2018

Synthesis, convergence, and differences in the entangled histories of cytogenetics in medicine: A comparative study of Canada and Mexico

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William Leeming and Ana Baharona. 2018. “Synthesis, Convergence and the Early Adoption of Cytogenetics in Medicine: A Comparative Study of Canada and Mexico.” Studies in History and Philosophy of Biological and Biomedical Sciences (71), 8-16. (Accepted Author Version)

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Title: Synthesis, Convergence and Differences in the Entangled Histories of Cytogenetics in Medicine: A Comparative Study of Canada and Mexico

Abstract: It is now commonplace for historians to say medical genetics began around sixty years ago with the synthesis and convergence of human genetics and cytological techniques in European centres which, in turn, were disseminated to centres in the United States in a more or less straightforward manner to become a new field of expertise in medicine and clinical research, i.e., cytogenetics. In this article, we show how the early histories of cytogenetics in Canada and Mexico unfolded against strikingly different backgrounds in clinical research and the delivery of health care. A key argument follows that the field of cytogenetics did not necessarily come together and develop the same way in all countries. The article begins with a brief background to the history of human cytogenetics. There follows two sections outlining the early adoption of cytogenetics in Canada and Mexico. Conclusions are then drawn using comparisons of the different ways local determinants affected adoption. This leads, in a final step, to suggestions for directions for future study concerning the ways circuits of practices, collaborative research, and transfers of knowledge have shaped the ways that cytogenetics has been organised in medicine around the world.

Keywords: Medical Genetics, Cytogenetics, Karyotyping, Transnational perspective on history, Entangled histories

1. Introduction

Within the clinic, medicine became geneticized since the 1930s when physicians incorporated genetics ("slowly at first, then with increasing vigor"), to explain health and disease. As Comfort has shown, medical genetics emerged as a hybrid of science and medicine "with the tensions, negotiations, and alliances between the competing styles and interests of the scientist and the clinician."[1] In this biomedical space, cells and chromosomes became places of knowledge production for explaining health and disease, inherited or congenital characters, inner or environmentaly produced. As Santesmases has shown, cytological evidence used by medical doctors, were the major contributions to the advancement of human genetics from a medical standpoint.[2]

Although the classic narrative acknowledges that medical genetics began approximately 60 years ago, at the end of the 1950s, with advancements in the science of human genetics preceding it from the end of World War II onward, [3] historians of science have not entirely, as Müller-Wille and his colleagues have argued, been been entirely successful in providing a coherent alternative to this widespread view. Nevertheless there is general agreement surrounding the idea that, although medical genetics was developed by the 1930s, the interplay of radiation damage and genetics expanded after the war. "WWII is a watershed in the history of heredity research when medical genetics began to privilege the individual over the collective, and population approaches

[1] Comfort (2012), pp. xii. For Comfort, this hybridization is one of the defining characteristics of twentieth-century healthcare. See, also, de Chadarevian (2013); Hogan (2016).

[2] Santesmases (2015).

[3] Harper (2008). .

replaced racial typologies."[4] The end of the World War II brought significant changes not only social and cultural, but also scientific and technological. As stated by Cambrosio and Keating, after the atomic bombs, Western medicine resulted in the emergence of new practices based on the direct interaction of biology (specially genetics) and medicine,[5] giving rise to postwar biomedicine characterized by focusing on cells and molecules. [6] In the post-war years, when there were growing international interests in studying the effects of radiation on human populations, human genetics was reconfigured. Indeed, Susan Lindee has described this phenomenon as "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." [7] More particularly, Diane Paul maintained the investigation of chromosomal anomalies in the late 1950s "laid the scientific groundwork for prenatal diagnosis." [8] In post-1945, knowledge on human heredity depended on the circulation of people, medical and experimental practices, and methods within very different disciplinary contexts. As Mülle-Wille and colleagues have said, "such transfers not only mediated interdisciplinary relations, they were also able to induce concurrent transformations in previously separated fields" that was the case of karyotyping techniques. [9]

[4] Gausemeier 'et al.' (2013), pp. 6.

[5] Cambrosio et al (2006). See also Keating and Cambrosio (2003).

[6] Gaudellière (2002).

[7] Lindee (2002), pp. 75.

[8] Paul (1998), pp. 141.

[9] Gausemeier 'et al.' (2013), pp. 9, see also de Chadarevian (2013).

The synthesis and convergence of human genetics and cytological techniques in European centres feature prominently in these accounts of the origins of medical genetics. These are said to have produced a new field of knowledge, i.e., cytogenetics, that would subsequently be disseminated to centres in the United States in the 1960s. Cytogenetics was in fact the first in a succession of new technological advancements that would permit scientists and clinicians to investigate diagnostically the genetic basis of disease. In a subsequent phase, cytogenetics, biochemical genetics, genetic counselling, and, after the mid-1980s, molecular genetics amalgamated into a formal medical specialty, i.e., "medical genetics," around which the researchers and service providers involved worked collectively to build an environment which provided the resources needed to ensure that governments and the public would acknowledge the value of the expertise being offered.

Our contribution to the history of early cytogenetics begins by broadening the scope of inquiry beyond the understanding that medico-scientific breakthroughs that originated in European centres in the late 1950s diffused in a more or less straightforward manner to become a new field of expertise in medicine and clinical research, i.e., cytogenetics. A key argument follows that the field of cytogenetics did not necessarily come together and develop the same way in all countries. Correspondingly, we believe it is inappropriate to suggest that developments in any single country can be regarded as exemplary for what has occurred elsewhere and against which developments in other national and supranational settings can be ranked and compared in relative terms. Indeed, historians of specialty formation in medicine in the past have convincingly shown that the phenomenon of medical specialisation is not by nature and by theoretical definition independent of local variants of the specialty practices to be found

in different national settings. [12] On a high level of generality, histories of medical specialties around the world have consistently indicated that individual specialties develop as more or less coherent sets of practices evolving from a more or less unitary perspective (i.e., professional medicine). However, detailed investigation has revealed the important contribution of complex intraprofessional arrangements and resource sharing relationships that are involved in achieving the emergence of closely defined obdurate structures and standards of practice. Accordingly, in what follows, we concentrate on the complexity of intraprofessional arrangements and resource sharing relationships that have contributed to the growth and development of cytogenetics in Canada and Mexico.

