Clinical Genetics in Nursing Practice

Third Edition

Felissa R. Lashley

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Dr. Lashley has authored more than 300 publications. Both prior editions of *Clinical Genetics in Nursing Practice* have received Book of the Year Awards from the *American Journal of Nursing.* Other books have also received *AJN* Book of the Year Awards including *The Person with AIDS: Nursing Perspectives* (Durham and Cohen, editors), *Women, Children, and HIV/AIDS* (Cohen and Durham, editors), and *Emerging Infectious Diseases: Trends and Issues* (Lashley and Durham, editors). *Tuberculosis: A Sourcebook for Nursing Practice* (Cohen and Durham, editors) received a Book of the Year Award from *Nurse Practitioner.* Dr. Lashley has received several million dollars in external research funding, and served as a member of the charter AIDS Research Review Committee, National Institute of Allergy and Infectious Disease, National Institutes of Health.

Dr. Lashley has been a distinguished lecturer for Sigma Theta Tau International and served as Associate Editor of *IMAGE: The Journal of Nursing Scholarship.* She is a fellow of the American Academy of Nursing. She currently serves as an editorial board member for *Biological Research in Nursing.* She received an Exxon Education Foundation Innovation Award for her article on integrating genetics into community college nursing curricula. She is a member of the International Society of Nurses in Genetics, and was a member of the steering committee of the National Coalition for Health Professional Education in Genetics, sponsored by the National Human Genome Research Institute, National Institutes of Health. She served as President of the HIV/AIDS Nursing Certifying Board. Dr. Lashley received the 2000 Nurse Researcher Award from the Association of Nurses in AIDS Care; the 2001 SAGE Award by the Illinois Nurse Leadership Institute for outstanding mentorship; and received the 2003 Distinguished Alumni Award from Illinois State University, and in 2005, was inducted into their College of Arts and Sciences Hall of Fame. She served as a member of the PKU Consensus Development Panel, National Institutes of Health. She serves as a board member at Robert Wood Johnson University Hospital in New Brunswick, New Jersey.

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To my own special loved ones—my F_1 generation: Peter, Heather, and Neal and their spouses, Julie, Chris, and Anne, but especially for my wonderful and awe-inspiring F_2 generation: Benjamin, Hannah, Jacob, Grace, and Lydia Cohen. I love you more than words can say. Thanks to my P_1 generation: Ruth and Jack Lashley for love and support through the years.

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Introduction

I wrote the first edition of this book more than 20 years ago, and the discoveries in genetics since then have been phenomenal. The new knowledge and applications of human genetics to health and to society have made it even more necessary that nurses "think genetically" in their practice and, indeed in their lives. Genetic factors can be responsible in some way for both direct and indirect disease causation; for variation that determines predisposition, susceptibility, and resistance to disease and also for response to therapeutic management. Genetic disorders can be manifested initially at any period of the life cycle. In addition, improved detection, diagnosis, and treatment have resulted in the survival into adulthood of persons who formerly would have died in childhood and who now manifest common adult problems on a background of specific genetic disease. Genetic disorders have an impact not only on the affected individual but also on his/her family, friends, community, and society. Genetic variation is important in response to medications, common foods, chemicals that comprise pollution in the environment, and food additives. Genes determine susceptibility to complex common disorders such as cancer, heart disease, diabetes mellitus, Alzheimer disease, emphysema, mental illness, and others. Genetic risk factors are also important in preventing disease in the workplace.

Nurses in virtually all practice divisions and sites can therefore expect to encounter either individuals or families who are affected by genetic disease or are contemplating genetic testing. Nurses must be able to understand the implications of human genetic variation and gene–environment interaction, as well as overt disease, as they assist clients in maintaining and promoting health, and preventing and treating disease. Each person has his/her own relative state of health, and not all persons are at similar risk for developing disease because of variation in genetic makeup, for example, in regard to cancer. Thus, optimal planning, intervention, and health teaching in the appropriate educational and cultural context for a given client or family must make use of this knowledge in order to be effective. It is with these points in mind that the third edition of *Clinical Genetics in Nursing Practice* was written. This third edition is even more of a labor of love than the prior editions, and provides current information while maintaining a reasonable size and scope.

