The Clinic Is My Laboratory: Life as a Clinical Geneticist

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Abstract

Clinical genetics is the application of advances in genetics and medicine to real human families. It involves diagnosis, care, and counseling concerning options available to affected individuals and their family members. Advances in medicine and genetics have led to dramatic changes in the scope and responsibilities of clinical genetics. This reflection on the last 50+ years of clinical genetics comes from personal experience, with an emphasis on the important contributions that clinical geneticists have made to the understanding of disease/disorder processes and mechanisms. The genetics clinic is a research laboratory where major advances in knowledge can and have been made.

Keywords

clinical genetics, history, medical genetics, principles, certification, genetic counseling
INTRODUCTION

The clinic is my laboratory. For clinicians, the clinic is a fascinating, ever-changing, unpredictable, evolving laboratory full of surprises—a place where your subjects, your patients, present amazing questions and results.

In a field like human genetics, where major advances have come from rigorous basic laboratory work and multidisciplinary international collaborations, clinicians sometimes feel that their contributions are less significant. There is also the misconception that clinical work is easier or less exacting than laboratory research. So let me say from the beginning that clinical research is probably even more challenging than laboratory research, because the clinician deals with that notoriously unreliable subject—the human being. Developing quantitative and reliable methodologies in clinical research has been challenging. Some of the most important observations have been descriptive, and methodologies have often been subjective—always a suspicious approach to hard-core objective scientists. Nevertheless, the advances made in the clinic and the new knowledge and methodologies that have emerged from clinical genetics during the last half century are every bit as stunning as the dazzling molecular work.

Clinical geneticists come from backgrounds in other medical specialties and subspecialties, and they often use skills learned through the old-fashioned medical model of apprenticeships. Histories, physical examinations, and laboratory tests are always the basic minimum, and surprises often show up. We continue to practice the art of medicine—the instinctive sense of what a particular individual or family needs. By carefully defining terminology, improving physical and laboratory measurement skills, adopting digital technologies, and collaborating with laboratory and social scientists, clinical geneticists have developed a whole new set of standards. Work with parent support groups, long-term follow-up, multidisciplinary clinics, and international collaborations are enabling clinical geneticists to define the variability among affected individuals as well as the natural histories of specific conditions and rare disorders.

As a clinical geneticist, I consider it my job to take all the new developments in population, basic, and molecular genetics and apply them to the human disorders, diseases, and conditions seen in the clinic. Then, working with real families, with all their wonderful peculiarities and uniqueness, I sort through which developments in genetics and medicine are relevant to that particular family in order to give them an appropriate range of reproductive and planning options.

I was honored to be asked to write about my personal experiences as they relate to the development of clinical genetics. I will do so by first revealing a bit of my personal history; then reflecting on what I see as the philosophy behind clinical genetics; and finally describing, decade by decade, the evolution of the field from the perspective of my personal involvement in it. Hold on to your seat!

EARLY LIFE

Like most people, I was influenced by my parents, my whole family, and my culture. My father was a liberal protestant minister who moved westward across the United States every five to seven years. He was a bit of a rabble rouser and an intellectual at heart, with a strong social conscience. My mother was a woman of her times, supporting her husband in every way but yearning to express herself, which she did through the care of her family, involvement in the church, and an interest in biology that she shared with her children. We were a relatively large family by today’s standards, with five children (myself, an older and younger brother, and two younger sisters) and a paternal grandmother who lived with us for as long as I can remember.

I was born in Boston just before World War II, and my earliest memories are of moving from a suburb of Boston to Manchester, New Hampshire. I remember rationing and coupons, horsegrown milk wagons, and making soap during the war. Although we had meat only once a week (for
Sunday dinner), we never wanted for love or necessities. As a minister’s child, I was expected to be on good behavior when in public (e.g., at church), to attend church and church school every week, and to “do well in all things.” Although there was that social pressure, there was also a strong sense of belonging to family and community. Wherever we lived, there were people who cared about us and accepted our liberal views. I do remember, however, at a very early age, not understanding why God was a man and likened to a father. Why not a mother? In church, under my breath, I often translated “he” to “she” in hymns and prayers.

My father had high academic expectations for us. My older brother always got A grades in school, and I was expected to produce them as well, particularly in math and science. I have always thought that having an older brother and a father who expected me to do well was a major advantage. I learned how to interact with males and how to not offend them, but how to get what I wanted! However, it was really my mother’s great wonder of the natural world, continual encouragement, and fascination with biology that stoked my curiosity about bugs, worms, animals, and plants of all types. By the time I reached high school (at which time we were living in Seattle), I knew I loved biology and was aiming to be a physician. It seemed a logical way to be engaged in science and “do good” at the same time. I became involved in student government in high school and consequently learned some political lessons. Because mine was a multiracial, inner-city school, I learned respect for individuals regardless of their background or social status.

Since my parents had lived in the Boston area and my older brother had gone to Yale, there was some pressure to go to an Ivy League college. My maternal grandmother had spent a year at Wellesley College in the late 1800s, so there was some leaning toward Wellesley, and when we visited the beautiful campus, my choice was made.

After easy As in high school, Wellesley was a scholastic challenge, particularly with the heavy load of science courses for the premed curriculum. It was also a bit of a social challenge, being shoulder to shoulder with prep school graduates from wealthy East Coast families.

Again, I learned to hold my own, this time among all females, shunning the overemphasis on “being feminine” and “catching a husband” and the pervasive intellectual one-upmanship. I was certainly sociable, but I learned to focus on my goal of getting into medical school. As a scholarship student, I worked at a variety of jobs throughout the academic years and summers. One of those jobs was working for a zoology teacher, making fruit fly media and counting tumors in fruit flies that were genetically predisposed to develop cancer. This was the beginning of my interest in genetics, in an era when the correct number of human chromosomes had not yet been defined.

MY ENGAGEMENT IN HUMAN GENETICS AND CLINICAL GENETICS

My first real interest in genetics was sparked by another zoology teacher, Miss Austin. She was a tough old maid, strict to detail, but whenever she talked about her summers doing research in Indiana, all the harshness evaporated, and she glowed with excitement about experiments demonstrating how bacteria could transfer genetic information. When I interviewed for medical school, one of my interviewers asked how many human chromosomes there were, and quoting Miss Austin, I replied, “Forty-six.” He was visibly impressed. I am not sure whether that is why I got into the University of Washington (UW) School of Medicine—but in retrospect, I rather hope so.

Because of Miss Austin, when I entered medical school, I chose medical genetics as an elective, which turned out to be an enormous piece of good fortune. Dr. Arno Motulsky, a relatively recent hire at UW, was establishing the Division of Medical Genetics, beginning the legacy of medical and human genetics at UW (113). He offered the elective to medical students for the first time that year. I was the only one who selected it, and so I had a weekly hour-long tutorial with Arno
about the new field of medical genetics. I loved it and talked incessantly about it to my fellow medical students, and the next year, 35 students chose this elective!

At that time, the National Institutes of Health was encouraging research by offering a paid extra year in medical school for medical students to do research. The UW School of Medicine was new and very research oriented, and eight of my classmates elected to take the extra year between their first two years (covering basic sciences) and second two years (covering clinical training). Arno had developed a postdoctoral fellowship training program in medical genetics at UW, and it was an exciting experience for a young medical student to rub shoulders with the fellows who later became luminaries, such as Phil Fialkow, Charlie Epstein, Fred Hecht, and Bob Murray. I married a classmate at the beginning of this extra year.

During that year, I worked on a project to see whether I could get bone marrow cells to make more fetal hemoglobin when grown under low oxygen (foreshadowing work on hemoglobin gene control). Arno’s view was that the laboratory was where real contributions to medical genetics would be made. Through Arno’s guidance and encouragement, I ended up with respectable results published in *Nature* (85). I gained a huge amount of respect for the hard work of laboratory investigators; however, my love during that year was the weekly medical genetics clinics, where real people with real problems came for the genetic information that was available in that era. Much has changed in the delivery of care in the clinic over the years, but that was the beginning for me. I am enormously indebted to Arno for his inspiration and wise advice. Our first daughter was born during our last year of medical school, and over the next six years, we had another daughter and a son. As a pediatrician, I learned an enormous amount from raising children, not to mention the fun of being a family.

