

MÉXICO EN EL UMBRAL DE LA ERA GENÓMICA

THE IMPACT OF THE GENOME PROJECT ON MEDICAL EDUCATION

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Only a man who lives at the North Pole could be ignorant of the Human Genome Project. And none can doubt that its impact will be profound in changing both principles and practice of medicine. But such advances are not *sui generis*. Historians tell us that when some new idea erupts into our consciousness, we will understand it better if we realize that there are precursors that led up to it.

Today the gene and its protein product(s) are the ultimate among diagnostic instruments, and their power to fathom pathogenesis gives them a central role in medical thinking. Table 1 shows how this central position was attained. Today the gene and its protein product(s) are the ultimate among diagnostic instruments, and their power to fathom pathogenesis gives them a central role in medical thinking. Table 1 shows how this central position was attained. The table shows the convergence of two paths of development: the increasing precision in the definition of the gene on the left and the internalization and refinement of diagnostic study in medicine on the right. At first the doctor asked the patient what ailed him and prescribed accordingly. Then someone thought to examine the body, at first in life, then in death took, after which followed investigations into physiological, biochemical and molecular aspects. Finally it became possible to find the gene: the key to pathogenesis. On the genetic side the statistical factor of Mendel was given operational meaning by the drosophilists as a unit of mutation, function, recombination and so on, functional meaning in the one gene-one enzyme formula and a structural definition in the co-linearity of the base pairs of the DNA with amino acids of the proteins. Finally we arrived at today's molecular definition of

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the gene alluded to above as of medical diagnostic utility. Biological and medical intentions have converged in the fulfillment of the genome project.

Table 1

Genetic	Medical
Statistical	Medical History
Operational	Physical Examination
Functional	Morbid Anatomy
Structural	Physiological-Biochemical Analysis
Molecular	Molecular Análisis
Genomics-Proteomics	

An impact on medical education:

So now we know we have 30,000 or so genes (1,2). And we know that some of these specify more than one protein. So are there 60,000 proteins, or more? Whatever the number, it is well beyond today's already insupportable burden for students. So genes and their products will have to be systematized, and the informatics people will see to that. But will they see to it in ways that always make medical sense? I ask because biological and medical goals are not the same. Biologists who teach the first two years of medical school emphasize how things work in, and provide generalizations for, the biology of species, not individuals. The teachers of the last two years are clinicians who teach biological aberrations in individuals - which raises a critical question. Are the generalizations of the pre-clinical sciences appropriate for the problems of medicine? In general, yes. Those rules apply to all of Homo sapiens, but we don't all abide by them equally. Each human being is unique in genes, development and experiences, and in the consequences of the specificities of all three, whether in health or in disease, in resistance or in vulnerability.

So there is a gap that philosophers might call epistemological; between the first and last halves of medical school (3). Whatever biologists teach has been subjected to hypothetic-deductive test. They don't give their impressions; they deal in

“facts”. But on the clinical side, the “facts” are gleaned inductively; cases of what is presumed to be the same disease are gathered and analyzed in regard to numerous qualities so as to produce a “classical case”, and the arbiter for admission of new cases is the experienced clinician. These two ways of thinking are very different.

A second component in this gap is the idea of individuality. Every patient has a unique history, clinical picture, course and response to treatment, as well as a unique reaction to the discomforts and uncertainties of disease. Biologists are generally indifferent to individual uniqueness. Species is their thing. So the student goes from the typological thinking of biology to the uniqueness of the individual. Those that make this leap see patients whole, as diverse people in need of the human touch of the doctor. Those who don't are more likely to see the patient as a “*case*” of a disease to be explained as molecules gone wrong.

There's little reason to suspect this gap of closing and some reason to suspect it of widening. Years ago basic science hadn't the power to dominate medical thinking and medical education reflected the ideas and experiences of clinicians less constrained by molecular detail. So students' thinking was modeled on that of the clinicians whom they wanted to be like anyway. The clinicians were their heroes.

