which to confront individual patients with their particular version of the disease they suffer.

---

Every profession has explanatory principles that inform its practical applications. These are unlikely to come explicitly to mind in the course of every day's work; they are not part of the array of facts that are arranged and rearranged in the solution of the problem of the moment. Rather they explain why the facts are arranged as they are. For example, the expression of hypothyroidism depends upon the age at onset of symptoms. That is the fact. The explanatory principle is that development imposes its stamp upon the clinical picture of any disease, and so the student sees this disease in babies and children during the pediatric rotation and in adults on the medical wards, and the differences are assigned to the developmental stage. But the genetic lens dissolves such stratification to remind the physician that the zygote has the same genes as the centenarian, give or take a few somatic mutations, and, depending upon cellular differentiation, such genes specify protein products that integrate to form a homeostatic apparatus that adapts appropriately over time and in response to innumerable experiences of the environment. Growth and development characterize the initial adaptations, the next stage is the steady state of adult life which gradually gives way in highly individual patterns to aging. If this lifetime trajectory can be perceived as a tube, a cross section representing any moment in the lifetime would represent for each a developmental or homeostatic matrix in which today's conditions are outcomes of influences of the past and the future will be influenced by those of today. This must be so because our genes constrain us to be the same person throughout our lives, no matter what our history. So the clinical picture is always a) constrained by the original plan, itself under limits imposed by the phylogenetic past, b) subject to modification by what the individual was before overt disease came to light. So the explanatory principle illustrated in this second view of hypothyroidism is that all diseases are characterized by a phylogenetic past, an ontogenetic past and conditions of the present. A similar version of disease, which he calls "homeostatist," has been reported by Goldstein.<sup>1</sup>

## **The Questions**

### *A. The Body as a Machine*

These questions, what disease does the patient have, how do I treat it and how can it be prevented, are true to the metaphor of the machine. If the machine is broken, the site and nature of the damage

must be found and named, and then an effort must be made to fix it. From the point of view of these missions, generalizations in the form of explanatory principles are best associated with each specific disease. There is little need to tie them all together except in such ways as that all diseases afflict the same machine; all machines have temperature, blood pressure, cerebrospinal fluid, produce urine and so on. Within diseases generalizations consist of lists of signs and symptoms and individual cases are judged in relation to the “classical case”, while values of anything that can be measured are arranged in histograms and means and dispersions are calculated. But means and dispersions characterize populations, not individuals, and are, therefore, representative of typological thinking in which the “type” prevails and individual variation is given less attention, or is ignored.

### *B. Through the Genetic Lens*

Since evolution and natural selection inform the answers to all of the questions asked when medicine is viewed through a genetic lens, the sequence in which the questions are asked is determined by their content and the answers to all derive from those given for the first.

#### **1. Why do we have disease and what is it?**

The question of “why” reasonably precedes that of “what” because the answers to why? are likely to constrain the forms disease can take. Whether or not these questions are commonly asked and answered in medical education is uncertain. What is certain is that they do not appear anywhere in textbooks of medicine, pediatrics, pathology or any of the specialties. One has to conclude that the answers are thought to be either too obvious to ask or of no consequence. But shouldn’t students learn something about disease as they enter into the study of diseases?

##### *a) Why disease?*

Why do we have disease? Why are we not, after all this time, adapted to everything? An answer to this “why” question that suits the machine way of thinking is that human homeostasis is likely to be incongruent with many experiences of the environment and may respond to their pressures by breaking down. Discovery of the molecular details of the break will lead to a way to mend it.

The geneticist agrees, but adds that we must know whence the incongruence arises. It arises from genetically specified variation in the protein products that constitute the elements of homeostasis.

---

These variations exist because each species requires a fund of variation to remain congruent with a variable and indifferent environment. Such variation is a result of mutation at the time of meiosis and we know that in the formation of gametes, the range of mutation runs from losses of whole chromosomes to harmless base pair substitutions. Upon fertilization, however, the zygote is subject to selection, favorable in the case of variants that improve homeostatic adaptation, unfavorable for those whose effects are to impair the capacity to adapt, which is to say, those that lead in individuals, to incongruence and perhaps disease. In between, and continuous with the favorable and unfavorable alleles, are variants of polymorphic frequency that are for the most part neutral in selection, but which, given appropriate circumstances, may contribute to diseases of complex origin. To preserve the symmetry of continuity, it should be added that in other circumstances the same genes are likely to have a favorable selective effect, however small. So the answer to the question of “why disease?” is, it is a consequence of an evolutionary imperative for variation without which the species is in peril of extinction.

Now, because this variation, so necessary for species survival, is expressed in individuals, typological thinking, which appeals to classes, not individuals, is inappropriate. A more apposite mode of thought is that which Ernst Mayr calls population thinking.<sup>2</sup> By this he means that populations are composed of individuals unique in genes, which, of course lead to uniqueness in development and experiences, so it is individuality that characterizes population thinking.

No doubt this relationship between variation and the viability of species was at least alluded to in college courses in biology, but it is uncertain that that viability was perceived to include susceptibility or resistance to disease. But even if it were, does it not need re-emphasis in medical school? Perhaps it may be asked, why bother? Such a concept does not influence diagnosis or treatment, nor prevention either. The case for “why bother?” will be made in the answer to all of the other questions, which will be seen to flow from the same evolutionary imperative.