The other center for medical genetics at that time was at Johns Hopkins Hospital in Baltimore, where Victor McKusick also ran a fellowship in medical genetics. So after medical school, we headed off to Baltimore, where I did an internship in medicine and pediatrics and then a fellowship in medical genetics.

The late 1960s was an exciting time in human genetics. Victor had many fellows from all over the world, most of whom were older and had already finished their specialty training. I knew that this was what I wanted to do—use my medical and genetics knowledge to help families understand their reproductive and care options. To do it well required broad knowledge of medicine, including obstetrics, pediatrics, and adult medicine, as well as broad knowledge of the field of human genetics, including evolution, population genetics, biochemistry, and cytogenetics (molecular biology had not been born yet).

At that time, Victor was sorting out the heterogeneity of connective tissue disorders, particularly various types of short stature. We became involved with the Little People of America (LPA), a support group for individuals of short stature. It is a model of what support groups can do for people with rare disorders.

The medical genetics clinic at Johns Hopkins Hospital saw families from all over Maryland and, in fact, from all over the world. I was interested in defining the natural histories of congenital anomalies, and I worked on achondroplasia (116), homocystinuria (110), diastrophic dysplasia (144), Marfan syndrome, and thrombocytopenia–absent radius (TAR) (84). Most of the patients were children, although through the Johns Hopkins research ward, we brought in many adults with disproportionate short stature for week-long multisystem evaluations. That led to better descriptions of their particular disorders.

When I realized that I did not always know the therapy for simple, common disorders, I began to understand how little I knew about general pediatric care. So near the end of my two years with Victor, I applied for a pediatric residency at Harriet Lane Clinic and was accepted. Johns Hopkins was an excellent place to train in pediatrics because the program is situated in the heart of the city,
where there was lots of pathology. House officers were given independence and responsibility. We learned from each other (Dave Valle, Jim Hanson, and I were interns together). We were on call (i.e., up all night) every other night. At night, we did all the laboratory tests ourselves so that we would understand what the results meant, and I once diagnosed tuberculosis from a bone marrow aspirate in the middle of the night. In retrospect, it seems rather primitive, but we did learn a lot.

At the end of those two years, we had another year before returning to Seattle. The genetics of growth hormone deficiency was being sorted out, and because of my work with individuals with disproportionate short stature, it seemed natural to do a year of pediatric endocrinology. I trained with Bob Blizzard, from whom I learned how to evaluate short stature, how to measure, and how to talk to parents and patients. But perhaps the most important lesson was the endocrine model of feedback systems, which has now become an identified mechanism in molecular biology.

In 1972, we returned to Seattle. My job was to develop medical genetics clinics at Seattle Children’s Hospital and throughout the Washington, Alaska, Montana, and Idaho (WAMI) region. Arno Motulsky had a large training program grant, and part of my job was to give the fellows a clinical experience. Seattle in the 1970s was a hotbed of creativity. David Smith had come to develop the field of dysmorphology, and there were many others interested in congenital anomalies, including Dave Shurtleff, Bruce Beckwith, Tom Shepard, Ron Scott, and Ron Lemire. They formed a journal club and an interdisciplinary working group in pediatrics, and all of the genetics fellows benefited. The many developments in genetics made this an exciting time. UW always had a marvelous basic science group in medical genetics, including geneticists such as Stan Gartler and George Stamatoyannopoulos. Medical geneticists worked as a broad-based interdisciplinary research team stretching from the UW School of Public Health (where Gil Omenn was dean) to molecular work (with UW becoming one of the genome centers).

In 1980, the opportunity arose to move to British Columbia (BC), Canada, to run the provincial genetics service. This was a unique chance to put genetics services on a population-wide basis, because Canada had universal health care and BC had a population-based registry of genetic disorders and birth defects. For the next nine years, I ran the University of British Columbia (UBC) Medical Genetics Clinical Unit, and we developed population-based clinical genetics services. Every clinical geneticist had a special area of interest, and the Department of Medical Genetics had several basic science arms.

In 1990, I became chair of the Department of Pediatrics, which gave me experience and insight into health care administration and education because I answered to both the dean of the UBC Faculty of Medicine and the president of the BC Children’s Hospital. I was able to continue my clinical research and oversee arthrogryposis clinics by negotiating to ensure I had a research associate. During the next ten years, I became involved in many professional organizations in pediatrics and human and medical genetics both nationally and internationally.

Once I stepped down as chair of the Department of Pediatrics, I returned to clinical research for four years before mandatory retirement (now a thing of the past). However, because I love what I do, I planned about ten years’ worth of projects related to arthrogryposis and have continued to work as hard as ever. Since my official retirement, I have also become engaged with UBC’s emeritus group, which has raised a whole new field of interest concerning aging academics (54, 58, 70).

At a time when there were very few women in medicine (much less in clinical genetics), I feel particularly privileged to have been supported and to have been able to play a role in the development of this new field. I have always felt that matriarchal and patriarchal approaches to leadership are complementary. I have also been fortunate to have fantastic staff members, collegial colleagues, and outstanding trainees. All clinical geneticists learn from their patients, and
in addition, I have learned an enormous amount from my children and grandchildren, who tell me regularly when my explanations lack clarity.

**PRINCIPLES OF CLINICAL GENETICS**

Clinical genetics is the exciting combination of cutting-edge genetics (molecular, population, and evolutionary genetics as well as epigenetics) and medicine with all of the remarkable technological and personalized medicine advances of our time. Over my 50 years of involvement, stunning discoveries have multiplied exponentially. It is therefore a challenge to identify the underlying principles of clinical genetics, because they continue to evolve!

**Real People with Real Problems**

First and foremost, of course, clinicians deal with real people with real problems. These people are always part of an extended family. Clinicians apply both new and old techniques from basic genetics, molecular genetics, and diagnostic genetics to specific families, each with its own unique situations and questions. Even if a specific mutation or chromosomal arrangement appears at first glance to be the same as those in other patients, different families have different sets of genomes, environments, and epigenomes. Just as importantly, their family dynamics, scientific understanding, and cultural background will be unique, and each individual may respond to news of a genetic problem differently.

Clinical geneticists face sadness and suffering: Each family seen in the clinic has been through emotional trauma, is facing difficult decisions, and will end up with less than ideal solutions. Remaining sensitive and open is challenging and requires training and practice. Providing the relevant information clearly and ensuring that each family member feels supported are special skills. Dealing with such significant problems might seem depressing, but providing families with new perspectives, multiple options, and reliable information for their life journey is enormously rewarding.

The available information and options change over time, as do the objectives of the individuals. Families need to keep asking questions, keep themselves informed, and be open to change.

**The Clinic Is a Laboratory**

The medical genetics clinic is a laboratory, but the tools are quite different from those used in a biomedical or technology laboratory: They are often qualitative and subjective. However, great progress has been made in developing universally accepted descriptive nomenclature (7, 8, 98, 119, 138), quantitative measurements (63, 75, 82, 99, 100), and standardized histories and physical examinations. The philosophy underlying the idea that the clinic is a laboratory includes the following.

**Much can be learned from a single abnormal person.** A great deal can be learned from studying an abnormal individual (e.g., one can define what is required to be considered “normal”). Studying the various systems involved in an affected individual with a particular disorder helps identify the pathways that affect those systems and how the abnormal gene has its effect.

**The natural history of a disorder reveals genes at work.** The natural history of a disorder is usually studied by evaluating 20–30 affected individuals throughout their lifetimes. This natural history needs to be established before undertaking therapy in order to reveal what is “normal” for
the disorder and allow appropriate surveillance for possible complications (32, 36, 41, 43). The basic genetic defect is modulated by other genes and the environment (including drugs and other therapies), and a single patient can provide new insights or unique findings.