Moving beyond the confines of what occurred in the United States, our study of early cytogenetics gives accounts of two countries where the taking up of cytogenetics was influenced by strikingly different backgrounds in clinical research and health care delivery. Unlike the United States, where a broad cohesive national strategy has notably never been developed for genetic health care, [13] the structural development of medico-scientific interest in cytogenetics in both Canada and Mexico has followed closely the prescriptions of national programs and government policies. At the same time, we submit, Canada and Mexico each represent very different cases. Whereas the path that Canadian cytogenetics followed would focus on diagnostic testing, counselling and the formation of laboratories in university-hospital settings, the development and growth of Mexican cytogenetics was strongly tied to clinical research and investigating the chromosomal basis of population health. We will see that in Canada, in what follows, that the emphasis was all on testing, counselling and the clinic, while there was much

[12] See, for example, Döhler (1993); Leeming (2001); Weisz (2006).

[13] See, for example, Lin-Fu and Lloyd-Puryear (2000).

greater funding and institutional emphasis on research in Mexico.. These differences allow us to say that the local contexts were important in the adoption and development of cytogenetics in Canada and Mexico, thus contributing differently to the global fields of human genetics and medical genetics.

2. Some Background: What is Cytogenetics?

Simply put, cytogenetics is "the study of structure, function, and evolution of chromosomes." [14] The term "chromosome" refers to any of numerous threadlike bodies, consisting of chromatin, that carry genes in a linear order in the nucleus of the cells that make up organisms. Carl Wilhelm von Nägeli was the first to describe thread-like structures in the nuclei of plant cells in the 1840s. Walther Flemming later published the first drawn illustrations of what he called "chromatin" in 1882. He used aniline dyes to make the structure of the chromatin more visible under the microscope. Eventually, in 1888, the term "chromosome" (Greek for "stained body") was employed by Wilhelm von Waldeyer. [15]

The consensus among historians of science is that cytogenetics originally took shape as a discipline around the idea that chromosomes were the physical carriers of the hereditary material of living beings. [16] More specifically, in the first decades of the twentieth century, the chromosomal theory of heredity, also known as Boveri-Sutton theory, merged Gregor Mendel's theory of heredity with the evidence then available concerning chromosomes to posit chromosomes as the physical sites on which "genes," as Wilhelm Johannsen called them in 1909,

[14] Smeets (2004).

[15] Cremer 'et al.' (1988).

[16] See, for example, Dunn (1965); Jacob (1982); Wallace (1992); Cremer 'et al.' (2006).

were positioned. It is noteworthy that Mendel's theory of heredity had previously been published in 1866 in the Margraviate of Moravia, but remained relatively unknown until it was rediscovered and experimentally substantiated in 1900 independently by Carl Correns, Hugo de Vries, and Erich Tschermak in the Netherlands and Germany. The merger with the chromosomal theory of heredity allowed for the genetic theories of the early twentieth century to be explained in cytological terms and for scientists to make experimentally testable predictions concerning the transmission of heritable traits across generations. It was Walter Sutton who subsequently coined the term "cytogenetics" to refer to the study of chromosomes; cytogenetics being a combination of the disciplines of cytology and genetics. [17]

Technical advancements in the nineteenth century in optical lenses, stains and tissue manipulation contributed significantly to the growth and development of cytogenetics. However, progress in human cytogenetics was slowed down due to an inability to arrive at consensus on the correct count of chromosomes in human cells. From the 1890s to the 1920s, the number of chromosomes reported varied from eight to over fifty. [18] Theophilus Painter published the number as forty-eight in a study of meiotic chromosomes in 1923, a number that was generally accepted for many years. In 1956, Joe-Hin Tijo and Albert Levan of Sweden provided what is today regarded as the correct number of forty-six. New techniques for analysing chromosome anomalies followed that gained the attention of clinical researchers such as the ones studied in this article.

[17] Gersen (2004).

[18] Hsu (1979).

Down syndrome was the first anomaly – an autosomal trisomy – to be identified using chromosome analysis. Jérôme Lejeune of the Centre National de la Recherche Scientifique (CNRS) of Paris showed a slide of a karyotype which indicated the presence of the anomaly at the International Genetics Congress in Montreal in August 1958. By the end of 1958 there were at least four groups at Uppsala, Edinburgh, London, and Harwell who were, like the team in Paris, actively studying chromosomes and a variety of syndromes. On Lejeune's return to France, the CNRS hurriedly published with the Academy of Sciences "as a matter of urgency, in order to overtake the Anglo-Saxon teams." [19] This was followed soon thereafter by papers detailing the identification of Turner syndrome and Klinefelter syndrome. [20] In what follows, we trace how the new techniques for analysing chromosome were taken up in two countries outside of Europe: Canada and Mexico.

3. The Beginning of Cytogenetics in Canada

Recognition of the opportunities for tumour analysis afforded by cytogenetics can be traced in Canada as early as the late 1920s. Pierre Masson, an eminent French histopathologist with an interest in human tumours, arrived in the province of Quebec in 1927 to become Director of Anatomic Pathology at Hôpital Notre-Dame and Director of the Department of Pathology at Université de Montréal. The founding of the Service of Anatomic Pathology at Hôtel-Dieu de Québec followed in 1946. [21] Even so, Jacques Gagnon, originally a pathologist at Université de Montréal, is generally credited with first bringing cytogenetic techniques back to l'Hôpital Ste-

[19] Gauthier 'et al.' (2009), pp. 320-321.

[20] Ford 'et al.' (1959); Jacobs 'et al.' (1959).

[21] Seemayer 'et al.' (2008).

