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SPECIAL ARTICLE

A History of Medical Genetics in Pediatrics

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ABSTRACT

Medical genetics emerged from a basic science only one half century ago. Scientists and physicians housed in a variety of basic science and clinical departments have accomplished many of the major advances in the study of genetic diseases in children. A scientific approach to human genetics emerged in 1948 with the establishment of the American Society of Human Genetics. Even before the use of modern laboratory techniques, Pediatric departments spearheaded the clinical description of simple genetic disorders, syndromes, and major malformations. The burgeoning of medical genetics as a specialty and its tremendous growth in departments of pediatrics was stimulated by major technological advances, such as the ability to visualize human chromosomes, the development of methods to study biochemical variations in blood and urine, cell culture, somatic cell hybridization, and molecular technology, all of which allowed for the diagnosis, treatment, and prevention of genetic disorders in children. Many pediatricians sought training in genetics, and training programs in medical genetics flourished in departments of pediatrics. The explosion of knowledge concerning the metabolic and molecular causes of genetic disease and understanding of their pathogenesis has led to a variety of specific diagnostic, preventive, and therapeutic approaches for alleviating the symptoms or preventing the complications of many of these disorders. Medical genetics is now recognized as a distinct medical specialty with its own American Board of Medical Specialties approved board (American Board of Medical Genetics) and clinical specialty college (American College of Medical Genetics). **(*Pediatr Res* 56: 150–159, 2004)**

Abbreviations

ABMS, American Board of Medical Specialties
AFP, α-fetoprotein
ASHG, American Society of Human Genetics
CGH, comparative genomic hybridization
PKU, phenylketonuria
SCID, severe combined immunodeficiency

Unlike other pediatric specialties, which usually started as offspring of internal medicine subspecialty development, medical genetics emerged from a basic science only one half century ago. Scientists and physicians housed in a variety of basic science and clinical departments accomplished many of the major advances in the study of genetic diseases in children. In this article, we trace the development of medical genetics as a scientific and clinical discipline and concentrate on contributions of pediatricians or from departments of pediatrics.

Genetics had its roots in the 19th century when, in 1865, Gregor Mendel, a monk and then abbot in an Augustinian monastery, discovered the laws of inheritance in garden peas, a feat that was overlooked until "Mendelism" was rediscovered in 1900 (1). Walther Flemming first visualized human chromosomes in tumor cells in 1882, and Waldeyer introduced the term "chromosome" in 1888 (2). During the 1880s, Roux, deVries, and Weismann developed the theory that chromosomes carry determinants of heredity and development, and in 1903, Walter Sutton and Theodor Boveri proposed the chromosomal theory of Mendelism. In this same decade, the concept of "inborn errors of metabolism" was introduced by Archibald Garrod, which he formally proposed in his Croonian lectures, published in 1909, discussing alkaptonuria, pentosuria, cystinuria, and albinism (3).

During the next half century, genetics developed as a basic science, with a focus on *Drosophila*, the mouse, and corn as experimental systems; most human studies were based on biostatistics and population-based mathematical analyses. However, during this time, Mendelian inheritance was defined in a number of disorders, such as albinism, brachydactyly, and symphalangism (4,5). During this era, the concept of "eugenics" evolved, resulting in a societal attempt to improve the gene pool and prevent

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dissemination of bad genes into future generations. This led to a variety of eugenic practices throughout the world, where individuals with mental deficiency as well as those with physical malformations were prohibited from reproducing, with programs of forced sterilization, etc. The eugenic movement culminated in the "justification" of the Nazi holocaust, but after the Second World War, eugenics and its base in human genetics fell into disrepute.

A scientific approach to human genetics emerged in 1948 with the establishment of the American Society of Human Genetics (ASHG), but it must be stated that the majority of its founding board of directors were members of the American Eugenics Society. Few medical doctors were involved in human genetics at that time, the majority being PhDs with backgrounds in formal (population or statistical genetics), *Drosophila*, or mouse genetics. Many of these PhD geneticists began studying the inheritance of single gene disorders in human, and some became excellent clinicians in the description of syndromes and birth defects. These included such individuals as Curt Stern in Berkeley, Norma Ford Walker in Toronto, and F. Clarke Fraser in Montreal (who gained an MD after his earlier PhD but never took an internship). Annual meetings of the ASHG began in 1948, and the first International Congress of Human Genetics was held in Copenhagen in 1956, with regular congresses occurring every 5 y since then.

