Medical Genetics at McGill: The History of a Pioneering Research Group

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Abstract. The McGill Group in Medical Genetics was formed in 1972, supported by the Medical Research Council and successor Canadian Institutes for Health Research until September 2009, making it the longest active biomedical research group in the history of Canada. We document the history of the McGill Group and situate its research within a broader history of medical genetics. Drawing on original oral histories with the Group's members, surviving documents, and archival materials, we explore how the Group's development was structured around epistemological trends in medical genetics, policy choices made by research agencies, and the development of genetics at McGill University and its hospitals.

Keywords. medical genetics, human genetics, biomedical group research, oral history, McGill University

Résumé. Le groupe de médecine génétique de McGill (McGill Group in Medical Genetics), créé en 1972, a reçu l'appui du Conseil de recherches médicales du Canada puis des Instituts de recherche en santé du Canada jusque septembre 2009. Cela en fait le groupe de recherche biomédicale le plus longtemps actif dans l'histoire canadienne. Nous présentons l'évolution de ce groupe en situant ses travaux dans le cadre plus large de l'histoire de la médecine génétique. À l'aide d'entrevues avec les membres du groupe, de documents et matériaux d'archives, nous examinons comment le développement du groupe s'est structuré autour des courants épistémologiques de la médecine génétique, identifions les choix effectués par les agences de recherche et retraçons l'évolution de la génétique à l'Université McGill et dans ses hôpitaux.

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On 5 November 2009, approximately 100 scientists and guests gathered in the Charles Martin Amphitheatre at McGill University for a symposium to celebrate the history of the McGill University Medical Research Council (MRC)/Canadian Institutes of Health Research (CIHR) Group in Medical Genetics (hereafter "the Group"). Formed in 1972 under the direction of F. Clarke Fraser and Charles Scriver, the Group operated through MRC and then CIHR[1] funding until September 2009, making it the longest funded biomedical research group in the history of Canada. While a focus on "medical genetics" loosely defined the Group for the duration of its tenure, its 14 members were specialists in various areas of biomedicine, including teratology, cytogenetics, biochemistry, population genetics, endocrinology, and molecular biology—fields of study that converged and diverged at different times from the 1960s to 2009. During its 37-year history, Group members published over 1400 articles that helped define and develop a still-inchoate field of research. Most articles were collaborative works co-authored by Group members and research associates. The Group's success and longevity was augmented by proficient and strategic grant writing, which provided Group members steady and expansive support for basic and clinical research.

In 2010, a team of researchers in the Department of Social Studies of Medicine at McGill University set out to document the history of the Group's work within the broader context of medical genetics in Canada. Our objective was to supplement existing national histories of Canadian genetics, a still-understudied domain, with the history of one particularly rich case study that would shed light on the field's development in Canada and North America generally. We examined a complete set of Group funding applications to the MRC/CIHR, surviving personal and professional correspondence, and policy documents related to the Group's activities and funding structure. One of our research methods involved oral histories; we conducted in-depth interviews with all 14 living Group members. These oral histories, which have been transcribed and deposited in the Osler Library for the History of Medicine, constitute a unique, original, and detailed repository of information about the history of human genetics in Canada. As historian Nathaniel Comfort has argued, oral histories are unique sources that "talk back." They convey data through memories created during the process of dynamic interactions between researcher and subject. In spite of recurrent caveats concerning the evidentiary status of oral histories, which question the trustworthiness of retrospective recollections of events, the insights they may yield cannot be excavated from papers or archival

documents, because they are a product of the oral history itself.[2] In this article, we draw from these oral histories and textual sources to analyze the history of the Group as its members documented its activities and as, years later, they saw it or—to be more precise—remembered it. We suggest that in the eyes of its members, the Group underwent several major transformations shaped by broader trends in medical genetics research—itself a "hybrid science," in Hubert C. Soltan's words—as well as local conditions at McGill and its hospitals.[3] During the first phase of consolidation, the Group established its identity as a cohesive collective pursuing and united by shared aims. It brought together two existing research programs, and through this combination achieved considerable success in obtaining funding and publishing what contemporaries acknowledged to be path-breaking work. Members were closely linked and in regular contact. During a second phase starting in the mid-1980s, the introduction of molecular biological approaches, increasingly heterogeneous training, local institutional pressures, and changing research funding policies transformed the Group into a loose collection of individuals and narrow subgroups whose collaborations were characterized by growing subspecialization and collaborator dispersal among different work sites.

THE GENETICS-BASED APPROACH TO MEDICINE: THE GROUP COMES TOGETHER

Human or medical genetics began to develop as a field during the interwar period when it was closely associated with the eugenics movement. Without losing its links to eugenics, the field after World War II became organized along new lines, around the American Society of Human Genetics [ASHG] founded in 1948 and its journal, the *American Journal of Human Genetics*. From about 1955-75, in Susan Lindee's words, "an explosion of new institutions, disciplines, databases, interventions, practices, techniques, and ideas turned technically driven human genetics from a medical backwater to an exotic and appealing medical research frontier."[4] By the mid-1950s, programs and divisions of medical genetics had been established at major universities.[5] Chromosomal explanations of Down syndrome, myeloid leukemia, and Phenylketonuria, among other conditions, proved relevant to clinical medicine and public health; declining mortality and morbidity rates from bacterial infections and malnourishments further allowed geneticists to argue for the growing importance of their work. The creation of genetic screening and counselling programs during the 1950s and 1960s provided an important entree to clinical medicine, particularly pediatrics. The American Board of Medical Genetics was incorporated in 1980 to accredit both training

programs and specialists in the field. Surveys showed that the proportion of North American medical schools with formal courses in genetics increased from 8.6% in 1953 to 86.5% in 1985.[6]