**Many genetic disorders are present at birth or during childhood.** Infancy, childhood, and adolescence are dynamic periods in life and growth. Physiology and growth change dramatically over early life. Normal growth patterns for each age and some ethnic groups have been established for most of the external structures of the human body (75). Part of a clinical workup involves quantifying the various measurements of the body and then plotting them against normal population parameters. Similarly, established norms for developmental landmarks and behavior (136) become part of the working description of an affected individual and the disorder.

**Identifying tissue-unique gene expression is important.** It has become clear that different cell types, tissue types, and organs have unique patterns of gene expression that are dependent on sex and time in development, and that this expression may also be epigenetically controlled and transgenerationally determined. Exploring these effects is at the heart of the clinic’s genetics laboratory.

**Documentation is essential.** Full documentation [such as photos (4), measurements (75), and organ system reviews] is essential not only for diagnosis (and therefore counseling) and good clinical records, but also as part of the research study of the natural history of a specific disorder. Clinical geneticists collect information and make a presumptive diagnosis rather than developing a hypothesis and testing it through laboratory experiments. Dealing with human beings requires a different set of rules concerning privacy, conflicts of interest, ethics, and interpersonal interactions.

**Doing Three Things at Once**

Academic clinicians are usually doing three things at once while seeing a patient or a family and providing care: trying to make a specific diagnosis, considering the best possible therapy that prevents complications, and looking for the basic underlying mechanism(s) of the disorder. Doing so is part of the art of medicine and a necessary component when providing clinical genetics health care services. It is also complex, of course, and complicated further by an ever-changing health care industry.

Academic clinicians also often have three concurrent responsibilities: providing care, conducting research, and teaching. Every family provides data about the natural history of a disorder as their care is provided, a solution to a challenge that they have discovered, a parent or family support group that they have found or founded, or an alternative therapy they have tried. This is research of a descriptive type—which, when combined with information from other families with the same disorder, may help to define the extent of the signs and symptoms of the specific condition. Most clinical genetics clinics are based in tertiary health service institutions, and there are almost always trainees of many levels (including medical students, residents, fellows, and genetic counseling students) who are observing and taking part in clinics and whom academic clinicians are responsible for teaching.

**Collaborations**

Clinical research on rare genetic disorders or diseases requires collaborations—often regional, national, or even international—to assemble enough families or affected individuals to draw
conclusions. But doing so raises several questions. For example, do all individuals need to have exactly the same mutation? And what systems, symptoms, and signs need to be described? Data are messy, and drawing conclusions is often difficult—but this descriptive natural history is the kind of information that families actually want!

Collaborations often include laboratory workers or investigators in order to define the parameters and accuracy of a diagnostic test or to identify the modified genes and pathways. However, collaborations may also be interdisciplinary and involve other specialties, such as cardiologists, pulmonologists, and physical therapists. Interdisciplinary research appears to be necessary to answer the complex clinical research questions that face clinical geneticists today. Diverse skills and methodologies need to be brought together in new ways.

**Required Training, Certification, and Recertification as a Medical Specialist**

Most developed countries now require that clinical geneticists undergo specific training and certification before being allowed to provide patient care and bill for services. The complexities of modern medicine require specialty and subspecialty certified training programs, specific board-administered examinations, and certifications of individuals responsible for care and the quality of that care (e.g., being liable for mistakes and eligible to be sued within the legal system).

Part of a clinical geneticist’s training is to learn about the broad range of disorders and heterogeneity that exist, learn the proper terminology for structural anomalies, learn to measure and describe accurately deviations from normal, and learn to appreciate the psychosocial dimensions of family dynamics in the face of genetic and nongenetic anomalies or disorders. The requirements, guidelines, and ethical considerations are complex and constantly changing as new knowledge influences clinical practice.

**International Networks**

Genetic discoveries belong to the world, and outstanding research discoveries come from every corner of the globe. The international genetics community communicates effortlessly in this new world of the Internet and digital data. One of the joys of being a clinical geneticist is having colleagues and collaborations all over the world. Affected individuals pop up everywhere, and describing and publishing these cases often leads to unexpected breakthroughs.

**Genetic Counselors**

With the growth of genetic counseling as a master’s degree and PhD specialty, research concerning counseling methodologies is emerging. Genetic counseling has always been a complex area, and research in this area has expanded to cover cultural and ethnic differences, intra- and interfamilial diversity, and the differing psychodynamic patterns within families.

Providing care is often a team effort. One always starts with a family history, and by asking the family what their questions are and ensuring that each family member has a chance to respond. Clinicians also draw from their own broad experience in order to raise and answer questions that the family may not know to ask.

**Whole-Family Counseling**

Although individuals may be referred or refer themselves to the clinic, clinical geneticists are always dealing with their whole family.
**Family history.** Clinical genetics work always starts with taking a family history. In fact, it is preferable to start taking the family history before the first meeting, because families often have to consult with a grandmother or the family historian to find out about miscarriages and infant deaths or exactly what Uncle Henry died of. This history then begins to reveal some of the natural history of the disorder.

A good family history is part of good medicine and good research. It may take several hours to complete, but it then becomes the basis for diagnosis, decision making, and even therapy. However, it is also confidential and must be respected as such, because not every member of the family has given permission for their personal information to be shared. In addition, family legends may not always be factually correct and should be treated with caution. Clinicians must remain aware of this uncertainty.

**Homework.** Clinical geneticists must do their homework [through library and online reviews and research, including in PubMed, Online Mendelian Inheritance of Man (OMIM), and GeneReviews] about the condition in question. Then, during the clinic visit, they must elicit specific questions from those present (the questions of a sibling are often different from those of the parents or the affected individual) and discuss the many issues and possibilities in a nonjudgmental fashion. It is an unspoken rule that clinical geneticists help the people in the clinic make the best possible decision for them and their family but do not give specific advice or judge the decisions. Family members, couples, parents, and children may come to terms with new information at very different rates.

What every affected individual and their family want to know (whether they can verbalize it or not) is what is going to happen over time—the natural history of the disorder if it is left untreated. Then, of course, they want to know what has been learned from other families about treatment and prevention.

**Parent support groups.** Because affected individuals and families share common concerns, it is natural for them to bond together in parent support groups (69). It can be an enormous help and comfort for parents to meet another affected individual, to see that an adult with the disorder functions well, and to discover a way to deal with a nagging problem.

On the Internet, families can almost always find a helpful group or another affected individual. Organizations such as the National Organization for Rare Disorders and the BioPontis Alliance for Rare Diseases, rare disease groups (30), Facebook, and genetics clinics are also resources for connecting people. Support groups encourage research about natural history, treatments, and basic mechanisms; organize registries; publish newsletters; have social gatherings; and raise money for treatment and research. They provide information to their members, often publishing pamphlets. However, such groups need reliable, informed clinical genetics advisors to avoid promoting unproven therapies, charlatans, and opportunists.

**Listening to families.** Parents and affected individuals often become experts on the disorder in question and so almost always know more about it than most doctors and researchers. Thus, it pays to listen to their ideas, questions, and observations and to make distinctions between what is known and what is speculation.

**Professionalism**  
Clinical geneticists are legally, ethically, and morally responsible for the health care and information they provide to a family. Standards of training, examining, and certifying competent
professionals have been developed in most modern health care systems. Clinical geneticists are expected to continue their education, keep up with new developments, and know the accepted guidelines for care of specific disorders. Not just anyone can provide this type of care, and most new diagnostic tests require expert interpretation.

Health care systems are constantly changing and vary significantly by country or jurisdiction. Clinical genetics is an essential part of modern health care, but because it is so specialized, it is usually provided in tertiary care centers by professionals who have undergone appropriate training.

Databases

Digital technology has had a major impact on access to information regarding genes, mutations, genetic disorders, control mechanisms, therapies, and epigenetics. To practice clinical genetics today, one must keep up with the ever-changing landscape of information. There are many journals dedicated to genetic information that can be accessed worldwide and often are published only online. Clinical genetics services can be provided almost anywhere in the world through outreach clinics and online consultations even though practitioners are based mainly in tertiary care centers.

