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A SCIENCE OF THE INDIVIDUAL: Implications for a Medical School Curriculum

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INTRODUCTION

> "There is no science of the individual, and medicine suffers from a fundamental contradiction: its practice deals with the individual while its theory grasps universals only." (63)

This observation was made by observers of the past who saw that because there was no science of the individual, there was no way to treat a patient as an individual. It is not clear what they thought that science of the individual was, but we know what it is today. It is the uniqueness of the individual—genetic, developmental, and experiential—that accounts for human variation, whether in health or disease.

Two Views of Disease

Before modern medicine, some doctors held the view that disease takes its form from the physiology of the patient (physiological) while others believed that diseases have independent specificity and come from nowhere to seize their prey (ontological) (63). Since ancient times these positions have been argued, the physiological forging ahead in the nineteenth century when familial diathesis was popular, and the ontological in the early twentieth century when the germ theory was all the rage. The entry into modern times was stimulated when, in the early decades of the twentieth century, investigators moved their attention from the organ to the cell, and the rest is a familiar history. Biochemistry was the first to be stimulated by this shift in focus. Then molecular biology broke away from biochemistry, genetics and biochemistry spawned biochemical genetics, and finally, in a new merger, molecular biology and genetics came together to produce molecular genetics, whose most prominent offspring is genomics.

A principal outcome of this progress was a descent in phenotypic analysis from the description of signs and symptoms to the relevant DNA and its trappings: The reductionist method has reached an ultimate level of disease explanation. These developments put an end to the ontological concept of disease and established the physiological concept by demonstrating gene-specified proteins as mediators

of both normal homeostasis and disease. Further, those proteins of disease are specified by genes of which there may be numerous alleles and a disease may be split by originating in variants at different loci. And today attention has shifted from monogenic to complex diseases, where we observe more than one locus involved—even multiple homeostatic systems whose integration is altered to make the individual susceptible to adverse effects of experiences of the environment (11, 14, 28, 57). So we are working our way into that "science of the individual" that has long been perceived as necessary to undo the contradiction between the individuality of the patients and the generality of the means to deal with their illnesses.

Genetics and Individuality

Genetics is the basis for the science of the individual or, in today's terms, individuality. We have begun to probe the individuality of more than 1500 inborn errors and of a rising number of complex diseases that predict a future of identification of genetic variation in all diseases. In many inborn errors we understand individuality of both disease and treatment. For example, we now appreciate that phenylketonuria (PKU), a classic "monogenic" inborn error, is highly complex with gradations of impaired phenylalanine metabolism and response to treatment, reflecting extensive allelic heterogeneity at the major locus (the *PAH* gene encoding phenylalanine hydroxylase) as well as variation at more than 10 other genes encoding proteins involved in the synthesis of the biopterin cofactor for PAH or in transport or alternative pathways of phenylalanine metabolism (61, 62). Obviously, complex diseases are next. Who, a few years ago, would have predicted a genetic basis for otitis media (13, 21), prostate cancer (48), or inflammatory bowel disease (32, 47, 51)? Pharmacologists are looking for disease alleles in complex disorders whose proteins could be targets for drugs tailor-made to nullify their adverse actions in individuals (23, 59). And, of course, genomics is employed in the characterization of a vast store of genes and their variants still unknown but certain to contribute to numerous disorders still genetically uncharacterized (18, 32a).

The Human Genome Project and Medical Individuality

These advances in the application of genetics to medicine are the first fruits of many to be harvested from the products of the human genome project (HGP) and its follow-on activities (18). Conceived in the mid-1980s and launched in 1990, the HGP has been an enormous success: We now have a finished sequence of more than 99% of the gene-containing (euchromatic) part of our genome and this has provided us with a list of 20,000–25,000 protein coding genes and with millions of single nucleotide polymorphisms (SNPs) (33). But this progress in understanding the human genetic complement is dwarfed by the challenges ahead, which include: (*a*) identifying all functional elements in the genome, a list that includes not only protein coding genes but also *cis*-acting regulatory sequences,

microRNA genes, other functional RNAs, and likely many kinds of elements not yet appreciated; (*b*) elucidating the function of all the RNA and protein products of the coding sequences and understanding how these products of individual genes are integrated into complex biological systems, some sophisticated, some less so, but all the result of evolutionary tinkering; (*c*) delineating the complete catalog of all genetic variation and its functional consequences; and (*d*) understanding the many ways variation in our genome interacts with variables in the environment through epigenetics and related mechanisms (4, 7, 35). Based on their record, we are confident that the protagonists of the HGP will meet these challenges; it will be up to medicine and medical educators to determine how best to use this enormous influx of human biological information for the medicine of the future (6, 67).

