American Pediatric Society's 2006 John Howland Award Acceptance Lecture

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I am most grateful to the American Pediatric Society for honoring this happily converted internist who saw the light thanks to the wisdom and encouragement of the late Horace Hodes, whom I had the pleasure of introducing for his Howland Award in 1982 (1,2). I am equally grateful for your honoring a geneticist, only the second, the first being Barton Childs in 1989 (3). He has been a role model for me since my getting into the field in 1956. There hasn't been a dull day since then.

I would like to devote my talk to the exponentially growing impact of genetics on pediatrics and all of its subspecialties, which, if not already, will soon become subspecialties of genetics. I will comment on these advances, some old and some new, which have had an impact on the basic understanding of human disease and an increasing influence on clinical research and practice in pediatrics. Much of this has come about by what I call thinking genetically, by which I mean approaching basic and clinical questions first from a genetic point of view with the goal of understanding disease on the basis of human variation. It is easily demonstrated that no two individuals, even including identical twins, are alike, first due to differences in their DNA, and then how their genetic makeup interacts with their internal and external environment.

Let me begin with infectious diseases, responsible for so much of pediatric pathology and childhood death. Among the more common of these worldwide are HIV/AIDS (4), tuberculosis (5), and malaria (6). It has become clear that susceptibility and resistance to and severity of these infections, as well as their response to therapy, are associated with a variety of mutations in cytokines, red cell proteins, and enzymes, many of which show great variation geographically and ethnically. As another example, meningococcal meningitis is generally more invasive and lethal in children with mutations in late components of the complement cascade (7) and in fucosyl transferase, which is important in mucosal protection against bacterial invasion. Also, herpes simplex infection is far more likely to result in severe encephalitis in patients with mutations in a recently discovered gene, UNC 93B1, which activates innate immunity (8).

In addition, the complexity of the immune response and the increasing number of identified primary immunodeficiency diseases (9), which influence the response and susceptibility to

microbes is becoming recognized as an important factor in the field of infectious disease. These genetic variations are also at the core of the growing caseload of children with allergies and, less commonly, of autoimmune diseases. An example, published just this month in *Nature Genetics* (10), is genetic variation in filaggrin, which, when mutated, allows percutaneous absorption of allergens resulting in atopic dermatitis and associated asthma.

Another common cause of pediatric pathology is the vast group of developmental disorders, including neonatal abnormalities, neurologic disease, and many of the problems arriving in the hands of our surgical subspecialists. The genes mutated in children with these malformations can in turn teach us about normal human development. For example, genetic abnormalities leading to forelimb anomalies have identified mechanisms of normal arm and hand development, as well as their association with defects in other organ systems. In neurologic disease, the common problem of epilepsy presents us with even greater complexity, where genetics and environment interact to alter prognosis and therapy.

Genetic variation is responsible for much, if not most, of endocrine disease. Beside the well-described monogenic conditions, such as adrenal and thyroid abnormalities, progress is rapidly being made in the dissection of the common problems of obesity, short stature, and delayed puberty, as well as type I and type II diabetes mellitus, the latter a current pediatric epidemic. As there has been success in therapeutic and preventive intervention in the monogenic conditions, the latter, genetically complex diseases, environmentally influenced, will no doubt yield to such interventions when we eventually more fully understand individual variation in susceptibility to these common maladies.

The work of my colleague, Bruce Gelb (11), and several other investigators has led to an understanding of a number of congenital and later onset cardiac problems, which teach us about normal heart development and will lead to therapeutic and preventive interventions, just as it has in the pulmonary field. The discovery of mutations leading to surfactant deficiencies in neonatal lung disease and those resulting in abnormal mucus in cystic fibrosis have already led to improved survival and better health in these previously mostly lethal diseases. Similarly, nephrologists are beginning to differentiate between various genetic causes of nephrosis and nephritis, which will lead to more rational treatments individualized to specific defects.