*b) What is Disease?*

Disease has already been defined as a consequence of incongruence of some aspect of homeostasis with the environment. We know the elements of homeostatic devices to be protein gene products, so

the variation that contributes to incongruence and disease must be expressed in the structure, amount and adaptive capacity of these protein unit steps of homeostasis.

In what follows, the emphasis is on the protein gene products and their role in homeostasis because the incongruence is not of the genes but of their products. We are accustomed to using such locutions as gene-environmental interaction when, in fact, the interaction is between homeostasis and the environment. The virtues of the distinction will be evident in answers to all of these questions. Now, since the unit steps as well as the whole of the homeostatic apparatus came into being according to the genetic plan, the forms that disease can assume must be both permitted and constrained by how that plan has influenced its products, their variations and their integration into workable devices. This seems to answer an age-old question of the definition of disease. On the one hand, disease has been defined since antiquity as having entity. That is, it is said to exist apart from the individuals it afflicts; it has its own essence.<sup>3</sup> Obviously in this definition, called essentialist, or ontological, individual variation is of little moment; it is the typological, classical case that expresses the disease's essence. An alternative concept, called nominalist, or physiological, and also dating from antiquity, has it that disease is an expression of how an individual has failed to adapt, and because all individuals are different, each person evinces a personal version of whatever the disease. Today the choice between these opposed definitions is easy to make. If disease originates in incongruence between variable homeostatic devices and equally variable experiences of the environment, then, because each individual is unique, the choice can only be nominalist. This argument will be strengthened in answers to the other questions; here we emphasize that the form the disease takes is a property of the individual who exhibits its signs. Such a definition also accommodates resistance to disease on the same grounds; variation in the protein unit steps of homeostasis confer congruence with the same conditions of the environment that provoke disease in the vulnerable. So susceptibility and resistance are based upon the same kind of variability and are equally expressive of individuality, and because variable, represent a continuity between health and disease, as well as between degrees of disease. And as a continuity, there is an incommensurable area of overlap wherein expression of its component variants is contingent, uncertain, and in respect to pathogenesis and prevention, to be treated with

---

caution. Here is the place for population thinking, a place for concern for the individual.

So, what is the lesson the answers to these questions teach? It is that at the basis of disease is the necessity of the species for variation while the clinical expression is a consequence of the failure of a variant homeostasis to adapt to some aspect of the geographical, biological, cultural or social condition of the environment. So disease is as much a consequence of variation in our social and cultural organization as biological, and management is best directed to whichever component is most amenable. It is a paradox that the genetic way is more sympathetic to prevention by social adjustment than is conventional medical thinking which embraces hands-on treatments. But because the student should have the wherewithal to think about the justification for each, these questions should be asked and answered.

## **2. Why this person and why this disease?**

Why should any particular person be singled out to suffer a particular disease? Patients ask, "Why me?", and the up-to-the-minute answer is provided by the media, usually with pontifical certainty and authority, "It's in your genes". And there is some truth in it. Investigators are able sometimes to find the genes, identify their products, place the latter in their homeostatic contexts thereby clarifying pathogenesis, and we all know that treatment is dictated by pathogenesis. But here there is another paradox; it is the patients with those conditions in which this solution is most likely that are the most resistant to treatment. That is the reason for the strenuous efforts to devise safe and effective means of gene therapy for monogenic disorders.

### *a) Proximate Causes*

Our techniques have been effective in exposing proximate causes in monogenic disease and they are being extended to the discovery and characterization of genes whose variant products are associated with disorders of more complex origin. So may we say that once we know the genes, we know the answer to "Why this person?" and "Why this disease?" The answer is yes, but it is only a partial answer. The genes have been there since conception and yet the onset of the disease was not at conception, may not be until old age, or may never be, though their possessor live to be 100 years old. So we need to know the particular experiences that have contributed and

their impact through development and over the years, on a homeostasis that has failed in some detail to adapt to them. These non-genetic influences vary no less than the genes, but in other ways: kinds, intensities and durations, for example. So the homeostatic matrix changes depending upon the experiential variables. That is, early changes in the matrix are likely to influence later changes, some in the direction of resistance, others toward vulnerability to influences to be experienced after many years, with implications for overt onset of disease. There is a growing movement in medicine to trace the origins of diseases of late onset to variations of early life. For example, nutritional and other differences in intrauterine life or infancy characterize people with heart attacks, hypertension and type II diabetes, all with onsets in mid to later life.<sup>3-10</sup> And why not? The genes have been there from the start and it is they that specify the proteins that characterize the capacity of homeostatic devices to respond diversely to experiences of various kinds and intensities, early or late, and of long duration and short. Evidently states of development, maturation and aging characterize people as individuals no less than the genes that played their part in attaining those states; again the need for population thinking. So the answers to the questions “Why this person?” “Why this disease?” are determined by a) the qualities of the genes and how their products have integrated in homeostasis; b) the history of the kinds, intensities and durations of experiences; and c) the history of the development, maturation and aging of the homeostatic matrix within which the day’s experiences are sorted out and accommodated — or not. The lists of genes can be duplicated exactly in more than one person as in twins, perhaps the experiences, too, more or less. But it is unlikely that the development and maintenance of the homeostatic matrix could be duplicated, so a person’s ontogeny, maturation and aging are significant contributors to uniqueness and diversity.