No one can predict this future precisely, but if genetic variants are associated with disease, and proteins reflecting the variation of the gene that specified them are the basis of pathophysiology and its individuality, genetics, as the science of the individual, will come to be perceived as a basic science of medicine and will enter the curriculum as such (67). The purpose of this paper is to consider the role of genetics and genomics in the medical curriculum. Our view is that the influence of genetics transcends proximate causes and medical specialties to form a context within which to comprehend them all. So, in addition to furnishing the wherewithal for its own medical specialty, genetics as the basis of the perspective of individuality should suffuse the whole of the medical teaching.

In doing so, genetics is at one with the other basic sciences, all of which appear in analyses of all diseases. But genetics goes beyond them in connecting the biological present with its past. Genes and genomes establish themselves through natural selection and evolution, with individuals the instruments of both (65, 66).Because health is represented in medicine by congruence of genetic individuality with a constantly evolving environment and disease with incongruence, references to selection and evolution are likely to turn up wherever genetics and genomics do. That is, genetics and genomics, as fundamental to the science of the individual, must be evident in any analysis of health and disease. Inasmuch as individuality is constituted of variation in molecular biology, anatomy, biochemistry, and physiology, the sciences with which medical curricula ordinarily begin, perhaps a foundation of genetics should precede them all. This paper is an argument favoring such an innovation. We begin with a skeletal description of medicine and of what a medical student faces in the first two years.

A DEFINITION OF MEDICINE

Modern medicine engages the scientific method in the study of physical and mental aberrations in individuals and their causes, treatment, and prevention. This entails investigating the patient's molecular, biochemical, physiological, anatomical, and psychological constitution as well as a history of the patient's illness, past health, family history, and social and cultural experiences, all in relation to details of physical, radiological, and other laboratory examinations. A diagnosis is reached

by comparing the description of the patient at hand with those of experience in the form of a "classical case," and a course of treatment and suggestions for preventing recurrence are outlined accordingly. In general, the doctor's orientation is toward the likenesses between cases that lead to certainty of diagnosis rather than differences that may be pointing to heterogeneity and individuality. For most of the history of medicine the latter has been somewhat impossible, awaiting the advent of method. Now genetics and genomics provide evidence for individuality (22, 45, 68), but, in general, the typological mind-set continues the tradition of fitting cases into types, as opposed to embracing the perception of individuality, which requires observing differences between cases. Infusing genetics and genomics should result in nontypological thinking and emphasis on individuality (5, 6, 67). This transition is under way, especially in the diagnosis and treatment of certain cancers (3, 49), but it is far from complete (5, 10, 31, 44).

What Does a Medical Student Face?

In most schools first-year medical students are taught principles of biology, including anatomy, molecular biology, biochemistry, and physiology, in a context of "how things work." This is entirely appropriate as a foundation for later learning of how things do not work. In general, it prepares the students well for pathology and pathophysiology in the second year. By then students have a grasp of human complexity, integration, and adaptability as well as resistance to influences that threaten these mechanisms, and they know that failure in these can lead to disease and premature death. It is less emphasized, however, that variations in these properties and capacities inhere in individuals, in whom they are a reason for both health and diseases.

In the second year, students who have learned the principles of how things work move on to disease in the individual, and to diagnosis by comparison with the hypothetical classical case. They are also confronted by the patient's evident social and cultural individuality and the necessity to adapt care accordingly. Here is where biology and medicine meet, where the quality of care is measured by the physician's recognition of the patient's individuality: molecular, physiological, personal, and cultural. The question is whether instilling in the students' minds an encompassing respect for biological variation will reinforce concern for the individuality of patients' adaptation to their disease and its management even while promoting the doctor-patient relationship in all aspects of medical care. The idea that individuality will enhance the doctor-patient relationship is critical because if medicine is to retain its humane features, it must be practiced in a scientific context that accommodates them. Individuality, originating in variation of genes, development, and experiences, is that context.