One of the first MDs to become a human geneticist was James Neel, whose studies ranged from hemoglobinopathies to complex disorders, such as diabetes and mathematical genetics in diverse populations (6). Neel was an internist, as were most of the other major medical figures in genetics in 1950s, including Victor McKusick at Johns Hopkins, Arno Motulsky in Seattle, and Alex Bearn and Kurt Hirschhorn in New York. There were few formally trained pediatricians in medical genetics in the 1950s, an outstanding exception being Barton Childs at Johns Hopkins. These adult-trained medical geneticists each developed training programs in genetics, with most of their early trainees being internists as well. However, with the explosive developments in the genetics of childhood diseases in the 1960s and 1970s, many pediatricians sought training in genetics, and training programs in medical genetics flourished in departments of pediatrics. Indeed, many of the second-generation internal medicine–trained geneticists joined departments of pediatrics, and they themselves trained numerous pediatricians over the years. Many of the early medical geneticists based in pediatric departments were originally trained as internists, including David Nathan, Charles Epstein, John Littlefield, Judith Hall, Ian Porter, and David Rimoin. Simultaneously, a number of pediatric-trained medical geneticists emerged, such as Charles Scriver, William Nyhan, Rodney Howell, John Opitz, Henry Nadler, Jurgen Spranger, Barbara Migeon, Jim Sidbury, Michael Kaback, and Murray Feingold. A number of highly productive genetics units were established in children's hospitals and pediatric departments throughout Europe. One of the first was established at the Royal Children's Hospital (Great Ormond Street) in London under the direction of J. Fraser Roberts, followed by Cedric Carter, Marcus Pembry, and Robin Winter. Paul Polani at Guys Hospital in London made major contributions to the field. Maurice Lamy developed an important genetics center at the Hopital des Enfants Malades in Paris, with the help of such luminaries as Maroteaux, Frezal, and de Grouchy. Clinical genetics flourished in Kiel, Germany, with H.R. Wiedemann and his student Jurgen Spranger, who subsequently developed a genetics center in the department of pediatrics in Mainz.

CLINICAL GENETICS AND DYSMORPHOLOGY

Even before the use of modern laboratory techniques, pediatrics departments spearheaded the clinical description of simple genetic disorders, syndromes, and major malformations. F. Clarke Fraser (7) was the first to point out "genetic heterogeneity" in 1956, when he demonstrated that two clinically similar cases might be genetically different. The description of genetic syndromes and subsequent genetic heterogeneity was led by a number of pediatricians and others working in pediatric departments, such as John Opitz, David Smith, Sydney Gellis, Judith Hall, Pierre Maroteaux, Jurgen Spranger, and David Rimoin. One of the most important contributors to pediatric syndrome description and classification was Robert Gorlin, a dental pathologist, who described many of the well-recognized syndromes involving the head and neck (8).

One of the most influential individuals to define the mechanism of birth defects was David W. Smith, a pediatrician and clinical geneticist. Smith coined the term "dysmorphology" for the study of genetic and acquired structural malformation syndromes with consideration of their cause and pathogenesis (9). He developed concepts of birth defects caused by abnormalities in formation, normal formation followed by disruption by external forces, or reversible deformation caused by external pressures. He trained a host of disciples, such as Kenneth Lyons Jones, Brian Hall, John Aase, Jim Hanson, and John Graham, who followed in his footsteps and made major contributions to the fields of dysmorphology and syndrome identification. Smith was trained in the basic genetics department at the University of Wisconsin, which also bred another highly prolific pediatric syndromologist—John Opitz. Whereas Smith had a relatively broad and simple mechanistic approach to the definition of syndromes, Opitz had a highly complex approach and made numerous accurate predictions as to the mechanisms of syndrome cause and pathogenesis, such as the developmental field concept and premutations (10).

The study of structural malformations in human was preceded by similar descriptions in the mouse, by individuals such as Joseph Warkany in Cincinnati (11). His studies led to the definition of both genetic and environmentally induced structural defects. A number of clinical geneticists and dysmorphologists became expert in the field of teratology and described numerous teratogenic syndromes caused by prenatal exposure to radiation, infections such as rubella, methyl mercury, folate deficiency, alcohol, drugs such as phenytoin and warfarin, maternal diseases such as diabetes, and Rh and ABO maternal-fetal incompatibility.

The burgeoning of medical genetics as a specialty and its tremendous growth in departments of pediatrics was stimulated by major technological advances, such as the ability to visualize human chromosomes, the development of methods to study biochemical variations in blood and urine, cell culture, somatic cell hybridization, and molecular technology, all of

which allowed for the diagnosis, treatment, and prevention of genetic disorders in children.

CYTOGENETICS

The beginning of modern human cytogenetics was made possible by the development of tissue culture, the ability to use peripheral blood after immunogenetic stimuli of lymphocytic mitosis, use of mitosis-arresting agents, hypotonic wash of dividing cells, and a variety of staining techniques. Aside from the discovery in 1956 (12) of the correct human chromosome number of 46, most of the descriptions of chromosome abnormalities came from departments of pediatrics in their study of abnormal children. The first of these was the finding by Lejeune of an extra chromosome 21 in Down syndrome in 1959 (13). This was quickly followed by the discovery of sex chromosome abnormalities including 45X in Turner syndrome (14), 47XXY in Klinefelter (15), and other numerical abnormalities of sex chromosomes. Not long thereafter, other autosomal trisomies were discovered, primarily of chromosomes 13 (16) and 18 (17). Another class of chromosome aberrations found early in cytogenetics was a variety of patients who had mosaicism and had two or more chromosomally different cell lines in their bodies. The most important of these were XY/XO in male pseudo-hermaphroditism (18) and XX/XO in X-chromatin positive Turner syndrome patients (19). A major class of abnormalities discovered through the study of children with congenital abnormalities was changes in the structure of chromosomes. These include isochromosomes in the case of the long arm of the X associated with Turner syndrome (20), deletions, including those of the short arm chromosome 5 in the Cat cry syndrome (21), and the short arm of chromosome 4 in the Wolf-Hirschhorn syndrome (22), as well as balanced and unbalanced translocations, the latter resulting in partial duplications and deficiencies of parts of chromosomes. One of the early forms of the latter resulted in extra material from chromosome 21, translocated often to chromosome 14 in cases of familial Down syndrome (23).