Nurses and other health professionals generally are still not educated in genetics. This educational deficit presents a barrier for receiving optimal services when it occurs in the consumer but is even more serious when it is present in those individuals *providing* health services. As far back as 1983, there was a call for the inclusion of genetics content in the curricula of Schools of Nursing, Medicine, and other health professions. With the efforts spearheaded by the National Human Genome Research Institute, National Institutes of Health, through the National Coalition for Health Professional Education in Genetics (NCHPEG), attention has been focused anew on the need for health professional competency in genetics. Today genetics is a topic discussed widely in the lay media—therefore health professionals must be able to understand this material and use it appropriately in their practices.

Clinical Genetics in Nursing Practice is written so that it can either be read in sequence, or, once the terminology is understood, as individual chapters out of sequence, because each chapter can stand on its own. The comprehensive bibliography includes the most up-to-date literature at the time of this writing as well as classic references and special older articles and books that are either still the standard or contain special examples or material that is unique. Genetic information and clinical implications are integrated for the nurse to use in

practice as the topic is discussed. Illustrative examples from my own experience and practice in genetics, genetic counseling, and nursing are given throughout. In this book, the term "normal" is used as it is by most geneticists—to mean free from the disorder or condition in question. The term "practitioner" is used to mean the appropriately educated nurse or other health care provider. Genetic terminology does not generally use apostrophes (i.e., Down syndrome rather than Down's syndrome), and this pattern has been followed. In some cases, detailed information is provided that may be more useful as the reader becomes familiar with a topic. For example, a reader may not be interested in transcription factors until he/she encounters a client with Denys Drash syndrome. Ethical, social, and legal implications are integrated throughout the book and are highlighted where they are particularly vital.

The first part of the book discusses the broad scope of human genetic disease including the Human Genome Project and future directions; gives an introduction to basic information in genetics for those who need either an introduction or a review; discusses human variation and diversity as it pertains to health, disease, and molecular applications in forensics and society; and covers the various types of genetic disorders, gene action, and patterns of inheritance. Part II discusses major genetic disorders in three categories—cytogenetic or chromosomal disorders, inherited biochemical disorders, which are usually single-gene disorders, and congenital anomalies. The third part discusses assessing and intervening with clients and families at genetic risk. This section covers the impact of genetic disease on the family, assessment of genetic disorders, genetic counseling, genetic testing and screening including essential elements in such programs as prenatal detection and diagnosis, agents and conditions affecting the fetus, the reproductive and genetic effects of environmental agents, and treatment of genetic disorders. The taking of family histories, an important early-assessment tool, especially for nurses, is emphasized. Part IV discusses the burgeoning role of genetics in common situations, conditions, and diseases. It discusses the common complex disorders, twins, drug therapy, the immune system and infectious diseases, mental retardation, aging and Alzheimer disease, alpha-1-antitrypsin deficiency and its role in emphysema and liver disease, cancer, diabetes mellitus, mental illness, and behavior and heart disease. Part V discusses the ethical impact of genetics on society and future generations. Included in this section is information on assisted reproduction. The last section provides listings of Web sites for groups providing genetic information and services for professionals and clients. A glossary and detailed index are also included. Illustrations, tables, and photographs are liberally used to enrich the text.

In thanking all the people who helped bring this book to fruition, there are so many that to name them runs the risk of omitting someone. Therefore, I am acknowledging my long-time friend and colleague, Dr. Wendy Nehring, who was always there with an encouraging word when work bogged me down. I also want to acknowledge Dr. Ursula Springer and Ruth Chasek at Springer Publishing Company, who not only believed in this project but also are so wonderful to work with.

Nurses, depending on their education, preparation, and jobs, play a variety of roles in aiding the client and family affected by genetically determined conditions. All nurses, as both providers and as citizens, must understand the advances in genetics and their implications for health care and societal decisions. Future health care has become more and more influenced by genetic knowledge and the understanding of how genetic variation influences human responses. No health professional can practice without such knowledge.

