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Point of View

Human and Medical Genetics in Brazil

To my beloved son, Dr. Luciano Heitor Beiguelman, *in memoriam.*

Bernardo Beiguelman

Abstract

The present paper intends to be a brief historical analysis of the conditions for the development of Human and Medical Genetics in Brazil.

Papers written by Brazilian authors on themes of Human Genetics were already found in the scientific literature published between the twenties and the end of the forties. They were usually concerned with the distribution of blood groups or the frequency of sickle cell trait in population samples. Nevertheless, they cannot be taken as landmarks of the development of Human Genetics among us, since their results did not influence the scientific thinking of our students to the point of stimulating the foundation of scientific schools dedicated to the study of genetic problems in humans.

Several reasons may be evoked to explain what hindered a better receptivity to those pioneer works, but one of which was, no doubt, that such papers have been published in journals of very restricted circulation. The case of the recently departed physician Jessé Accioly, from Bahia, is typical. He published the results of his studies on the inheritance of the sickle cell trait and sickle cell disease in 1947, as a full paper, in the *Arquivos da Universidade da Bahia*. This paper remained unrecognized for many years, while the note on the same subject published in the same year by James Neel in *Medicine* bestowed international notoriety and a great impulse to the career of this North American geneticist, also recently deceased.

The low effect of the Brazilian papers on genetic markers in humans in the first half of this century for stimulating the development of Human Genetics can also be attributed to the fact that most of them were written by authors who already had a medical specialization. Such situation contributed to circumscribe their works to the field of specialization of their authors, such as Immunology, Hemotherapy, Forensic Medicine or Clinical Hematology. Moreover, some of these papers resulted from fortuitous incursions of their authors into the field of Human Genetics. It is also clear that the lack of continuity of research in Human Genetics might be due to the lack of a stimulating environment. In Brazil of the first half of the 20th century research centers in Physical Anthropology were missing and there were almost no courses on Statistics applied to biomedical sciences.

In the thirties and forties, the organization of the first Brazilian centers for genetical work were under the leadership of Carlos Arnaldo Krug, in the *Instituto Agronômico de Campinas* (IAC), of Frederico Gustavo Brieger, in the *Escola Superior de Agricultura "Luiz de Queiroz"* (ESALQ), in Piracicaba, SP, and of André Dreyfus, in the ancient *Faculdade de Filosofia, Ciências e Letras da Universidade de São Paulo* (FFCLUSP). Since the beginning these centers had high academic quality and were mostly committed to investigations on genetics and plant breeding, genetics of *Drosophila* and bees, as well as chromosomal studies in invertebrates. The absence of research on Human Genetics have been expected at IAC and ESALQ due to the agricultural purposes of these institutes. However, it might seem curious that this type of research had not been started at FFCLUSP, specially when it is well known that André Dreyfus, one of the most brilliant, lucid, creative and stimulating intellectuals of that period, was very conversant with the literature on Human Genetics current at that time. It is thanks to him that the library of the *Instituto de Biociências da Universidade de São Paulo* still contains a wealth of bibliographic documentation on this subject, dating from the first decades of the 20th century.

Nevertheless, taking into account that, until the forties, Human Genetics was strongly influenced by Eugenics, which provided a "scientific" basis for racism and intolerance towards handicapped people, it is understandable that André Dreyfus had not sought in being involved with the preparation of researchers in this area. In this context it is important to remember that the influential *Annals of Human Genetics*, published in England, was previously the *Annals of Eugenics*, and that the *Journal of Heredity*, the official publication of the American Genetics Association, was frankly in favor of the eugenic movement and became the principal organ for "scientifically based" articles on

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Eugenics. The "scientific" arguments for the Immigration Restriction Act which passed in 1924 came from the Eugenics Record Office at Cold Spring Harbor (Allen, 1975). This Act limited drastically the entrance into the USA of immigrants coming from Eastern Europe and the Mediterranean countries, on the allegation that they belonged to populations genetically inferior to the Anglo-Saxon and Nordic individuals. Between 1915 and 1930 several laws were passed in USA which prohibited some kinds of interracial marriages, while in 1933, in 26 US states there existed 63 different sterilization laws for various social "misfits": mentally deficient, among whom there were included individuals culturally retarded, criminals, psychiatric patients, epileptics, and patients with leprosy or syphilis (Whitney, 1933; Landman, 1933).