Currently, molecular analysis and its relationship to medical treatment are emphasized in teaching. Integrating those details with the patient's sense of his or her humanity and personhood is sometimes overlooked. An outlook based on individuality is more likely to be attentive to this need and so ought to be cultivated from the start. This may appear to some to be special pleading for genetics, but it has

a biological basis. It is that each human life begins as a conceptus composed of little more than genetic material capable of endowing proteins with both options and constraints for variation in development, homeostasis, and adaptation to the variety of the individual's experiences of the environment throughout that life. Further, the DNA is the instrument of continuity of both individual lives and those of species, and, through its capacity for mutation, the source of those variants that constitute individuality, itself the substrate for selection and evolution.

Medicine and Evolution

But why should a medical student care about evolution? Because evolution formed the human being who is the patient, in contours and in genetic, molecular, biochemical, and physiological constitution—the very attributes the doctor studies to make a diagnosis. And having shaped that constitution and its abundant variation, evolution stamped the forms and limits of manifestations of disease.

It has been said, and not only by historians, that whomever is to understand the object of his study must know its history. In studying the basic sciences, the students hear references to genes and other attributes held in common by human beings and an array of other organisms varying from bacteria to mice. Genomics is widening that range, describing biological relationships between *Homo sapiens* and hundreds of other organisms. Why is this useful to a medical student? Because it is through evolution that all of those organisms have developed their own brand of congruence with the environments they inhabit, as well as their own kinds of incongruences that lead to disease. It is individuals that are selected, individuals with traits that led, however indirectly, to reproductive success. It is individuality upon which evolution is based. So, as we learn more about our own biology and its variable capacities to adapt to the more rapid evolution of cultures and societies, the necessity to perceive medicine in terms of individuality based on genetics, development, and experiences of life becomes increasingly obvious. And the description of such a relationship, molded by variation and ever more apparent as the student's education moves from the biology of congruence to that of incongruence, constitutes a logical beginning for the curriculum.

To appreciate this new genetics embraced by genomics, we begin where it began.

HUMAN GENETICS, EARLY AND LATE

Genetics was in the curriculum of only a few schools of medicine before the 1950s, at which time inborn errors and chromosome anomalies began to constitute the principal forms of what came to be called "Genetic Diseases" (52). Growth of medical genetics was slow but steady; a study in the late 1970s revealed that 77 of 106 medical schools had a genetic component in their curriculum, and later polls showed increases (15, 55). Today all medical schools recognize a role for genetics, and its prominence in medicine is attested by the birth and maturity of several

organizations: the American Society of Human Genetics, the American College of Medical Genetics, the American Board of Medical Genetics, and numerous journals devoted to medical aspects of genetics. This is plain evidence of progress and standing in the medical community. It is the path taken by all specialties that embrace both clinical duties and the pursuit of molecular answers to medical puzzles. That is what medical geneticists are doing now in the age of genomics. Most papers in the *American Journal of Human Genetics* report searches for genes, usually in diseases of complex origin. As for education, representatives of the Association of Professors of Human and Medical Genetics, and of the American Society of Human Genetics, came together to list in detail the content of a course in genetics for medical students (http://genetics.faseb.org/genetics/aphmg/aphmg1.htm). The recommendation is that all such students must (not should, but must!) learn to think genetically about disease as they do about the molecular or biochemical aspects of diseases. This is all the more necessary for genetics given its role in both basic science and clinical medicine.

The professors suggest a separate course during the basic science year, as well as representation throughout the whole four years. They provide a comprehensive list of genetic lore to form the basis for the course and emphasize the necessity for constant colloquy with patients and their families. Any medical school that heeds their urging is on the right track.