It is impossible for an individual to keep up with everything in the rapidly expanding field of clinical genetics, and hence most clinical geneticists are part of groups in which different individuals acquire different expertise and ongoing clinical research interests. The ability of even the most seasoned clinical geneticists to make clinical diagnoses is being overwhelmed by the wealth and depth of new knowledge. Even the gestalt skill of recognizing the facial features of a particular syndrome is being usurped by facial recognition programs, which give the probability that their suggestion is correct. Fortunately, there are new tools and electronic databases that help to make the expanding knowledge base accessible.

DECades of change

The 1960s

The 1960s was when it began! Clinical genetics could not exist before the study of human genetics. Of course there had been Mendel and Darwin, Galton and Bateson, Garrod and Avery, and visionaries such as Waddington, Morgan, and Fisher, but it was not until the correct number of human chromosomes was determined that it became feasible to apply genetics to human conditions (115). In the 1960s, the discovery that syndromes that had already been described clinically were associated with chromosomal abnormalities created a reason to consult with clinical geneticists and to learn in more detail about the potential medical complications and the consequences for families. From a personal perspective, I feel that I was present as the field of clinical genetics began to evolve.

In the United States, Kurt Hirschhorn, Victor McKusick, and Arno Motulsky had the vision to set up medical genetics training programs for post-medical-doctoral fellows, while Charles Scriver and Clarke Fraser did so at McGill University in Canada. Many places in the United Kingdom and Europe had PhD programs in human genetics. The field had fallen into some disfavor because of the eugenics movement of the early twentieth century, but as the medical benefits became obvious, families increasingly wanted information about genetics. Interestingly, the clinical genetics training programs in the United States began in departments of internal medicine, even though the newly recognized metabolic disorders and growing list of chromosomal disorders presented most often in childhood. Technological advancements in those areas were improving the diagnostic abilities of pediatricians.
As described above, I fell in love with medical genetics in medical school in the early 1960s, when I was pursuing a master’s degree with Arno Motulsky. Although Arno and UW were strong on laboratory research, I was most excited by the clinic—the questions that real people had about their real problems. The questions of the families in the 1960s penetrated the vast unknowns of newly described conditions, and there was a great need for clinical research to help answer those questions. It is fair to say that much of the 1960s was about describing new conditions in clinical terms (i.e., the clinical phenotypes).

Also as mentioned above, after finishing medical school, I went to Baltimore to do an internship in medicine and pediatrics and then a fellowship in medical genetics with Victor McKusick. Much has been written about Victor—he was a consummate clinician, so that every round, every clinic, every consultation, every journal club, and even new entries in MIM (later OMIM) were multidimensional experiences. Along with taking a medical history, a family history, a physical exam, laboratory work, and a photograph, patients (and their families) were provided with genetic counseling and other medical advice; they were often part of a research project and not infrequently provided clues about the basic mechanisms of rare disorders. Victor was an exuberant writer, so his fellows were instructed to do a literature review and write up almost every case. The camaraderie and energy among the fellows was a model for a lifetime of work. The challenge of discovering something that Victor did not already know was an inspiring task.

Each fellow published many papers under Victor’s tutelage. For one clinic, I was assigned a family from the eastern shore of Maryland who had been diagnosed with atypical Fanconi anemia but, after careful observation, turned out to actually have TAR. Reviewing atypical cases of Fanconi anemia seen at Johns Hopkins and published in the literature enabled me to summarize 40 cases and define this newly identified disorder, its unique clinical features, and its natural history (84). Writing it all up was another learning experience. When the 11th draft of the manuscript was returned to me with many, many red marks, I asked Victor (or, actually, Dr. McKusick—we never dared to call him Victor) whether it was always this hard to write an article, and he replied, “Actually, I think it gets harder!”

One of the things that was intriguing about TAR was that the disorder had structural anomalies (missing radius with the thumb present) and an ongoing problem of low platelets, which at the time we thought involved different processes (125). The paper describing TAR was published in 1969 (84), but it would take until 2007 to understand the unusual basis of its autosomal recessive recurrence risk with biallelic involvement (in which one parent usually contributes a deletion of chromosome 1, and the other parent usually contributes either a single-gene mutation or a common polymorphism on an undeleted chromosome) and to realize that a single gene can function differentially in multiple pathways (104).

In the early 1960s, Victor had established a liaison with the Jackson Laboratory in Bar Harbor, Maine, which was the home of multiple mouse strains and many types of mammalian research. Together, they started a two-week summer course on mammalian and human genetics—a broad review course with an emphasis on the cutting edge. Victor’s fellows were expected to attend. The faculty was “the best and the latest” from around the world. The atmosphere was relaxed, and there were many opportunities to informally converse with the emerging leaders in human, medical, and clinical genetics. Victor’s fellows put on a demonstration model clinic so that nonclinical attendees could see some of the challenges of clinical genetics. I later had the pleasure of becoming a faculty member for these courses and teaching them for over 20 years, providing an emphasis on the clinical challenges of medical genetics.

While I was a fellow, Victor convinced the March of Dimes to take on birth defects (because they had been so successful at conquering polio), and thus the March of Dimes birth defects conferences began. Luminaries from around the world were invited and came to Johns Hopkins
to explore human malformations and their mechanisms. I first met Bob Gorlin, Dave Smith, Dave Rimoin, John Opitz, Jürgen Spranger, and many others at those meetings. There were few women in medicine and medical genetics in those days. Many original concepts were born and new disorders described during those meetings. The atmosphere was open, informal, lively, and congenial. We fellows presented individuals with rare findings for discussion. These were wide-ranging conversations based on personal experiences as well as literature from the past and from foreign countries. One of Victor’s enduring legacies was to publish the proceedings of these conferences, and we fellows acted as editors (a valuable experience in discrimination, grammar, and meeting deadlines). I published the first case of homozygous achondroplasia in these proceedings (77).

Victor had an abiding interest in connective tissue disorders, one subgroup of which were the chondrodysplasias. Dave Rimoin had been a fellow with Victor for two years prior to my arrival and had worked hard on distinguishing various types of growth hormone deficiency and disproportionate short stature. Peter Beighton and I inherited Dave’s office, and we both became involved in the workup and evaluation of individuals with chondrodysplasias and connective tissue disorders. That commitment meant attending the regional and national meetings of the LPA, a support group for individuals less than 4 feet 10 inches tall. I learned a lot from that group and its members. I loved being a medical resource, and after spending three or four days with groups of affected individuals, I learned to distinguish the fine points and natural histories of various disorders. More importantly, as a professional, I learned the key questions for families and affected individuals: What will happen over time? Can a complication be prevented? Why did this happen to me?

This was the inspiration for studying the natural histories of rare disorders and working with support groups. Working with support groups is clinical research at an elevated level. I watched families and affected individuals help each other, provide solutions that they had discovered to various problems, warn each other about spoiling children who would need to be tough as adults, and band together to support research and disability rights and raise public awareness. Many support groups have subsequently developed for rare diseases, but I think the LPA was the first that empowered affected individuals to help themselves. The local and national meetings provided opportunities for developing leadership. Many important papers came from that period as the clinical features (proportions, measurements, X-ray findings, etc.) and natural histories of disorders such as diastrophic dysplasia (144), achondroplasia (116), and pseudoachondroplasia (76) were first defined.

The 1970s

The 1970s were a heyday for cytogenetics and metabolic disorders. Newborn screening was introduced, and banding revolutionized cytogenetics by identifying deletions, duplications, and translocations. Molecular genetics was in its infancy, with recombinant, cloning, and sequencing technologies being developed. Introns and isoforms were just being recognized. As I moved from Baltimore back to Seattle in order to develop a full-service medical genetics clinical program, outreach clinics were soon to be introduced in the Pacific Northwest. By mutual agreement among the states’ health care providers and trainers, the UW School of Medicine would train physicians for the WAMI area, which meant establishing clinical teaching services across these states. Prenatal diagnosis by amniocentesis was becoming available for cases of advanced maternal age and at-risk families (5, 109). Advances in ultrasound technologies enabled the diagnosis of structural anomalies as early as 12 weeks. We even used X-rays to diagnose TAR early in the second trimester (118) and measurements of the humerus to diagnose achondroplasia by 16 weeks (80).
By the mid-1970s, we had developed a consultation service at Seattle Children’s Hospital, prenatal diagnostic services together with obstetrics at the university hospital, and outreach clinics across the WAMI area. The original medical genetics clinic at the university hospital gradually moved toward adult diseases, such as cancer and heart disease, and we became the model of clinical genetics services for a geographic area.