Canadian institutions and individuals played a central role in the field's development during this era. Several prominent Canadian researchers were founding members of the ASHG and served on its Board of Directors.[7] The Canadian College of Medical Geneticists was established in 1976 and in 1989 medical genetics became a specialty recognized by the Royal College of Physicians of Canada. These events followed decades of institutional development, research, and debate on the standing and relevance of genetics to medical education and practice. The two leading institutions in this regard were the University of Toronto and McGill University; together these trained more than half the individuals who established medical genetics training or service sites in Canada.[8] We know a great deal about the fertile tradition of genetic research begun in the 1930s at the University of Toronto by Norma Ford Walker, a tradition that Fiona Miller characterizes as at once "anomalous and marginal."[9] William Leeming suggests that Walker lacked formal biochemical laboratory support, and medical genetics at Toronto remained fragmented. Consequently the field in Toronto "failed to keep pace with other multidisciplinary centres in North America."[10]

We know considerably less about the McGill and the Montreal stories. By 1970, university centres existed in many parts of Canada,[11] but there is little doubt that the field was most fully developed at McGill, which boasted the country's first Department of Genetics, established in 1934 with a grant from the Rockefeller Foundation. It was in this department that Clarke Fraser earned his PhD, inaugurated the field of teratogenetics, and in 1951 became the director of the newly created Department of Genetics at the Montreal Children's Hospital, a department formally affiliated with McGill's Medical Faculty. When the International Congress of Genetics held its first meeting in Canada, in 1958, it was no accident that its organizers chose Montreal as the meeting site. The establishment of the Group in 1972, with Fraser as director and colleague Charles Scriver, a leading biochemical geneticist, as its co-director, cemented ties between clinicians and academic researchers, and solidified McGill's position of prominence.[12]

The Group formed in 1972 at the recommendation of Malcolm Brown, the President of Canada's Medical Research Council from 1966 to 1977. The undisputed leaders of the Group were Charles Scriver and Clarke Fraser.[13] At this time, work in medical genetics was splintered among various sites at McGill University and its affiliated hospitals. However, the formation of the Group consolidated institutional and financial support and led to the timely convergence of two distinct programs of research. The first dealt with teratological abnormalities and

the second with the biochemical bases of inborn errors of metabolism. Prior to the Group's formation, Fraser's work in teratology and that of Scriver in biochemical genetics had made both men instrumental in defining the field of medical genetics in Canada. Their strategic collaboration reflected the priorities of medical genetics research of the period—increasingly combining the study of chromosomal abnormalities, teratogenetics, and biochemical genetics.[14]

In a speech to the American Society of Human Genetics, Dorothy Warburton declared Fraser to be "Canada's first medical geneticist," although Fraser himself credited Ontarians Norma Ford Walker and Madge Macklin—it was Macklin who first coined the term "medical genetics" in the early 1930s—for creating the foundation upon which his work built.[15] Fraser earned his Master's and PhD degrees in 1942 and 1945 in genetics at McGill and then completed his medical degree at the same institution in 1950. His research came to focus on what he called "teratogenetics," a field of study that examined prenatal exposure to environmental agents causing malformation and maldevelopment. Indeed, Fraser's discovery in 1950 that the newly available "wonder drug" cortisone could cause cleft palates in mouse embryos launched teratogenetics as a field.[16] He translated much of his laboratory-based research into clinical practice, studying and treating defects in cleft palate and lip, congenital heart defects, neural tube defects, and other congenital malformations. In 1951, Fraser established the Department of Medical Genetics at the Montreal Children's Hospital, which offered one of the first genetic counseling services in Canada.[17] The importance of Fraser's contributions and his international stature yielded an impressive succession of accolades. He was elected President of the American Society of Human Genetics in 1961, won its Allan Award in 1979, and received the March of Dimes Award for Contributions in the Field of Birth Defects in 1987. In Canada, he was awarded the Blackader Award of the Canadian Medical Association in 1968, the Order of Canada in 1985, and the Prix de Québec in 1999.[18]

Charles Scriver was born in Montreal in 1930 to a prominent family of medical professionals. Both his mother and father were respected physicians and researchers at McGill, and they influenced his decision during the 1950s to move away from the humanities and geography, the focus of his undergraduate degree at McGill, to the study of medicine. After earning his medical degree at McGill in 1955, and completing residencies at the Montreal Children's Hospital and Harvard, Scriver increasingly focused on biochemical genetics and pediatrics. During his year in Boston, he discovered a type of seizure disorder in children that was responsive to the injection of vitamin B6. He continued his research in London, England, working with Charles Dent and John Walsh, two prominent figures in the study of chromatographic methods

for detecting inborn errors of metabolism. Returning to McGill in 1961, Scriver worked in the de Belle Laboratory of Biochemical Genetics at the Montreal Children's Hospital. His training in chromatographic techniques would lead to the discovery and classification of over 20 inborn errors of metabolism during his career.

In the late 1960s and early 1970s, Scriver and his colleagues conducted studies of rickets in children in Quebec. Rickets is a childhood disease characterized by stunted growth and serious bone malformations. American biochemist Harry Steenbock had demonstrated in the 1920s and 1930s that the fortification of irradiated foods with vitamin D, the so-called "sunshine vitamin," could prevent rickets. This finding led to widespread changes in the manufacture of dairy products and other food staples in the United States, changes that by 1945 had halved the country's incidence of this disease. Scriver's research found that rates of the disease were significantly higher in Quebec than in other populations (the risk of rickets increases in geographic areas where harsh winters may limit a child's UV exposure). With the help of Arnold Steinberg, a Montreal businessman and philanthropist, these studies encouraged the fortification of milk, which became mandatory in Canada, virtually eliminating the disease by the late 1970s.[19] Scriver's contributions to the development of medical genetics in Quebec also included participating in the co-construction of a unique university-government collaboration: Le Réseau de Médecine Génétique du Québec (The Quebec Network of Genetic Medicine), established as a pilot program in 1970. Scriver and Carol Clow (also from McGill), along with colleagues at Laval and the chairs of pediatric programs at four Quebec medical schools, persuaded the minister of health, Claude Castonguay, to create and fund an organization dedicated to the early screening of newborns for a variety of genetic and congenital disorders, along with parental education and patient treatment. The Quebec Network, which involved Quebec's four medical schools and its Ministry of Health, was formalized in 1971 and would expand to include prenatal diagnosis. Its formation amplified Scriver's stature in provincial and federal medical research circles, and provided a successful example of a government-industry medical partnership in Quebec at a time when such collaborations remained rare.[20] His visibility, like that of Fraser, led in 1972 to a personal invitation from Malcolm Brown, President of the MRC, to apply for group status. Scriver recalled: "We [felt] that maybe we should try to respond to the invitation from the [MRC] to form [and] create groups of shared interest."[21]