This is what most schools are doing and it is successful (39). Genetics is established in medicine and will fill a necessary role in solving questions of cause and prevention of disease. But genetics limited to a medical specialty does not reflect Sewell Wright's characterization of genetics as the "root stock" of biology (69). That is, genetics, as fundamental to the science of the individual, must be seen to draw its relevance from evolution and selection, or else where did Mendelism come from? Where mutation, variation and disease, and genomics, too? Dobzhansky's observation that "Nothing in biology makes sense except in the light of evolution" (20) is emphatically inclusive of medicine. That is not to say that the clinician should refer to evolution in the diagnosis and disposition of every patient, but that these processes, whence come the individuality of human diseases, are what they are because living organisms including *Homo sapiens* have been adapting individually for so long and to such a range of experiences of the environment.

Fifty years ago nearly all known proximate causes were environmental. Then, with the characterization of inborn errors and chromosome anomalies, a class of "genetic" diseases emerged and medical texts carried separate sections, sometimes back to back, on "genetic" and "environmental" diseases. Now we recognize that from the moment of conception an individual exists in relation to a range of environments in which outcomes depend on genetically variable homeostatic devices that respond to elements of the environment that vary in kinds, amounts, and durations, interactions that encompass all stages of human development, maturation, and aging. For the most part these interactions lead to a continuity of congruence in life, but incongruence between homeostasis and experiences may lead to

disease and, within this continuity, usually congruent, sometimes incongruent, is recounted the experience of the individuality of each life. Do these observations justify teaching medicine in a genetic context?

WHAT JUSTIFIES A GENETIC CONTEXT FOR MEDICAL TEACHING?

The medical curriculum has traditionally begun with anatomy, biochemistry, physiology, and pharmacology. The principle is that the basic science teachers expose the human being in its normal state and then pass the student on to clinical teachers by way of pathology. Keeping in mind how the normal works, pathologists and physicians can show the student the dysfunction of the abnormal. But weaving together the normal and the dysfunctional had to be unsatisfactory until molecular biology, often introduced at the beginning of the first year, could enable pathology to be perceived as pathophysiology and the student could observe abnormality at the molecular level. But where did those molecules come from? They were specified and given their character by each individual's genes, themselves inherited from parents and ancestors within species and on into the evolutionary interspecies past, thereby providing a continuity in the form of a biological memory of life.

Of what interest is that memory to a physician, and why should a genetic perspective be presented at the beginning of the curriculum?

1. One reason is that the options and constraints conferred upon human proteins take their origins from those of prior species, and a physician who understands the molecular physiology of the past is more likely to differentiate the feasible from the infeasible at all levels of diagnosis, management, and prevention of disease. We already draw inferences about disease and treatment from many such organisms and, given that comparative evolution is a major preoccupation of genomics, we shall know much more in the near future.
2. That memory includes mutational variation, the wherewithal for congruence with a range of also evolving environments, and the basis for variation exemplified in individuals who are grist for the mill of selection both favorable and unfavorable. The former is the means for evolution, the latter for disease.
3. It is appropriate to begin with genetics, a discipline that deals with the qualities of the molecules, cells, and organs that coalesce through development into an individual who matures, ages, and dies. All of these processes derive their capacities for responding adaptively (or disadaptively) from the genes.
4. Physicians see disease as the archenemy, and so it is, but a grasp of genetic individuality and its origins reveals that much of variation is good or bad depending on the quality of an individual's experiences of the environment. So

a gene can contribute to both health and disease depending on the conditions of life. Thus, human individuality, some of which we see and use in daily life to identify one another and to form the variety in our relationships, and which is a product of the options and constraints exerted on the formation and behavior of proteins by their genic specifiers, is no less a property of disease than health. No doubt this observation is made on grounds of molecular biology alone. Molecular biology has provided the infrastructure, the framework, and the context for many new curricula, but it is genetics and genomics that generalize the idea of individuality and its role in disease by connecting it to the biological memory.

5. Beginning medical education with genetics should exert a powerful centripetal force for bringing a scattered medicine together. Diseases of the heart, brain, bone, and senses each exhibit their own repertory of mechanisms of pathophysiology at the molecular level, and the molecules and their functions each tend to differ from those of the others. Hence, obstetrics, pediatrics, medicine, and all the other clinical specialties have their own molecular problems to deal with, so the insight of a specialist doctor narrows in detail. But the genes, differing only in the arrangement of their components underlie and conceptually draw together all branches of medicine into the individualities of the relationships of those genes with the conditions within which they act. So the early recognition of this unity in medicine in distinction to its obvious fractionation can help the student keep complexity within bounds.
6. Medical students begin their study with visions of promoting human health, which is why veteran teachers of basic sciences make appropriate references to disease. In that vein, beginning the curriculum with the genetic perspective gives the students an early insight into the origins of disease, and thus into human variation.

