Medical Genetics and the First Studies of the Genetics of Populations in Mexico

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ABSTRACT Following World War II (WWII), there was a new emphasis within genetics on studying the genetic composition of populations. This probably had a dual source in the growing strength of evolutionary biology and the new international interest in understanding the effects of radiation on human populations, following the atomic bombings in Japan. These global concerns were shared by Mexican physicians. Indeed, Mexico was one of the leading centers of this trend in human genetics. Three leading players in this story were Mario Salazar Mallén, Adolfo Karl, and Rubén Lisker. Their trajectories and the international networks in human genetics that were established after WWII, paved the way for the establishment of medical and population genetics in Mexico. Salazar Mallén's studies on the distribution and characterization of ABO blood groups in indigenous populations were the starting point while Karl's studies on the distribution of abnormal hemoglobin in Mexican indigenous populations showed the relationships observed in other laboratories at the time. It was Lisker's studies, however, that were instrumental in the development of population genetics in the context of national public policies for extending health care services to the Mexican population. In particular, he conducted studies on Mexican indigenous groups contributing to the knowledge of the biological diversity of human populations according to international trends that focused on the variability of human populations in terms of genetic frequencies. From the start, however, Lisker was as committed to the reconstruction of shared languages and practices as he was to building networks of collaboration in order to guarantee the necessary groundwork for establishing the study of the genetics of human populations in Mexico. This study also allows us to place Mexican science within a global context in which connected narratives describe the interplay between global trends and national contexts.

KEYWORDS Rubén Lisker; Mario Salazar Mallén; Adolfo Karl; medical genetics; population genetic surveys; indigenous populations; hemoglobin variation; G6PD deficiency

HUMAN genetics was part of the emergence of biomedicine in the mid-20th century and underwent a sea change following World War II (WWII), giving rise to multicentric interlaboratory studies and clinical trials, the establishment of scientific research groups, and medical and research networks in which collective production of knowledge occurred (Cambrosio *et al.* 2006, Keating and Cambrosio 2007). The postwar collaborative networks, supported by both international and national agencies, established new ways to circulate practices, knowledge, and tools in which physicians and human geneticists contributed to the characterization of human populations by studying variation in genetic frequencies.

During these years, extensive serological and blood-group distribution studies took place with the intention of measuring human genetic variability, underlain by growing international interest in understanding the effects of radiation on human populations. One of the early centers for the study of the genetic structure of populations was Mexico. This story is recounted here.

From the 1940s onwards, Mexican physicians adopted a scientific perspective for studying human heredity and environmental factors associated with certain pathologies in Mexican populations and particular family trees. The first publications in which formal knowledge of genetics was applied to humans, and in which the appearance of certain illnesses or conditions was correlated with hereditary genetic factors, appeared toward the end of the 1940s. These studies paved the way for the development of knowledge on human heredity that contributed to the introduction of medical genetics to Mexico, and the development of population genetics

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Professor Lisker passed away on December 2015, and I dedicate this manuscript to his memory.

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there (Barahona 2009). As Comfort (2012) has shown, the development of medical genetics was therefore strongly linked to that of human genetics, a process called the “medical turn” in human genetics, which occurred in the middle of the 20th century in the years following WWII. “The narrative of the medical turn in human genetics implies that genetics colonized medicine. . . physicians actively imported genetics into their discipline—slowly at first, then with increasing vigor” (Comfort 2012, p. xii). Out of this turn, Mexican physicians-turned-geneticists Mario Salazar Mallén, Adolfo Karl, and Rubén Lisker consolidated the emerging model of human genetics in the clinic and in scientific research in postwar Mexico (1945–1970).

As we will see, they assimilated the knowledge and practices learned abroad and introduced them to national needs while taking part in various international collaborative networks. It was Lisker’s studies, however, that were instrumental in the development of population genetics in the context of national public policies for extending health care services to the Mexican population, given the fact that in the 1950s and 1960s, Mexican human populations were studied for anthropological, ethnographic, or economic ends; but rarely from a genetic perspective. He established one of the largest genetic research programs to focus on indigenous people during the 1960s and 1970s. Lisker’s motivations cannot be explained without either their national context or without reference to international and global concerns. Of particular interest was his long-term effort to carry out research on indigenous populations in order to provide insights into the biological history of the human species, disease patterns, and biological relationships among populations.