Because specialty physicians came for medical genetics training, our group of fellows in training at UW was broadly based. I was responsible for their clinical training and set them to multidisciplinary projects, such as an organ system evaluation of Turner syndrome, leading to a landmark publication on the natural history of Turner syndrome (96), the creation of a Turner syndrome clinic, and long-term study by Virginia Sybert.

During those early days, I became interested in arthrogryposis because of a pair of monozygotic twins who came for genetic counseling. One twin had multiple congenital contractures, and one did not; the latter was going to marry and wanted to know his risk of having an affected child. Both men were bright and highly functional. Literature searches were hard in those days: One went to the library and pulled big volumes (Index Medicus) off the shelf, looked through the alphabetically arranged subjects, and then went to the dusty stacks, where bound volumes of old journals were housed, in order to find the article. No photocopying was available back then. We would later come to recognize that amyoplasia—the most frequent type of arthrogryposis, which is characterized by multiple congenital contractures—is often discordant among monozygotic twins.

At the time, not much had been written on arthrogryposis—mainly lethal familial cases, and nothing like these two young men. So I hired some summer students, who pulled 1,800 cases cataloged as arthrogryposis from among the Seattle Children’s Hospital records and those at the Shriners Hospitals for Children in Spokane and Portland (31, 44, 67). I have worked ever since to sort out the heterogeneity among such patients. With the help of Lynn Staheli, we established a multidisciplinary clinic that has become a model of standardized care for arthrogryposis and still runs at Seattle Children’s Hospital. We also wrote a book for families and therapists, which is now available online (139). We defined many specific clinical entities and their natural histories, and more recently have contributed to finding more than 330 genes that, when mutated, can lead to decreased fetal movement and subsequently multiple congenital contractures (83). Similar clinics and clinical research on rare diseases were being established at many centers in the 1970s, and individual clinical geneticists became experts on particular disorders (e.g., the contributions of Vic Ricardi and Jan Friedman to neurofibromatosis).

During this period, a new type of clinical genetics specialist was born: the genetic counselor. Sarah Lawrence College, under the leadership of Joan Marks, developed a master's degree program in genetic counseling, and I had the pleasure of being on the advisory board. I was impressed with the seriousness and breadth of the curriculum and the quality of the trainees, and we began to hire the graduates to help with the ever-increasing workload. They were skilled in obtaining family histories, gathering relevant literature, and communicating with families. However, the diagnostic and medical care role still belonged to, and was the responsibility of, the clinical genetics physicians. These well-trained counselors were an enormous boon in a busy clinic, and genetic counselors have since developed specialized skills for specialty clinics, such as those for cancer, cystic fibrosis, and cardiovascular disease.

Our medical genetics group in Seattle played an active role in the explosion of new knowledge in cytogenetics (11, 120) and metabolic diseases. We described numerous new syndromes, such as Pallister-Hall syndrome (15, 86). Working with our local LPA group, we diagnosed many new types of chondrodysplasias and defined the natural histories of others (32, 36, 41, 43, 137). Our prenatal diagnosis group increased in expertise and diagnosed many new clinical entities in utero (80, 109, 118).
One of the remarkable things about Seattle in the 1970s was the diversity of individuals whose interests aligned with those of geneticists and who were able to contribute their skills to clinical and research work. Bruce Beckwith, Dave Shurtleff, Ron Lemire, Ron Scott, Tom Shepard, and Dave Smith were all active in pediatrics at Seattle Children’s Hospital. Dave Smith had his own fellows, and they were trained in dysmorphology—a unique combination of descriptive skills, embryology, teratology, and clinical diagnostic acumen. Shortly after I arrived in Seattle, Dave Smith and Ken Jones described fetal alcohol syndrome. It was a time when rubella and thalidomide embryopathies had exposed the vulnerability of the embryo/fetus. Our clinic at Seattle Children’s Hospital saw several cases of warfarin embryopathy, and we went on to describe the various features that resulted from exposure at different times during gestation (88, 121, 122).

As the clinical genetics services expanded, we began to ask how common genetic disorders were among admissions to children’s hospitals (89) and to specialty services such as neurology clinics (10) and neonatal intensive care units (106). The answer was that they were quite common overall, even though specific disorders were rare. Over the years, this has become more obvious. There are now clinical geneticists in every specialty at both adult and children’s hospitals. All specialties are now taking up the principles of clinical genetics, and clinical geneticists are finding new challenges in interpreting the findings of the new technologies (38).

In the late 1970s, there was a growing need to certify individuals with appropriate training to provide genetics services in order to be able to bill appropriately for their expertise and for the interpretation of increasingly complex laboratory tests. In 1979, Dave Rimoin led the establishment of the American Board of Medical Genetics, now called the American Board of Medical Genetics and Genomics, and I served as its first vice president. Following the example of other medical specialties, we established an examination procedure for clinicians, laboratory directors, and counselors. Much later, in 1991, with the blessing of the American Medical Association, the American College of Medical Genetics (now the American College of Medical Genetics and Genomics; the Canadians had already established their Canadian College of Medical Geneticists, in 1976) was established by individuals who had passed the examination. Diplomats of the college have subsequently established standards of care, standards of training, laboratory standards, continuing education requirements, working papers on relevant issues (such as ethical controversies), various therapies, and screening procedures. Most developed countries have followed this model of medical recognition for clinical geneticists, and many clinical geneticists have dedicated countless hours to the ongoing process of training, examining, providing continuing education, and updating standards of care.

As more clinical geneticists became involved in describing congenital anomalies, it became clear that there was a need for common terminology and nomenclature (138), and a landmark meeting was held in Seattle to address this issue. As a relatively young clinician, I was honored to be a part of that process, and I marveled at the collegial give and take. The results have stood the test of time and are still used today. Jürgen Spranger’s illustration from 1982 (Figure 1) still nicely clarifies the differences between malformations, disruptions, deformations, and dysplasias; over the years, the different mechanisms of these processes have become clearer.

The David W. Smith Workshops on Malformations and Morphogenesis were also established in the late 1970s. They have served as a nidus illuminating the underlying mechanisms of congenital anomalies for almost 40 years. Initially, Roger Stevenson, John Graham, Ken Jones, Jim Hanson, and I ran the meetings, but gradually we have passed them on to younger generations (28). Subsequently, similar meetings examining the mechanisms involved in congenital anomalies have been established in many regions around the world.

As the 1970s drew to a close, hints of the importance of nontraditional mechanisms, such as mosaicism (11, 76, 120), in producing congenital anomalies began to arise. The discordance seen in
monozygotic twins (57, 108) distressed those who used single-gene differences to explain genetic differences between monozygotic and dizygotic twins. We began to develop growth charts for specific disorders because accurate physical measurements of affected individuals became important for diagnoses (82, 99, 100, 137).

With the growth of clinical genetics, in 1977, John Opitz established the *American Journal of Medical Genetics*, which focused on clinical reports. Several other clinically oriented journals have launched since then, but John made a point of encouraging reports from developing countries.

For me, the 1970s ended with a sabbatical year in Seattle spent working on arthrogryposis. I made real progress at separating various types of arthrogryposis on a clinical level thanks to my research associate (Susan Reed) and the multidiscipline clinic. I found that one-third had only limbs involved, one-third had limbs plus other body areas involved, and one-third were lethal or led to severe developmental delay (31). Of the living individuals affected with arthrogryposis, one-third also had amyoplasia—a newly recognized disorder identified from clinical observation (91, 93, 127). I distinguished different entities on a clinical basis (90, 92, 94, 95), Lynn Staheli devised new orthopedic therapies for specific deformities, and the rehabilitation group discovered the importance of stretching and splinting—all now mainstays of care for individuals with arthrogryposis.