In 1969 and 1971, methods of chromosome banding led to far more accurate descriptions of chromosomal abnormalities, particularly those involving structural changes. This led to the concept of contiguous gene deletion syndromes by Roy Schmickel (24). Although fluorescent banding techniques were used extensively in the early 1970s, to this day, G-banding is the most common method of studying chromosomes from blood and other tissue.

It was soon found that virtually all malignant cells carried various chromosomal abnormalities, a finding predicted in 1914 by Boveri (25). The first of these was the Philadelphia chromosome, diagnostic of chronic myelogenous leukemia by Nowell and Hungerford (26). Janet Rowley (27) later discovered this to be due to a translocation between the long arms of chromosomes 9 and 22, leading to uncontrolled activation of a gene partly responsible for cell division, thereby leading to uncontrolled growth of myeloid cells. Careful study found many similar instances of balanced and unbalanced translocations in leukemia and lymphoma involving various chromosomes and various cell growth genes. These have become indispensable tools in the accurate diagnosis and tailoring of therapy in various oncologic disorders, especially in the childhood leukemias and lymphomas. High-resolution banding in prophase was developed in 1977 by Francke (28), Yunis (29), and the Manilovs, which improved delineation of microdeletions in solid tumors, such as Wilms and retinoblastoma.

In the past few years, new technology has led to even more refined diagnosis of chromosomal imbalances. These have included the use of fluorescent probes (fluorescence in situ hybridization) for the purpose of accurate identification of chromosomes and their parts, as well as the mapping of genes to specific sites on chromosomes. These have revealed specific chromosomal abnormalities in diseases such as Langer-Giedion, Prader-Willi, DiGeorge, and Beckwith-Wiedemann syndromes. Variations of this method have led to detection of small duplications and deletions by comparative genomic hybridization (CGH), both in individuals and to an even more important extent in cancer cells. In addition, techniques have been developed for multicolor identification of chromosomes so that a single fluorescent study can identify multiple abnormalities, including those involving translocations, in a single cell, particularly important in complex chromosomal abnormalities in malignant cells. Recently, even greater refinement and accuracy have been achieved by hybridization of DNA or RNA to microarrays, leading to discovery of over- and underexpression of specific genes in malignant cells. Major advances in the understanding of the pathogenesis of Down syndrome has been accomplished in departments of pediatrics by Charles Epstein, David Cox, and Julie Korenberg and in understanding chromosomal imprinting by Arthur Beaudet and Judith Hall.

One of the most important applications of all of these cytogenetic techniques has been in the prenatal diagnosis of chromosomally abnormal fetuses, allowing families the options of terminating such pregnancies and allowing them to pursue pregnancies with chromosomal normality. Cecil Jacobsen in DC, Neal McIntyre in Cleveland, and Henry Nadler in Chicago were pioneers in this area.

BIOCHEMICAL GENETICS

The field of biochemical genetics dates back to Garrod (3), who in the early part of the 20th century coined the term "inborn errors of metabolism." The field has grown to such a degree that the eighth edition of *The Metabolic and Molecular Basis of Inherited Diseases* (30) now fills four large volumes. The great majority of these disorders are prevalent in the pediatric population, and often they cause problems in the newborn or the infant. Many of them are responsible for mental retardation and, to a greater or lesser degree, physical abnormalities. The first inborn errors to have their enzyme deficiency discovered were glucose-6-phosphatase deficiency in glycogen storage disease type I (31) and phenylalanine hydroxylase in phenylketonuria (PKU) (32) followed by the description of lysosomal enzyme disorders in the 1960s. The development of new electrophoretic and chromatographic methods in protein and enzyme biochemistry led to the rapid elucidation of many enzyme deficiencies in amino acid and organic acid metabolism in the 1960s and 1970s. Because these disorders affected

primarily children and there was rapid development of methods for the treatment and prevention of the associated mental retardation, departments of pediatrics became the natural site for their study and care. This resulted in the training of numerous pediatricians in biochemical genetics and the establishment of divisions of medical genetics within departments of pediatrics. Major advances were made in the study of inborn errors in pediatric centers in Baltimore, Boston, New Haven, Chicago, Denver, Montreal, San Diego, Los Angeles, and Philadelphia. The early investigators in biochemical genetics, such as Barton Childs, Harry Harris, Rodney Howell, Charles Scriver, and Leon Rosenberg, trained numerous young physician scientists, who became experts in inborn errors of metabolism and built active units in pediatrics departments throughout the United States.