The key elements in this story are the trajectories of Salazar Mallén, Karl, and Lisker and the international networks in human genetics that were established after WWII. In the particular case of malaria eradication in Mexico, these scientists sought validation and credibility for their work in medicine and genetics, which was intertwined with economic and political arguments, to pursue their personal scientific agendas (Cueto 2007). Thus, these Mexican human geneticists of the mid-20th century mobilized scientific resources and laboratory practices in the context of international trends and national priorities in a way that led to significant discoveries in the field internationally. The story illustrates the still largely-unrecognized importance of Mexico’s role in a global movement to deliver the benefits of scientific knowledge to millions of people.

I will present my narrative in two parts. In the first, I shall refer to the first studies on the distribution of genetic markers in the Mexican Mestizo and Indian populations in the 1950s, in the pioneering work of Mario Salazar Mallén and Adolfo Karl. In the second, I shall focus on Lisker’s studies at the Nutrition Illnesses Hospital (Hospital de Enfermedades de la Nutrición, or simply the HEN) on the characterization of indigenous Mexican populations, using the knowledge he had acquired early in his career during stays in Chicago and Seattle. I shall attempt to demonstrate that Lisker’s research

was perfectly aligned with the developments that were occurring in other parts of the world, although he was concerned with national priorities. His studies were important both at the national and the international level inasmuch as his research on the genetic characterization of Mexican groups contributed to global knowledge on the genetic diversity of American populations.

Mario Salazar Mallén and Adolfo Karl’s First Genetic Characterization of Mexican Human Populations

Population genetics was the first branch of medical genetics developed in Mexico by a group headed by Mario Salazar Mallén (1913–1976) at the General Hospital of the Ministry of Health and Medical Attention, and at the National Cardiology Institute. Salazar Mallén studied at the School of Medicine, National Autonomous University of Mexico (UNAM), where he received his degree in 1936. One year later, he moved to New York to specialize in allergies and internal medicine. Upon his return in 1938, he founded the first Mexican Allergy Service at the General Hospital; he is also considered to be the founder of the Mexican Allergological School. He was the first hematologist to carry out research on blood-group distribution; a pioneer of human population genetics in Mexico. In addition, he was the first chairman of the Mexican Human Genetics Association, founded in 1968, whose founding members included his former student Rubén Lisker.

In particular, he wished to understand the heredity and distribution of certain pathologies with regard to immunological illnesses. The first publications of this group date from 1948, when “Studies of pharyngeal flora in groups of children in Mexico City with reference to the existence of hemolytic streptococcus” appeared, then “Psychological factors in illnesses,” “Immunological study of ancient bone remains,” “The problem of auto-sensitization and the pathogenesis of some essential processes,” “Some problems in the doctrine of allergies,” and several others (see Fernández del Castillo 1959), but undoubtedly the most-important works are those published in 1944, 1949, and 1952.

In his 1944 paper, he published a study on the distribution of the ABO groups in indigenous and mixed-race populations (Mallén and Portilla 1944). It’s worth noting that in 1945, Alexander Wiener and a Mexican colleague J. Preciado Zepeda also published a study on the individual blood differences in Mexican Indians, with special reference to Rh blood types and Hr factors (Wiener *et al.* 1945). New York physician Wiener had begun the study on the Rh factor at the beginning of the 1940s, trying to classify the Rh alleles using familiar subscripts of letters and numbers (Comfort 2012). Being a blood group expert, Wiener worked with samples of serum factors from Afro-American, Jewish, Chinese, Australian, and Mexican populations and the data were incorporated in Arthur Mourant’s survey on the distribution of human blood groups (Suárez and Barahona 2013; see also Mourant 1954). Salazar Mallén was aware of Wiener’s work on

different indigenous populations around the world and wanted to conduct similar studies in Mexico.