In this section we argue for a genetic context within which to teach medicine. But is such a context justified if only a fraction of disease is influenced by genetic variation? In the next section we suggest a genetic component in all disease.

EVIDENCE FOR GENETIC VARIATION IN ALL DISEASE

Are there any diseases in which the genes do not play a role? Currently, this question is not answerable and will not be until we understand what all our genes do and how the pathogenesis of all diseases plays out, but it seems likely that genetic variation contributes to the illness of every sick person. What is our evidence?

1. Everything we are and do, from creative thinking to autonomic function, is mediated by biological systems comprised of proteins, and nearly all pathogenesis is mediated by alterations of these systems. Even such classic

"environmental" diseases as those caused by infectious agents involve the homeostatic devices that counter the pathologic effects of the infectious agent. The protein components of these systems are specified by genes, each with protein coding and *cis*-acting regulatory segments. Many genes have a repository of common variation and all are susceptible to mutations with deleterious consequences on the function of their protein products. This variation, some normal, some abnormal, and some abnormal only under certain circumstances, influences all disease. The only exceptions to a primary role for proteins of which we are aware are the small number of disorders caused by defects in genes whose final product is an RNA [e.g., cartilage-hair hypoplasia syndrome (56)], but even these disorders are the result of abnormal variation in the genes that encode these RNAs and include a pathophysiology that involves many protein systems.

2. Given the degree of integration in the human body within and between homeostatic devices, within and between cells, within and between organs and organ systems that constitute the individual, how can any disease fail to be influenced by more than one protein and therefore more than one gene?
3. There is also clinical evidence that genetic variation contributes to all disease. We often observe that certain diseases tend to run in families, suggesting a role for the genes. This familial tendency is well documented for many common disorders of adult life, including hypertension, coronary artery disease, neuropsychiatric disorders, and inflammatory bowel disease. The ultimate test for a genetic contribution, namely some formal analysis of familial aggregation, may be difficult to accomplish, particularly for disorders with late onset, but a lesson learned over and over is that the more you look for genetic factors contributing to disease, the more you find. For example, genetic variation has been shown to play a role in the autoimmune disorders one by one (27). For each complex phenotype, as evidence for engagement of the proteins in a particular system is acquired, genes encoding other components of the same or related protein systems become candidates. An example of this "ripple effect" in the advancement of our understanding is coronary artery disease. From the initial careful clinical studies of early-onset, familial myocardial infarctions (29, 30) to the breakthrough in 1974 implicating the low-density lipoprotein (LDL) receptor (8, 9), we now know more than a dozen loci encoding proteins involved in lipid metabolism, each with multiple alleles, (16, 53) as well as genes for clotting factors, endothelial cell proteins, and no doubt many others (40).
4. The discovery of hundreds of abnormal alleles for many genes causing monogenic disorders (e.g., *CFTR*, *PAH*, *BRCA1*, etc.) suggests a rich source of alleles of deleterious consequence (2, 54) (Human Gene Mutation Database, http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html). While not frequent, these alleles either in heterozygotes or in individuals who are compound heterozygotes for two or more alleles of mild consequence, may well contribute to the

sets of genes involved in complex disease, and may account for their heterogeneity, too. For example, heterozygosity for *ABCR* alleles first identified as a cause of Stargart's disease, a rare, monogenic, early-onset form of macular dystrophy, has been suggested to contribute increased risk for the much more common age-related macular dystrophy (34, 42, 64).