Justine after studying in 1959 with Jérôme Lejeune at the CNRS in Paris. [22] Louis Dallaire would subsequently set up a service laboratory for the Montreal Children's Hospital in 1964 before moving on to set up similar facilities at l'Hôpital Ste-Justine and l'Université de Montréal. Louis Dallaire had originally applied for graduate work in human genetics after obtaining his physician qualifications and completing, first an internship at Université de Laval in Quebec City and, second, a paediatric residency at the Montreal Children's Hospital. Following this he went on to study cytogenetics with Paul Polani at Guy's Hospital, London, and Michael Court Brown at the radiation unit of Edinburgh Western General Hospital. Dallaire subsequently returned to Canada to become Mead Johnson Fellow in medical genetics at the Montreal Children's Hospital while pursuing doctorate studies under the supervision of F. Clarke Fraser, then staff geneticist at McGill University.[23]

The resources obtained to support the establishment of the cytogenetic facilities at l'Hôpital Ste-Justine, l'Université de Montréal, l'Université de Laval, and the Montreal Children's Hospital all came from established pathology and paediatric departments of the respective university-hospital settings that housed them. In each case, the number and variety of illness groups being investigated were very limited – too limited to justify independent budgets. Accordingly, cytogenetics staff found themselves grouped together with the staff geneticists of the hospitals who were called upon to perform syndrome analysis and prenatal diagnosis and, secondly, laboratory personnel who carried out biochemical assays to test for metabolic disorders. Syndrome analysis and the testing for metabolic disorders, like chromosome disorders,

[22] Fraser 'et al.' (1992); Harper (2008); Leeming (2004).

[23] Telephone interview of William Leeming with Louis Dallaire (16/11/1998).

may or may not be genetic in nature. The salient point is that, in the 1960s, the precise definition of genetic diseases was still in question as was the extent to which the genetic basis of disease could be investigated. Placed side-by-side, those individuals involved in cytogenetics, syndrome analysis, prenatal analysis, and biochemical analysis increasingly came to view themselves as being enmeshed in a common enterprise. Within a decade they took steps that would give rise to the organisation of a province-wide network of genetics-related health care services that became known as Le Réseau de la Médecine Génétique du Québec (The Quebec Network of Genetic Medicine).

Le Réseau de la Médecine Génétique du Québec was formed in October 1969 on the recommendation of four heads of the paediatrics departments at the Centre Hospitalier Universitaire de Laval, Le Centre Hospitalier Universitaire de Sherbrooke, the Montreal Children's Hospital and l'Hôpital Ste-Justine. In addition to Dallaire, Le Réseau included Claude Leberge, who had taken his medical and paediatric training at Laval, followed by Ph.D. studies under Victor McKusick at The Johns Hopkins University, Richard Gagné, cytogeneticist and staff geneticist at the Centre Hospitalier Universitaire de Laval, Charles Scriver of McGill, who set up the de Belle Laboratory of Biochemical Genetics at the Montreal Children's Hospital, and Carol Clow of McGill. The original mandate of Le Réseau was to develop a centralised program for the early detection of metabolic diseases in newborns. By the mid-1970s, Le Réseau provided a range of diagnostic services, counselling and treatment for a variety of paediatric disorders including chromosomal anomalies. [24]

[24] For details about the beginnings of Le Réseau see de Grandpré (1974).

It is reasonable to conclude that Quebec was the first province to establish cytogenetics in Canadian medicine. However, it would be wrong to assume that cytogenetics disseminated from Quebec to the rest of Canada in a kind of centre-periphery relationship. Since 1972, Canada's health-care system has been predominantly publicly financed and delivered by a combination of funds and policies originating at the federal level and operating at the level of the provincial governments. [25] Federal law mandates health insurance coverage and contribution levels, but physicians' associations contract with provincial funders. Medical associations are generally free to oversee the allocation of spending among general practitioners and specialists. Most hospitals are private, non-profit corporations, although some hospitals are maintained by the federal government (e.g., the Department of National Defence) or provincial and territorial governments (e.g., psychiatric hospitals). All hospitals in the territories are administered federally. It was against the backdrop of the formative period of the establishment of a national health insurance system that genetic health care services in Canada took shape. At the same time, each provincial genetic health care service followed its own unique scheme of local development.

Of the eleven sites in Canada that provided some combination of genetic counselling and laboratory services in 1970, only three in Quebec were set up by individuals who had studied in Quebec. [26] The remaining eight sites (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Nova Scotia, Newfoundland) were set up by individuals who originally trained in the UK and/or the United States. While the university-hospital setting at Toronto, Ontario was a major point of training in genetic counselling, cytogenetics and biochemical genetics did not achieve mature status until the 1980s. The Atlantic Provinces (Nova Scotia, New Brunswick,

[25] For details see Clarke (2012), 267-86.

[26] For detailed histories concerning the different sites in Canada, see Leeming (2004).

P.E.I., Newfoundland) made a lot of resource-sharing arrangements for counselling and laboratory services, with a centre at Halifax (Nova Scotia) and one at St. John's (Newfoundland) acting as centralised services for people from multiple provinces. By contrast, the case of cytogenetics in the province Manitoba is exceptional in so far as experts were recruited from abroad and interprovincially to start up genetic services. It thus merits more attention.

In 1960, the head of the Winnipeg Rh Laboratory, Bruce Chown, and the head of paediatrics, Harry Medovy, at the University of Manitoba recruited Irene Uchida, trained in genetics at the University of Toronto, Ontario and subsequently in Drosophila genetics in Madison, Wisconsin. [27] Once in Winnipeg, Uchida secured a grant of $250,000 for five years from the National March of Dimes Foundation (United States) to do cytogenetics research on Down syndrome. With these funds, she hired a group of local laboratory technicians and assembled a group of postdoctoral fellows in cytology who were working in the Department of Plant Science at the University of Manitoba. Through the 1960s, she pursued research, did some genetics instruction in the Department of Paediatrics, and helped to set up a cytogenetics service in what eventually became the Department of Medical Genetics at Children's Hospital of Winnipeg. When she departed Winnipeg in 1969 to start up a chromosome laboratory at the new medical school at McMaster University in Ontario, Harry Medovy set about recruiting John L. Hamerton, then head of the cytogenetics section of the Paediatric Research Unit of Guy's Hospital Medical School in London, England.[28] Hamerton had been recommended to Medovy by a London (Ontario) neuroanatomist, Murray Barr, who had met Hamerton in 1958. Hamerton, in

[27] Hamerton (1992).