Further publications of Salazar Mallén are those that appeared in 1949 and 1952, using agglutinin as a marker in seven indigenous populations and one mixed-race population in the Federal District for the characterization of blood groups (Salazar Mallén 1949; Arteaga *et al.* 1952). Salazar Mallén collaborated with the Instituto Nacional Indigenista (INI, National Indigenous Institute), which provided the infrastructure to take the blood samples and the management of the indigenous populations.

Salazar Mallén was partly supported at this time by a grant from the British Council to visit Dr. Robert Russell Race's laboratory at the Medical Research Council in London in 1951, where Race not only gave him advice and training, but "a generous amount of the testing sera" (Arteaga *et al.* 1952, p. 357). This collaboration was influential on Salazar Mallén's future projects as Race was a renowned human blood expert, who had published *Blood groups in man* in 1950 with his eminent serologist wife Ruth Ann Sanger; an authoritative book that was used as a mandatory reference for ensuring safe blood transfusions.

By 1959, Salazar Mallén and colleague Teresa Arias published a study in the influential journal *Science* on the inheritance of the Diego blood group in Mexican Indians (see Box 1).

Box 1

The Diego blood factor was discovered by Levine and collaborators back in 1954 in the blood of a Venezuelan mother whose baby had hemolytic disease and died three days after birth. After conducting some blood tests intended to find a rare blood factor in the child and parents' blood, researchers found a new type classified as a "family" blood type and named it "Diego" after his father's surname. Initially considered to be rare, further investigations traced this group from the Venezuelan family to many other indigenous populations in Latin America and to the Mongolian race in Asia (Levine *et al.* 1954; for a history of the Diego blood group see Junqueira and Castilho 2002). It is now known that the Diego system is composed of 22 blood factors or antigens carried on the band 3 glycoprotein also known as AE1 (Anion Exchanger 1) located in human chromosome 17. The genetic background to all the polymorphisms is a single nucleotide change in the band 3 gene that gives rise to an amino acid substitution in the protein due to a mutation in the SLC4A1 gene (Poole 1999; Bégat *et al.* 2015). The Diego antigen is common in indigenous people of the Americas and East Asians and people with some ancestry in those populations, but not found in other human populations (Layrisse and Wilbert 1961).

By the 1950s, it had been proven that the Diego factor was present in the blood of Caucasians in very low percentages, and from 5% in Chinese populations to 45% in Brazilian Indian populations, but not in exclusively-derived black populations, Australian aborigines, or in Polynesians. The relatively high frequency of this blood group in South America had genetic, anthropological, and clinical implications. Because it was an important marker for understanding the diversity of indigenous populations, and also because these studies had not been done in Mexico before, Salazar Mallén and Arias embarked on a project to describe the Diego blood group in indigenous populations. They tested 152 blood samples from 30 nonrelated Tlaxcaltecan Indian couples and 62 children with some slight Spanish mixtures, and concluded that the Diego blood factor was present in 20.39% (Salazar Mallén and Arias 1959). This finding supported previous investigations in Brazilian Indians (Junqueira *et al.* 1956) and in Chinese and Japanese populations (Layrisse and Arends 1956).

Following the line of research established by Salazar Mallén, in 1957 Adolfo Karl at the Escuela Nacional de Ciencias Biológicas of the Instituto Politécnico Nacional (National School of Biological Sciences of the National Polytechnic Institute), published the first study on the distribution of abnormal hemoglobins in a group of Mazatecs in the river basin of Papaloapan. Using the horizontal gel electrophoresis technique, he analyzed 123 samples of indigenous clotted blood samples that were selected on the basis that there was no close family relationship between the individuals from whom they had been taken. These individuals were between 8 and 85 years old and the samples were taken from 17 populations in the area of Papaloapan. The results of this study demonstrated the prevalence of hemoglobin type A, without the presence of fetal or abnormal hemoglobin. His conclusions were "a) that in the Mazatec group of indigenous Mexicans there is a high frequency of the gene or group of genes that induce the formation of hemoglobin A, b) that the individuals studied are, very probably, homozygotic for said factors, c) that it does not appear that there are gene mechanisms or those of another nature that block or inhibit the normal formation of hemoglobin A, and d) that, for the moment, it is not possible to put forward any information on the hereditary mechanism of hemoglobin A" (Karl 1957, p. 86). These studies were related to those observed in other research laboratories at the time, but they did not have an impact on Mexican genetics until other groups began to publish by using more markers and new techniques such as gel electrophoresis to measure genetic variability in Mexican populations.