### *b) Remote Causes*

Elements involved in incongruence and pathogenesis are proximate causes. Other kinds of causes that contribute to individuality in disease are remote causes, and it is these that impose specificity on the case. So the answer to “Why me?” is, “because you have the genes and the experiences that have led to this disease, but you also came by those proximate causes in ways that differentiate you from anyone else with those same genes or those experiences. That is, a number of events and conditions had to come together to specify you as one to have the disease.”

---

What are these remote causes? To begin with, the gene or genes whose products act as proximate causes in this individual who asks, “Why me?” had to exist somewhere in order to turn up in the patient’s genotype. So mutation and recombination are remote causes. For example, if the CFTR gene had not mutated to  $\Delta F508$ , then presumably, cystic fibrosis would be less frequent or milder. Or, acknowledging its existence, if chance or design had not worked to increase its frequency, we should see much less of the disease. Next the  $\Delta F508$  allele had to be present in the population whence the cystic fibrosis patient was drawn, and it or other mutants had to be present in both parents. So all the forces that shape the gene pool, mating systems, ethnicity, founder effect, and selection are remote causes that ensure that the genetic proximate causes exist, both at all and in the specific individual under scrutiny.

Not all remote causes are genetic. Social and cultural patterns are a source. For example, smoking is a proximate cause for much disease but the reasons why the smoker smokes despite incessant warning against it are remote causes, having to do with individual decisions in response to advertising, peer pressures, the motivations of both tobacco farmers and manufacturers of tobacco products, as well as the tolerance of a society that accepts their continued sale, a tolerance that until recently, included that of organized medicine. All of these have been accepted expressions of our culture and they are remote causes of disease.

The cultural differentiation of dietary habits is another source of remote causes. Some societies promote diets that contribute to disease in susceptible people; immigration into them can be dangerous. The Pima Indians are an example. They had their particular genotypes which were congruent with their diet. But the discovery of oil on their property brought affluence and in its train came an unaccustomed diet, automobiles and indolence. The result? An extraordinary prevalence of Type II diabetes with all its associated woes. Genes, gene products and dietary factors are all proximate causes. What distinguished the Pima Indians is that they went from poverty to riches, which traduced their cultural identity with disastrous results. So the answer to “Why me?” and “Why this disease?” transcends the list of genes and experiences that through development make the questioner unique, to include where those genes came from, how they conspired to arrive in this particular person and what led to their concatenation with particular experiences to emerge in time as this unique case of a set of signs and symptoms

we call by a particular name.

An advocate of the machine approach might say that remote causes are irrelevant, and so they are in the clinic or emergency room. To a patient with a heart attack or a hemorrhage, nothing could be of less interest. But to a student just beginning to form some concepts about disease they are of paramount importance. First, they help in tracing the unique path taken by an individual to arrive at the diseased state, an exercise in population thinking that shows the contingent nature of disease. Second, remote causes tie the individual case to a particular biological past and social present and make of the case a unique person. The biological past is exemplified in the phylogenetic origin of the specific variant genes possessed by the patient and in the qualities of the gene pool whence they were derived while the cultural present is exemplified in the mores of the society to which the patient belongs. Those engaged in preventive medicine know this and they work with remote causes to prevent disease. In pediatrics, pills and poisons are proximate causes of toddlers' disease and death, but the availability to the child of these substances is no less responsible. Similarly the disposition of the baby into the back seat of the car has reduced the trauma of which the proximate cause is the automobile accident. Geneticists, too, who engage in counseling must deal with beliefs and attitudes as well as the concentration of genes in ethnic and other isolates, so the student observes that remote causes link the biological with the cultural origins of disease and reveal, as nothing else can, the basis of medicine in society.

Perhaps today we have scientific validation for the intuitions of the clinicians of the past who seemed to regard every patient as a unique example. Fifty years ago a well known teaching motto was, "the patient is a person," although there wasn't much beyond the social identity to go on. Today we know patients to be biologically, developmentally, culturally and socially unique.

### **Why this disease at this moment?**

The afflicted person who asks "why me?" might also ask, "Why now?" There are no propitious times to be sick and with the exception of old age, illness is seldom anticipated. But we know disease to occur at all times of life and that the list of illnesses and their expressions tends to differ with age. The lore also has it that some diseases are milder in youth, others in mid to late life. But if we

---

assess the burden of disease in terms of a) duration of life, b) limitation of reproduction and c) permanent disability, burden seems to lighten with the years. No doubt death is a devastating thought at any age, especially when expectation is high for a long life. So what kind of burden is this that is greater when the death is in utero than when in the flower of life? Obviously the burden defined above is biological and stems from evolution. It is an expression of a human dilemma, one we seldom perceive or give much attention. We all live two lives. In one, a biological life, each one of us is an inheritor, generator, custodian, executor and transmitter of the most human treasure, our genome. In the other, a social life, each of us uses his/her individual biological endowment to make a life for ourselves, organizing ourselves into families, communities, societies and cultures, in the interest of this second, social, and to each of us, most important, life. But we cannot ignore the biological side of life if for no other reason than that disease is a part of it. Clearly these two lives are interdependent, the biological allows us to be social and we use our social powers to direct our biological lives. And obviously medicine is the social agency we have created to deal with the consequences of our participation in evolution, and, recognizing that disease is a life-long problem, we have stratified it according to age at onset. The tiers are, obstetrics, pediatrics, adolescent medicine, internal medicine and geriatrics. These tiers are basically biological, but it was social decisions that created typological distinctions that ignore the unity and continuity of disease. It is a social decision to expose students to each tier without reference to the others. But nature has stratified disease too, for biological reasons that give answers to the question, "Why now"? This arrangement is best described in the careers of a cohort of conceptuses, all conceived at the same time and pursuing life according to endowment and opportunity until the last one is dead.