Established in 1960, and subsequently incorporated under the Canadian Government Organization Act, the MRC reported to Parliament through the Minister of National Health and Welfare, and functioned to "support and promote research and development in the health

sciences, except public health research, in Canadian Universities and their affiliated institutions."[22] The MRC Groups Program, founded in 1966, followed a trend initiated by the US National Institutes of Health, which had since 1960 devoted an increasing proportion of its funding to collaborative group projects thought to be more stable, more focused on pragmatic problems, and more interdisciplinary, while producing higher quality results.[23] The MRC program sought to consolidate the work of two or more established investigators who aimed to collaborate on what the MRC called "especially productive areas of medicine."[24] Group members were expected to pursue their research within the framework of the team's objectives. In the 1972 Report of the MRC President, Malcolm Brown noted that the group's program was meant to seize "special opportunities and to permit on occasion the establishment of a team that could not be brought together within the usual university framework."[25]

As the founding Directors of the new Group, Scriver and Fraser had close personal and professional ties to the MRC. Scriver's parents both knew Brown well, and Fraser had been chairman of its Genetics Committee for close to five years prior to 1972. When asked why he and Scriver decided to submit the first application for group status in 1972, Fraser said, "I knew the [MRC] … and I guess they knew me. I must say, the [MRC] treated me very well."[26] Because each had developed successful and influential programs in their respective research areas in the 1950s and 1960s, Fraser and Scriver were well positioned in the following decade to become involved in the MRC groups initiative.

Fraser worked at the Montreal Children's Hospital where he had created a Medical Genetics Division in 1950. Fraser recalls in his memoir how McGill's Departments of Pediatrics and of Genetics supported the creation of this new unit.

> I had been discussing the ways and means with the professor of Pediatrics, Alton Goldbloom, and his second-in-command and successor, Alan Ross … during my final year in medicine. It was their vision of how genetics would fit into pediatrics that made the whole thing possible. Wally Boyes, then Chairman of the Genetics Department at McGill, went along. Links between the [Montreal Children's Hospital] Medical Genetics Division and the McGill University Genetics Department, where I maintained an office and lab, always remained strong.[27]

Given uncertainties about how medical genetics would fit into the existing institutional and disciplinary structure of McGill University, Fraser wrote that forming the Medical Genetics Division "was not always easy … The vigorous expansion of studies in human genetics posed some threat to other areas of genetics, and not all members of the genetics department were as convinced as I was that medical genetics was

taking off."[28] The institutional context was indeed complex. The unit at the Children's hospital eventually led to the establishment in 1965 of the Human Genetics Sector in the McGill Department of Genetics, "which remained part of the Genetics Department as far as teaching was concerned, but had its own budget for its research activities."[29] By 1970, human geneticists were consolidated in the newly arranged Department of Biology, which brought together zoology, botany, and genetics. According to Fraser, this consolidation provided a framework under which human geneticists, including members of the Group, could maintain autonomy within a larger departmental structure. However, it was not until 1979, following the formation of the Centre for Human Genetics, that such an administrative framework would fully "[provide] a focus for those working in human genetics."[30]

Geneticists were becoming increasingly conscious of the need to apply knowledge about genetic disease to benefit individual patients. Scientists had already made significant strides in amassing information on diagnosis, risk, and prognosis through chromosology (revealing, for instance, the chromosomal aberrations linked to Down syndrome) in the late 1950s, and cell genetics (in which the study of cultured cells enabled, for example, the prenatal diagnosis of genetic disease by amniocentesis) in the 1960s. Genetics now sought to parlay research into active treatment that would yield observable results.[31] The Group's initial application for MRC funding reflects this impetus, for its stated goals were to "bring all relevant knowledge in the various fields of genetics to the benefit of the patient" by, among other things, identifying the characteristic morphology of every chromosome in the human complement and by identifying the biochemical bases of new diseases and syndromes.[32] Fraser emphasized the practical importance of this shift. "I got a little frustrated [with] ward rounds and case conferences and saying this patient has a recessive disorder, and the chances of it happening again are one in four to subsequent siblings, and that's as far as you could go. If you know what the gene is doing maybe you could do something about it. So, when Charles Scriver appeared on the scene … he was the answer to my prayers."[33] Now genetics could have medical applications: "I was very glad to see [Scriver] on board because *it opened up a new field* [emphasis added]; opened up the possibility of presenting some of these disorders, or at least treating them in an intelligent way … and I confess that I probably [didn't] know as much biochemical genetics as I should [have], because whenever something like that came along, I sent it up to his lab and let him deal with it."[34] Scriver also spoke equally positively of his early experiences working alongside Fraser: "The prediction was that Scriver and Fraser could not work together because they would be two independent competing factions, and the predictions were totally wrong," he said. "[W]e loved working with

each other. It was easy, and we left each other to do what we could do as individuals, [although] … our joint work was greater than [its] parts."[35]