These studies would be, from these years onward and especially during the 1960s and 1970s, performed by other groups; especially Lisker and his collaborators in the HEN, with emphasis on population genetics of genetic markers; by Dr. Salvador Armendares and Dr. Fabio Salamanca at the Mexican Social Security Institute with an emphasis on cytogenetics; and by Alfonso León de Garay in the Genetics and Radiobiology Program of the National Commission of Nuclear Energy, with an emphasis on genetics and radiobiology.

Figure 1 Rubén Lisker ca. 1995. Taken from Pérez Tamayo 2008. With permission of Universidad de Colima, Mexico.

Collectively, these studies contributed tremendously to the development and consolidation of human genetics in Mexico,¹ particularly as carried out by Rubén Lisker.

Dr. Rubén Lisker Yourkowitzky in an International Setting

Dr. Rubén Lisker (1931–2015) was born in the city of New York, United States, and arrived in Mexico at six months of age. A descendant of a Ukrainian–Jewish family, he held American nationality until the age of 18, and would not have had problems in becoming a Mexican citizen as his father Felipe already was one. After the Russian Revolution, Felipe Lisker had studied medicine but abandoned his degree after the second year, immigrating to the United States as a student; he arrived in Mexico in 1926 when expelled from the United States for not having his papers in order. He was later able to establish a hardware store in Corregidora Street in the center of Mexico City. Don Felipe was married to Olga Yourkowitzky in 1929, whom he had met previously in the United States (R. Lisker, April 2008, personal communication; see Barahona 2009) (Figure 1).

When Lisker finished high school, he entered the School of Medicine of the UNAM in 1948. There he was a student of Mario Rebolledo Lara, who gave lectures on medical therapeutics at the General Hospital; and, crucially, Mario Salazar Mallén, who gave classes on various medical disciplines. He was awarded his degree with the thesis “Immunological response in malnutrition”, his advisor being Dr. José Laguna García. When he finished his degree in 1954, he wished to enter the HEN (later the Salvador Zubirán National Nutrition Illnesses Institute in 1978, and the Salvador Zubirán National Medical Sciences and Nutrition Institute, SZNMSNI, in 2000), but he was not accepted as an intern, so he decided to study in the United States instead.

Lisker went to the Michael Reese Hospital in Chicago, Illinois, from 1954 to 1957 as a medical resident (in the first year he worked as a rotating intern and for the following months as a research assistant in the Hematology Department;

see Barahona 2009); specializing in hematology with Karl Singer, a Viennese physician who had immigrated to the United States and was a specialist in human hemoglobin. In these years he met Arno G. Motulsky, a German–Jewish immigrant physician who had been a pupil of Singer’s a few years before; whose collaboration and friendship lasted many years (R. Lisker, April 2008, personal communication; see Barahona 2009).

In Chicago, Motulsky was particularly interested in sickle-cell anemia and its genetics. In 1953, he was invited by Robert Williams to set up a medical genetics division in the department of Medicine at Washington University in Seattle. The division started operations in 1957 and specialized in glucose-6-phosphate dehydrogenase (G6PD) deficiency. Like anemia and thalassemia, G6PD deficiency is a biochemical–genetic response that helps protect against malaria (Box 2). This condition was discovered in the 1920s among workers on South American banana plantations run by the United Fruit Company (Comfort 2012). For Motulsky, the study of the G6PD deficiency was a very promising new line of research to study the genetic basis of the response to various drugs (Motulsky 1957, Motulsky and Campbell-Kraut 1961). His article on blood reactions to drugs is considered a founding document in the field of pharmacogenetics, the study of genetic variation in response to drugs (Comfort 2012). These studies were particularly important and influential in Lisker’s work, as we will see below.