5. Many millions of SNPs have now been identified and, even if most are functionally neutral, the absolute number of those with recognized functional significance is still large and provides a source of genetic variation that is likely to influence common complex diseases (11, 28, 32a, 57). The list of SNPs with functional significance contributing to complex traits is growing daily and includes the P12A polymorphism of PPARγ that contributes to type I diabetes (1, 24), the factor V Leiden polymorphism that increases the risk for deep-venous thrombosis (38, 58), the chemokine receptor 5 (CCR5) variants and their resistance to HIV infection (12), and the APOE4 variant that contributes to Alzheimer's disease (19, 41). A current bottleneck in appreciating the significance of this variation is our limited ability to characterize the functional significance of many SNPs. After all, who can say whether a given SNP is "normal"? The word normal refers to a protein that has passed the selective test; that is, it completely fulfills its allotted function over a wide range of conditions or stresses. But when we do not know what that function is or how the variant might influence its fulfillment, or other intrinsic or extrinsic factors that stress the function, we cannot say whether a given variant is "normal," "abnormal," or "abnormal only under certain circumstances."

Finally, the obvious variability—biological, functional, and social—of all human beings leads inescapably to the view of individuality of all diseases. If each of us is easily distinguished by the way we look, act, and perform, why should we not expect similar individuality in the ways and extent to which we get sick and respond to treatment? Thus, if teaching medicine within a genetic milieu is justifiable, in part by evidence favoring a component of genetic variation in all disease, what should that context be?

GENETICS IN THE CURRICULUM

A Genetic Context

We have made a case for teaching medicine in a context of genetics and genomics. That is, the subject should be taught in recognition of the individuality of sick people who have met the demands of disease variably by individually expressed homeostatic devices. This offers a context within which to teach all subjects, both preclinical and clinical: It is the science of the individual.

But what is meant by "a genetic context"? The word "context" is derived from the Latin word *contexere*, which is defined as the verb "to weave." This is a

particularly felicitous definition because by tying variation in molecules to variations in expressions of disease, genetics weaves basic science and clinical medicine together as nothing else can. As we have pointed out, the genes, in the form of a conceptus, represent the continuity of life from the evolutionary and parental past to the present, and they continue that mission through individualized developmental and maturational translations to aging and an individual's end. And whatever experiences of the environment the developing, maturing product of that conceptus has will be mediated by a unique set of proteins, which, in fulfilling whatever function they are assigned, do so within the limits of the options and constraints imparted by the unique set of genes that specify them. That is a context for medicine and one that embraces equally: (*a*) congruence of our species with its environments and variation, leading to degrees of incongruence including disease; (*b*) variation of individuals and their families in accommodation to the varieties of gene pools; (*c*) individuality of organisms attained in part in meiosis, recombination, and union of parental gametes to form a conceptus, in part in development and maturation, and in part in the influence of that individuality on adaptation to living; (*d*) influences of individuality on treatment and prevention of diseases to the extent permitted or promoted by variable proteins; and, finally, (*e*) genomics in its mission to reveal all functional elements in our genome and the extent of variation in these elements between members of our species and that of exposing the mechanisms of evolution and their meaning for medicine.

BRINGING THE CONTEXT TO THE STUDENT

How will this suffusion of genetic thinking into the whole of the medical curriculum be accomplished? No doubt there are as many ways as there are schools. Our suggestion is to begin the curriculum with lectures presenting and justifying the above or some similar context, then, again in ways suitable for the school, to work toward its application, where appropriate, in all courses. It should be clear that the purpose of such introductory lectures, even if given by geneticists, is not to teach genetics per se, but to introduce some of the generalizations of the biology of medicine. It might be objected that the subjects of these lectures are beyond the students' present knowledge, but they need not be; today's students have had biological sciences in college and are eager to begin.

Having introduced the student to the origins of individuality, how can this context be expanded and reinforced in the subsequent four years of medical school? We think there is no best way to accomplish this goal; rather, each school will have to adopt a strategy that fits best with the overall design of its curriculum and with the expertise and interests of its faculty. What is clear, however, is that it will require the commitment of a broad segment of the faculty. In contrast to the introduction of a new course, which can be achieved by one or a few interested members of the faculty, transmitting this point of view will be most effective if the students hear a few words about variability and its consequences in every lecture and around every bedside. The genetics faculty should be an excellent resource

for concepts, examples, and other teaching material, but all faculty members who adopt this goal will be able to identify aspects of their subject matter in which variation is prominent as an influence on health and disease and on the interaction of individuals with experiential variables.