In fact, Fraser and Scriver's collaboration proved essential to their ability to secure funding from the MRC, which was still in the process of figuring out how, exactly, the genetics-based approach to medicine would fit into the organization of medical funding in Canada.[36] Not everyone agreed with the group-based approach taken by both the MRC and NIH. Even at McGill there was significant opposition. Patrick Cronin, McGill University's Dean of Medicine, for instance, speaking on behalf of himself and another colleague, wrote to John Firstbook, Executive Director of the Association of Medical Colleges in 1974: "I am not at all convinced that any of the 'numerous advantages' of groups can be proved. Where is the evidence? … To my mind, research groups are really expensive and probably cost more than the individuals could get by themselves."[37] During MRC consultation sessions in 1974, concern was expressed that group grants constituted a form of elitism in biomedical funding during an ostensibly precarious time of re-structuring at the MRC.[38]

Despite such concerns, group funding continued, in part because the inter-disciplinary partnership between Fraser and Scriver reflected wider trends in genetics research. Historians have shown how medical genetics developed rapidly in the 1960s and 1970s due to collaboration between researchers of chromosomal abnormalities and biochemical geneticists seeking to understand and treat genetic disease.[39] "After 1960," William Leeming writes,

> the basic division of labour involved in biochemical testing followed a pattern similar to that of chromosome analysis: individuals with backgrounds in chemistry were recruited to perform a service function in 'biochemical laboratories,' and a new occupational category appeared: 'biochemical geneticists.' Physicians would look for tell-tale signs and symptoms (e.g. failure to thrive, developmental delay, ocular abnormalities) that might be indicative of metabolic disease. A geneticist would be consulted regarding the family history and, if a laboratory evaluation was in order, blood or urine was obtained and shipped to the laboratory where it would undergo testing.[40]

This early collaboration among Fraser, Scriver, and their colleagues was especially significant in that it both combined specialized research domains and consolidated one of the first federally funded centres in Canada for the study and treatment of the genetic components of disease. This grew out of their earlier work in genetic counseling, their study of patterns of genetic disease in families, as well as new trends in North American genetics more generally.[41] The Group was thus shaped by and in turn shaped further this renewed genetics-based approach.

THE GROUP IN ACTION: RESEARCH AREAS AND EPISTEMOLOGICAL TRENDS

In its first grant applications, the Group emphasized unity and shared objectives: "To utilize regional opportunities at McGill University and in Québec aiding in interdisciplinary genetics work and linking hospitals and departments; to support national and international programs and services that could link research programs; and to consolidate the research program such that facilities would be set up for programs of diagnosis, counseling, and treatment of patients."[42] Under Scriver's direction, the Group's research was initially held together by biochemical approaches to the study and treatment of genetic disease. Early Group members—including David Rosenblatt, Reynold Gold, and Peter Hechtman—conducted research in related fields: prenatal diagnosis; cell culturing; folate and vitamin B12 metabolism; keratin genetics; and the biology of differentiation and development.[43]

Between 1972 and 1981, all Group members were trained by, or worked closely with, Scriver. Gold, for example, came to McGill to work with Fraser but, due to his interest in biochemical genetics, he shuffled his workspace at the Montreal Children's Hospital to be closer to Scriver. He was eventually recruited to be a member of the Group because of his focus on keratin genetics, which was, according to one of the Group's grant applications, "a virtually untouched field in human biology and genetics" at that time.[44] Gold left in 1976 to pursue new projects in Toronto despite productive interactions with Harriet (Susie) Tenenhouse, who joined the Group as a research associate in 1972. Gold fondly recalled his work with Tenenhouse, who would later become one of the Group's principal investigators: "The collaboration … was wonderful because she was a fantastic experimentalist … everything was accurate and precise and the interaction between us was a very good example of how a group [could work]."[45] This collaborative study of an abnormality in keratin biosynthesis constituted one area of expertise within the Group.

A student of Scriver's, Rosenblatt completed his medical degree at McGill in 1970. Later, at the recommendation of Scriver, Rosenblatt spent four years at Harvard and MIT as a post-doctoral scholar learning skin fibroblast culturing techniques for the study of metabolic processes. He returned to McGill and joined the Group in 1975 specifically to apply this training to the study of metabolic diseases. This expertise proved to be a major asset to the Group, as did the tissue bank that he began to assemble at the beginning of his career, and which continues to be a source of data for rare genetic diseases around the world.[46]

Rosenblatt had collaborated with Scriver even before leaving for his post-doctoral position in Boston, in particular for "a project where

[we] were looking at different patients with PKU, using an amino acid analyzer to look at phenylalanine-to-tyrosine ratios to see if they could be distinguished into different groups. The first publication I had was published in *Nature*[47] as a result of that work with Scriver."[48] Scriver was an important mentor to Rosenblatt, which was the primary reason Rosenblatt became involved in the Group and medical genetics research more generally. "My entry into the area," Rosenblatt later remarked, "was not driven primarily by an interest in medicine or genetics, but by exposure to a mentor who would discuss with you a career path … [I] saw the enthusiasm of the work, the enthusiasm of Scriver … and was riding on his experience and his mentorship."[49] Rosenblatt remembered the first 10 years of his career as "highly, highly sheltered. I was living in this cocoon of the Group, and Scriver protected me from … any clinical responsibilities."[50]

The Group's goals remained consistent during its first decade, focusing on the research, treatment, and delineation of phenotype patterns of various teratological syndromes (Fraser),[51] biochemical genetics and inborn errors of metabolism (Scriver and Hechtman), folate and B12 metabolism and prenatal diagnosis (Rosenblatt), cell culturing (Rosenblatt and Pinsky), and vitamin D metabolism (Tenenhouse). In 1981, Tenenhouse, a research associate with the Group since 1972, was recruited as a member to support the Group's focus on biochemical genetics. She had also completed her PhD work in biochemistry at McGill and conducted research using Mendelian models to study renal phosphate transport and vitamin D metabolism in X-linked hypophosphatemic states.[52] During these early years, Tenenhouse suggested, the Group was unified by geographic proximity and the dynamism and congeniality of Scriver's leadership: "When Scriver was director of the Group, [it] was much smaller … [w]e did a lot of things together, from eating lunch together in the cafeteria, to attending seminars together, and participating at national and international meetings together. We were a much more unified entity in those days." As the demographics of the Group's composition shifted, so, too, did its focus. Tenenhouse reflected that: "when more people joined the Group and their areas [of expertise] were a little different … [the Group] was no longer [so unified]."[53] In 1981, the Group also recruited Leonard Pinsky, the first member not located at the Montreal Children's Hospital, a change that initiated the geographic dispersal and separation of researchers who had previously worked in closely situated laboratories.