Box 2

The G6PD enzyme catalyzes the conversion of glucose-6-phosphate during the utilization of glucose by the erythrocytes. In this step, a molecule of NADPH is generated, which is necessary for maintaining the concentration of reduced glutathione in erythrocytes, indispensable in turn for the integrity of the cell membrane. The discovery of Carson and his collaborators published in 1956 on the relationship between hemolytic anemia and the presence of illnesses such as favism (acute hemolytic anemia after ingestion of broad beans), was important for the use of this marker in human genetics (Carson *et al.* 1956). Currently, more than 100 variants of this enzyme are known, which may manifest itself due to extreme or moderate deficiency, and is a sex-linked characteristic.

Upon his return to Mexico in 1957, Lisker worked part time at the HEN at the invitation of Dr. Luis Sánchez Medel, head of the Hematology Department and friend of José Laguna, whom Lisker had met in 1956 at the International Hematology Congress in Boston, United States; but to earn a living he founded the Specialized Clinical Analysis laboratory in October 1958. Here they performed biometries; bone marrow,

¹ This paper focuses only on the work of Lisker; for Armendares and Salamanca on cytogenetics see Barahona 2009, 2015a. For de Garay on genetics and radiobiology see Barahona *et al.* 2005; Barahona and Ayala 2005a, 2005b; and Barahona 2006, 2009, 2015b.

bilirubin, and anemia analysis; blood analysis of newborns for incompatibility of blood between mother and child; among others. He left this laboratory, however, in 1965 to study at the Medical Genetics Division of the University of Washington in Seattle, United States, with Motulsky. Thanks to Dr. Salvador Zubirán and Dr. Guillermo Soberón, two leading authorities of the medical Mexican community, he obtained a scholarship from the National Institutes of Health (NIH) for postgraduate studies from 1965 to 1966. Upon his return in 1967, he founded the Genetics Department of the HEN, becoming its first director. This department would become the Rubén Lisker Genetics Department in 2007, when he became Professor Emeritus of the SZNMSNI (R. Lisker, April 2008, personal communication; see Barahona 2009).

Genetic Characterization of Mexican Populations

In the 1960s, critical awareness began to grow about the difficulties of defining geographical groups in man. Using a handful of genetic markers (such as blood groups), human geneticists hoped to study human variation more precisely than anthropometric and anthropological methods permitted (Lipphardt 2014). After WWII, many institutions and founding bodies allocated enormous financial sources for genetic research on populations around the globe. Prominent human geneticists promoted human variation studies in many countries including Dobzhansky in Brazil (Barahona and Ayala 2005a, Lipphardt 2014), Luca Cavalli-Sforza (1980), and Rubén Lisker in Mexico (Barahona 2009). Many debates concerning the new trend of using gene frequencies in physical anthropology in the postwar years drew attention to the importance of correlating data from both disciplines to have a more accurate picture of human evolution (Lipphardt 2014). One of the leaders of this trend was Cavalli-Sforza, whose studies on the genetics of human populations using linguistic data produced a body of data from which many correlations would be followed up (Cavalli-Sforza 1980). This approach was very influential in many studies around the world, including those of Lisker.

During the 1950s, information on the genetic structure of Mexicans came from two sources. On the one hand, from medical studies on congenital errors of the metabolism or chromosomal aberrations and, on the other, from anthropological studies with the objective of a biological characterization of certain populations (Lisker 1981). The physical data held by the anthropologists came from studies of phenotypic characteristics whose variability was readily apparent (color and type of hair, eye shape, and so on), but were unfortunately linked to racial ideas. This was why it was essential for Lisker, in consonance with other global trends in human genetics at the time, to have “neutral” genetic data that allowed him to know how much of the variability was due to genetic structure and how much to environmental factors. He was particularly interested in providing information not merely of anthropological interest, but because it was useful knowledge for medicine (in both a preventative and curative

nature) in order to design medical policies specific to those populations for which there were growing concerns about the eradication of anemia and malaria (paludism). This was a clear intersection of the development of post-WWII biology and medicine (biomedicine), and the political project of post-revolutionary Mexico (see Cueto 2007).