The ways in which this suffusion of individuality can be achieved vary in the extent that they require alteration of the existing structure of the curriculum. Introducing this context would not require significant structural change in the curriculum; the faculty would simply be encouraged to emphasize variation and individuality in all aspects of what they currently teach. In the basic sciences, when proteins are the subject, the student needs only to be reminded of their potential for variation and that variation may lead to disease. In biochemistry and physiology, where pathways, modules, and networks of proteins are the object of scrutiny, variability will come naturally. If there are postlecture discussions the effect of the inevitable variation would be a natural object for speculation. In many schools inborn errors are already a natural exhibit in biochemistry or molecular biology, so variation is not new. What may be new is its extent: the recognition that variation is there in every individual and that, when there is disease, each person's version of it must differ, whether subtly or obviously. It may also be unusual to talk freely about variability as an evolutionary phenomenon, a necessity for the life of species despite its adverse effects on certain individuals within the species.

On the clinical side, the context may seem less obviously pertinent. Although on one hand we know that in all diseases there is clinical variability, both subtle and obvious, and that the variants may require individual attention in treatment, such differences may not be perceived to stem from etiological variation. On the other hand genetic heterogeneity is now recognized and there is increasing recognition of the relationship of genetic variation to the specificity of drug treatment. There is a favorable environment for this approach: genetics and genomics have become watchwords, widely employed both in medicine and in lay discourse, even comic strips. So there is a climate receptive to individuality, and increasing evidence of it.

This climate of individuality or "personalized" medicine is more and more apparent in clinical practice. One instance is provided by recent work in essential hypertension identifying genetic polymorphisms that aid in understanding the pathophysiology and have the potential to improve the treatment of this common disorder. Although hypertension is an elevation in systemic blood pressure, each patient reaches that phenotype by different paths, each determined by a unique combination of genetic makeup and experiences of the environment. The most common form, essential hypertension, has been associated with genetic variation in renin-angiotensin, aldosterone, G-protein signaling, and adrenergic responses (46). Up to 15% of individuals with essential hypertension have been suggested to have abnormal regulation of the aldosterone/renin axis, and many of these patients have polymorphisms in aldosterone synthase or adrenal 11 beta-hydroxylation (25).

Individuality is also apparent in the treatment of hypertension. Genetic influences on drug pharmacokinetics are well described for many therapeutic agents

commonly used in the treatment of hypertension and other disorders. Newly identified polymorphisms in genes involved in the alpha-adrenergic, beta-adrenergic, nitric oxide, renin/angiotensin, aldosterone, and angiotensin converting enzyme (ACE) systems influence the antihypertensive effect of diuretics, beta blockers, alpha blockers, ACE inhibitors, and angiotensin receptor blockers (60).

Similarly, an understanding of genetic variability in both the host and the infectious agent is already a crucial component to providing optimal therapy for patients infected with HIV (12, 50). Current guidelines recommend testing isolates of HIV for genetic mutations that confer drug resistance in order to determine appropriate therapy (37).

Factual Overload and De-Emphasis of Critical Thinking

Although we have not stressed it to this point, a common criticism of medical school curricula in reports published over the past century is an excessive emphasis, especially in the first two years, on factual information that seems, at least to the student, irrelevant to the practice of medicine. There is no sign that the growth of this glut is slowing; to the contrary, genomics and other forms of big science promise to increase the acquisition of new facts dramatically. Corollaries of this factual overload are that it fosters rote memory and noncritical thinking. We argue that providing a consistent context of genetic principles from the outset of medical school will diminish the need to bombard students with all the facts, decrease the need for uncritical regurgitation of this information, and provide a framework in which the student can assemble facts into logically consistent sets or integrated levels of understanding. In this paper we argue for a genetic context. Over the student's career, new facts, and there are bound to be many, can be critically evaluated and retained or discarded depending on how they fit in the framework provided by the principles. In this way, especially with guidance from teachers, the student can develop an intellectual framework that will enable lifelong skills in critical thinking.