In addition to the inborn errors of amino acid and organic acid metabolism, numerous other metabolic fields evolved in the 1970s and 1980s, with the description of lysosomal enzyme disorders (*e.g.* mucopolysaccharidoses), peroxisomal enzyme defects (*e.g.* Zellweger syndrome), urea cycle defects (*e.g.* citrullinemia), carbohydrate metabolic disorders (*e.g.* glycogen storage diseases and galactosemia), purine and pyrimidine defects (*e.g.* Lesch-Nyhan syndrome), and disorders of mineral metabolism (*e.g.* Wilson's disease and hemachromatosis) (30). The development of cell culture techniques and somatic cell genetics, including the development of selective media, such as HAT (hypoxanthine-aminopterin-thymidine) by John Littlefield (33), and the concept of complementation, paved the way in the 1960s for many of these biochemical discoveries, such as the definition of the enzyme defect in HPRT (hypoxanthine guanine phosphoribosyl transferase) in Lesch-Nyhan syndrome and the enzyme defects in the mucopolysaccharidoses (30) The 1970s and 1980s witnessed the description of numerous enzymatic defects in diseases involving carbohydrate, protein, and lipid metabolism, many of which took place in departments of pediatrics. In addition, pediatricians made important discoveries in basic genetic principles using the new somatic cell technology, such as the clonal proof of the Lyon hypothesis by Davidson, Niitowski, and Childs (34) and the demonstration of the noninactivated terminal end of the short arm of the X chromosome by Larry Shapiro (35).

IMMUNOGENETICS

Serologic testing of blood cell antigens was the first advance in laboratory-based clinical genetics. In 1901, Landsteiner described the ABO blood groups, and in 1940, Levine and Weiner described the Rh system. 1941 proved to be a highly important landmark in pediatrics, with Levine's discovery that erythroblastosis fetalis was due to Rh incompatibility between mother and child (36). The introduction of Rhogam led to a precipitous fall in the incidence of kernicterus, a then highly prevalent cause of neonatal brain injury. The blood group systems also proved to be highly effective markers in genetic linkage studies, with the Duffy blood group being the first human autosomal gene to be mapped (37).

Many of the discoveries of the fundamentals of human immunogenetics, such as the structure and variation of immunoglobulin molecules and the different subtypes of T and B cells, derived from the description and study of the numerous inherited childhood immunodeficiency diseases (38). The earliest of these is Bruton X-linked agammaglobulinemia (39), recently shown to be due to mutations in a lymphocyte specific kinase (BTK) (40), which has led to a better understanding of the control of immunoglobulin synthesis and B cell development. A large number of defects leading to abnormalities of both B and T cells have been described, many of which lead to severe combined immunodeficiency (SCID). The most common of these is, again, X-linked and together with Bruton agammaglobulinemia explains the predominance of boys among immunodeficient children. An important autosomal recessive cause of SCID is deficiency of a purine salvage enzyme, adenosine deaminase, the study of which has led to a better understanding of T cell development (41) and has allowed therapy by enzyme replacement in affected children. Most cases of SCID can be cured by bone marrow transplantation if an appropriate genetically matched donor is available. These diseases have also become a leading candidate for trials of gene therapy, successful in the case of X-linked SCID and promising in adenosine deaminase deficiency. A pure T cell deficiency can be produced by a deletion in chromosome 22 associated with a variety of other abnormalities (DiGeorge syndrome). Another primary T cell defect is caused by a different purine salvage enzyme, purine nucleoside phosphorylase (38).

An additional important aspect of immunogenetics derives from the study of lymphocytes in tissue culture, which led to the discovery of the mixed lymphocyte response. This, together with the understanding of the genetics of HLA, has led to many successes in the field of tissue and organ transplantation. HLA typing has also provided diagnostic testing for ankylosing spondylitis and has been a great aid in the investigation of autoimmune disorders, such as type 1 diabetes.

A major effort is currently devoted to the study of the genetic component of allergy, including food allergy, asthma, and other common problems in children, all of which seem to be increasing in frequency. Similarly, there is the beginning of understanding of the genetic component of autoimmune diseases, which also seem to be on the rise.

MOLECULAR GENETICS

2003 marked the 50th anniversary of Watson and Crick's landmark paper on the structure of DNA (42). This half-century has witnessed the rapid evolution of molecular genetics, culminating in 2003 in the total sequencing of the human genome. Major milestones along the genome superhighway were the description of the genetic code in 1966 by Nirenberg, the discovery of restriction enzymes and their use in mapping DNA in 1970, the invention of the Southern blot in 1975, the first cloning of human genes (chorionic somatomammotropin and the α and β chains of Hb) in 1977, the description of restriction fragment-length polymorphisms and their use in gene mapping in 1980, and the invention of PCR by Mullis in 1986 (1). These discoveries all paved the way for the Human Genome Initiative as a multinational public and private coop-

erative venture, leading to the first publication of the human genome draft sequence by teams led by Francis Collins and Craig Venter in 2000 (43,44).