[28] Telephone interview of one of the authors with John L. Hamerton (21/03/1999).

turn, assembled a team of individuals from England to work with three local laboratory assistants in Winnipeg. Funds were solicited and received for laboratory equipment purchases from the Children's Hospital Research Fund (Winnipeg). By the early 1970s, Hamerton had been successful in acquiring two major research grants: a Public Health Research Program grant to survey the births at the Women's Hospital (Winnipeg) for chromosome abnomalies over a three year period, and a Medical Research Council (MRC Canada) grant for somatic cell genetic studies to develop cell hybrids and mutant cell lines. The MRC also awarded an additional major equipment grant. A formal genetic counselling clinic was started in 1969 by Hamerton in conjunction with a service cytogenetics component run out of a cytogenetics research laboratory.

While it can be said that there was considerable difference in the way that the structural development of institution-based interests in cytogenetics began in the various Canadian provinces, it is noteworthy that each provincial site was established in a university-hospital setting – often a paediatric department – which provided what might best be described as a "protective niches" in which cytogenetic laboratory facilities could be nurtured. These facilities remained small and entirely reliant on the larger departments that housed them until the early years of the 1970s when a concerted effort was made to assess the rate and direction of genetic health services at the national level in Canada. This occurred when the geneticists involved in genetic counselling realised that they were spending proportionally less time in their research laboratories and more time in the clinics they were assigned to. A survey by questionnaire circulated by the Genetics Society of Canada confirmed that an increase in demand for genetic counselling had occurred and attributed the increase to innovations in laboratory and prenatal counselling services. The idea of creating a formal organisation to develop and maintain standards of genetic health services emerged from this that resulted in a coalition of scientists

and clinicians providing counselling and laboratory services to form a corporation to be known as the Canadian College of Medical Geneticists (CCMG). The CCMG would go on to pave the way similar developments in the Netherlands, the United States, Finland, Sweden, Germany, France, and Denmark. The application for the incorporation of the College was recorded by the Ministry of Consumer and Corporate Affairs on January 13, 1976. The same year, the CCMG made a formal application to the Royal College of Physicians and Surgeons of Canada for the recognition of Medical Genetics as a new medical specialty.

It was not until 1988 that the Specialty and Manpower Committee of the Royal College supported the creation of medical genetics as a free-standing specialty in Canada. By that time, eighteen centres in eight provinces were providing counselling and laboratory services. All belonged to university-hospital affiliated programs, with the exception of three centres in Ontario. In addition, nine provinces had established outreach programs whereby staff from genetics centres was dispatched on a regular basis to hold clinics sites in outlying areas. Of the sixteen Canadian universities with faculties of medicine, seven offered Royal College accredited residency training programs in medical genetics, and seven offered training programs accredited by the Canadian College of Medical Geneticists. In practical terms, this meant that holders of MD degrees could either apply for certification as medical genetics specialists after completing a defined period of specialty residency in a program recognised by the Royal College, or, after obtaining certification as specialists in another area of practice recognised by the Royal College, apply for certification as clinical geneticists recognized by the Canadian College of Medical Geneticists. Ten years after specialty recognition, only two staff geneticists were employed in provincial genetics centres with just Royal College training in medical genetics. At the same time, a healthy percentage (44%) of the MD-geneticists was certified by both bodies, indicating a

relatively high level of acceptance in the field for the RCPSC medical geneticist category. The other fifty three per cent of clinicians providing counselling and consultation in genetics centres, by contrast, were made up of individuals who had entered the field prior to specialty formation in 1989.

As a final point, it is significant that the occupational role of MD-geneticists evolved in relation to the roles of other medical specialist categories. In brief, two broad sets of activities can be identified. The first set falls under a general category of prenatal care in pregnancy and childbirth, and overlapped with the services of obstetrics and gynaecology. Activities in this set continue to be referred to by their function: 'prenatal diagnosis'. This can be distinguished from what is called 'general genetics'. General genetics is a catch-all category for activities involving infants, children and adults. As a set of activities unto itself, it can be further divided into three subsets. Activities in the first subset overlap with the area of neonatology. This involves the diagnosis and management of congenital anomalies and diseases in newborns. The second subset takes up broader paediatric concerns and focuses on the diagnosis and management of disorders in children. Finally, the third subset deals with adult-onset diseases and screening for carriers of heritable conditions. In this regard, the nature of the interface with other medical specialists shifts depending on whether the patient is a pregnant woman, an infant, a child, or an adult.

4. The Beginning of Cytogenetics in Mexico

Spanish-born Mexican pediatrician Salvador Armendares is reputed to be the first Mexican physician with postgraduate studies in human genetics. After obtaining his B.Sc. in 1950 at the National Autonomous University of Mexico (UNAM), Armendares specialised in pediatrics at

the Children's Hospital of Mexico in 1956, working from 1961 to 1962 as a pediatrician and researcher at the Medical National Center (CMN) Gynecology and Obstetrics Hospital #2 and later on at the CMN Pediatric Hospital, both belonging to the Instituto Mexicano del Seguro Social (IMSS). In 1964, he was granted a fellowship from UNAM to spend two years as a graduate student at the British Medical Research Council in Oxford, England, under the supervision of Alan C. Stevenson. Stevenson, at the time, was the dean of the Council and considered one of the first physicians to work in the fields of human and medical genetics.