CONCLUSION

To return to the beginning and the recognition by doctors of the past of the need for a science of the individual, we are acquiring the means for such a science now, but general acceptance of its need and value lags. This is not due to any deficiency of the teaching of medical genetics in the curriculum, but is a function of a tradition of typological thinking about biology and disease that does not accommodate variation. And yet there is genomics hovering over us with its thousands of genes and their many thousands of combinatorial controlling elements, and its study of how the genes of hundreds of species fit into the grand scheme of evolution, so a change in medical thinking that accommodates variation is required. We have suggested one way to proceed. It is to suffuse the curriculum with genetics, beginning with a few lectures that outline a context of genetics and genomics

within which the rest of the curriculum fits naturally. Although this may sound extraordinary, it involves at its core only the recognition of variation in all systems stemming from proteins specified by genes. This is not to say that individuality must be salient in all teaching but that it should lurk in the background of the teaching whether of ophthalmology, orthopedics, cardiology, or another field. For example, there is variation in the anatomy, physiology, and diseases of the eye, and the joints and the beat of the heart. It is a dynamic variation, originating in the adaptation of gene-specified proteins to conditions met as a conceptus, and amplified and further varied thereafter through development, maturation, and aging. It is immensely complicated, but by approaching medicine in a context of variation we are moving to resolve that contradiction between the singularity of the patient and the generality of treatments and prevention.

We also emphasize the origins of the science of the individual in natural selection and evolution. These subjects have not been of prime interest in medicine. For example, they do not appear in the indexes of the most prominent textbooks of medicine or pediatrics. There has been no obvious reason to include them in the curriculum in any comprehensive way, but they are the biological history of our species, and if we are to understand ourselves in health and disease it must be in the light of how we came to be as we are. It may be said that a curriculum already filled with the necessary has no room for the unnecessary. Is evolution necessary? Does it have practical application? What could be more practical than understanding the form and function of humanity and the shapes and limits of disease? Our tendency at the moment is to answer only the "how" questions. After all, their answers point to disposition. But evolution asks "why" questions that direct our attention to individuality and the origins of disease: why me, why this disease, and why now in my life (43). For example, there is a gradient of phenotypic effect, probably related to the age of reproduction, in which catastrophic diseases, strongly genetic in origin, occur early in life; 75% to 80% of human disease occurs in utero, whereas old age is a time of chronic diseases more strongly associated with experiences of living, themselves susceptible to discovery and change. In describing this change in etiology with age, the geneticist would say that the heritability had declined, heritability being an expression of the extent of the genetic contribution to the variation in a population. This suggests a motto for medicine: We work always to raise the heritability in the direction of 1.0. How? We give more attention to nongenetic elements of cause that may be susceptible to discovery and modification. In so doing we reduce the frequency of disease by eliminating the preventable cases, leaving only the hard-core, strongly "genetic" disease. Indeed we are already doing that. Mortality curves are being rectangularized, which is to say people are surviving into old age, either without disease or with chronic diseases controlled (26). And, to add to these feats, a comprehensive plan, perhaps of the scope of the Genome Project, was recently suggested to search for those experiences of living that contribute to disease, in aid of plans for prevention (17). This will be an epidemiological study that will designate elements of the environment as risk factors, which must be followed by the genetic question, "risky for whom?"

This prolongation of life, sometimes without disease, often in relative comfort, is one of medicine's most glowing successes, attained, it should be added, with little reference to heritability. This is characteristic of the medicine that marches to the laudable tunes of alleviation of suffering, preservation of life, and cure and prevention of disease. Attention to these aims is what we all want when we are sick and go to the doctor. But medical school is different. In medical school the teaching in basic sciences is rooted in generalizations and principles. But teaching about disease is less so. Each disease has its own generalizations [age at onset, organs involved, signs, symptoms, and the like (36)], but there is little attention to principles of disease: Why do we have disease? Who has which one and why, and when in life? But what of it?

Principles give context to facts. We allude to the students' complaints of the burden of the facts, and medical schools responded by trying to lighten the load. Another way is to tie a lighter burden of facts to principles. That is what we propose in this paper. The genetics perspective, which is strongly principle driven, is the way to individuality, a consequence of evolution's need for variability, that originates in variable genes that specify variant proteins reflected in individuality at many physiological levels including who we are, our strengths and weaknesses, our careers in disease, and so on. One might be tempted to say, "But that's what molecular biology, biochemistry, and physiology do." But, of course, they do not, as they lack the principle of variability. That variability and its relationships to the individuality of health and disease is the reason for teaching medicine in a genetic context.

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