During the past 25 y, numerous genes responsible for genetic diseases of childhood onset were identified and cloned, with such early examples as Duchenne muscular dystrophy (45), chronic granulomatous disease (46), and cystic fibrosis (47). These pediatric disease–based discoveries have occurred throughout the biomedical establishment not only in departments of pediatrics but also in basic science and most specialty departments in academic medical centers, as well as industry. Some of the early work in the molecular genetics of human disease was done on the hemoglobinopathies in pediatrics departments in Boston (David Nathan and Stuart Orkin) and Baltimore (Haig Kazazian). The discovery of the genes responsible for thousands of diseases has revolutionized all of medicine and has led to the identification of their etiologic defects, allowing new insights into methods of disease diagnosis, prevention, and treatment. It has also had a major impact on our understanding of cancer, with numerous human oncogenes and tumor suppressor genes being described, such as the genes responsible for retinoblastoma, neurofibromatosis, chromosome breakage syndromes, breast and ovarian cancer, colon cancer, etc. The rapid increase in the number of diagnostic tests that could be performed by molecular techniques led to the need to develop clinical, laboratory, and ethical standards for their wide dissemination. The American College of Medical Genetics now publishes regularly updated Standards and Guidelines for Clinical Genetics Laboratories (http://www.acmg.net). Recognizing the clinical challenges resulting from this explosion of diagnostic tests and the need for broad-based public policy development to help the United States address the benefits and challenges of genetic knowledge and genetic testing, the federal government created the Secretary's Advisory Committee on Genetic Testing in 1998, with representation from the genetics, academic laboratory, ethics, and industrial communities. In 2002, the Secretary's Committee on Genetics, Health and Society replaced this with a broader mandate. Both committees were chaired by Edward McCabe.

COMMON DISEASE GENETICS

A great deal of work has recently been published as to the diagnosis of predisposition or susceptibility to common diseases with a genetic component (48). Among these are hypertension, asthma, type 2 diabetes, obesity, and psychiatric disorders, the majority of which have their clinical onset in adulthood. Although numerous associations have been reported in the literature of specific polymorphic changes in a variety of genes in some of these diseases and many others, careful analysis shows that only a small percentage of these polymorphisms are reliable diagnostic predictive markers (49). In addition, the ethical questions for such diagnostic screening are still under debate, especially their application to children. Nonetheless, with the development of whole genome chips over the next few years, these are very likely to become a significant component of medical practice.

PREVENTION OF GENETIC DISEASE

Genetic Counseling

The first tool that the geneticist had for the prevention of genetic disease was genetic counseling. This was done primarily by the physician or PhD medical geneticist and in the early days was one of their few practical tools. With the growth of prenatal diagnosis and genetic screening programs resulting in the increased needs for genetic counseling, a new profession with education at the master's level evolved in the 1970s. These individuals were first called "genetic associates" and later became known as "genetic counselors." The first of these programs was developed at Sarah Lawrence University in Bronxville, NY, by Melissa Richter and Kurt Hirschhorn and subsequently headed by Joan Marks. These professionals have now become an essential part of the genetics team and deal with all forms of genetic disease. Training programs for genetic counselors have developed throughout the country.

Screening Programs

Genetic counseling was traditionally performed in individual family units who had a family history of a genetic disease, for example, after the birth of the first child in the family with a known genetic disorder or a syndrome for which the cause was still uncertain. A variety of population-based screening programs that can detect or prevent the birth of a child with a genetic disorder or allow for early treatment have been developed. With the development of filter paper blood collection and the bacterial inhibition test developed by Guthrie (50,51), the newborn screening program for PKU was the first of these screening programs to be developed since therapy by dietary manipulation had been found to be successful by Hans Bickel in Germany (52). Before too long, all states had developed newborn screening programs to detect PKU and eventually several other treatable disorders, such as galactosemia, maple syrup urine disease, hypothyroidism, and hemoglobinopathies. These screening programs flourished because of the energy of such pediatricians as Louis Elsas, Charles Scriver, Richard Koch, George Donnell, Neal Holtzman, Richard Erbe, and numerous others throughout the world. They have led to the prevention of thousands of cases of mental retardation and neonatal death. With the recent development of tandem mass spectrometry, new expanded screening programs are being tested in a number of states, which will allow for the early detection of numerous other potentially treatable disorders, such as medium chain acyl-coA dehydrogenase deficiency. The power of this screening is the detection of treatable disorders before avoidable death or permanent disability, such as mental retardation, has developed. When early treatment was shown to improve the symptoms of the disorder, population-based screening programs for other disorders, such as sickle cell disease and cystic fibrosis, were developed. A variety of other presymptomatic population screening programs have been developed, some based on the ethnic predilection for disease or the presence of new molecular markers. The basic requirements for such programs are a diagnostic test

that is easy to perform and the ability to intervene with therapy to ameliorate the symptoms or prevent complications.

For many of the disorders that are not amenable to therapy, prenatal diagnosis can be performed for couples who have had an affected child. With the discovery of the enzyme defect in Tay-Sachs disease by John O'Brien (53) in 1969 and the development of a simple blood test to detect carriers, Michael Kaback (54) conceived of a population-based heterozygote screening program among Ashkenazi Jews so that couples who both were carriers and thus at risk for bearing children with this lethal neurologically devastating disorder could detect their one-in-four chance of carrying an affected fetus. They could then elective to terminate the pregnancy, thus avoiding the disaster of having a first affected child before knowing that they were at risk. Subsequent monitoring of each pregnancy then allowed them selectively to have only unaffected children and avoid the disaster of having an affected child. The Tay-Sachs screening program was first started by Kaback in the Baltimore-Washington area and California and then rapidly spread around the world. The tremendous effectiveness of this program can be measured by the fact that the incidence of Tay-Sachs disease has been reduced by >90% in the Jewish populations of the United States, Canada, and Israel and is now significantly more common in non-Jews than in Jews (55).