Armendares and Stevenson had become acquainted when Stevenson had come to the School of Medicine of UNAM to present plans for the World Health Organization (WHO) sponsored "International Project on Congenital Malformations." Human geneticists James V. Neel, J. A. Fraser Roberts, Stevenson and epidemiologist William J. Shull had previously met in 1959 in Ann Arbor, Michigan to plan a simple prospective study of the malformations occurring in a consecutive series of births in hospitals in several countries. The WHO agreed to support the Project with Stevenson as the principal investigator. Sixteen countries were chosen to participate, including Mexico. The WHO sent letters to the Ministries of Health for a number of countries explaining the goals of the research goal and requesting participation. After sending the invitation letter to each country's Ministry of Health, a visit was paid by WHO personnel to recruit obstetricians and pediatricians who might be interested in taking part in the study. The main requirements for the centers chosen were that they had to be maternity hospitals large enough to guarantee the efficiency of the study. This meant that the maternity hospitals would have to be rather large, expecting a minimum of 10,000 births over the two years of the project.

Argentina, Chile, Colombia, Mexico and Panama were among the Latin American countries taking part in this research. [29]

The collection of data began in 1961 and ended in 1964. This involved the recording of each single birth in white cards, and similar yellow cards for the second member of a twin pair (for the second and third members of triplets on the front and back). The cards were printed at Oxford in English, Spanish, Serbo-Croat and Czech. They were serially numbered and posted in batches to the various centers. After completion, the cards were returned to Oxford, indicating the cause of death and up to six malformations of each child along with the other information from each birth. Physicians were asked to describe any malformation found to avoid a single diagnostic term. If a syndrome was mentioned they were asked to describe all the malformations found in the child as well as to give a general diagnosis.[30] This study encouraged the pursuit of population studies on certain chromosomal anomalies, like Down Syndrome, that had not previously been done in Mexico.

Among the findings of the International Project on Congenital Malformations that were of particular interest in the context of Mexico were "the large contribution of neural tube defects to foetal wastage in most countries and the significant correlations of frequencies of these defects

[29] The participant Mexican hospitals were the Gynecology and Obstetrics Hospital #1 Gabriel Mancera, the director of which was the obstetrician and gynecologist Luis Castelazo Ayala (a physician well known to Armendares), and Gynecology and Obstetrics Hospital #2, whose director was the neonatologist Juan Urrusti Sainz, a friend and university contemporary of Armendares. See Insert Reference.

[30] Stevenson 'et al.' (1966), pp. 20.

over the twenty-four recording centres; the unexplained correlation in frequency between neural tube defects and dizygous twinning; the marked association of consanguinity of parents with increased stillbirth rates and frequency of early death of the infant, these frequencies being highest where parents are most closely related; and the demonstration that, if malformations known to be due to the expression of single recessive gene mutations are ignored, consanguinity of parents is demonstrably associated in these data with neural tube defect frequencies only." [31] Other malformations recorded were harelip and cleft palate, malformations of the gut, malformations of urogenital tract, and Down Syndrome. In the latter, unless careful clinical examinations were carried out in the newborns, studies were supplemented by dermatoglyphic and chromosome data. It is worth noticing that, according to the study, there was a relative high frequency of Down Syndrome in Mexico. The study also showed that in Mexico City the proportion of all pre-28th week losses that occurs between the 17th and 27th weeks was much higher than elsewhere, indicating that further analysis of the information collected might serve to identify the characteristics of a high-risk group of mothers and give clues to the etiology.

Second, and concurrently, the International Project on Congenital Malformations permitted Armendares to join and contribute to the international research networks on human and medical genetics. Soon after his return to Mexico from England, Armendares was able to establish the first Unit on Human Genetics (Unidad de Genética Humana, UGH) and, a couple of years later, the first graduate program on medical genetics for physicians endorsed by the UNAM. Although initially it did not include investigation, once consolidated in the 1960s, research groups began to be formed especially at the General, Gynecology and Obstetrics, and Oncology Hospitals. According to Mateos and Beyer, it was in 1966 that the Scientific Research

[31] Stevenson 'et al.' (1966), pp. 29.

Department (Departamento de Investigación Científica, DIC) was established in the IMSS, funded by a million-dollar donation from the Ford Foundation. [32] This department paved the way for the development of cytogenetics in Mexico with a strong emphasis in medical practice because it provided the budget, the space and the spirit to found the first unit in human genetics in the country.

Colombian-born Mexican physician Fabio Salamanca and Mexican physician Leonor Buentello were the first generation that graduated from the program and soon joined Armendares at the unit. It´s worth noticing that Salamanca had studied physiology at the National University of Colombia and, years later, taken a diploma on cytogenetics at the University of Minnesota under Jorge J. Yunis's suprervison. On her part, Buentello graduated from the School of Medicine at the UNAM, and graduated on virus genetics at Freiburg, Germany under Richard von Hass's supervision. The three of them were the nucleus of the UGH, and began the adaptation, standardization and stabilization of the techniques developed at the time for the study of human chromosomes. These were used to tackle the specificities of local needs and to develop precise diagnostic protocols to provide accurate genetic information to Mexican patients for the development of future treatments and prophylaxis (preventive medicine). Armendares (the only of the three who had practiced medicine at the hospital) was the first to associate karyotyping with genetic counselling, interpreting test results and technical language for the patients or their parents at the hospital. [33] Furthermore, the three began to attend international conferences and

[32] Mateos 'et al.' (2012).

[33] Insert Reference.

publish in international journals that contributed to the global knowledge on human genetics.[34] By the end of the 1960s the UGH moved from its original location in a small room in the basement of the Paediatric Hospital to an adjoining bigger area where more people were hired and more equipment acquired. In 1970 the UGH consisted of ten researchers, twelve technicians and assistants, and up to twelve doctoral and postdoctoral students.

Influenced by the research he conducted at Oxford with Stevenson, Armendares' genetic research agenda at the UGH included population genetics in congenital illnesses, and particular disorders such as abnormal growth in Mexican children, malnutrition as a cause of chromosomal alterations, and Turner Syndrome, which was not well understood. He also worked on the early diagnosis of Down Syndrome. Prior to the adoption of karyotyping, children with Down Syndrome in Mexico were diagnosed by looking for a smaller size in the iliac index of the hip. [35] The location of the unit in the hospital was of crucial importance inasmuch as it allowed human geneticists and physicians to combine the clinical practice with the laboratory in a two-way-traffic. Furthermore, the standardization of the up to date techniques at the UGH was very important because they made the karyotype accessible to scrutiny and close examination.