In 1981, when Pinsky was invited to join the Group as its Co-Director with Scriver, he was the Scientific Officer of the Human Genetics Committee at the MRC, as well as the Director of the Centre for Human Genetics. The Centre for Human Genetics was formed in 1979 to consolidate medical genetics within McGill's Department of Biology. Its

mandate was to provide institutional and academic support for medical genetics, and, among other things, to coordinate genetic health care at McGill University and its affiliated hospitals.[54] Pinsky trained as a physician in Montreal during the 1960s, working with Fraser for four summers during his training. He recalled that, during these summers, "I developed more and more interest in my belief that genetics was the answer to a lot of the world's medical problems."[55] Early in his career he wrote two career-defining papers in medical genetics, outlining the importance of the genetics-based approach to medicine.[56] While working as a researcher in the Cell Genetics Laboratory at the Jewish General Hospital's Lady Davis Institute, Pinsky was among the first researchers at McGill and its affiliated hospitals to grow human diploid cells for the purpose of studying genetic disease. His contributions to the Group, from 1981 to 1991, much like Rosenblatt's, were in the areas of somatic cell genetics and the culturing of skin fibroblasts, with a particular focus on androgen receptor histology and sexual maldevelopment. Pinsky's expertise in these areas was critical for the Group because it allowed it to participate in what was becoming a major re-orientation of genetics research in North America during this period: previously focused on the transmission of hereditary characteristics, research had become increasingly focused on DNA transcription and expression, which would be central to the turn to molecular genetics in the 1990s.

With the recruitment of Pinsky, a member of the Group was, for the first time since 1972, located geographically and academically apart from the Montreal Children's Hospital. In his interview, Scriver suggested that this diffusion was a consequence of the Group's accomplishments: "We were successful enough," Scriver recalled, "that our activities spread beyond the physical space of the Children's Hospital and the academic space of pediatrics … [a]nd we wanted to see genetics get into other areas of medical care and medical education and research."[57] The situation seems nonetheless to have bothered Scriver because Pinsky recalled that: "At various times … and during my interaction with the Montreal Children's Hospital, I was invited to… leave the … Lady Davis Institute" in order to work alongside other Group researchers.[58] Despite such pressure from Scriver, Pinsky remained at the Lady Davis. The Group's expansion into the Lady Davis Institute, then, represented its first successful attempt to recruit a high-profile medical geneticist—thereby increasing its visibility and profile—and to incorporate new areas of medical genetics into the Group's research activities.

Pinsky's recruitment and the move beyond the confines of the Montreal Children's Hospital thus allowed the Group to participate more actively in the molecular revolution in biology. This revolution, institutionalized in the ambitious Human Genome Project that began in the 1990s and sought to map all genes in the human DNA, coalesced

around new laboratory techniques, and was driven by growing interest among scientists and clinicians but also policymakers, patients' groups, and the lay public. Such interest was based on the underlying hope that mapping the structure and function of genes at the molecular level would generate essential knowledge about genetic mutations that cause disease.[59] At stake for the Group was nothing less than the risk of losing MRC support if it failed to make this transition. By the mid-1980s, new molecular techniques such as recombinant DNA and gene cloning, followed in the late 1990s by techniques for the study of gene expression and DNA sequencing, were being progressively adopted by medical geneticists across North America.[60] These developments required a shift from biochemical to molecular approaches, one that began with the renewal application of 1976, where Peter Hechtman was added as the Group's expert in "molecular and biochemical genetics."[61] Hechtman also completed his PhD under the supervision of Scriver, and was the first PhD laboratory geneticist added to a Group composed primarily of "geneticist-physicians."[62] His recruitment into the Group was significant as part of a broader trend bringing PhDs and laboratory scientists into biomedical research areas previously dominated by physician-researchers.[63] But it did not provide a solution to the need for molecular expertise. As Hechtman recalled:

> When I signed on in the early 1970s, biochemistry was going to be the answer to everything. But it didn't take long—let's say [until] 1978, maybe '79, that the first papers came out in which it was apparent that molecular biology was now a lab science that could be applied to all kinds of biological or medical problems … if the Group had its eyes on me as the guy who was going to make them into molecular biologists … they must have been disappointed because I [didn't] take to new technology very easily.[64]

Pinsky's recruitment helped, but competition was raising the stakes as other Canadian institutions adapted rapidly to the "molecular turn." According to Hechtman, the Group was particularly determined to keep pace with a group of researchers at the Children's Hospital in Toronto under the direction of Louis Siminovitch, who had "developed a very strong molecular biology program. They had Rod McInnes, who is now [at McGill], Roy Gravel, who was part of the Group … [and] there's no question that in terms of molecular biology competence, that group raced way past what we were able to do."[65] Rosenblatt similarly recalled that the Group "was concerned about [its] competitiveness … [because] … Lou Siminovitch had changed everything in Toronto, had made everybody … drop their projects" to train in molecular biology technologies.[66]

Mounting pressure to incorporate molecular approaches was the impetus behind the recruitment of Rima Rozen for the Group's 1986

renewal application. Born in the Soviet Union, Rozen moved to Montreal in 1960 and pursued an undergraduate degree in genetics through the McGill Department of Biology, later completing her PhD in genetics under Scriver's supervision. With the latter's encouragement, Rozen pursued her interest in metabolism during a one-year post-doctoral fellowship at Yale University. There, she learned molecular biological techniques in the laboratory of Leon Rosenberg, a prominent researcher recognized for his pioneering work using molecular biological approaches to identify inborn errors of metabolism.