No new number's here. But today, the students come from the molecular generalizations of the basic sciences to a reductionist analysis of pathogenesis that accounts for signs and symptoms. Who are they going to copy now?

In the past, the clinician began his approach to a case with the signs and symptoms and probed downward toward the physiological, biochemical and molecular levels of expression. Today, genomics is teaching us to begin with the gene, then to characterize its protein to account for pathogenesis and its consequent signs and symptoms. That requires a change in thinking that enhances the danger that the disease itself and its molecules may be the object of primary interest, rather than the individuality of the patients who suffer the disorders.

How to resolve these dilemmas. There is no question they need attention. Observers of medical education have noticed a degree of stasis in the system and look forward to change. (4-8)

So what do we do? One way to go might be to bring biology and medicine into closer accord by defining disease, which is the central focus of medical thinking, in ways that fit biological thinking. This would require little change in the organization of the medical school, but considerable change in the thinking of medical teachers, both biologists and clinicians. Not easy, but to fail to make the effort is to fail the students. What is the way?

A concept of disease:

There must be a concept of disease that could at once facilitate the student's shift from basic science to disease and provide principles that, in accommodating the whole range of disease, could give medicine the same sort of foundation of generalizations as those upon which biology depends. And in so doing, biology and medicine would be brought into a greater degree of intellectual consonance.

A Context:

Assuming the value of such principles, upon what are they based and in what context can they be assembled? They seem naturally to be based on genetics, and an appropriate context is expressed in the ideas of Ernst Mayr, an evolutionary biologist at Harvard. (8) Mayr perceives biology as divided into two areas differing in concept and method. One, functional biology, is concerned with the operation and interaction of molecules, systems, organs and cells. Causes are proximate, the viewpoint is inward and questions are commonly preceded by how; how does the organism function? The other, evolutionary biology, is concerned with the history of functional biology, its causes are called ultimate because they originate and marshal the proximate causes, and its questions are prefaced by why: why in the sense of, what are the conditions of the past that have made it possible to pose and answer the how questions. The two biologies meet at the DNA, so that the

functional deals with everything after transcription, while the evolutionary centers on the history of the DNA and the conditions of the environment within which organisms have attained their present state. If this sounds like a description of genetics; it is. But it's a different kind from that we're used to. Medical genetics is applied genetics. This genetics is the basic science for medicine.

Mayr did not include disease in his model, but disease is no less biological than the ideal state, so there should be no difficulty in applying his principles to biological abnormality. So in relation to disease, the proximate causes are a) the products of the variant genes, and b) the experiences of the environment with which they are incongruent. Remote causes are a) the mechanisms of mutation and the causes of fluctuations through time of the elements of the gene pool, including selection, mating systems, founder effects and drift, and b) the means whereby cultures and social organization evolve. In disease, the variant gene products and the experiences of the environment with which they are incongruent, account for characteristic signs and symptoms, but in making available the particular proximate causes assembled by chance in particular patients, it is the remote causes that impart the stamp of individuality to the case.

The How Questions:

In testing the Mayr model we begin with functional biology. Its questions begin with how; for example, how do genes influence disease. The answer is, by way of the variability of their products.

Proteins are the mediators of pathogenesis. Proteins are specified by genes, and genomics leads by way of proteomics to integrated homeostatic devices composed of protein units, which, as the product of the gene, are inescapably, the fundamental units of life. Table II lists unitary functions of proteins. Space precludes more than a word about these.

Obviously, proteins have business other than disease. It is the perversion of those normal roles that constitute disease, so the protein is the effector of the gene's intent and of its impact as a variant.

Then, the protein is a unit of both the phylogenetic and the developmental history of the individual, and, since homeostasis is designed to maintain the open system in an indifferent environment, the protein is a unit of history of the moment. If so, then it is our duty to analyze the disorder of each patient in three time scales at once; that of the genes, the maturation of state and that of the conditions of the moment. All three will affect the clinical state. The principle here is that disease is in us and of us and not something that comes from the outside to attack us.