[34] In 1980, Armendares and Buentello left the UGH and entered the Anthropological Research Institute (Instituto de Investigaciones Antropológicas) of the UNAM as a full-time researcher and technician respectively. Here they founded and worked in the area of anthropological genetics until Armendares' death in 2010. When Armendares left the unit, Salamanca was appointed its director, a position that he holds to the present. For further details of Armendares', Buentello's and Salamanca's academic careers, see [self-reference].

[35] Armendares 'et al.' (1967).

Unquestionably, Armendares learned karyotyping techniques in his training at Oxford. Among the most important were the ones developed by Moorhead and colleagues in 1960 for chromosome preparation using heparin as an anticoagulant – of common use in all the blood culture techniques at the time. [36] He also adopted the use of phytohemagglutinin, a protein obtained from Phaseolus vulgaris, as a mitotic initiator. [37] In Armendares laboratory these techniques were used for leucocyte cultures from peripheral blood. These techniques, for example, allowed Armendares and colleagues to do more complete work on Down Syndrome, introducing karyotyping as a tool for a more precise diagnosis. [38] On the other hand, more attention was paid to techniques for identifying Turner Syndrome. Articles on gonadal dysgenesis in patients with Turner Syndrome had been published as early as 1972. Using gonadal biopsies, Armendares and Salamanca found that most presented the XO genotype, but a series of chromosomal variants appeared in the population studied at low frequencies.[39]

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[36] Moorhead 'et al.' (1960).

[37] Nowell (1960).

[38] Armendares 'et al.' (1968).

[39] Màrquez-Monter 'et al.' (1972). It is worth noticing that Héctor Márquez-Monter was a pathologist who studied at the Anderson Hospital in Houston, Texas. He was Head of the Pathology Department at the Biomedical Research Unit of the CMN where he hired physician Alejandro Cuevas Sosa in 1967 to work with Armendares. Cuevas had been studying with Margery Shaw at the Houston Institute of Health, a remarkable physician and lawyer best known as one of the first to perform genetic counselling in the clinic. Upon his arrival, Cuevas Sosa began the study of familial extracentric bisatellited chromosome due to a translocation between

Other materials and methods were used in later studies for the first time in the country. For example, buccal smear wab samples stained with aceto-orcein were used for the X chromatin determination, and peripheral blood lymphocyte culture was used for chromosomal analysis of seventy-four patients from the Pediatric Hospital. These new techniques allowed the geneticists at the unit to relate Turner Syndrome with different chromosomal variants.[40] This work received more than sixty international citations between 1973 and 1985. [44]

As part of the innovation pursued by Mexican geneticist at the Unit, other studies were performed towards understanding the frequency of certain illnesses with the occurrence of chromosomal alterations, for example, a study published in 1971 on child malnutrition and the effect of protein calorie deficiency on genetic material. [45] It was found that there was a significant increase in structural anomalies of chromosomes in connection with malnutrition, a pending agenda of Post-Revolutionary Mexican governments. These results drew the attention of

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the short arms of two acrocentric chromosomes, using leucocyte cultures carried out according to Moorhead and collaborators, and autoradiography on the mother cells according to Schmid. See Moorhead 'et al.' (1960); Schmid (1963); Armendares 'et al.' (1969).

[40] Armendares 'et al.' (1972).

[44] These works led to publication of the monograph Turner Syndrome. Diagnosis and Therapeutic Handling in 1979 by Armendares, which gives a detailed description of the medical characteristics of the syndrome, frequency in the population, its chromosomal classification, clinical characteristics and the correlation of the phenotype to the karyotype, sexual development, intelligence quotient and treatment. It is important to mention that these studies were the first of their kind in Mexico. Armendares (1979).

[49] Pardue 'et al.' (1970).

researchers both inside and outside Mexico, contributing to the development of this line of research in both humans and in laboratory animals. Years later, the same authors performed a study with other colleagues, published in 1979, to observe the frequency of structural chromosomal abnormalities in children with severe malnutrition. They used the frequency of sister chromatid exchange (SCE) as a more sensitive method for detecting certain types of environmental mutagens. They also used the Perry and Wolff staining technique with Giemsa stain published only a few years before in 1974. [46] The results obtained did not show overwhelming evidence of an increase in SCE in malnourished as compared to normal children. However, what they did find was that the proportion of third or subsequent cell division metaphases were significantly higher in malnourished children in comparison to the control group. This was compatible with the observations of Armendares and colleagues that in mixed cultures of malnourished and normal subjects, metaphases from the former are always more numerous than the latter. [47] This suggested the possibility that even if the cell cycle is faster in children than in adults, it is much faster still in malnourished children. [48]

Finally, in their work on the C band human chromosome study, Armendares, Salamanca and Buentello were capable not only of adopting but also of significantly improving a newly acquired technique to study chromosome abnormalities for a local context. In 1970, Pardue and Gall described a procedure to localize C-bands in human chromosomes using sodium hydroxide as a denaturalizing agent. [49] The next year several papers appeared informing about the drastic

[49] Pardue 'et al.' (1970).

[49] Pardue 'et al.' (1970).

[49] Pardue 'et al.' (1970).

[49] Pardue 'et al.' (1970).

changes in chromosome architecture caused by this substance. Margery Shaw and colleagues made several modifications reducing the concentration and time of exposure. [50] In 1974 Salamanca and Armendares developed a new staining technique using barium hydroxide, which showed up the C-bands of chromosomes to make this process simpler and more practical. The study was carried out on metaphase chromosome from normal and abnormal males and females. Chromosomes preparations were obtained according to the usual procedures in blood samples, and then treated with barium hydroxide. With this technique many metaphases were observed in each study because, even though barium hydroxide was as harmful as NaOH for the chromosome structure, it was more soluble and its solubility could be increased with the rise in temperature. This technique allowed each chromatid to be observed with its own centromere.[51]Armendares and his colleagues would subsequently take advantage of this improved technique to perform future studies.