The anthropological interest of the study of abnormal hemoglobins was that some of these were known to have a well-defined geographic and ethnic distribution. For example, hemoglobin S (HbS) was typical of the Northwest and central Africa, and was found at all sites where there had been immigration of black Africans. Hemoglobin C was typical of Western Africa, while hemoglobin E was almost exclusively from Southeast Asia. Correlating these data with those obtained for Mexican populations, Lisker and collaborators wished to establish degrees of racial admixture. He used sampling as a criterion and also, unlike previous studies, the linguistic classification of former Boas student, Mauricio Swadesh.

In order to carry out these studies, Lisker sought guidance from Swadesh, an American cultural anthropologist working at the UNAM at the time. Lisker later recalled: “I remember that I asked him: Whom do I study? How can I do it? What is the rational necessity of this problem? He provided me with his publications and informed me that at the time there were five large Mexican linguistic groups and that each of these, except the Tarasco, had subdivisions with distinct geographical areas. Thus, I knew their main characteristics... I first studied genetic markers in indigenous populations, and then those of mixed race in the Mexican Republic. I have dedicated 35 or 40 years of my life to the study of genetic markers.” (Pérez Tamayo 2008, pp. 104–105; Swadesh 1959). This approach of using the linguistic similarities among populations to be correlated with genetic similarities was of great importance because he could then use the results to test a hypothesis about historical interactions among different populations or ethnic groups, and also use them for establishing medical policies. Among the most-important genetic markers, his main studies were on the G6PD deficiency and on human serum albumin.

Influenced by Motulsky’s work, the characterization of certain hematological traits in indigenous populations was one of Lisker’s original lines of research and was published in a series of articles that appeared between 1962 and 1966 - (Lisker *et al.* 1962; Rodríguez *et al.* 1962; Rodríguez *et al.* 1963; Lisker *et al.* 1965a, 1965b, 1966). In a survey of the Mixtec area, they found two individuals with the G6PD deficiency. Both belonged to the Mixtec linguistic area and were residents of Jamiltepec, on the Costa Chica of Oaxaca, where malaria had not yet been eradicated. This finding, however, apparently contradicted those for other populations. For example, this G6PD deficiency was very rare in mixed-race populations; and in close to 600 indigenous populations, including a Mixtec group in which malaria did not occur due to the high altitude at which this population lived, the deficiency was nonexistent. Thus, it was of great importance

Figure 2 Rubén Lisker in the Malaria Eradication Campaign, ca. 1965. Taken from Pérez Tamayo 2008. With permission of Universidad de Colima, Mexico.

to establish the relationship between the geographical distribution of hemoglobin variants and malaria epidemiology (Figure 2).

Lisker and his collaborators suggested that the presence of malaria could be acting as a selective agent, and that the mixture of this population with black groups who had lived in this region since the 16th century, whose essential nucleus was the population of Cuajinicuilapa, could explain the presence of the deficiency. The partial answer they found for the G6PD deficiency was obtained when, thanks to the National Campaign for Eradication of Paludism, the Ministry of Health decided to study the area for G6PD deficiency as a preliminary step prior to implementing general treatment with primaquine. Lisker and his collaborators took samples from a total of 1931 adult men in search of HbS and G6PD. The results published showed that, despite the fact that in the recent past the area had had a uniform incidence of malaria, there were marked differences in the frequency of both characteristics in neighboring cities (Lisker *et al.* 1965a). The findings suggested that the relative presence of HbS and the G6PD deficiency were related to the distance from Cuajinicuilapa. Like Salazar Mallén, Lisker asked for the collaboration of the INI and the Escuela Lingüística de Verano (Language Summer School), with the infrastructure to take the blood samples and the management of the indigenous populations. The INI anthropologists and the medical geneticists linked urban and rural settings, and also linguistic and cultural approaches to the study of human biological diversity. (For an anthropological perspective of Lisker's work, see Suárez and Barahona 2013).