### *A Gradient of Selective Effect*

Distributions of ages at death are U-shaped. The nadir coincides with puberty more or less and so the diseases embraced in the two limbs of the U are, on the left prepubertal, and on the right those of adult life. These diseases differ in many ways. Table I contrasts some characteristics of pre- and post-pubertal disease. A kind of unity in disease is demonstrated in identity of the qualities shared by diseases in both columns; all participate in all characteristics. The differences are of quantity, not quality and there is continuity

and overlap. Such a unity is presumably a consequence of the universality of pathogenesis, a result of homeostatic incongruence; classification of diseases according to cellular differentiation is, in a sense, merely a matter of subtyping. And this unity is clearly a property of phylogeny. No doubt plants have diseases that people cannot have, but those disorders must arise in the same homeostatic incongruence due to variation in competence of the same kinds of protein gene products. Pathogenesis is universal.

Both qualitative and quantitative differences within and between diseases also represent continuity of disease, a property of the continuity of development, maturation and aging. This continuity is reflected in the careers of our cohort of conceptuses in which the most profound and burdensome disorders have their onset earliest, the least last, with a decline in this selective gradient throughout life.

Why do diseases differ across the gradient? The first nine months of the life of the cohort is spent in an environment of minimal perturbation protected by the uterus and amniotic sac as well as a placenta dedicated to the welfare of embryo and fetus. So if there is disease, it is more likely to be associated with genic or chromosomal variants that are disadvantageous no matter what the environment. After birth the baby begins to have experiences that increase in scope and variety as life moves on, so disease is increasingly associated with experiences that test a declining repertory of genetic variability in the cohort. This, the geneticist would say, represents a life-long decline in heritability, a property defined as the degree to which the variation contributing to a trait in a population is genetically determined. It is characteristic only of populations, not of individuals. Heritability is represented in Table I in which, for example, monogenic diseases, often impervious to whatever the condition of the ambient environment, appear most often among prepubertal diseases, while disorders of complex origin, multigenic and multifactorial and responsive to variation due to migration and secular change, are more likely to appear on the post-pubertal side. So heritability declines throughout the life of the cohort; the diseases with onsets later and later in life are less and less likely to segregate in mendelian fashion or even to have a positive family history. This pattern is also observed within diseases with broad spans of ages of onset.

We measure life span from birth rather than from conception, and in our society, intrauterine life, infancy and childhood are perceived as preliminaries to the important phases of life that come when we

---

are adults. The moment of conception and its temporal relationship to birth are conjectural, but even were we to know its precise date, it would only prove that we were some months older than we say. But if we were able to take a biological rather than a social look at our gestational life, we might revise, even reverse, the weight given to early as opposed to later life. Since development is a historical process, whatever happens late must be within constraints imposed by what happened early, even though plasticity is among the characteristics established early on. We know very little of the molecular basis of human development, but biologists are plumbing the developmental depths of the mouse, drosophila and *C.elegans*. Such studies must have an impact on our thoughts about disease and the gradient of selective effect; the former because events early in life are bound to affect susceptibilities later on and the latter because given the lack of mutational discipline in gametogenesis, selection is likely to land its heaviest blows early in life. And that is what happens. Human fecundity is estimated to be about 25%<sup>10</sup>. About one quarter of conceptuses never implant. A further 30% are lost imperceptibly in early post-implantation, and another 15%-20% abort noticeably or are stillborn. So the vast preponderance of human disease is experienced *in utero*. There may be those to whom fetal wastage is not real disease, defining the latter as that which occurs or is evident after birth. But such a definition is negated by chromosomal analysis of early abortuses which shows that a large majority of the cases of, for example, XO Turner syndrome or trisomy 21 Down's syndrome that exist *in utero* never reach term.<sup>11</sup> So are they wastage if unborn and disease if they emerge alive? But that is a subsidiary point. The principal point is that three fourths of our cohort is gone by term and most of that mortality is presumed to be due to genetic incongruence. One half of all abortuses have been shown to be associated with chromosomal abnormality but all chromosomes are not represented in the distribution, suggesting that only some such abnormalities are tolerated at and after implantation, and even fewer appear at term.<sup>10</sup> So it may be that most intrauterine disease is chromosomal, but given the precision required in the construction of the homeostatic apparatus, who can doubt that there are monogenic disorders too. And the birth of babies with non-segregating congenital anomalies without chromosomal abnormality suggests multigenic disease as well. These observations are illustrative of the principle of continuity. The view through the genetic lens includes not only what is and what can be, but what is not, what could be and what may never

become. Why a disease does not exist represents a dimension in our concept of what disease is.<sup>11</sup>

So here is evidence that genetic variation in the cohort begins to decline in utero. Indeed the majority of human disease is intra-uterine. What of post-natal life? After birth, genetically determined incongruence appears in the form of metabolic diseases. The newborn infant is now required to regulate metabolic processes without maternal help, so the inborn errors make their appearance. Seventy percent of these are expressed by three years, over 90% by the end of puberty, and only about 1% appear after 40.<sup>12</sup> Again there is a decline in genetic variability as the remnant of the cohort grows toward fulfillment of its reproductive role, and there is a further decline in adult life expressed in the preponderance of diseases of complex origin.