Another major class of biochemical genetic disorders are the hemoglobinopathies, primarily sickle cell disease and thalassemia, both of which are prevalent in specific populations. The success of the Tay-Sachs screening program led to a trial of a similar program for sickle cell disease in the 1970s. However, it was quickly abandoned for a variety of reasons, including that sickle cell disease does not result in early death or mental retardation, and screening, with the goal of prenatal diagnosis and elective termination of affected fetuses, was considered by some political bodies as representing genocide in the black population. Antonio Cao (56), a pediatrician in Sardinia, established a population based thalassemia-screening program based on the model of the Tay-Sachs program. This was subsequently adopted by many Mediterranean and Southeast Asian countries, and the incidence of thalassemia has been significantly lowered throughout these regions. Carrier screening programs have since been developed for other disorders, such as cystic fibrosis, Canavan disease, etc., as biochemical and molecular techniques for carrier detection and prenatal diagnosis are developed.

As new markers for recessive diseases become available, carriers of more and more traits can be screened for on a population basis. These programs are often most effective when dealing with a disease with an ethnic predilection, such as Tay-Sachs in Jews and thalassemia in people of Mediterranean or southern Asian extraction. Population screening for multiple diseases simultaneously have been developed, such as the "Kosher Kit" first developed by Robert Desnick at Mt. Sinai for screening multiple diseases in Ashkenazi Jews (*e.g.* Tay-Sachs, Canavan, cystic fibrosis, Neiman-Pick, Gaucher disease). With the evolution of micro-array technology, multiplex screening that will be applicable to all populations will likely evolve.

PRENATAL DIAGNOSIS

The cytogenetic, biochemical, and molecular findings and techniques described above all have led to highly effective diagnostic and screening programs for chromosome abnormalities, inborn errors of metabolism, and now structural diseases in children. A major method of genetic disease prevention is prenatal diagnosis, which is designed to detect chromosomally and genetically abnormal fetuses in pregnancies at risk. Prenatal diagnosis was first suggested by Fuchs (57) in 1956 using sex chromatin analysis in amniocytes. This was followed by Breg and Steele's (58) demonstration of the culturability of amniocytes obtained by amniocentesis. This technique has allowed many families to attempt pregnancies in the face of high genetic risk, when they previously would not have considered a pregnancy or would have terminated accidental pregnancies.

Amniocentesis, whereby a sample of amniotic fluid is obtained, usually with ultrasound guidance through the abdominal wall, was the first method of prenatal diagnosis that was developed. The cells derived from this fluid are then cultured and subjected to chromosome analysis and, when indicated, biochemical or molecular analysis. The fluid itself can also be used for the study of various biochemical constituents, *e.g.* α-fetoprotein (AFP) which, when elevated, raises the suspicion of an open neural tube defect. The field of prenatal diagnosis was developed during the late 1960s and 1970s, and much of it took place in pediatrics departments, by such individuals as Henry Nadler in Chicago, Michael Kaback in Baltimore and Los Angeles, and Aubrey Milunsky in Boston.

During the past decade, chorionic villus sampling, a method for earlier prenatal diagnosis (at 9–11 wk gestation), has gained in popularity, because decisions of termination can be made before fetal movements are felt and before others are aware of the pregnancy. This procedure is performed by inserting a cannula through the cervix or through the abdominal wall and obtaining some chorionic villi from the edge of the placenta by suctioning. More recent attempts have been and continue to be made to do these prenatal studies on fetal cells circulating in maternal blood, by pediatricians such as Dianna Bianchi, avoiding the relatively low risk of unwanted termination (59). This technique, however, has not been perfected as yet because of the small number of cells and difficulty in their purification and isolation.

An exciting development has been the field of preimplantation diagnosis. This has become widely used in conjunction with *in vitro* fertilization, whereby one or two cells that are removed from an eight-cell embryo can be studied for specific gene defects that lead to inborn errors of metabolism and by fluorescence *in situ* hybridization technique for abnormal numbers of chromosomes in the common aneuploidies (trisomy 21, 13, 18, XXX XXY, XYY, XO). The drawbacks of this technique are the inability to observe other chromosomal abnormalities and the necessity of holding the embryo for a somewhat extended period of time before implantation while awaiting the results. The first of these can be overcome by applying CGH, which allows a complete molecular karyotype to be determined from a single cell. An even more accurate

technique is to combine CGH with appropriate micro-arrays, which allow the detection of small deletions and all possible numeric abnormalities. Most recently, the second drawback has been experimentally overcome by performing this technique on a polar body (60), allowing a derived conclusion as to the chromosomal constitution of the ovum. The ovum itself can be held in abeyance before *in vitro* fertilization, which leads to greater success than delaying implantation of an early embryo.

Prenatal diagnosis has traditionally been done when a couple are at risk for a known single gene or chromosomal disorder because of family history or because of maternal age. Screening of these samples for AFP became an effective method of detecting and thus potentially preventing neural tube defects. When the presence of abnormal maternal AFP levels were detected in maternal serum in both neural tube defects and chromosomal disorders, population-based maternal serum screening for AFP and several other markers such as human chorionic gonadotrophin and estriol were established. Epidemiologic studies of neural tube defects suggested that low folic acid levels might be a predisposing factor. Through the energy and persuasive abilities of two pediatricians, Godfrey Oakley of the Centers for Disease Control and Prevention and Richard Johnston of the March of Dimes, legislation was passed in the U.S. Congress mandating fortification of flour with folic acid, resulting in a major decline in the incidence of neural tube defects.