These studies included other towns in the region close to Cuajinicuilapa, such as Ometepe in Guerrero, and San Pedro Mixtepec and Pochutla in Oaxaca. Malaria had been endemic in this region until very recently, where the presence of 90% of the parasitosis was due to *Plasmodium vivax*, and 10% to *P. falciparum*. These cities turned out to be representative, as the frequencies of HbS and G6PD were high (Cuajinicuilapa),

intermediate (Ometepe and San Pedro Mixtepec), and low (Pochutla). The blood samples were taken by the personnel of the INI, who at the time were working in the malaria eradication campaign (Cueto 2007), from adult men at random (on the condition that they had been born in those towns) and from children from newborns up to 12 years of age. The samples were then taken to Lisker's laboratory in Mexico City and used for other markers such as haptoglobins and transferrins, antigens from the Diego and V blood groups; and the Gm factors associated with myeloma proteins. It is important to mention that Lisker was familiar with the work of Arthur G. Steinberg of the NIH, who by 1965 had already published results for genes Gm and Inv, which determined the series of gamma globulins present in normal individuals, using electrophoresis techniques. In their 1965 article, Lisker and his collaborators mentioned that some serum samples were obtained directly from Dr. Steinberg and analyzed according to his 1962 procedure, and in the acknowledgment paragraph of this article, they thank Dr. Giblett and Dr. Steinberg for the technical assistance given at their laboratories in the United States to solve their research problems (see Steinberg 1962 and Steinberg *et al.* 1967).

These studies enabled discovery of the phenotypic frequencies of HbS, G6PD deficiency, haptoglobins 2-1 (mod), Gm (c+), and antigens Diego and V (Lisker *et al.* 1965a). These markers turned out to be significant as, for example, the Diego antigen was coded for a gene almost exclusive to East Asian-derived populations and with a high frequency in Amerindian populations, especially South American ones. "The system of Gm groups is extremely valuable for characterizing human groups, as there is not only variability in the frequency of their antigens, but they are also transmitted by different alleles in the main ethnic groups" (Lisker 1981, p. 24).

Lisker and his collaborators also focused on the identification of another component in the blood, human serum albumin (the main protein of human blood plasma) to detect polymorphisms characteristic of Mexican populations. Serum albumin had been widely used as a genetic marker to characterize ethnic groups since the beginnings of the 1960s. Screening for variants of albumin (and other macromolecules) was of great aid to anthropological studies in establishing the relationship between genetic composition and linguistic similarities. By the time Lisker started conducting his studies, at least two dozen variants of human serum albumin had been reported, but only two of them: the common albumin A, and a rare variant, albumin B, were fully characterized.

Using the new technology of starch gel electrophoresis developed by Poulik (1957) a few years before, Lisker, Liisa Melartin, and Baruch S. Blumberg² from the Cancer Research Institute of Philadelphia, United States, discovered new

² American scientist Baruch Samuel Blumberg won the Nobel Prize in Medicine or Physiology in 1976 for his contributions to the origins and spread of infectious diseases. He discovered the hepatitis B virus and subsequently developed the vaccine.

variants for albumin in the blood. These studies, published in the influential journal *Nature* in 1967, included 281 individuals from mixed-race communities in the Federal District; 20 Mazatecs from Huautla de Jiménez; 123 Zapotecs from Guelatao de Juárez, Pochutla; and 263 Mayas from Yucatán. Thanks to the technique used, Lisker and his collaborators described the new “Mexico albumin”, which moved more slowly in the gel than albumin A (considered to be the wild-type) but more quickly than the one called albumin B described in European and American populations. The results showed the presence of a variant of the Mexico albumin among the Zapotecs of Guelatao and Pochutla, while 10 other variants were found in the mixed-race populations studied. They also found that in one of the variants for the Mexico albumin, an individual and three of his or her children presented a new variant together with albumin A. They explained this as a case of autosomal codominance consistent with other data reported previously. This study allowed them to confirm the heritability of this characteristic. “It might be possible to identify families with three or more variants to determine whether there is segregation in one or more loci. Moreover, using data from other families for variants of albumin B and Naskapi, the data obtained suggest linkage between the albumin and the Gc gene. These (Mexican) populations may serve to carry out more detailed studies on this linkage” (Melartin *et al.* 1967). This conclusion was important because the Naskapi albumin had been described as a common variant in high frequency in the Naskapi Indians of Quebec and in many North American tribes, but it had not been found in white or black American populations, or in European populations (Melartin and Blumberg 1966; Melartin *et al.* 1968). For Lisker, the causes of variability were not clear at the time, but he put forward that various factors could be involved, such as breeding of indigenous groups with white and black populations, which would explain the percentage of nonindigenous genes in the groups studied.