During the sabbatical year, I also took a course on medical anthropology and discovered the frequency of birth defects among anthropologic artifacts and legends (29). I gained respect for
the aboriginal view that individuals with birth defects had special powers. They often became shamans or seers in their cultures, whereas in our scientific culture, birth defects provide insights into normal development.

The 1980s

In the early 1980s, I began to consider moving. Clinical geneticists were being recognized as important for every tertiary care center. Molecular genetics was beginning to emerge. Genetic linkage had become useful in pinpointing the locations of genes involved in diseases, and genes were being sought for specific monogenic diseases. Because there were still very few clinically trained individuals, job opportunities were plentiful. I was intrigued with Canada’s universal health care system and had become disappointed with the US insurance system, which systematically (in small print on the bottom of the policy) denied care when a child was born with birth defects. Family after family that I saw were being financially strained or going bankrupt because of this policy.

I chose to move to Vancouver because it was possible to estimate the frequency of genetic disorders within the province, and a program to provide full medical genetics services throughout BC was being developed. A birth defects registry was already well established in BC, with multiple sources of data entries, including birth certificates, hospitalizations, and clinics. It seemed possible to develop a model of care in this new specialty within the province. There was even a separate Department of Medical Genetics at UBC, and Pat Baird was a dynamic leader.

Shortly after I arrived in 1981, the clinical genetics unit moved to a newly built, modern BC Children’s Hospital and BC Women’s Hospital and Health Centre. Our offices were next to the prenatal diagnosis unit. We established a full-service unit, including ward consultations, outreach clinics, and diverse laboratories (embryo and fetal pathology, diagnostic and counseling clinics, etc.) (5). Each of the medical genetics physicians had a special interest and became a resource for the rest of the group on that topic (including intersex conditions, dermatology, metabolic disease, dwarfism, neurologic disorders, and arthrogryposis). Each genetic counselor provided counseling services to a pediatric specialty clinic (cleft palate, cardiac, cystic fibrosis, cancer, deafness, etc.) in which they became expert and able to recognize unusual patients who needed to be referred for a full medical genetics consultation. We had regular case conferences to discuss unusual findings or laboratory results and journal clubs to assure that we kept up with the latest developments. We established a filing system of records by diagnosis (this was before computers) and tracked statistics for numbers and types of families seen. We tracked the amount of time required to take a family history and prepare for the suggested diagnoses of the upcoming family, clinical and postclinical time spent to get laboratory results, and time spent to write family and referring-doctor letters, as well as whether a return visit was necessary. By doing regular outreach clinics around the province, we came to know the referring physicians, began providing educational sessions to the physicians and nurses in the area, and saved travel time and loss of income for the affected families. This model has been duplicated in many other places.

We also established the number of clinical genetics physicians needed as a ratio to the population size. As the Canadian College of Medical Geneticists matured into a training and certifying body, these data were useful for planning and justifying the training of additional clinical geneticists for each province.

During the 1980s, major progress was made on distinguishing various types of arthrogryposis (16, 24, 33, 35, 37, 126). Our group (as did many others) published many clinical descriptions of new syndromes and conditions. We also published updates on how to prevent complications of described conditions (2, 40, 123, 128, 140). New teratogens [including vitamin A (34), valproic acid (14), and malathion (39)] were recognized. Under the newly established guidelines of the
Canadian College of Medical Geneticists, the American Board of Medical Genetics, and the American College of Medical Genetics, more training programs were established both for medical geneticists and for genetic counselors.

The possibility that folic acid supplementation could prevent neural tube defects also arose in the 1980s. Canada became part of an international trial to examine this question, and the clinical genetics and prenatal diagnostic services of BC were included (114). This allowed us to accumulate a great deal of information and to recognize subgroups of neural tube defects with increased risk (79, 103, 114, 130, 131). Based on mouse work done in BC that showed multiple neural tube closure sites, we published our BC data on human families in which fetuses exhibited vulnerabilities at certain developmental sites (143). The data led to fortification of grains with folic acid in Canada and the United States, which cut the rate of neural tube defects by at least half in much of North America.

Human and medical genetics was becoming a mainstream specialty of public health interest (38). Interest in the frequency of genetic disorders and birth defects as a cost to the health care system led to the awareness that birth defects were the leading cause of infant mortality. Newborn screening programs began to be used to detect and treat metabolic diseases early enough to prevent debilitating complications.

Having been part of several studies to establish the “normal” growth curves for various chondrodysplasias, we had a growing awareness of the value of comparative measurements (75) of all body areas (particularly the craniofacies) for making diagnoses, learning about natural histories, and evaluating various therapies. Two hardworking clinical genetics fellows (Ursula Frosters and Judith Allanson) and I began to search for normal measurements of every body part. This work eventually culminated in the Handboook of Physical Measurements, which is now a required text for every clinical genetics unit. The original publication included tables for abnormal conditions, and the number of conditions has increased with subsequent editions (e.g., 75). However, the deficiencies of the handbook are still that most data (other than height, weight, and head circumference) are cross sectional rather than longitudinal and that most data are from individuals of Caucasian European ancestry. Data from other ethnic groups are desperately needed.

The concept of quantitative measurements underlies many advances in clinical genetics. Originally, we believed that experienced practitioners would be able to use their intuition to make correct diagnoses. As laboratory tests improved and pooling of data between centers expanded, the desire to be more objective increased. More quantitative measurements, routine standardized photographs (4), and defined nomenclature (98) all helped. For instance, ears that are truly low set in the skull are extremely rare; when they appear to be low set, it is usually because of a short neck, extra tissue at the neck, or a tall cranium.

Because we were trying to distinguish subtypes among our families with Noonan syndrome, when UBC and the BC clinical genetics unit hosted the David W. Smith meetings, we asked attendees to bring pictures of their patients with clinically diagnosed Noonan syndrome (no genes were yet known in the 1980s). We thought that there were four subtypes, and lo and behold, when we reviewed the 100 or so photos, we established that there were indeed four—but they were age related, occurring in the same individual at different ages and in multiple members of the same family (3, 147). This meant that we needed to look for age-related changes in the physical features of every syndrome and condition—an important insight that made longitudinal quantitative measurements in humans even more important.

Because of the wonderful cooperation in Canada among all the medical genetics units and departments, we were part of important prenatal diagnosis studies to assess the safety of amniocentesis (12) and, later, of mid-trimester amniocentesis versus early amniocentesis. The Medical Research Council of Canada (which later became the Canadian Institutes of Health Research) funded
these important studies, the results of which then became part of standard prenatal diagnosis and care.

During the 1980s, cloning techniques led to the availability of synthetic growth hormone. I served on the editorial board of *Growth, Genetics, and Hormones*, a free journal published by Genetec for goodwill and to increase awareness about hormones in general and growth hormone in particular. It was a useful journal for publishing information about chondrodysplasias, intrauterine growth restriction, and the use of growth hormone for conditions other than growth hormone deficiency. It turned out that growth hormone does not ultimately increase stature in individuals affected by achondroplasia, intrauterine growth restriction, or Turner syndrome; at the time, however, it was important to explore this line of therapy. Because of my interest in the natural history of Turner syndrome, I was asked to be on the advisory board of a Canadian trial of growth hormone to treat girls with Turner syndrome. This carefully matched study found that, after several years of expensive treatment, treated girls gained less than an inch of height (129). An interesting and still unanswered question that came out of the study was whether the origin of the remaining X chromosome in these girls (paternal versus maternal) made a difference.

During the 1980s, I began teaching at the Jackson Laboratory mammalian genetics summer course in Bar Harbor. Many other short courses on human genetics subsequently evolved in Europe, South America, and Asia. These courses helped the nongeneticists working on genetic problems and the new trainees from the Americas, Europe, and many other regions to learn about the latest developments and meet evolving experts.