Improvement in ultrasonographic technology has also led to the ability to detect and indeed diagnose numerous dysmorphic syndromes and skeletal dysplasias *in utero*. Fetal echocardiography has led to the prenatal detection of congenital heart disease and arrhythmias, which allows for fetal therapy of arrhythmias, preventing the development of hydrops fetalis, and the early planning of medical and surgical therapy for congenital heart defects.

TREATMENT OF GENETIC DISEASE

The explosion of knowledge concerning the metabolic and molecular causes of genetic disease and understanding of their pathogenesis has led to a variety of specific therapeutic approaches for alleviating the symptoms or preventing the complications of many of these disorders (61,62). The understanding of metabolic pathways has led to a number of different forms of therapy for metabolic disorders, which have succeeded in saving a number of infants who otherwise would have died or would have been severely compromised. After the discovery of the enzyme defect in diseases such as PKU and galactosemia, dietary restriction of the specific substrate that was not being metabolized (phenylalanine and galactose, respectively) was shown to be highly effective. In other disorders, substrate depletion has been effective in acute situations with the use of dialysis, exchange transfusion, or plasmapheresis, such as the urea cycle defects. In the 1970s, Leon Rosenberg (63) defined a group of "vitamin-responsive inborn errors" in which co-factor supplementation was found to be effective in some cases (*e.g.* pyridoxine supplementation in homocystinuria). In other aminoacidopathies, restriction of protein- or substrate-enhancing techniques was used. Examples of these include several of the urea cycle disorders, with restriction of protein and diversion of ammonia from urea production, described by Saul Brusilow (64). The therapy, although effective when followed carefully for the life of the patient, is not easy and not pleasant, and admissions to pediatric services for repeated salvage are common. Augmentation of enzyme activity has also been found to be effective in certain inborn errors, such as the use of phenobarbital to reduce bilirubin levels in hereditary hyperbilirubinemic states. Enhanced elimination of toxic substrates was found to be effective in disorders of mineral and iron metabolism, such as Wilson disease, and hemachromatosis product replacement therapy has also been highly successful in a number of genetic disorders, such as diabetes, growth hormone deficiency, hemophilia, and hypothyroidism. In recent years, enzyme replacement therapy has been proved to be effective in Gaucher disease, and enzyme replacement therapy for a number of other storage diseases, such as Hurler and Fabry syndromes, are now in clinical trials and will soon be widely available. The discovery of the genes responsible for specific diseases and the subsequent elucidation of their pathogenesis should quickly allow for the development of small-molecule pharmaceutical advances to normalize the phenotype in many of these disorders.

Some disorders, including some inborn errors and hemoglobinopathies, which are expressed in the bone marrow, can now be cured by bone marrow transplantation, especially when a histocompatible sibling is available. Although bone marrow transplantation still carries a risk of mortality of up to 20% and morbidity as a result of graft *versus* host disease of up to 50%, when successful, it may be preferable to lifetime adherence to difficult and sometimes not totally effective other forms of therapy.

A great deal of publicity has occurred in the past decade concerning the promise of direct and specific cure of genetic diseases through gene therapy (61). Animal experiments have led to the development of a variety of viral vectors to carry the replacement gene to bone marrow or the diseased tissue; however, there have been few successes yet in the human. Problems have existed in targeting the gene to the appropriate location, regulation of gene activity, immune responses, and the demise of several subjects. To date, the only human disease in which gene therapy has proved to be effective is combined immunodeficiency disease; however, this success has recently been marred by the development of leukemia in several subjects. It is likely that this decade will see major technologic advances in gene therapy that will be applicable to many genetic disorders and allow us to reap the therapeutic rewards of the human genome initiative.

PROFESSIONALIZATION OF MEDICAL GENETICS

Human genetics as a distinct discipline is little more than 50 y old. The first professional organization of human geneticists was the ASHG, which was founded in the late 1940s. This was primarily a research organization and was relatively small until the 1970s. The rapid growth in biochemical genetics and cytogenetics at that time led to a great expansion in the number of pediatric geneticists working in clinical depart-

ments, as well as a smaller number of obstetricians interested in prenatal diagnosis. By the end of that decade, it became obvious that medical genetics had truly become a medical specialty in its own right and that certification of clinical geneticists was important for the recognition of practitioners of medical genetics by the greater medical community and the government and other insurance providers.

David Rimoin was asked by the ASHG to form a committee to seek the best mechanism to certify medical geneticists and accredit their training programs. Because the American Board of Medical Specialties (ABMS) had not been accepting any new specialty boards for a number of years, the committee decided to form an independent board to be known as the American Board of Medical Genetics, which would certify clinical geneticists, PhD medical geneticists, genetic counselors, and cytogenetics and biochemical genetics laboratory geneticists. It also took on the role of accrediting training programs in medical genetics. The National Board of Medical Examiners was hired to develop the examinations, and this arrangement continues to the present day. The great majority of the clinical geneticists who sought certification were pediatricians.