An official policy of sterilization had also been adopted in 1928 in Canada (Alberta Province), 1929 in Denmark, Finland and Switzerland (Vaud Canton), 1932 in Mexico (Vera Cruz Province), and in 1933 in Nazi Germany (Landman, 1933; Müller-Hill, 1993). However, it was in Nazi Germany that the eugenic movement had the voluntary, enthusiastic and disciplined participation of numerous geneticists, some of whom very eminent, for the fulfilment of the most grisly atrocities which occurred without opposition in a climate of growing terror: 1) dismissal of all Jewish and half-Jewish civil servants, state employees and society's employees (1933); 2) passing of the "law for the prevention of progeny with hereditary defects, which allowed for compulsory sterilization in cases of congenital mental defects, schizophrenia, manic-depressive psychosis, hereditary epilepsy and severe alcoholism (1933); 3) proclamation of the "law for the protection of German blood and German honor" which prohibited marriage as well as extra-marital sexual intercourse between Jews and citizens of German or related blood (1935); 4) in 1937 all 385 German colored children born to Negroid and German parents were surgically sterilized in university hospitals, according to a plan proposed in 1935; 5) suspension of the law on compulsory sterilization in 1939 in favor of an euthanasia law allowing the murder of the physically or mentally retarded by carbon monoxide or by shooting; 6) the systematic and brutal murder of most European Jews (six million people of all ages), at first by slow starvation or by shooting (1939-1941) replaced from 1942 to 1945 by an efficient killing machine in extermination camps, employing gas-chambers and crematoria.

In the thirties Brazil did not remain immune to the ominous activity of the eugenicists. At that time there was a Brazilian Eugenics Central Commission based in Rio de Janeiro, and its official journal (*Boletim de Eugenia*), printed in Piracicaba, SP. This journal published Portuguese translations of articles written by Nazi German geneticists, notes written by Brazilian Professors praising the sterilization laws passed in Nazi Germany and in favor of "eugenic methods" against handicapped, criminals and social misfits in Brazil, as well as articles speaking out against marriage between White and Negroes, as well as against Japanese immigrants in Brazil. In accepting that differences between human beings are biologically determined, Brazilian eugenicists, like their northern hemisphere colleagues and Nazi mentors, also assumed that some human beings and human races should be classified as superiors, because of their hereditary endowment, whereas others should be considered inferiors and with no value to society. Superiors and inferiors should not be equal under the law. It is thus apparent that in the thirties and forties in Brazil there was no climate to the development of Human Genetics in the Department of Biology of the ancient FFCLUSP, which, at the time, was, perhaps, the most important center for the promotion of genetic studies in Brazil.

Soon after the end of the Second World War, in 1945, the revelation by the press and cinema of part of the horrors which were committed in the Nazi concentration and extermination camps served to silence the eugenicists, but it also determined a decline of interest in studies on Human Genetics. This decrease of interest lasted for many years in the universities of the civilized world. However, with the development of Biochemical Genetics at the end of the forties, it became evident that not only was it necessary to retake the research on inborn errors of metabolism started by Garrod in 1908, but it also became clear that there were numerous biochemical detectable genetic differences in normal people, which served to make attractive the study of genetics in human beings. It was not only the detection of human polymorphisms, but also the demonstration that they could be associated with diseases, that unleashed an avalanche of research whose objective was the knowledge of the mechanisms responsible for the maintenance of these polymorphisms and the study of the evolutive factors in Man (mutation, selection, genetic flow and genetic drift). In turn, the regrettable entering of humanity into the nuclear era, by means of the horror of the Hiroshima and Nagasaki destruction, stimulated the study of genetic effects of radiation and other mutagenic agents on humans.

It became evident that the experience accumulated by "drosophilists" who worked on genetic polymorphisms, selective mechanisms, inbreeding effects, and linkage could be transferred without any great difficulties to the study of these problems in human beings. Moreover, human beings have been considered a better model than any other for the study of the general genetic problems, since they offered the advantage of providing the best conditions for the investigation of their ancestors, descendants and collateral relatives, and for obtaining detailed information from anatomic, physiologic and biochemical points of view.