But the decrement is not uninterrupted; the decline in heritability is not monotonic. In each phase of life the genetic selective impact is greatest early, least at its close.<sup>12</sup> For example, disasters of late pregnancy are more likely to be associated with maternal factors; dietary, social, toxemia or placental disorder, while disease and death after infancy is more probably due to poisons, accidents or homicide. In adult life there are a few more or less monogenic diseases or more or less monogenic cases of multifactorial disorders that stand out because onset is at a particularly healthy time of life in the 40s say, or on the threshold of old age, the 60s perhaps, while for older people aging narrows homeostatic capacity to resist and maintain.

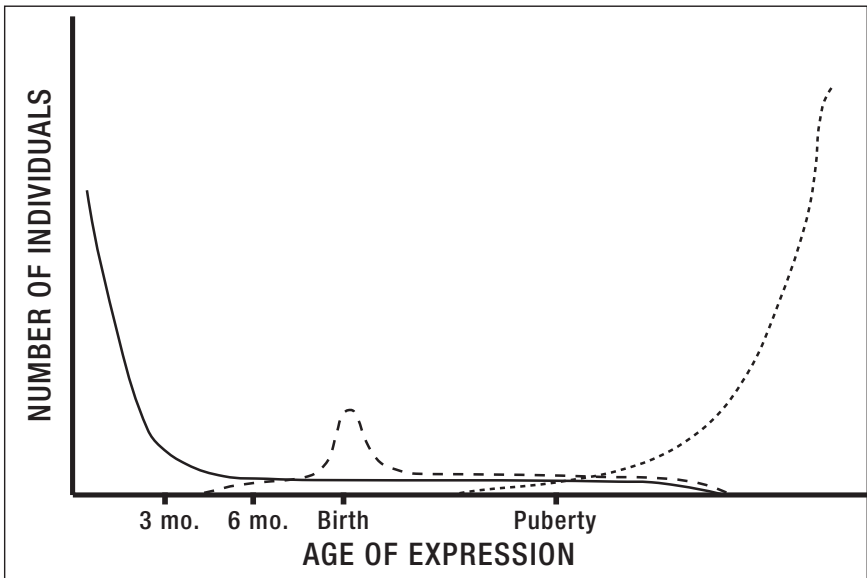
A glance at Table I reveals that most of the properties shown there are responsive to the gradient of selective effect. For example, diagnostic specificity, at its peak in monogenic disorders, diminishes with the decline in heritability. An example is gout. There is a decline in family history, severity and blood uric acid level as age at onset rises<sup>13</sup>. Those that appear in childhood are well defined inborn errors, while cases of adult life become less well defined, milder, have fewer affected relatives and lower serum uric acid as age at onset rises, and when onset is in old age the gout is likely to occur in non-familial cases who are under treatment with diuretics for hypertension.

Similar stories can be told for other properties in Table I. But no sooner do we edge, however slightly, toward the typological than

---

nature reveals our folly. For example, although monogenic disease is characteristic of prepubertal disease and multifactorial of adult life, there is the overlap shown in Figure I. Asthma and rheumatoid arthritis are multifactorial disorders that are characteristic of later life, but show up in early life, while Huntington's, a monogenic disease, turns up late. The figure also suggests that diseases with onset in intrauterine life may not be expressed until late. For example, an absent kidney may turn up only at autopsy.

**Figure I.**



### **Treatment**

When viewed through the genetic lens the question of treatment becomes, "How can we restore this person to his/her unique steady state?" differing thereby from the conventional question in its attention to the particularity of the patient. Obviously for some disorders, who a patient is is of no moment, treatment is much the same for all. Medication can be changed, or doses adjusted, according to the apparent response, so the physiological and pathological path traversed by the patient to arrive at overt disease may not matter. Heterogeneity of cause and pathogenesis leading to the same symptomatology, however, make exceptions, but heterogeneity is not congenial to the typological thinker.

How well does the rule that treatment is dictated by pathogenesis work? Apart from infections and deficiency diseases in which, in any case the treatment is directed to cause, the record is mixed. But generalizations can be made. Treatment according to pathogenesis is least successful when heritability is high and most successful when heritability is least. Those single-gene disorders of infancy where the pathogenesis is entirely self-contained, as in Tay-Sachs disease where the accumulation of ganglioside is uninfluenced by any aspect of the extracellular environment, are examples of the former. The pathogenesis is known and there is no way to intervene. The best results are obtained in disorders where no damage is done *in utero* or post-partum and where pathogenesis can be influenced by external manipulation. Phenylketonuria (PKU) is an example in which appropriate dietary handling allows the affected to assume a more or less normal role in life. But studies done by Hayes<sup>14</sup> and 10 years later by Treacy<sup>15</sup> revealed that only about 12% of monogenic inborn errors have such a result. Another 40% can be improved by manipulation of one kind or another which means that about one half are resistant to any treatment now in use. That is why, recognizing that treatment must be directed to cause rather than pathogenesis, gene therapy is being given such intense scrutiny.