Rozen returned to the Department of Pediatrics at McGill and became a member of the Group. Her recently acquired expertise in new molecular biological techniques for the study of PKU, cystic fibrosis, and developmental disorders made her extremely valuable. The MRC grant application of 1986 highlighted her work and called attention to the Group's growing interest in molecular genetics. "Rozen will study expression of the ornithine aminotransferase gene in mutant phenotypes," the application stated, "causing human gyrate atrophy; she will work also with all other PIs [Hechtman, Tenenhouse, Rosenblatt, Pinsky, and Scriver] on their molecular projects."[67] According to Rozen, "I was recruited back to develop molecular genetics, because there was no one in this area at [the Montreal Children's Hospital]. So here was this new skill set, and I was bringing more molecular activity into the Group. The Group needed to have a modern evolving area of research."[68] Most of the other Group members would go on to train in recombinant DNA techniques, and the Group would become "more molecular" from the mid-1980s onwards, but Rozen's expertise was essential during this pivotal period of technological and epistemic change.[69]

Following the recruitment of Rozen, an aging Scriver, already contemplating retirement, referenced in letters to Group members the need to recruit more molecular geneticists to secure future funding in a field whose boundaries and foci were being redefined. In July 1987, for example, he wrote:

> Our first upcoming problem is membership and leadership of the Group for the 1991 renewal. I hope to remain a participant but we should have a new profile. We can keep our commitment to "physiological genetics," but we need to show a much higher profile in the current convention—which is molecular genetics and medical genetics … we won't be renewed if we don't change. Even though my leadership may have some value now, we need evidence of molecular leadership in the future.[70]

Sensing the pressure to adopt state-of-the-art technologies or to risk losing MRC funding, Scriver wrote another letter to the Group in October 1987: "I'm taking the proposal to recruit a medical/molecular geneticist seriously. This person … will be recruitable [sic] in his/her own

right through McGill, and will also fit the bill for the MRC renewal application four years from now."[71] One year later, when the Group's leadership and academic directions were still in transition, Scriver wrote once again, seeking to construct a unifying research theme: "Our team's [theme]," Scriver wrote, "is 'the structure of human genetic variation.' It complements the other themes. The common theme (for all components) is molecular genetics."[72] Ironically, the Group's "common theme" in molecular biology after the late-1980s in practice fragmented the Group geographically and academically, as it recruited new members, such as Emil Skamene, who were located at various sites across the McGill campus and who often worked in unrelated and hyper-specialized research areas.

The Group recruited Skamene in 1991 because of his research on genetic mechanisms of resistance to a variety of infectious diseases. "I knew [the Group members] were interested in what I would call today Mendelian or monogenic traits," Skamene remembered. "They were interested in newborn malformations; they excelled in biochemical genetics … one gene—one disease phenotype."[73] Using a multigenic approach, Skamene studied listeria, mycobacteria, malaria, salmonella, and tuberculosis at the Centre for Host Resistance formed in 1988 at the Montreal General Hospital. Trained in immunology, not genetics, he was not at the time of his recruitment in close contact with most of the Group members. When asked why he thought he had been invited, Skamene responded: "I don't know what exactly Charles [Scriver] said [when I was recruited], but I am sure it had to do with my experimental strategies on how to dissect these multigenic traits into a series of unigenic systems that interact. [This] became attractive as an expansion of [the Group's] purely monogenic themes, which were extremely important but from a practical point of view pertained only to a tiny proportion of the population."[74] His multigenic approach, Skamene suggested, was a "natural extension" because "it was a way to look at common diseases of adult life" that diversified the scope of the Group.[75]

Before retiring as Co-Director of the Group in 1994, Scriver was involved in recruiting a new member and Director, Roy Gravel, to contribute to the Group's growing focus on molecular approaches to genetic disease.[76] Gravel had already built a reputation for his expertise in PCR and gene cloning techniques for the study of Tay-Sachs, Sandhoff disease, and folate and vitamin B12 metabolic deficiencies at the Hospital for Sick Children in Toronto and at the Montreal Children's Hospital Research Institute, where had worked since 1989. His first involvement with the Group in 1994 was influenced by his interactions with Rosenblatt and Rozen, who had developed programs in related research areas. Gravel, who directed the Group from 1994 to 2001, recalled: "we had a core group of David [Rosenblatt] and Rima [Rozen] and ourselves

studying B12 and folate and we were very integrated in the nature of that work. But the truth is, the Group was really made up of a diversity of different kinds of areas … [and] we were just [a] … small cohort that tended to work closely together."[77]

Along with the "molecular turn," two institutional developments promoted research fragmentation. The first was a decision to expand the Group beyond pediatric medicine. The Group's 1986 application for renewal omitted "consolidation" as an objective, and emphasized instead the expansion of research and services beyond the Montreal Children's Hospital. This shift both shaped the Group's future and reflected changes that had already taken place. The rationale for expansion was that it would "extend [the Group's] sphere of influence to benefit the training program and the interactions of [its] work," for "[t]he multifocal approach contribute[s] to interactions between the Group and a greater part of the McGill Community."[78] The new orientation followed the creation of the Centre for Human Genetics in 1979, which was the first attempt by clinicians and researchers to provide an *independent* administrative structure for medical genetics at McGill. The subsequent formation of the Division of Medical Genetics in the Department of Medicine in 1986, under the leadership of Rosenblatt, allowed the Group to expand from Pediatrics to the study and treatment of adult medicine. This Division offered diagnostic services for patients in Montreal to screen for Huntington's disease and adult polycystic kidney disease using recombinant DNA technology. Despite its undoubted usefulness, this expansion temporarily threatened the Group's eligibility for funding.