—FELISSA ROSE LASHLEY, RN, PHD, FAAN, FACMG

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Basics of Genetics and Human Genetics

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Human Genetic Disease

Genetic disease knows no age, social, economic, racial, ethnic, or religious barriers. Although many still think of genetic disorders as primarily affecting those in infancy or childhood, genetic disorders can be manifested at any period of the life cycle. The contribution of genetics to the common and complex diseases that usually appear in the adult such as cancer, Alzheimer disease, and coronary disease has become more evident in the past few years. The advances in genetic testing that are increasingly rapidly transferred to clinical practice, and innovative genetically based treatments for some of these diseases have changed the practice of health care. Improved therapeutic modalities and earlier detection and diagnosis have resulted in patient survival into adulthood with what were formerly considered childhood disorders. For example, about one third of patients with familial dysautonomia (an autosomal recessive disorder with autonomic and sensory nervous system dysfunction) are adults, the median survival age for persons with cystic fibrosis is over 30 years, and more than half of persons with sickle cell disease are adults.

In addition to the affected individual, genetic disorders exact a toll from all members of the family, as well as on the community and society (see chapter 8). Although mortality from infectious disease and malnutrition has declined in the United States, the proportion due to disorders with a genetic component has increased, assuming a greater relative importance. Genetic disorders can occur as the result of a chromosome abnormality, mutation(s) in a single gene, mutations in more than one gene, through disturbance in the interaction of multiple genes with the environment, and the alteration of genetic material by environmental agents. Depending on the type of alteration, the type of tissue affected (somatic or germline), the internal environment, the genetic background of the individual, the external environment, and other factors, the outcome can result in no discernible change, structural or functional damage, aberration, deficit, or death. Effects may be apparent immediately or may be delayed. Outcomes can be manifested in many ways, including abnormalities in biochemistry, reproduction, growth, development, immune function, behavior, or combinations of these.

A mutant gene, an abnormal chromosome, or a teratologic agent that causes harmful changes in genetic material is as much an etiologic agent of disease as is a microorganism. Certain genetic states are definitely known to increase an individual's susceptibility and resistance to certain specific disorders, whereas others are suspected of doing so. Genes set the limits for the responses and adaptations that individuals can make as they interact with their environments. Genes never act in isolation; they interact with other genes against the individual's genetic background and internal milieu, and with agents and factors in the external environment. Conneally (2003, p. 230) expresses this by saying, "No gene is an island." For example, persons who have glucose-6-phosphate dehydrogenase (G6PD) deficiency (present in 10%–15% of Black males in the United States) usually show no effects, but they can develop hemolytic anemia when exposed to certain drugs such as sulfonamides. In another example, the child with phenylketonuria develops signs and symptoms after exposure to dietary phenylalanine. In the same manner, diseases thought of as "environmental" do not affect everyone exposed. Not all

individuals who are exposed to a certain amount of trauma develop fractures. One of the determining factors is bone density, about 85% of which is normally governed by genetic factors. An extreme example of genes' effect on bone density is that of osteogenesis imperfecta type III in which the affected person is prone to fracture development with little or no environmental contributions.

Genes are important in an individual's susceptibility, predisposition, and resistance to disease. Some examples include the following.

- persons who are Duffy negative (one of the blood groups) are resistant to malaria caused by *Plasmodium vivax;*
- persons in Papua, New Guinea, who develop tinea imbricata, a fungus infection, must inherit a susceptibility gene and must also be exposed to the fungus *Trichophyton concentricum* in order for that susceptibility to manifest itself;
- possession of HLA-B27 leads to susceptibility for development of ankylosing spondylitis;
- the association of increased levels of pepsinogen I and the development of duodenal ulcer but protection against some extrapulmonary tuberculosis;
- the association of a certain homozygous defect (Δ32) in *CCR5* (the gene that encodes a coreceptor for HIV formerly called *CKR5*) in Whites results in high resistance to HIV infection, and in its heterozygous form delays the onset of AIDS in persons already infected, as does the more-recently recognized *CCR2* V64I variation;
- heterozygosity of the human prion protein gene appears protective, as most persons developing iatrogenic Creutzfeldt-Jakob disease are homozygotes at position 129;
- West Africans persons with certain variants of *NRAMP1* (the natural-resistance-associated macrophage protein 1 gene) appear more susceptible to tuberculosis;
- persons with alpha-1-antitrypsin deficiency are susceptible to the development of emphysema and/or certain hepatic disorders; and
- boxers who possess an apolipoprotein E ε4 allele appear more susceptible to chronic traumatic encephalopathy than those who do not possess it.