It is in disorders of lower heritability that treatment by medication or other management is most likely to work, and the lower the heritability the greater the success. Table I reveals that it is in post-pubertal disease that migration socio-economic status (SES) and secular change become prominent and success of treatment increases. These successes parallel the gradient of selective effect so that, for example, the later the onset of type II diabetes, the less complicated the treatment. Some late onset cases of this disease may be treated by diet alone.

### **Prevention**

The final question is, "what can we do to maintain adaptation in this patient, or in others who have no apparent disease?" This question is adjunct to the treatment questions, and at the very center of the genetic way of perceiving disease. Prevention has an honorable place in medical thinking and we owe to its practitioners the health of the nation. Genetics, however, exposes a different level of opportunity for prevention, that of the specific individual genetically vulnerable to particular experiences. Some of these experiences have been discovered by epidemiologists who proclaim them to be

---

risk factors. For this the geneticist is grateful, but also asks, "Risky for whom?" So there is a growing list of genes discovered in relatives of patients with undoubted disease that are presumed to represent vulnerability to that disease, and sometimes experiences specific for that vulnerability are also known. Medicine has been receptive to this kind of information, as has the public, as well as companies that offer kits for on the spot testing. In addition there are those who test whole populations, the better, they say, to bring these preventive boons to a greater number. These possibilities have raised questions of ethics. They are based on the difficulty of deciding, for each particular person, the extent of the vulnerability, if any, given the presence of particular genes and associated non-genetic risk factors. The possession of knowledge about genes without an understanding of their implications for each particular person is the issue.

But why? Why doesn't every woman who has the BRCA1 gene need to know it, or even to consider a preventive mastectomy? The reasons are individual and have to do with penetrance, a drosophiline word that means that a gene failed to produce an expected phenotype. But penetrance is a property not of the gene but of the capacity of the homeostatic device, of which the gene's product is a unitary element, to accommodate to its inadequacy. Penetrance is, thus, a measure of the variability of other elements of homeostasis which may act to negate the incompetence of one gene product, or to enhance it. Nor can we necessarily assume that were we to know all of the relevant genes we could predict with certainty, because the products of all are acting in a homeostatic matrix that has been influenced by the particularities of development or of maturity and aging. The outcomes of aging are no less influenced by genetic and non-genetic variability than those of development, and they begin, insidiously in the fourth decade and accelerate thereafter. So as an influence in prediction aging will assume a greater role as we come to understand it.

The genome project is going to expose a great many genes whose products will be characterized as to homeostatic function, and sooner or later the extent of their variability and their association with diseases will be known. We need, in addition to the project that is enumerating the genes, an epidemiological-genetic project of similar scope, power and glamor to canvass the environment for the experiences that bring genetic vulnerability to overt disease, and in whom that prospect is likely. Such knowledge is of paramount

importance for prevention. The record of treatment of monogenic disorders is not encouraging while that with disorders of low heritability and late onset suggests that much can be done. So we need to know the kinds, intensities and durations of experiences of the environment that are capable of provoking disease in which ones of the genetically vulnerable, and how they do it. Armed with such information we might promote a medicine dedicated to raising the heritability of disease in the direction of 1.0. If successful, the residue would consist of the intractable monogenic disorders, and the monogenic cases of disease of more complex origin, whose hopes would reside in the hands of the gene therapists.

### **An Example**

Rickets is an often cited example of a disease whose heritability rose spectacularly.<sup>16</sup> It is a disease of the culture, occurring in infants robbed of the sun by the conditions of city living and subsisting on inadequate diets, and after vitamin D was discovered, the disease was a consequence of poverty. But the establishment of well baby clinics and the addition of vitamin D to food caused rickets to all but disappear, leaving a few children moderately resistant to ordinary doses of vitamin D, and a variety of monogenic types of metabolic disturbances with rickets a part of the phenotype. So the heritability of rickets has risen, not exactly to 1.0 because of rickets in babies who are breastfed and lack any food containing the vitamin or because of the dislocations of low SES. But not withstanding these few cases, it is a success story of the first magnitude and shows the virtues of prevention when the proximate cause is an environmental variation.

But however dedicated we may be to raising the heritability of disease, we must expect no miracles. The principle of continuity suggests that there will be awkward diseases and cases thereof, only partially responsive to changes in living and of intermediate heritability, perhaps because the products of several genes with much heterogeneity are involved. Still, the logic of biology is on the side of prevention. Starting with a knowledge of individual genotypes, the products of the genes they specify, the homeostatic devices those products form in development, the environments to which they are adapted as well as those to which they are vulnerable, the logic favors a redesign of those disadaptive environments. But change in individual lives is not the end of it. Prevention on any large scale will require new attitudes on the part of both the

---

public and organized medicine. Somehow the public will need a more realistic appreciation of what is possible and what not, and organized medicine will have to take an activist part in whatever redesign of social organization is necessary. The lack of its participation in the steps to control the use of tobacco is an example of its reluctance to assume such a responsibility. In the end, the fate of tobacco is a social decision, but medicine might have led the charge against it. As long as the medical ideal is that of fixing the broken machine, other agencies, within and outside medicine, assume responsibility. But were prevention to become medicine's primary aim, a far greater social engagement would be required, an obligation to participate in how society is structured the better to promote the health, not only of the population at large but of individuals. Of course, in the present context, with the dominance of the machine mentality, such talk is just nonsense. But in a medical education based on the genetic origin of both species and the individual variability within and between them, the logic of prevention, when defined in measures to raise the heritability, will be seen by the students to imply a strong medical advocacy for a social intervention not limited to socially minded physicians, but by the profession as a whole, acting in response to a biological imperative.