In May 1987, the MRC's Report of the Visiting Team to Assess the Group on Medical Genetics advised that: "The guidelines of the MRC state clearly that the laboratories of the members of the Group should be located in a single site. The laboratories of this Group, however, are at four different locations … *the Group probably violates every canon of organizational theory*, yet retains an investigative vitality through its imaginative leaders."[79] As the MRC further reported, "This new development of the medical genetics unit reflects that the MRC Group is working well and fostering creative new initiatives."[80] Not everyone agreed that fragmentation and intellectual vitality could co-exist. A letter from Scriver to the Group in August of 1987 expressed concern about "whether we can convince the MRC ever again that we are really a Group when we exist in three sites. We have to consider the costs and benefits of our current 'decentralization.' Centralization at the [Montreal Children's Hospital] will be obligatory by 1991, or no Group renewal, is my guess."[81] Non-renewal did not occur in large part because the MRC was itself changing course, as we shall see.

Responding to Rosenblatt's expansion into the Department of Medicine and its affiliated hospitals, Scriver warned: "The 'Rosenblatt Unit' is a good development in that it expands human genetics into areas where it is needed. But it divides us into parts where we were once whole [Montreal Children's Hospital]. Therefore, in terms of limited resources, we are competing between ourselves."[82] Nonetheless, other needs predominated and the Group continued to evolve into a loose association of research teams located in various sites. One competing priority was placing the sprawling and fragmenting field of medical genetics at McGill within a viable administrative structure. Following the expansion into adult hospitals, a university Department of Human Genetics was formed in 1993 under the mandate to centralize medical genetics and to support the durability and bureaucratic efficiency of the field. Rosenblatt later explained: "I was very much a strong advocate for the creation of the University Department," because it "create[d] a structure that has longevity."[83]

At about the same time, a major change in grant policy at the national level further promoted the growing fragmentation of the Group. In 1994, the Group Grants Program stopped providing operational funds for core facilities to groups, offering instead individual research grants. This had a profound impact on the scientific activities of the Group and on other research teams throughout Canada. Members now had to secure MRC/CIHR funding for individual projects before being invited to participate in the Group, an affiliation that provided members with additional funding opportunities. Gravel explained that, due to this change in policy, "[We] … evolved from a group that was funded to do the operations of research, core facilities, training programs" to one in which "people were expected to have their own independent grants to run their research programs."[84] This change in policy encouraged individuals to pursue separate lines of research. It also permitted Gravel to take up a position at the University of Calgary in 1999, while remaining a Group member until it disbanded in 2009.

In oral histories reflecting on this final period of Group activity, many members focus on the lack of research integration and the absence of personal interactions within the Group. Andrew Karaplis, for example, who was the only new addition on the 1998 renewal application and the first endocrinologist in the Group trained in experimental medicine (PhD, McGill, 1987) in the Group, had very little contact with most of the members.[85] He had worked briefly with Tenenhouse, which he thought was the reason he was invited to join: "Susie [Tenenhouse] and I had collaborated on generating a knockout mouse of the renal sodium phosphate co-transporter," he said, "and I think at that point, she wanted … to bring some additional members into the medical genetics

group with similar research interests."[86] Yet, apart from his work with Tenenhouse, Karaplis had few interactions with Group members. "The [multiple] locations [of the Group] were very difficult in many respects," Karaplis recalled, because

> I was at the Lady Davis Institute, while the rest were at the [Montreal] Children's [Hospital]. Also, our interests were different. We had very little commonality. … [T]he main facility that we all shared [was] the histology service that was set up at the Children's. So, occasionally, I would use it to get tissue samples processed there. But the interaction was rather limited in many other respects.[87]

Eric Shoubridge, who joined the Group in 2001, remembered that Tenenhouse and Karaplis "were kind of off doing their own thing. And so we weren't really a group in that sense, I don't think. We [were] all working on different aspects of metabolic problems."[88]

Under the direction of Rozen, the Group recruited three new members for the 2001 application—Shoubridge, Robert MacKenzie, and Mark Trifiro—who continued the Group's hyper-specialization in molecular medical genetics. All three new members, along with Gravel, Rosenblatt, Rozen, and Karaplis, worked with the Group until funding ceased in 2009. While an interest in metabolism and health linked Shoubridge's research[89] with the themes of the Group, his interaction with other members was limited because of his specialization in mitochondrial diseases. "They invited me to join," Shoubridge suggested, "because nobody … was doing what we were doing … the patients we saw at [the Montreal Neurological Institute] were [mostly] adult patients … with mitochondrial DNA problems."[90] The formation of subgroups was a characteristic feature of the Group's organization by this time: "We used to have regular meetings … [b]ut we weren't working as a kind of team, focused on the same thing, because we all had our own individual projects."[91]

After completing his PhD at Cornell University in 1969, and following a post-doctoral fellowship at Berkeley (1969-1971), MacKenzie spent his career in the Department of Biochemistry at McGill developing model systems to understand folate-mediated processes.[92] A self-declared basic scientist with little connection to medical genetics, or medicine in general, MacKenzie was recruited into the Group, he suggested, because his research overlapped with that of Rozen and Rosenblatt's: "[the Group] was actually bringing together an interaction that I already had with David [Rosenblatt] and Rima [Rozen]."[93] Over the course of his career, MacKenzie became interested in folate-mediation in mitochondrial DNA, which created another connection with Shoubridge. Tenenhouse similarly reported that the "folate group" produced a number of significant collaborative projects, but members without internal collaborators had to develop alternatives outside McGill, and frequently outside Canada.[94]