The concept of genetic risk factors, as well as the environmental risk factors usually considered, has thus become important.

EXTENT AND IMPACT

Results of surveys on the extent of genetic disorders vary based on the definitions used, the time of life at which the survey is done, and the composition of the population surveyed. More data are discussed in chapter 9. Researchers have estimated the incidence of chromosome aberrations to be 0.5% to 0.6% in newborns, the frequency of single gene disorders to be 2% to 3% by 1 year of age, and the frequency of major and minor malformations to range from 4% to 7% and 10% to 12%, respectively, at the same time. It is estimated that overall about 50% of spontaneous abortions are caused by chromosome abnormalities as are 5% to 7% of stillbirths and perinatal deaths. These are discussed in chapter 5. Rimoin, Connor, Pyeritz, and Korf (2002) cite the lifetime frequency of chromosomal disorders at 3.8/1,000 livebirths; single gene disorders at 20/1,000; multifactorial disorders at 646.4/1,000; and somatic cell (cumulative) genetic disorders (including cancer) at 240/1,000, meaning that deleterious genetic changes ultimately affect disease in nearly everyone!

Historic studies are still relevant because they provide information that predates the advent of prenatal diagnosis (which allows for the option of selective termination of pregnancy, preimplantation genetic diagnosis, and embryo selection) thus distorting information about genetic disorders at birth and after because of selection. A 1981 longitudinal study by Christianson, van den Berg, Milkovich and Oeshsli (1981) of pregnant women enrolled in the Kaiser Foundation Health Plan followed offspring to 5 years of age. Their definition of "congenital anomalies" was very broad and encompassed conditions of prenatal origin including "structural defects, functional abnormalities, inborn errors of metabolism, and chromosome aberrations" that were definitely diagnosed. They classified these anomalies as severe, moderate, and trivial. "Trivial" included conditions such as supernumerary nipples, skin tags, and umbilical hernias, and are excluded from consideration. Obviously, late-appearing disorders were not included.

Twenty-seven percent of those offspring who died before 1 year of age had an anomaly, as did 59% of those who died between 1 year of age and 5 years of age. There was a fivefold increase in the cumulative incidence of congenital anomalies between 6 days of age and 5 years of age. At 5 years of age, the incidence rate of severe and moderate congenital anomalies as defined was 15%. The incidence was higher among children weighing 2,500 g or less at birth. As high as this may seem, it still does not include conditions usually developing later (e.g., hypercholesterolemia, diabetes mellitus, Huntington disease). Another study by Myrianthopoulos and Chung (1974) found an overall incidence of congenital anomalies of 15.56% in infants at l year of age. These researchers included minor anomalies. In a New Zealand study of 4,286 infants, Tuohy, Counsell and Geddis (1993) recorded the prevalence of birth defects defined as "a significant structural deviation from normal that was present at birth" in infants alive at 6 weeks of age. The prevalence was 4.3% of live births.

According to the charts of patients evaluated between July 1981 and February 1995 at a medical center covering central and eastern Kentucky, 4,212 patients were seen. As classified by Cadle, Dawson, and Hall (1996), the most common chromosomal syndromes were Down syndrome, trisomy 18, Prader-Willi syndrome, fragile X syndrome, Turner syndrome and trisomy 13. The most common single-gene defects were Marfan syndrome, Noonan syndrome, neurofibromatosis, ectodermal dysplasia and osteogenesis imperfecta. The most common teratogenic diagnoses were fetal alcohol syndrome, infant of a diabetic mother, fetal hydantoin syndrome, and maternal PKU effects. In the category of other congenital anomalies, unknown multiple congenital anomaly syndromes were followed by spina bifida, cleft lip and palate, and microcephaly. Sever, Lynberg, and Edmonds (1993) estimated that in the United States 100,000 to 150,000 babies are born each year with a major birth defect and, of these, 6,000 die during the first 28 days of life and another 2,000 die before 1 year of age. In active surveillance of malformations in newborns in Mainz, Germany from 1990 to 1998, major malformations and minor errors of morphogenesis were found to be 6.9% and 35.8% respectively. Risk factors significantly associated with malformations were: parents or siblings with malformations, parental consanguinity, more than three minor errors of morphogenesis in the proband, maternal diabetes mellitus, and using antiallergic drugs during the first trimester (Queisser-Luft, Stolz, Wiesel, Schlaefer, & Spränger, 2002). Koster, McIntire, & Leveno, (2003) examined minor malformations as part of their study, finding an incidence of 2.7%. They also detected a recurrence risk for minor malformations of about 7% in women whose index pregnancy had a mild malformation.