## **Conclusion**

The answers to the questions as perceived through the genetic lens point to a conceptual basis for medical education that includes the metaphor of the body as a machine and goes beyond it. It is expressed in ideas and generalizations that form a framework that makes coherent a sea of facts. Conjuring with concepts defines education, memorizing and arranging facts defines training, and the emphasis on facts is a frequent criticism of our teaching.<sup>17-19</sup>

Table II contrasts some characteristics of the thinking of medicine dominated by the concept of the body as machine, with those of a synthesis of medical and genetic thought. It is the second of these that constitutes the framework of ideas and generalizations. Such a synthesis of diverse modes of thought could not have been composed in the past because of a lack of satisfactory connections between nature and the expressions of disease. But now, genetics, which Vogel and Motulsky perceive to be the "leading basic science for medicine"<sup>20</sup> is available to expand our thinking and elaborate our concepts. In what follows the superscripts refer to the number of the concepts in Table II.

All of the concepts derive from evolution.<sup>1</sup> Disease, a consequence of the need of a species for variation,<sup>2</sup> is described in individuals in three time frames:<sup>3</sup> that of phylogeny whence came the genes and their products, development, maturation and aging which determine an evolving homeostatic matrix, and the present, wherein are found experiences with which individual<sup>4</sup> homeostatic variation is incongruent.<sup>2</sup> The store of variability in the species is such as to require a nominalist definition of disease<sup>2</sup> and to require that it be perceived in a populational vein.<sup>4</sup> Further, the three time frames make no sense outside environmental systems that have their own homeostatic controls. Thus disease can be comprehended only in relation to social and cultural organization.

Diseases take their characteristics and qualities from the continuity of homeostatic matrices<sup>5,6</sup> observed throughout the lives of individuals, themselves a reflection of a gradient of selective effect expressed in a decline throughout life in the heritability of disease.<sup>6,8</sup> Effectiveness of treatment increases as the heritability declines, so the logic of prevention is expressed in a preeminent medical aim to drive the heritability in the direction of 1.0, leaving the residue to gene therapists and genetic counselors.<sup>7,8</sup>

So the answers to the questions, “Why me?”, “Why this disease?”, and “Why now?” are answered in terms of evolutionary imperatives.<sup>1</sup> Individuality and population thinking stand out in these descriptions of the characteristics of disease,<sup>4</sup> an emphasis that suggests the possibility of a return to the individuality of patients that characterized the teaching of a medicine that marched to the strains of “The Patient is a Person”. No return to the grand rounds of the past is suggested, nor to the C.P.C., only that medical teaching translate the individuality of molecules into the individuality of personhood,<sup>4</sup> a connection that nature makes and that is reflected in how the consequences of an incongruent homeostasis and disease are disposed uniquely in each unique person. In this, emphasis is given to neither reductionist analysis nor to integrating synthesis. The one is meaningless without the other and the relationship of congruence to incongruence is intelligible only in the context of both.<sup>9</sup>

The question of implementation is deliberately left open. Others will have other thoughts, other formulations, and changes in medical education always vary with each institution. Genetics is already forcing changes in our thinking and the fruits of the genome project will

---

have profound further effect. The question examined here is how to organize our thinking to give our students the intellectual equipment to adapt to the diversity of changes that are upon us.

**Table I**  
**Differences between Prepubertal  
and Postpubertal Diseases**

	<b>Prepubertal</b>	<b>Postpubertal</b>
Mode of inheritance	Monogenic	Multifactorial
Age at onset	Early	Late
Frequency	Rare	Frequent
Latency	Short	Long
Affected relatives	Numerous	Few
Diagnostic specificity	High	Low
Number of diseases	Very many	Fewer
Burden	Great	Less
Sex differences	Occasional	Frequent
Influence of migration	No	Yes
Secular change	No	Yes
Effects of SES	Some	More
Success in treatment	Some	More
Heritability	High	Low
Predictability	High	Low

---

**Table II**

**Concepts or ways of thinking  
in the machine and synthetic modes**

<b>Characteristics of Thinking</b>	<b>Machine</b>	<b>Synthesis</b>
1. Reference	Engineering	Evolution
2. Disease	Essentialist	Nominalist
3. Time Span	Synchronic	Diachronic
4. Individuality	Typological	Populational
5. Causes	Proximate	Proximate-Remote
6. Continuity	Discontinuous	Uninterrupted
7. Management	Interventionist	Preservationist
8. Heritability	Irrelevant	Gradient
9. Analysis	Reductive	Integrative