This advantage served to attract to Human Genetics not only students with a background in *Drosophila* genetics, who opted at the end of their course for another field of investigation, but also attracted consecrated scientists who had been studying *Drosophila* for many years. This world-wide shift also occurred successfully in the fifties in Brazil, allowing the achievement of studies on many auto-

somal or sex-linked polymorphic systems for evaluating the genetic composition of Brazilian populations, selective effects, rates of mutations, consanguinity, genetic load, epidemiology of congenital defects, radiogenetics, genetic studies in isolates, gene flow, and the investigation of genetic components responsible for susceptibility/resistance to infectious diseases. The publications of Brazilian authors who worked on these important themes gained immediate international recognition and the respect of foreign peers. The apogee of this success was reached between the sixties and eighties. Taking into account a combined criterion of quality and quantity of papers on Human Genetics, Brazil was included at that time among the first five most productive countries in research on Human Genetics, being ranked just below the United States of America and the United Kingdom.

These themes, so beloved of Brazilian geneticists, did not touched the medical community in Brazil, not even when the research dealt with inherited diseases, probably because, for investigating the pathogenesis of these disorders, geneticists followed an audacious and unusual methodology in Medicine, since under the name ***trait*** there were summarized all signs and symptoms of the patient under analysis. In the eyes of the clinicians, always dealing with individual problems, this simplified labeling, that apparently ignored the variations of the clinical picture of each patient, seemed to be an excessive abstraction and a complete heresy.

Such resistance remained in the medical community even when genetic heterogeneity was demonstrated in apparently homogeneous clinical disorders, allowing geneticists to foresee different pathogenesis for the different clinical genetic entities they were able to recognize. For the medical community it was difficult to accept a biological science in which, as in physics and mathematics, the artificial concepts used for working out hypotheses are a consequence of the need of applying statistical analysis to interpret reality for obtaining laws that, when applied to the real world, represent natural phenomena with a high degree of exactitude.

The medical community did not give any clear signs of accepting the new wave of research on Human Genetics which emanated from the Departments of Biology of the ancient *Faculdades de Filosofia, Ciências e Letras*, even when it became clear that a biochemical interpretation for an inherited disease should be investigated whenever its pedigree analysis supported a monogenic transmission. Otherwise stated, this lack of acceptance of Human Genetics among clinicians remained even when it became clear that the indication of monogenic inheritance for a disease, together with the knowledge of its physiopathology, could enable either the discovery of an enzyme defect or the detection of a structural protein abnormality responsible for the manifestation of a clinical condition, and the definition of its pathognomonic sign.

Genetics only started to be frankly accepted in the medical community from the sixties onwards, after the advent of Human Cytogenetics. Notwithstanding the chromosome complement of normal individuals had been discovered in the fifties (Tjio and Levan, 1956), three years before the discovery of the first human disease due to chromosomal alteration (Lejeune *et al.*, 1959), Human Cytogenetics only acquired strength in the sixties, after Moorehead *et al.* (1960) described a technique for short-term culture of lymphocytes, which allowed the settlement of this specialty in many laboratories world-wide, even in those with a limited budget. It was the facility of this technique which allowed the extraordinary development of Human Cytogenetics in Brazil in the early sixties, enabling our geneticists to compete creatively in the same field that was flowering in countries of the northern hemisphere.

Human Cytogenetics had an unexpected impact on Medicine mostly because it enabled the elucidation of the etiology of many sporadic and even familial diseases with no Mendelian transmission, through the investigation of structural or numerical chromosomal abnormalities. Here it seems important to stress that in spite of the fact that most of the geneticists had no medical training, they not only introduced karyotype analysis in the medical armamentarium, but also a specific semiology for diseases resulting from chromosomal aberrations, as a consequence of their karyotype-phenotype correlation studies.

However, the immediate acceptance of Human Cytogenetics by the medical community seems also due to the fact that chromosomal aberrations are *visible under the microscope*. This materialization of the genotype changes was fully pursuant to the psychological tendency of most people to resist against dealing with abstract notions, such as those which had dominated Genetics reasoning for a long time. At a time when we were far from the technology of DNA analysis, which allows the investigation of the structure and function of human genes and the diagnose of inherited diseases by examining the abnormal genes themselves, one can imagine the great impact provoked by the possibility of observing and photographing some genetic changes.