Genetic factors therefore play a role in both morbidity and mortality. Various studies have attempted to define more closely the extent of such involvement. Again, estimates are influenced by definition, population, type of hospital (community or medical center), and methodology. A 1978 study by Hall, Powers, McIlvaine, and Ean divided diseases into 5 categories: (1) single gene or chromosome disorders, (2) multifactorial/polygenic conditions, (3) developmental anomalies of unknown origin, (4) familial disorders, and (5) nongenetic disorders. The first four categories accounted for 53.4% of all admissions, whereas the first two categories alone accounted for 26.6% of all admissions. A 1981 Canadian study by Soltan and Craven classified diagnosis at discharge into four categories—chromosomal, single gene, multifactorial, and others, classifying such conditions as atopic sensitivity and hernias under others. In regional hospitals, patients with genetic conditions were 17.7% and 16.3% of the total in the pediatric and acute medical services, respectively. The average length of stay for pediatric patients with disorders with a genetic component was about twice that of the nongenetic, but on the medical service the length of stay was about the same for both genetic and nongenetic disorders. Older studies have had the following results: In a Canadian pediatric hospital, Scriver, Neal, Saginur, and Clow found that genetic disorders and congenital malformations accounted for 29.6% of admissions, whereas about another 2% were "probably genetic." In 1973 Day and Holmes found that 17% of pediatric inpatients and 9% of pediatric outpatients had primary diagnoses of genetic origin, and in 1970 Roberts, Chavez, and Court found that genetic conditions were involved in over 40% of hospital deaths among children. Yoon and colleagues (1997) in as well as Harris and James (1997), Hobbs, Cleves, and Simmons (2002) and

McCandless, Brunger, and Cassidy (2004) found that patients with birth defects and/or genetic disorders had longer hospital stays, greater morbidity, greater inpatient mortality, and higher expenses. In the United States overall, congenital malformations, deformations, and chromosomal abnormalities accounted for: 1–4 years of age, 10.9%; 5–9 years of age, 5.9%; and 10–14 years of age, 4.8%. These did not include most Mendelian disorders (Arias, MacDorman, Strobino, & Guyer, 2003). In Israel, Zlotogora, Leventhal, and Amitai, (2003), reported that in the period from 1996 to 1999, malformations and/or Mendelian disorders accounted for 28.3% of the total infant deaths among Jews and 43.6% of non-Jews. This did not account for pregnancy terminations. Hudome, Kirby, Senner, and Cunniff (1994) in examining neonatal deaths in a regional neonatal intensive care unit found 23.3% of the deaths were due to a genetic disorder. Review of the deaths during the five year period indicated that the contribution of genetic disorders was underrecognized. Further classification of mortality was: single primary developmental defect (42%), unrecognized malformations pattern, (29%), chromosome abnormality (18.8%), and Mendelian condition (10.1%). Cunniff, Carmack, Kirby, and Fiser (1995) examined the causes of deaths in a pediatric intensive care unit in Arkansas. They found that about 19% of deaths were in patients with heritable disorder. Stevenson and Carey (2004) found that 34.4% of mortality in a childrens hospital in Utah were due to malformations and genetic disorders while another 2.3% had such conditions but died of an acquired cause such as a patient with trisomy 21 who died of pneumonia. Classification of mortality in their study included malformations of unknown causes (65.6%), chromosome disorders (16.7%), malformations/dysplasia syndromes, (11.7%), and single gene and metabolic defects (6.1%). McCandless and colleagues (2004) examined admissions in a childrens hospital. They found that 71% of admissions had an underlying disorder known to be at least partly genetically determined. Genetically determined diseases were divided into those with a well-recognized genetically determined predisposition (51.8%) and those with clear cut genetic determinants (48.2%) and 96% of those with a chronic illness had a disorder that was in part, genetically determined. They also found that the 34% of admissions that had a clear genetic underlying disorder accounted for 50% of the total hospital charges and had a mean length of stay that was 40% longer.