I was due for a sabbatical in 1988–1989 and had the pleasure of going to the Genetics Laboratory in the Department of Biochemistry at the University of Oxford. They were strong in basic genetics, clinical genetics, and mouse genetics. John Edwards made sure I met luminaries such as Mary Lyon, Bruce Cattanach, and Tony Searle at Harwell. Intrigued with genomic imprinting, we produced a human homologous imprinting map based on an understanding of imprinted regions in the mouse that predicted many of the subsequently discovered imprinted areas of the human genome (132, 133). I attended the clinical conferences when Dick Lindenbaum, John Edwards, and laboratory fellows discussed new findings (22) and saw many cases of arthrogryposis from the United Kingdom and Europe. Because I was a university fellow at Green College, I had the pleasure of meeting Dian Donnai, Kay Davies, David Weatherall, John Walton, and Cecil Green. Perhaps the most important part of the sabbatical was visiting many medical and human genetics departments in the United Kingdom and attending many different types of European meetings, including those of the European Society of Human Genetics, the Royal Society, and the Clinical Genetics Society. I was impressed with the depth of clinical knowledge and research abroad.

During the sabbatical, I wrote several landmark papers: two on human imprinting (45, 46) and one on mosaicism (42). The latter predicted that mosaicism is responsible for patchy disorders and that mutation survival would be dependent on tissue-, sex-, and time-in-development-specific gene expression (25).

As the decade closed, there were many hints of other, nontraditional genetic mechanisms that would be clarified further as more technologies developed—such as the critical genomic area that is always paternally inherited in Prader-Willi syndrome but always maternally inherited in Angelman syndrome. Other human syndromes had suggested similar differential parental contributions, and such contributions were also being found in mice.

### The 1990s

At the beginning of the 1990s, as molecular genetics came into its own and the sequencing of the whole human genome became a goal, I became chair of the Department of Pediatrics at UBC. I
had never thought much about becoming a chair, since I enjoyed clinical work and clinical research so much. Many clinical genetics units are within pediatric departments, but even though UBC had a separate Department of Medical Genetics, the Department of Pediatrics was facing many important challenges at that time, and I was a trained pediatrician prepared to climb the academic ladder.

Over the next ten years, I learned an enormous amount about universities, hospital administrations, and health care delivery. The chair of a clinical department within a medical school that is part of a university answers both to the university (for teaching and research) and to the hospital (for patient care)—in other words, one has two bosses with quite different agendas and expectations. I daresay I learned to adapt my approach depending on whom I was talking to and what the issue was.

As in clinical genetics, there were human resource issues in pediatrics. The hospital administration thought that we had more than enough pediatric subspecialists for the whole province. We needed data to show them otherwise, and we set about performing an activity/time study for our department members and collecting information from other provinces. We learned that most subspecialists in Vancouver worked more than 80 hours a week and that, based on the ratios in other provinces, we had about half the number of subspecialists we needed for the population of BC. This was then the topic of that year’s Canadian Paediatric Society’s Ross Conference, the data from which have been used around the world to set standards for the number of pediatric subspecialties required for a given population base (51, 53, 111).

I had not realized that chairs are asked to be on so many committees and working groups—professional, provincial, national, and international. As a consequence, they are able to meet many amazing people, see many varied models, and end up with a network of contacts on many issues and topics. Chairs are often accused of never being home, but travel goes with the territory.

I learned to write summaries of meetings, produce yearly reports, and track finances carefully. I worked in both pediatrics and human and medical genetics professional organizations in the 1990s, both nationally and internationally (48), and it was possible to bring ideas and processes from one group to share with the other. One of the important aspects of these medical professional groups is that they help their members stay current on the latest advancements in science and technology, which then leads to changes in clinical practice. Professionals are very conscious of their responsibility to assure good medical health care, and they continually explore and debate new findings and their implications for changing or developing guidelines. Relevant to clinical genetics, I was involved with the American Academy of Pediatrics as it developed superb guidelines for the care of achondroplasia (20, 87), Turner syndrome (21), and trisomy 21 (18); for the prevention of neural tube defects (17); and for prenatal diagnosis (19). These guidelines are revised and updated every few years. Relevant to pediatrics, medical genetics professional groups have developed guidelines for newborn screening (1), DNA banking (27, 81), genetic diagnosis of minors, and many other topics.

I was part of the efforts to use consistent terminology in clinical genetics (119, 138) with regard to the chondrodysplasias (with regular updating conferences and publications) (7, 8) and, lately, with regard to all congenital anomalies (98). Additional parent support groups emerged (69). Clinical geneticists worked with them in many capacities and, in turn, learned much from the families about the various conditions.

While I was chair of the UBC Department of Pediatrics, I had the good fortune to have a research associate, and so I was able to continue my clinical genetics research related to arthrogryposis, including defining various subtypes (23, 26, 47, 52, 61, 64–66, 68, 71, 74, 97, 101, 107, 134). I also focused on parent-of-origin effects (46, 59), anomalies associated with twinning (49, 50, 60), and nontraditional forms of inheritance [such as microchimerism (56), imprinting (45),
and developmental origins of health and disease (DOHaD) (59)]. Databases were growing, and
e-mail was beginning to be used routinely, making collaborations and clinical consultation easier.
Genes whose mutations caused various disorders were being identified (9, 72, 73), and the Human
Genome Project had begun.

I was asked to write many chapters for the growing number of textbooks in pediatrics and
medical genetics. Human Malformations and Related Anomalies (141) and Arthrogryposis: A Text Atlas
(139) (an overview book for families on various aspects of arthrogryposis) were first published in
the 1990s. Both were award-winning books.

The UBC Department of Medical Genetics was growing, with many new faces and clever
ideas. Michael Smith, from UBC, won the Nobel Prize in 1993. Many visitors came to see how
our clinical services worked, and clinical geneticists from around the world came to Vancouver
for sabbaticals, resulting in useful observations such as reviews of the aspects of various syndromes
(135) and a defined approach to standardized behavioral workups (136).

Technical advances in genomic work led to the discovery of an increasing number of genes
related to an increasing number of disorders. In the meantime, we clinicians continued to describe
new clinical features of rare disorders and to define new syndromes. However, even as the number
of known disease-causing genes increased, the clinical features of many disorders were being poorly
reported in the literature. The role of clinicians in identifying specific diagnoses was less valued
by those who discovered the genes, and the lack of good clinical descriptions made identifying
affected individuals even more difficult. I wrote an editorial in Nature Genetics pleading for adequate
descriptions of clinical features in publications so that families could benefit from the whirlwind
of discoveries (55), but I am not convinced there has been much improvement (6)! The special
insight of clinicians in recognizing unique or unusual affected individuals is a hard-won skill that
deserves more recognition.

As the 1990s ended, the technical advances in genomic research multiplied, and it became
possible to think of all genes as part of pathways and to believe that their networks are knowable.
However, as with all new discoveries, more questions than answers arose. How is tissue-, sex-, and
time-in-development-specific gene expression regulated? How often do errors arise? What is the
role of all of the nontranscribed but highly conserved human DNA sequences?

The 2000s

The new millennium appeared along with a draft of the human genome and the end of my term
as chair of the UBC Department of Pediatrics. There were great hopes for the application
of molecular genetics to diagnosis and therapy. It was time for a sabbatical and regrouping, and this
time I went to the University of Cambridge as a visiting fellow of Christ’s College and became more
aware of the concept of fetal determinants of adult disease, later called developmental origins of
health and disease (DOHaD). It was becoming clear that the interactions of the environment with
geneic predisposition, together with chance and stress, may produce multigenerational effects
without changes or mutations in the DNA sequence. These epigenetic effects were observed first
in socioeconomic studies and later in epidemiology studies. As the chromatin structural changes
that occur with epigenetic modifications have been defined, the roles of the environment, stress,
and transgenerational effects have begun to clarify.

In 2000, I first became aware of the stunning findings of David Barker, whose epidemiologic
work showed that intrauterine growth restriction from a variety of causes leads to early-onset
cardiovascular disease, obesity, hypertension, and diabetes (59). Earlier work on genomic im-
printing had suggested the existence of parent-of-origin effects, and these effects were considered
epigenetic because they are related to the regulation of gene expression. Now that the human
genome sequence has been defined, tissue-, sex-, and time-in-development-specific gene expression profiles, sometimes referred to as the functional genome, have become the next challenge. Technological advancements have led to a better understanding of chromatin structure, and major changes in chromatin structure could be correlated with disease states, but these differences may also be the result of different environmental exposures. Epigenetic differences may be passed on from generation to generation without any changes in the DNA sequence, and they clearly play an important but poorly understood role in the clinical phenotype. There are also other non-traditional genetic effects, such as mosaicism (25, 42) and microchimerism (56), and significant sex differences in gene expression from the time of conception. These mechanisms underpin the mammalian evolutionary advantage of flexibility in response to environmental change.