The increasing research activity of the members of the UGH and the rapid development and adaptation of cytogenetics at clinic settings were very important for the institutionalization of human genetics in Mexico. In 1968, the Mexican Association of Human Genetics (Associación Mexicana de Genética Humana, AMGH) was established with a strong medical component. The Association brought together specialists in the field to promote human resource development and research, as well as the teaching of human genetics in Mexico. Its founding members were Salvador Armendares, Leonora Buetello, José María Cantú, Alejandro Cuevas, Mario Gonzalez Ramos, Susana Kofman, Hector Márquez Monter, Antonio Quiroz, Adolfo

[50] Drets 'et al.' (1971).

[51] Salamanca 'et al.' (1974).

Rosado, Mario Salazar Mallén, Carlos Zavala, Maria Teresa Zenzes and Rubén Lisker. Besides these, the corresponding foreign members were also elected. The interdisciplinary nature of human genetics allowed the inclusion of specialists in other fields such as biochemistry, biology, and chemistry. [52] Undoubtedly, the creation of the AMGH gave considerable weight to the formation of national and international academic networks, and was an important forum for the discussion and dissemination of genetic knowledge.

In terms of influence beyond Mexico, the organization of the V International Congress of Human Genetics held in Mexico in October 1976, was very important as a site of transnational collaboration. The first Congress was held in 1956 in Copenhagen as an effort to bring together human geneticists from all over the globe to contribute in all aspects of human genetics, including clinical practice, research, and education, and to foster international networks of collaboration that allow the circulation of people, methods and practices. Due to the international collaborations and positioning of Mexican human geneticists, the Permanent Committee of the International Conferences of Human Genetics, headed by James Neel, Salvador Armendares, F.C. Fraser, J. de Grouchy, and Lionel Penrose among others, the committee decided to give Mexico the opportunity to host the meeting. The Mexican Organizing Committee include the father of populations genetics in the country Mario Salazar Mallén, Salvador Armendares and his close collaborator and friend Rubén Lisker, Héctor Márquez Monter, José María Cantú and Fabio Salamanca among others. This congress was the first to be hosted by a Latin American

[52] It is noteworthy that other groups or institutions which appeared later, such as the Center for Studies in Health and Law at the Institute of Legal Research of the UNAM in 1992, and the Mexican Society of Genomic Medicine in 2003, reintroduced the fundamental principles of the AMGH.

country, and in its 5 day duration, there were presented more than 200 works on different aspects of human genetics. It is worth noticing that the Mexican geneticist not only were at the time working at the UGH, but in other research institutions that were developping human genetics in clinical practice, such as the Children's Hospital and the Pediatric Hospital, and many different state institutions.

Years later, in 1976, the National Council of Experts in Human Genetics (Consejo Nacional de Especialistas en Genética Humana, A.C.) was established, which became the Mexican Council of Genetics (Consejo Mexicano de Genética, CMG) in 1998. This was part of the Regulatory Committee of Medical Specialties (Consejo Nacional de Especialistas en Genética Humana, A.C.), which incorporated 47 Mexican councils and was governed in turn by the National Academy of Medicine. There were basically two objectives behind the creation of the CMG. The first was to bring together specialists in human genetics, and the second was to evaluate specialists who wished to pursue genetic medicine in a peer review system in order to ensure high standards of knowledge and training to detect health problems for hereditary diseases and genetic counselling. Genetic counselling has been restricted to tertiary hospitals, meaning those who give specialised care and conduct research. Counselling in these institutions, in principle, can only be given by doctors or specialists certified by the CMG, and is restricted to the establishment of family trees, as well as cytogenetic, biochemical and molecular studies to establish the probability of patients or their children inheriting a genetic disorder. The CMG was thus established as a certification body and conceived as an organization that supports and distinguishes medical genetics specialists from other areas. The CMG has kept close ties with the AMGH owing to the fact that a considerable number of members belong to both organisations.

Today, unlike other groups, the CMG offers courses to its members in organisations such as the National Institutes of Pediatrics and Nutrition, the General Hospital, CMN HP, and the Western Center for Biomedical Research – the last two being a part of the IMSS. As a result of the development of human genetics, the program for Registry and Epidemiological Surveillance of External Congenital Malformations was established in 1977. Years later, in 1984 it was changed to the National Reference Center for Congenital Malformations in Health (Centro Nacional de Referencia de Malformaciones Congénitas en Salud, CNRMCS) as a hospital system proposed by the state, which included the Ministry of Health, the IMSS and the ISSSTE. This registry started with the goal of having an up-to-date record of malformations, risk factors and teratogen monitoring environments. However, by the late 1980s, it had fallen behind with respect to keeping reliable records of genetic disorders in Mexico.

5. Concluding Remarks and Future Directions

The Johns Hopkins geneticist Victor McKusick famously said in the early 1960s that cytogenetics "gave us our organ." [53] McKusick was alluding to the fact that medical specialties have typically each taken on an organ of the body as the focus of their treatment practice. Thus, cardiologists have taken possession of the heart as their site of practice and nephrologists the liver. On the other hand, it is not clear that the chromosomes constitute an organ site in a manner that properly corresponds to hearts, livers, etc. Chromosomes are sites on which the genes are located, and cytogenetics have focused on studying the genetic basis of disease as a phenomenon of the entire body. Furthermore, whereas past historical studies on medical specialisation have typically focused on specialties that already have mature institutional

[53] Cited in Comfort (2012), p. 165.

histories, medical genetics in general – and cytogenetics in particular – is a recent addition to medicine. Accordingly, we have mostly stayed within the limits of national frameworks in this article to tell the histories of pioneering individuals who brought new techniques, experimental procedures, and methods of cytogenetics to Canada and Mexico. In this context, their histories show the narrowing of the interest area of individuals involved in creating a specific area of expertise, i.e., cytogenetics. This has been useful to the extent that it shows the narratorial plurality of new techniques, procedures, and methods being applied to serve different local, regional and national purposes. On the other hand, once established as a specific area of expertise, the narrowing down of cytogenetics to smaller routine component parts can also be seen to have resulted in a variety of roles performed by individuals operating within organisational settings that pre-exist cytogenetics. We have discussed some of these relationships, but, for reasons of limitation of space, have not fully explored their implications from the unitary, global perspective of medicine.