An important outcome of some of these studies has been the realization that, from chart audit, relatively few patients or families received genetic counseling and this is still true to some extent today. To ensure that this shortcoming is recognized, the discharge protocol should include the following questions that address the issue: Does the disorder have a genetic component? Was the patient or family so advised? Was genetic information provided? Was genetic counseling provided? The latter two questions could be deferred if the time was not appropriate, but part of the discharge plan for that patient should include referral for genetic counseling, and the family should be followed up to ensure that this was accomplished. A summary of the genetic information and counseling provided should be recorded on the chart or record, so that others involved with the patient or family will be able to reinforce, reinterpret, or build on this information. Recognition of genetic condition can also provide the opportunity for appropriate treatment and guidance.

GENETIC DISEASE THROUGH THE LIFESPAN

Genetic alterations leading to disease are present at birth but may not be manifested clinically until a later age, or not at all. The time of manifestation depends on the following factors: (a) type and extent of the alteration, (b) exposure to external environmental agents, (c) influence of other specific genes possessed by the individual and by his/her total genetic make-up, and (d) internal environment of the individual. Characteristic times for the clinical manifestation and recognition of selected genetic disorders are shown in Table 1.1. These times do not mean that manifestations cannot appear at other times, but rather that the timespan shown is typical. For example, Huntington disease may be manifested in the older child, but this is very rare. Other disorders may be diagnosed in the newborn period or in infancy instead of at their usual later time because of participation in screening programs (e.g., Klinefelter

TABLE 1.1 Usual Stages of Manifestation of Selected Genetic Disorders

	Life cycle stage				
Disorder	Newborn	Infancy	Childhood	Adolescence	Adult
Achondroplasia	X				
Down syndrome	X				
Spina bifida	X				
Urea cycle disorders	X				
Menkes disease		X			
Tay-Sachs disease		X			
Lesch–Nyhan syndrome		X	X		
Cystic fibrosis		X	X		
Ataxia-telangiectasia			X		
Hurler disease			X		
Duchenne muscular dystrophy			X		
Homocystinuria			X		
Torsion dystonia			X	X	
Gorlin syndrome			X	X	
Acute intermittent porphyria				X	
Klinefelter syndrome				X	
Refsum disease				X	X
Wilson disease			X	X	X
Acoustic neuroma (bilateral)				X	X
Polycystic renal disease (adult)					X
Adenomatous polyposis					X
McArdle disease					X
Huntington disease					X

syndrome), or because of the systematic search for affected relatives due to the occurrence of the disorder in another family member, rather than because of the occurrence of signs or symptoms (e.g., Duchenne muscular dystrophy). Milder forms of inherited biochemical disorders are being increasingly recognized in adults.

HISTORICAL NOTES

Human genetics is an excellent example of how the interaction of clinical observation and application with basic scientific research in genetics, cytology, biochemistry, and immunology and today's bioinformatics and technological advances can result in direct major health benefits and influence the formation of health and social policies. Examples of the use of genetics in plant and animal breeding can be found in the bible and on clay tablets from as early as circa 3000 B.C. The Talmud (Jewish law clarifying the Old Testament) contains many references indicating familiarity with the familial nature of certain traits and disorders, but it reveals little or no awareness of basic principles. In the 1800s, patterns of disorders such as hemophilia and polydactyly were observed. In 1866 Mendel published his classic paper, which remained largely unappreciated until its "rediscovery" in 1900 by Correns, DeVries, and Tschermak. In the late 19th century, Galton made contributions to quantitative genetics and described use of the twin method. In the early 1900s, Garrod's concepts of the inborn errors of metabolism led eventually to Beadle and Tatum's development of the one-gene/one-enzyme theory in 1941. The 1950s, however, marked the beginning of "the golden age" of the study of human genetics. During this period, the correct chromosome