The sabbatical provided me with a chance to develop other projects, such as defining a form of extreme short stature. I could follow up on a request from the LPA to review cases of severe intrauterine growth restriction and extreme adult short stature—a condition known as Majewski osteodysplastic primordial dwarfism type II (58, 78). According to the Guinness Book of World Records, an individual with this type of dwarfism was the smallest human being ever—less than three feet tall as an adult.

In the 2000s, things began to change for clinical geneticists who were trying to make diagnoses for their patients. As molecular diagnosis of single-gene disorders became possible at an increasing rate, the drive to make gene-specific diagnoses escalated. Companies and tertiary care center laboratories began to develop diagnostic panels that included known gene mutations for particular types of problems (connective tissue, dwarfism, cardiovascular, dermatologic, renal, and so forth); then, when several mutations in a specific gene were recognized, efforts to sequence the genes began to replace the mutation panels; then it became possible to examine genes in pathways; and as a result, the rate of diagnosis continued to improve. Because individuals with multiple disorders or developmental delay were often suspected of having chromosomal deletions, duplications, and rearrangements, molecular evaluations of chromosomal changes using comparative genome hybridization and dense single-nucleotide polymorphism arrays became widely used.

As the Human Genome Project neared completion, the potential to sequence the whole human genome of an individual became a reality; then, as technical advances reduced the associated costs, such sequencing became feasible for health care. Whole-exome sequencing became available first, but the problem was (and still is) how to interpret the results (142). Many clinical observations were unreported, and the clinical features associated with specific genetic changes were often poorly defined. Clinicians must dig through obscure reports and review photographs, incomplete medical histories, and laboratory results in order to try to interpret molecular changes that were reported as potentially abnormal but of unknown significance.

During the 2000s, I had the pleasure of being on the Medical Research Council of Canada, which recognized the importance of genome work as it transitioned to become the Canadian Institutes of Health Research. I was on the founding board of Genome Canada as it wisely chose to invest in sequencing the natural resources of Canada (e.g., salmon, wine grapes and yeasts, and evergreen trees) because it was so behind on human genome work. I was also the chair of the Science Advisory Board of the Canadian Ministry of Health when genetics services were becoming mainstream. During the late 1900s and early 2000s, maternal serum screening for chromosomal anomalies was introduced. Now, increasingly, measures of fetal health are available through the use of cell-free fetal DNA in the mother’s serum for specific diagnoses of aneuploidy (146).

A significant challenge for clinical geneticists is to incorporate medical advice along with genetic risks and reproductive options in the context of limited access to resources (146). The health care systems in North America are constantly changing as new tests, technologies, and knowledge arrive. Clinical geneticists need to know which medical genetics costs are covered in their regions,
as this varies across different jurisdictions and different health insurance companies. The health service providers are interested in minimizing costs and often refuse to provide genetic diagnostic tests unless it will change the management of the individual, yet we know that genetic disorders involve whole families and that the testing of apparently unaffected individuals is often important. Only comprehensive health care providers that are interested in prevention recognize the public health role of genetics. This can lead to significant savings in cost and suffering by avoiding diagnostic odysseys (multiple batteries of tests over many years) and by rapidly establishing specific diagnoses. The Undiagnosed Diseases Network of the US National Institutes of Health and the Canadian Organization for Rare Disorders aim to make genetic diagnostic efforts a standard part of care, but it will be many years before this becomes a reality (30).

**THE FUTURE**

So where is this all going? Former US president Barack Obama and Francis Collins (director of the National Institutes of Health) pointed us in the direction of personalized or precision medicine (102). This implies that we are beginning to know enough about genes and their control to utilize the new information in sensible ways—and of course, for many situations, this is true, including identifying predisposition to adverse drug reactions (117), targeted cancer therapy, newborn screening, and determining the cause of single-gene disorders.

However, the transgenerational effects of epigenetic programming in complex disease traits (which have been shown to affect at least three generations) suggest that many evolutionary effects on mammals (including humans) are just beginning to be understood. Ethnic predispositions and frequencies of diseases need to be studied in an atmosphere of nonjudgment and nondiscrimination. Modern humans first migrated out of Africa at least 60,000 years ago, and major genetic divergences have occurred since then (lactose tolerance, loss of skin pigment, and alcohol tolerance, to name a few), not to mention the interbreeding with other hominids (2% of the European human genome is Neanderthal, and 4% of the Asian human genome is Denisovan).

Understanding our relationship to microorganisms and how interdependent we are undoubtfully will lead to new preventions and new therapies. And finally, how are we mammals clever enough to tolerate at least 4–5 mutations to our DNA with every cell division? It cannot be simply that “bad” cells die; recent work on skin fibroblasts indicates that they tolerate huge numbers of oncogenic mutations. Some amazing interaction, recognition, or tolerance must exist within the tissues of our bodies.

Clinical genetics began as a “soft” science. It has transitioned to defining the consequences of genetic variation on a proteome-wide scale, and now engages all levels of science in providing families with information (13). Clinical geneticists must have a broad background in genetics and medicine. They have the challenge and enjoyment of always trying to keep up. For example, as knowledge of genetic modifiers emerge, accurate diagnoses and predictions become much more difficult (115).

We live in a time when a new profession is needed to interpret the results of whole-exome and whole-genome sequencing of individuals—just wait until epigenetic changes need to be interpreted! Just as importantly, what about changes in the genome outside known genes? Coding genes make up only 2% of the human genome, yet much of the other 98% is highly conserved. What secrets will the noncoding genome hold to help clinical geneticists provide information to families?

All chronic diseases are both multigenic and multifactorial, and both the environment and previous exposures play important roles. The challenge will be making an accurate diagnosis and identifying appropriate intervention (117). The solutions are almost entirely interdisciplinary.
Many new ethical questions have arisen, and engaging families in the discussion is essential (105). How should children be treated differently (27)? The diagnosis includes or depends on a phenotype that used to be strictly physical, but increasingly includes psychological, physiological, genomic, and epigenomic descriptions. Even the term phenotype has been taken over by biochemists, molecular biologists, and physiologists—as it rightfully should, in this era of precision medicine. Thus, the concept of a differential diagnosis has expanded for clinicians, but the responsibility of providing accurate diagnoses, interpretations of test results, and information for families has become even more challenging and difficult, and even more important!

Interestingly, some diagnoses still appear to relate primarily to environmental exposures, stress, and chance. Geneticists suspect underlying genetic predispositions and complex interactions. Many disorders that were thought to be complex or multifactorial are turning out to simply represent a very large number of single-gene disorders, each of which has its own interactions with the environment (e.g., developmental delay and early-onset seizures). Many genes have multiple functions at different times in different tissues. They also have different domains, performing different jobs.

Knowledgeable gatekeepers are necessary so that clinical genetic tests are provided only when proper history, clinical findings, and indications have been established. Neither hospital administrators nor the public (through media hype) have the background and knowledge to make such decisions, much less provide interpretation and counseling.

Being a diagnostician of complex rare disorders will continue to be a challenge (112, 124). As the multiple pathways, modifying genes, and variants become better defined and transgenerational effects better understood, research on therapies and natural history will be as vital as ever. Teamwork and bioinformatics will continue to be essential. New ways to provide services will develop (145). New clinical geneticists will need to follow the training guidelines of their regional college, board, or certifying body. They will be skilled in bioinformatics and biostatistics, knowledgeable about monogenetic and complex traits, and aware of environmental susceptibilities; utilize interdisciplinary team members; and know about the psychological aspects of disease. Answers to present questions will raise endless new ones.

Thus, I see a bright and exciting future for clinical geneticists. Pick an area of interest, read, explore, become an expert, pair with laboratory colleagues, and enjoy!

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