In 1995, the ABMS accepted medical genetics as a full specialty, not simply as a subspecialty of pediatrics. They insisted that they would not certify nondoctoral individuals, and thus an independent American Board of Genetic Counselors was formed to provide certification for this important group of master's degree professionals. In an attempt to provide a forum for continuing interaction and coordination between the growing numbers of medical genetics organizations, the Council of Medical Genetics Organizations was formed and meets annually to discuss common issues. In 2000, a combined residency training program in pediatrics and medical genetics was approved by the ABMS and the individual residency review committees, and a 5-y program was established whereby candidates could become board eligible in both pediatrics and medical genetics. A similar 5-y combined training program in internal medicine and medical genetics has also recently been approved.

In 1990, it became apparent that clinical geneticists had to organize their own clinically oriented organization, similar to the American Academy of Pediatrics and the American College of Physicians, if they were to be treated as full specialists by the federal government in its Medicare and Medicaid programs, the American Medical Association and its current procedural terminology committee, and the payers and general providers of medical care. David Rimoin was again asked by the ASHG to form a committee to accomplish this task and, the American College of Medical Genetics was founded in 1991 and promptly admitted to the Council of Medical Specialties.

In 1962, Congress created the National Institute of Child Health and Human Development with one of its major missions being "examining problems of birth defects and mental retardation." This led to the funding of numerous research and training grants that helped establish genetics divisions and major research programs on genetic diseases within departments of pediatrics.

In 1968, the National Foundation, later known as the March of Dimes–Birth Defects Foundation, turned to the elimination of birth defects as its mission, after their triumph in developing the polio vaccine. The March of Dimes funded the Annual Clinical Delineation of Birth Defects meetings, which, for the first 5 y (1968–1972), were held by Victor McKusick in Baltimore and became the main gathering place for clinicians who were interested in genetic diseases and birth defects. In 1960, Victor McKusick organized an annual course in Medical and Mammalian Genetics held in Bar Harbor, ME, under the auspices of Johns Hopkins School of Medicine and The Jackson Laboratories. This course has educated >4,000 pediatricians and other specialists on the basics of medical genetics over these many years.

In the 1980s, the David W. Smith Malformation and Morphogenesis meetings became the major meeting for pediatricians who are interested in malformation syndromes and dysmorphology (9). The first Smith meeting was held in San Diego, when it was already clear that Dave Smith was sick with cancer. Kenneth Lyons Jones organized that meeting both to celebrate Smith and also to start something that would continue as a celebration of his memory.

The Society for Inherited Metabolic Disorders was founded in 1978, largely through the efforts of Dr. Donough O'Brien. This group has met annually since then, and the majority of its membership are pediatricians. Over the years, medical genetics and dysmorphology became regular subspecialty sections at the Society for Pediatric Research and American Pediatric Society, where research findings by pediatric geneticists could be presented. The productivity of this group of individuals grew so quickly that more than one third of all E. Mead Johnson Pediatric Research awardees have been medical geneticists or worked on genetic diseases. In the past decade, a number of presidents and vice presidents of the American Pediatric Society have been geneticists, including Charles Scriver, Larry Shapiro, Michael Kaback, and Judith Hall.

Stimulated by Ed McCabe and Beth Pletcher, the American Academy of Pediatrics also recognized the importance of medical genetics in the care of children by establishing The Section on Genetics and Birth Defects in 1990. This section "enables those Fellows of the American Academy of Pediatrics who are primarily interested in pediatric genetics to meet for the purpose of discussing ideas, developing programs and projects, which will improve the care of infants, children and adolescents with genetic disorders or birth defects and educating primary care pediatricians about the role of genetics in their practices." This committee has published a number of guidelines for the care of children with genetic disorders.

Over the years, societies of human and medical genetics have developed throughout the world. As genetics societies were formed in numerous individual countries throughout the world, they have become regionalized. The American Society of Human Genetics has always included members from throughout North America, and a number of its presidents have been Canadians. The European Society of Human Genetics was established in 1967 by a small group of outstanding European geneticists and now includes representation from >30 national European genetics groups. Human genetics so-

cieties have been developed in Australia, throughout Asia and India, the Middle East, South Africa, and throughout South America.

The first International Congress of Human Genetics was held in Copenhagen in 1956 and followed every 5 y thereafter. The congresses had long been organized by a self-appointed international workgroup of human geneticists. After a great deal of controversy on the organization of the congress in Rio de Janeiro, the International Federation of Human Genetics Societies was founded in 1996 as an umbrella organization of multinational regional societies dedicated to all aspects of human genetics, including research, clinical practice, and professional and lay education. The three founding Full Member Societies—the ASHG, European Society of Human Genetics, and Human Genetics Society of Australasia—agreed to rotate the responsibility of organizing International Congresses of Human Genetics in their region at 5-y intervals.

CONCLUSION

The relevance of medical genetics to pediatrics is becoming even more important with the exciting new work in developmental genetics and the finding of many genes that control embryonic and fetal development. Medical genetics now involves all aspects of fetal and childhood development and disease, and its techniques are used by all pediatric subspecialists. In the years to come, the new genomics and proteomics promise to unravel the mysteries of growth and development and provide many new weapons against childhood disease and disability.

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