An exciting development has been the genetic dissection of gastrointestinal and biliary disease, including the understanding of the intricacies of the formation and secretion of bile and

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its components by my colleague and chairman, Fred Suchy (12). Other advances are the recent finding of genetic components of inflammatory bowel disease (13), already leading to the search for individually designed therapeutic strategies. A previously poorly understood problem, lactose intolerance, has recently yielded to genetic study. As you know, most of the world is unable to properly digest dairy products due to this defect, whereas most of the people deriving from northern and western Europe thrive on milk and its derivatives. Not only has the genetic change allowing lactose tolerance been discovered, but, recently, my son, Dr. Joel Hirschhorn, worked out that this mutation is only a few thousand years old, and spread in the European population contemporaneously with the establishment of the dairy industry in northern Europe, making the cow a powerful selective force in our recent evolution (14).

It is becoming clear that oncologic diseases are not only universally due to acquired genetic changes in cancer cells but are in many cases associated with germ line genetic changes leading to susceptibility to cancer. This is particularly true in childhood cancers, such as retinoblastoma, Wilms' tumor, lymphomas, and brain tumors. Recent molecular analyses, such as genomic and expression arrays, are beginning to identify individual abnormalities as possible targets for specific therapies. A recent successful example is the use of Gleevec in the treatment of chronic myelogenous leukemia (15).

It is in the field of inborn errors of metabolism that the greatest advances have been made in new therapeutic interventions. While we have had replacement therapy in our armamentarium for a long time, such as thyroid hormone for cretinism and insulin for diabetes, recent work in enzyme replacement therapy, as for Gaucher and Fabry disease, much of it developed by my friend and colleague Robert Desnick (16), has led to enormous clinical benefits and will be useful in other conditions. While gene therapy has not moved as fast as was hoped, early success in some immunodeficiencies holds promise for future applications. Stem cell therapy, hopefully in a few years, is certain to broaden our treatment of genetic disease.

In the future, perhaps the major group of pediatricians who will become geneticists will be those in primary care and in neonatology. Recent and future discoveries, greatly due to the success of the Human Genome Project, will find their applications in general pediatrics and medicine. When individual patients' genome sequence can be routinely obtained with appropriate ethical protections, and perhaps stored on a plastic card carried in their wallet, each person's susceptibility mutations will be recognizable allowing early application of preventive approaches to keep people healthy. This, of course, will be most important in children, so that physicians can act before permanent damage occurs. In neonates, it may lead to more rational and effective screening. Another application will be in therapeutics, a field in which we learn every week of newly discovered mutations leading to either detrimental reactions or resistance to medicines used for common or rare diseases. This, too, will be a role of the primary care doctor, to individualize therapy not only for the subtype of disease, but for the variation in response to drugs.

Finally, let me stress the change in genetic thinking that is occurring and that all pediatricians must adopt. Until recently,

we thought of genetic diseases as a few obscure, rare and untreatable conditions. Even these should be looked at differently. While most monogenic disorders are rare, as a group they represent a significant proportion of pediatric illness. Also, while we think of these as being simply the result of single mutations, it is clear that they show great variation due to the action of modifying genes and environmental interactions, allowing interventional strategies. But most important is the growing recognition that most, if not all, common diseases are caused to a greater or lesser extent by genetic changes, whose understanding will lead to more rational preventive and therapeutic approaches in childhood with a large impact on health and disease in adults. Pediatricians will then have an important role in preventing diseases not traditionally within the scope of pediatrics. All this will only happen if we think genetically and approach all of our basic and clinical activities with the question of what genetic mechanisms are at play. It is time for all pediatricians to become as excited as I have been over the past 50 y about the future of pediatrics, which has been and is rapidly changing, greatly in response to the advances in genetics, to some of which I have had the pleasure of contributing.

In closing, let me again say how incredibly honored and grateful I feel to have been chosen for the Howland Award, the greatest achievement in pediatrics. I am also enormously pleased that this is occurring in the presence of my love for 53 y, my occasional collaborator and my constant supporter and severest critic, my wife, Dr. Rochelle Hirschhorn, my three children, Melanie Vetter, J.D., Lisa Hirschhorn, M.D., MPH, and Joel Hirschhorn, M.D., Ph.D., and my grandchildren.

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