---

## References

1. Goldstein, D.S., *On the dialectic between molecular biology and integrative physiology: toward a new medical science*. PERSP.BIOL.MED.40, 505-515, 1997.
2. Mayr, E., *The Growth of Biological Thought*. Harvard Press, Cambridge, 1982, p.p. 45-47.
3. Marmot, M.G., *Early life and adult disorder: research themes*. BRIT.MED.BULL., 53, 3-9, 1997.
4. Barker, D.J.P., *Fetal and infant origins of adult disease*. BRIT.MED.JOUR.PRESS, London, 1992.
5. Frankel, S., Elwood, P., Sweetman, P., Yarnell, J., Smith, G.D., *Birthweight, body mass index in middle age, and incident coronary heart disease*. Lancet, 348, 1478-1480, 1996.
6. Edwards, C.R.W., Benediktsson, R., Lindsay, R.S., Seckl, J.R., *Dysfunction of placental Glucocorticoid barrier: link between fetal environment and adult hypertension?* Lancet, 341, 355-357, 1993.
7. Lever, A.F., Harrap, S.B., *Essential hypertension: a disorder of growth with origins in childhood?* J.HYPERTENSION, 10, 101-120, 1992.
8. Pettitt, D.J., Aleck, K.A., Baird, H.R., Carraker, M.J. Bennett, P.H., Knowler, W.C., *Congenital Susceptibility to NIDDM: role of intrauterine environment*. DIABETES, 37, 622- 628, 1988.
9. Martyn, C.N., Gale, C.R., Jespersen, S., Sherriff, S.B., *Impaired fetal growth and atherosclerosis of carotid and peripheral arteries*. Lancet, 352, 173-178, 1988.
10. Jacobs, P., *The role of chromosome abnormalities in reproductive failure*. Reprod. Natr. Dev. supp. I., 63s-73s, 1990.
11. Vogel, F., Motulksy, A.G., *Human Genetics*, 3rd, Ed., Springer-Verlag, Berlin, 1997, pp 297- 298.
12. Costa, T. Scriver, C.R., Childs, B., *The effect of Mendelian disease on human health: a measurement*. AM.JOUR.MED.GENET., 21, 231-242, 1985.
13. Yu, T-F, *Diversity of clinical features in early arthritis*. SEMINARS IN ARTHR.RHEUM., 13, 360-, 1984.
14. Hayes, A., Costa, T. Scriver, C.R., Childs, B., *The effect of Mendelian disease on human Health II: response to treatment*. AM.JOUR.MED.GENET. 21, 243-255, 1985.
15. Treacy, E., Childs, B., Scriver, C.R.. *Response to treatment in hereditary metabolic disease: 1993 survey and 10 year comparison*. AM.JOUR.MED.GENET., 56, 359-367, 1995.
16. Scriver, C.R., *Changing heritability of nutritional disease: another explanation for clustering*. In, *Genetic Variations and Nutrition*, Karger, New York, 1990. Simpolous, A. Childs, B., eds. p.p. 60-71.
17. Muller, S., Cooper, J.A.D., *Physicians for the 21st century. Report of the project panel on the general professional education of the physician*. JOUR.MED.ED. SUPP; 1-200, 1984.
18. White, K., *The Task of Medicine*. Kaiser Family Foundation, Menlo Park, Col., 1988.
19. Cantor, J.C., Cohen, A.B., Barker, D.E., Shuster, A.L., Reynolds, R.C., *Medical educators views on medical education reform*. JAMA, 265, 1002 - 1006, 1991.
20. Vogel, F., Motulsky, A.G., *Human Genetics, 3rd Ed.*, Springer Verlag, Berlin, 1997, p2.

**DISCUSSION HIGHLIGHTS:**

- In discussing genetics, everyone needs to use the same language. We need agreement that human genetics is the science of human biologic variation, that medical genetics is the science of human biologic variation as it relates to health and disease, and that clinical genetics is the part of medical genetics concerned with the health of individuals and their families. Dismorphologists — some of whom know genetics, some of whom don't — look at the science of structural defects.
- In the 1950s, genetics was a division of medicine but by the 1990s medicine had become a division of genetics. That shift should make it easier to implement the new genetic focus, but only if there is an unified response from education at the university, beginning with the undergraduate level. The content of genetics courses must be consistent. Current preparation is so diverse and uneven that too much remedial time in medical school is spent on information and concepts students should have acquired as undergraduates. In medical school, the basic principles of human genetics must become part of an integrated curriculum that is emphasized and incorporated through all four years of training.
- Many groups and associations are already pushing to include more genetic information in the medical curricula. What is needed is a specific plan of action.
- The sheer volume of new genetic information will force a change in medical thinking. It will be impossible to resist the avalanche of thousands of genes, each with a product that fits into a homeostatic device and that is part of an integrated system. Medicine will have to assimilate that information which, by its very nature, will change thinking. Change is inevitable.
- The concept of a genetic lens was first described more than 20 years ago, but without the supportive matrix of ideas that now exists. Even today, though, it may be difficult to reach medical students with this concept. Medical students not only have a tremendous amount of information to master, they also tend to resist philosophical ideas that are not fully documented. The one gene, one enzyme thinking of the molecular biologist is easy for the medical student to grasp, but it does not fit well with the

---

homeostatic mechanisms described by Barton Childs. For instance, many genes are associated with heart attacks, but it is not clear how these genes fit together, what gene-environment, or even what gene-gene, interactions are involved. While the overall concept of the genetic lens may be useful, it does not fit easily into the simple medical school teaching — especially since in the medical school what is not absolutely necessary to patient care is devalued. Immediacy is the emphasis; prevention gets little attention.

- Though Dr. Childs advocates a change in ideas, not a change in curricula, medical students are taught by people who reinforce the idea that what matters is molecular biology, not the genetic point of view. The real challenge will be to change the thinking of the faculty.
- In practice, a genetic perspective will make no difference to the physician who already views each patient as unique. But those who simply see the patient as “a bag of molecules,” will need to see the patient as a highly integrated system of molecules. This shift will make a difference in the way medicine is practiced.