Some Group members worked in highly specialized domains remote from the Group's other research areas. Mark Trifiro was recruited in 2001 specifically because of his years of training as a medical endocrinologist, with particular expertise in recombinant DNA techniques for the study and treatment of androgen insensitivity syndromes.[95] Following his appointment at the Jewish General and Lady Davis Institute, Trifiro forged particularly close connections, both geographic and professional, with Pinsky, by then at the end of his career at the Lady Davis Institute. "I had a good clinical practice in the hospital and [at] the Lady Davis Research Institute with Pinsky right next door," Trifiro said, "so I think Len [Pinsky] was really, really important in guiding me."[96]

The Group continued to receive CIHR funding until 2009. By then the collaborative group program had been discontinued and replaced by team grants based on new strategic priorities and demanding more focused collaboration than the Group manifested during its final decades.[97] Much had changed during its long existence: many of its members, their outreach in terms of national and international collaborations, the number and the increasing specialized nature of the research areas they covered, the methods they used to do so: in short, the Group had become a collection of teams, whose common denominator was no longer a specific research front but, rather, a more loosely defined discipline, human genetics, which, since the pioneering era of Scriver and Fraser, had acquired its academic "lettres de noblesse."

CONCLUSION

The Group exemplified in many ways the development of medical genetics in Canada. Its consolidation reflected both research trends on the ground and agency funding policies during the 1970s. Led by two of Canada's most prominent researchers in this small emerging field, it benefited from the continent-wide emphasis on continuous funding for focused, stable, and interdisciplinary research collectives. The Group thus became central to Canadian genetics during the 1970s. When in the 1980s and 1990s, the field expanded dramatically and exploded into numerous subspecialties, so did the Group, which lost the close-knit character and common purpose of its early years. Like other groups, it struggled to keep up with the "molecular turn" that was transforming the field. In the expanding, sprawling, and fragmented new world of Canadian medical genetics, it probably became somewhat less prominent. Nonetheless, the Group adapted successfully and remained highly productive. The MRC evaluation of 1987 continued to remain accurate until the Group's final dissolution. In spite of violating "every canon of organizational theory" (if such canons actually existed), the "Group is working well and fostering creative new initiatives."[98]

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NOTES

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43 McGill Group in Medical Genetics: Group Application, submitted 29 February 1972.
44 McGill Group in Medical Genetics: Group Application, submitted 29 February 1972.
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46 Rosenblatt has been Chairman of the Department of Human Genetics at McGill (formed in 1993) since 2001, and runs one of only two diagnostic facilities in the world for patients with inborn errors of vitamin B12 and folate metabolism. He was also the longest-standing member of the Group (1975-2009).
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50 David Rosenblatt, personal interview, 1 December 2009.
51 Fraser left McGill and the Group in 1982 to take up a position at Memorial University in St. John's, Newfoundland. He returned to McGill as Professor Emeritus in 1985 and continued with the Group until his retirement.
52 Tenenhouse joined the Group as a research associate in 1972, served as a core member from 1981 until 2004, and retired from McGill in 2009. In 2010, she was awarded the C. P. Leblond Award of the Network for Oral and Bone Health Research for her contributions to the field.
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64 Peter Hechtman, personal interview, 30 September 2010.
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69 Rozen was a member from 1986-2009, and would later go on to direct the Group for its final two terms (2001-2009). She continues to conduct research at McGill and the Montreal Children's Hospital Research Institute on enzymes in folate synthesis and molecular events in gene expression, and, in particular, the MTHFR gene and its effects on various diseases and defects.
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72 Charles Scriver, personal letter to MRC Group in Medical Genetics, 28 July1988.
73 Emil Skamene, personal interview, 5 August 2010.
74 Emil Skamene, personal interview, 5 August 2010.
75 Emil Skamene, personal interview, 5 August 2010. Skamene did not continue with the Group on the 1994 application for renewal, but remains at the time of writing the Director of the Centre for Host Resistance, Director of the McGill University Health Centre, as well as Senior Scientist of the Montreal General Hospital Research Institute.
76 After close to 50 years in the field, Fraser retired from McGill University in 1994, ending his 20-year involvement in the Group (1972-1982; 1985-1994). Scriver left as the Group's Director that same year, marking the end of his 22 consecutive years in a leadership or co-leadership role (1972-1994).
77 Roy Gravel, telephone interview, 4 February 2011.
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81 Charles Scriver, personal letter to MRC Group in Medical Genetics, 5 August 1987.
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83 David Rosenblatt, personal interview, 1 December 2009.
84 Roy Gravel, telephone interview, 4 February 2011.
85 Karaplis trained as a physician at McGill University (MD, 1984), and throughout this career has studied bone and mineral metabolism, with a particular expertise in molecular biological approaches to rickets and osteoporosis. He was a member of the Group until 2009, and continues his research on 24-Hydroxylase inhibitors in patients with X-linked Hypophosphatemic rickets, as well as the role of PTHrP and PTH in skeletal osteoporosis, at the Lady Davis Institute.
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87 Andrew Karaplis, personal interview, 30 November 2010.
88 Eric Shoubridge, personal interview, 8 October 2010.
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92 Robert MacKenzie, telephone interview, 2 February 2011.
93 Robert MacKenzie, telephone interview, 2 February 2011.
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95 Trifiro arrived at the Montreal Jewish General Hospital in 1991 after his residency work in endocrinology at Harvard between 1981 and 1986, and his post-doctoral training at the Clinical Research Institute of the Jewish General Hospital in Montreal. In 2007, Dr. Trifiro was appointed to the position of Chief of Endocrinology at the Lady Davis as part of his ongoing goal to merge his molecular endocrinology and medical genetics research with clinical practice.

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