An important point to be taken away from the article is that what look like coherent sets of practices in each country began as loose networks of resource dependencies, personnel, and organisations which can be re-configured within the context of local research and health care delivery systems. While proficiency in early cytogenetic techniques required training and practice, the work of the cytogeneticist required little specialised or expensive equipment or supplies. Chromosome analysis, or "karyotyping," involved photographing what is seen through the barrel of a microscope and reordering the chromosomes in accordance with a system of chromosome designation. In the early years this meant literally cutting out the photographic images of each chromosome, gluing them in order on another piece of paper, and re-photographing the arrangement for purposes of analysis and filing reports. In the 1960s the

number of chromosomal anomalies that the cytogeneticist was responsible for investigating was quite limited: Down syndrome, Turner syndrome, Klinefelter syndrome, Wolf-Hirschhorn syndrome, cri du chat syndrome, 5p trisomy, 13 q monosomy, 18p-syndrome, 18q-syndrome, and 21 partial monosomy. [54]

In Canada, cytogenetics facilities began as relatively small affairs in the 1960s operating in what we have described as the "protective niches" of university-hospital settings which provided the resources necessary to nurture what, from the perspective of the institutions housing them, was promising clinical research. But, that being said, it becomes increasingly easy to lose sight of the individuals working in these facilities after 1970 when the roles of cytogenetics staff members became routinely defined and new job categorisations appear in the division of labour of the university-hospital settings employing them. The article shows that a push towards ideal-typical standards of practice and recognition of expertise occurred with the development of a mutual awareness among Canadian practitioners of counselling and laboratory services as they became increasingly aware that they were involved in a common enterprise. The emergence of closely defined obdurate structures and standards of practice subsequently appeared with the establishment of a self-regulating body of de facto specialists: the Canadian College of Medical Geneticists (CCMG). Specialty formation was subsequently formally achieved with recognition by the Royal College of Physicians and Surgeons of Canada for medical genetics as a new free-standing medical specialty. At the same time, it is significant that while the occupational role of MD-geneticists evolved in relation to the counselling of patients, the role of PhD-geneticists became more limited in perspective. PhD-geneticists would become part of a class of technical experts functioning only in consultation with the MD-genetics and MSc trained genetic

[54] Harper (2006), p. 156.

counsellors. While they continued to administer and manage testing facilities, they would cease to be directly involved in the counselling of patients.

By comparison with our account of cytogenetics in Canada, there is a markedly pronounced emphasis on the role of the clinical researcher in our account of Mexican cytogenetics. Mexico has been remarkably prolific in the development of new knowledge and techniques at both the national and international levels.

It is important to note that prenatal diagnosis and the services of general genetics are accessible in most Mexican states – but not all. [55] By the early 1990s, there were one hundred and thirty-one specialists certified by the Mexican Board of Human Genetics of which ninety-seven were registered physicians. At the same time, most of the specialists (ninety-eight) were concentrated in the four largest Mexican cities: Mexico City, Guadalajara, Monterrey, and Toluca. Further to this, prenatal diagnosis and genetic counselling was available only in one of the public hospitals (Mexico City) and a few private hospitals. The main reason for the restrictions in access has been the illegality of abortion in most of the Mexican states.

As in our Canadian account, we began our account of Mexico by focusing on pioneering efforts. The focus is here on developments at the National Autonomous University of Mexico (UNAM) and the Instituto Mexicano del Seguro Social (IMSS). Salvador Armendares brought cytogenetics to these institutions after studies at the British Medical Research Council in Oxford, England in the mid-1960s. He was also involved is enmeshing Mexico, along with Argentina, Chile, Colombia, and Panama, in the World Health Organization sponsored "International Project on Congenital Malformations." At the same time, it is clear from our account that the

[55] Carnevale 'et al.' (1998); Penchaszadeh 'et al.' (1998); Kofman-Alfaro 'et al.' (2004).

same conceptual and technological innovations that impelled the structural development of institution-based interests in Canada attracted the interests of governmental bodies and policy makers both inside and outside of Mexico. We make mention of, for instance, the establishment in the mid-1960s of the Scientific Research Department at the IMSS, funded by a million-dollar donation from the (U.S.) Ford Foundation. This coincided with an increased emphasis at the UGH on clinical research directly pertaining to general genetics and preventive medicine as well as investigation of the structural anomalies of chromosomes linked with malnutrition.

All in all, it is the involvement of Canadian and Mexican cytogeneticists in the formation of national and international circuits of practices and collaborative research that suggest promising directions for future historical investigation. We have only begun to touch on how Canada and Mexico have been indirectly involved with one another in the growth and development of cytogenetics through early exchanges of cytogenetic knowledge, techniques, and people. In addition to the early relationships in Britain and France, Canadian and Mexican cytogeneticists have been part of a wider, entangled history involving cytogeneticists from a multitude of countries including (and not limited to) Sweden, Italy, Germany, Israel, the United States, Paraguay, Argentina, Brazil, Chile, Uruguay, Colombia, Ecuador, Peru, Costa Rica, and Japan. What Jürgen Kocka describes as "processes of mutual influencing, in reciprocal or asymmetric perceptions, in entangled processes of constituting one another" need further exploration if we are to more fully understand the inexorable push to become part of a larger movement to develop cytogenetics as a specialised field of laboratory medicine. [56] This, we submit, has involved individuals and localities whose interactions deserve to be recognised and studied in more than just one journal article.

[56] Kocka (2003), pp. 42. See also Barahona (2017); Müller 'et al.' (2009); Pernau (2012).

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