The description of different polymorphisms of albumin, like the Mexican and Naskapi variants, and the use of new methodologies such as the starch gel electrophoresis that allowed more precise analysis, clearly established the relevance of comparative studies of different human populations for understanding the historical movements of Native American groups (Smith *et al.* 2000). Because albumin is the major carrier of many physiologically-active substances and drugs in the blood, it was conjectured years later that some variants could have different properties of medical importance (Franklin *et al.* 1980).

Conclusions

I have attempted to show how research into the genetic structure of populations was initiated and developed in Mexico from a simultaneous dialog between the local context responding to national needs and concerns, and a global approach to studying human biological diversity; the latter made by the international networks through which scientific

resources were mobilized in order to enter into a transnational material culture.

Salazar Mallén and Karl were very important personalities in the introduction and development of medical genetics to Mexico; Salazar Mallén’s studies on the distribution and characterization of ABO blood groups in indigenous populations were the starting point for understanding certain illnesses, like hemolytic anemia, from a scientific perspective. Karl’s studies on the distribution of abnormal hemoglobin in Mexican indigenous populations confirmed the relationships observed in other laboratories at the time and helped lay the foundations for the later work by Lisker and others. These studies were soon followed by the ones of Lisker and his group on the characterization of human indigenous populations.

Owing in part to the influence that his studies in Chicago and Seattle had upon his thinking, Lisker was instrumental in the development of population genetics in Mexico. This research would not have been possible without the techniques he employed that were then brought to and implemented in the HEN. These studies broadened knowledge on the distribution of certain indigenous and mixed-race groups, and provided first-hand information on the distribution and frequency of the erythrocytic G6PD deficiency; of abnormal hemoglobins, such as HbS; and of certain serum proteins in these same population groups.

Several lines of research in population genetics were carried out between 1968 and 1985 at the Genetics Department of the HEN. The one related to the genetic characterization of various indigenous and mixed-race groups through the use of genetic markers, however, was the most important, as it furthered understanding of the genetic structure of the Mexican population and the identification of hemoglobin variants in various indigenous groups (Jones *et al.* 1968; Lisker *et al.* 1972, 1985; Lisker 1984).

In several of his books, but especially in *Genetic Structure of the Mexican Population. Medical and Anthropological Aspects*, Lisker insisted on the medical importance of genetic characterization of Mexican populations and documented several studies that included all the work performed by him and his work group. Among them were the discovery of certain variants not previously described; such as the Mexico albumin, the Castilla, Chiapas, Federal District, and Tepic G6PD; which enabled him to establish that the Mexican population was an ethnographic mosaic from a mixture of Amerindian, European and African populations (Lisker 1981; see also Armendaris and Lisker 1993). Lisker’s studies demonstrated what was suspected from other studies: there are no pure indigenous populations in Mexico, all have some degree of mixture with white populations, essentially Spanish, or with black populations mainly on the coasts. The work of Lisker and his collaborators drove the development of medical and population genetics in Mexico, and his group was considered a leader in human genetics at an international level.

From the start, however, Lisker was as committed to the study of shared languages and practices, for reconstructing the demographic history of Mexico, as he was to networks of

collaboration in order to guarantee the necessary conditions for establishing human genetics in Mexico. The combining of linguistic and genetic work to establish the histories of different populations is now a major tool in the world of demographic studies. Recognition of the work of Lisker and his predecessors and colleagues helps to give the history of Mexican science, within a global context, its proper due.

Coda

Professor Lisker passed away on December 2015. This article is to commemorate his life and work and introduce geneticists who might not be familiar with him to what he contributed. Rubén Lisker not only inspired and supported many young researchers, but was able to win the respect and friendship of his colleagues and the medical community throughout his life. Rubén was a generous person, who told me about many of the events I narrate in this account. I am very grateful to have been one of his friends.

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