Next, as a result of gene variation, the protein is a unit of individuality reflected in variations in each patient's signs and symptoms as well as in molecular analysis. And such is the extent of the variation that each patient is likely to represent a unique version of his disease. So the principle here is that each of us has our own disease.

I must also mention the role of the protein in promoting coherence in medicine. If all pathogenesis is mediated by proteins and all proteins are variable, we have a way to grasp the nature of all diseases, no matter how unlike in their signs and symptoms. So, the many principles illustrated in this section are summarized epigrammatically as: a) By their proteins ye shall know them and b) the language of nature is expressed in proteins. The DNA merely supplies the letters and words.

The Why Questions:

So the how questions are grist for the mills of investigators of pathogenesis who say that its elucidation leads to treatment. But the why questions are more often heard from patients: Why me, why this disease and why now?

Why Do We Have Disease?

Species must adapt or die. Adaptation requires variation, and since the mechanisms for supplying it cannot know in advance what will be necessary, mutation is random. And why not? Individuals are expendable; the fecundity of our own species is only 25-30 percent. So the principle is, a variable species is a viable species.

Why This Disease and Why Me?

The specificity of an individual's disease is a reflection of genomic and developmental differentiation and variation responding to kinds, amounts, and durations of experiences of the environment. So the answer to these questions is, it depends upon who you are and how you live. That is, who, in the genetic and maturational sense, you are, and how, you fit in to the world you occupy.

Why At This Time?

The human mortality curve is U shaped, with its nadir at puberty. This is again a question of species survival. We tend to think of life only after birth, but nature sees with a more penetrating eye. Intrauterine death and that of infancy and childhood prepare the species for a successful reproductive period. After that important work is done, disease has no selective meaning. Table III contrasts the qualities of pre- and post pubertal diseases. The differences are a reflection of natural selection on the left and its release on the right. The genetic contribution, heaviest in prepubertal life, declines throughout life. Which means that non-genetic causes increase in moment? So the principle here is that early in life we are at the mercy of our genes, later in life we become increasingly victims of how we live. So an aim for medicine should be to eliminate all causes emanating from the environment, leaving to the gene therapists those due to genetic causes unassisted by experiences of the environment.

Prevention and Treatment:

A strong element in the appeal made to the US congress for support of the genome project was the logic of treatment of disease: Find the incongruent molecules and then design a counter-molecule and the disease is cured. No doubt there will be some glittering successes, but we have yet to test our grasp of the complexity of mechanisms and our capacity to intervene without damage, so an expectant attitude is probably wise. Still the logic is there and efforts should be made. But the logic of genomics appeals more strongly to prevention where if the genes and the proteins that represent vulnerability can be found, steps could be taken to find the agent that turns vulnerability into disease. I am not making a case here for any early successes for prevention, but for the logic, which suggests that given the chance, prevention may one day assume the primacy now accorded treatment. The principle here is this logic. It is the essence of genetics and has been increasingly revealed in medicine as the trends illustrated in Table I moved toward their convergence.

Conclusion:

In conclusion such a concept of disease brings medicine into closer approximation with biology, to the benefit of students making the leap from basic to applied science. Such a conceptualization is only possible in an era of genomics, and its logic carries medicine beyond treatment to prevention and to the humane concerns that are natural to medicine. For example, the duties of medicine as we perceive them are three. First we see to that which threatens the life and health of the patient; i.e. diagnosis, treatment and prognosis. Then we look for causes, and third, we seek to relieve the impact of disease on the lives of patients, their families and the public. I suggest that an unexpected benefit of genomics will be recognition that the more weight we give to the third of these duties, the less will be the burden of the first.

Finally, the fruits of the genome project bring us face to face with our profound kinship with and dependence upon, the biological world. It is now plain that that

world was not made for mankind, rather mankind was made by that world, and it is one in which we serve ourselves best by serving it. That lesson is at the heart of genetics and biology. It should be at the heart of medical education too. The principle here is that the health of the world is - or will be - reflected in the health of our species. That is a cardinal principle of all biology; it should be a powerful, compelling principle of medicine. Let's teach the uses of the genome project to that end too.

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