Another impressive event that occurred in the sixties started with a paper by Steele and Breg Jr. (1966) which enabled the development of techniques for evaluating the chromosomal and biochemical constitution of human fetal cells obtained by amniocentesis after the first trimester of pregnancy. This was a great advance in comparison to Riis and Fuchs (1960) work, which allowed only the investigation of X-chromatin in fetal cells. At that time it was unimaginable that it would be possible the precocious prenatal diagnosis of genetic abnormalities with the present degree of accuracy, using ultra-sonography to follow with details the evolution of the conceptus within the uterus and for applying techniques for the direct study of human DNA. Moreover, the ability to diagnose chromosomal and inherited diseases by analyzing cells obtained from biopsies of the corial villi was only unequivocally demonstrated almost 20 years after Steele and Breg Jr.'s (1966) paper.

The fact that many abnormal karyotypes were associated with congenital defects, together with the demonstration of the importance of Y-chromosome and other monogenic alterations in sexual determination and differentiation, explains the reason why the acceptance of Human Genetics in the medical community started with pediatricians and endocrinologists, followed by obstetricians, while other Brazilian specialists usually thought of Human Genetics as an esoteric science. The full acceptance of Human Genetics by the Brazilian medical community was only achieved when it became undoubted the importance of Genetic Counseling to the practitioners of many medical specialties, and after the research activities on Pharmacogenetics, Immunogenetics (which stopped being restricted to Immunohematology), Genetic Epidemiology, Mutagenesis and Teratogenesis, Oncogenetics, Developmental Genetics, Behavioral Genetics, Genetics of Degenerative Diseases, and Twin studies increased among us.

As a consequence of the initial resistance of medical professionals to Human Genetics, it is understandable why only in 1959 it was possible to create, for the first time in Brazil, a course in Human Genetics at the *Faculdade de Medicina da Universidade de São Paulo* (FMUSP), and in 1963, at the *Universidade Estadual de Campinas* (UNICAMP), the first and, up till now, the only Medical Genetics Department in a Brazilian medical school. Unfortunately, UNICAMP's initiative has not been followed by other Brazilian universities, and only a few have even introduced specific courses on Human Genetics in the curriculum of their medical schools. Even the USP, which had the conditions to transform the course on Human Genetics into a Department, preferred to transfer this course to the *Departamento de Biologia* at the *Instituto de Biociências*. At the Ribeirão Preto campus of the USP research in Medical Genetics started in 1959 in the *Departamento de Clínica Médica* of the *Faculdade de Medicina*, but a course on Medical Genetics began officially in 1970, at the *Departamento de Genética e Matemática Aplicada à Biologia*.

The *Conselho Federal de Educação* (CFE) may have contributed to this situation by not including Human or Medical Genetics as part of the requirements for the minimum curriculum of medical schools, only recommending that "at least the notions of Cytology, Genetics, Embryology and Evolution" should there be taught (Resolution No. 8 of October 8, 1969). Fortunately, however, a large number of medical schools, especially those in the public universities, did not restrict themselves to the CFE recommendations, but maintain courses in Medical Genetics during at least one semester. This is evidently not enough to prevent high losses both in research and in the implantation of stronger training in Medical Genetics.

In fact, residencies in Medical Genetics, recognized by the *Conselho Nacional de Residências Médicas,* are only offered in Brazil by UNICAMP, USP (Ribeirão Preto campus), the *Instituto Fernandes Figueira* (Rio de Janeiro), the *Universidade Federal do Rio Grande do Sul* (UFRGS) and *Fundação Faculdade Federal de Ciências Médicas* (Porto Alegre, RS). Moreover, almost all graduate courses in Medical Genetics are conducted at Biology Institutes. As a consequence, the leadership of the largest proportion of creative scientific production in Medical Genetics in Brazil takes place in Institutes of Biology and not in the Medical Schools. This is the case of the innovating contributions on muscular dystrophies (*Instituto de Biociências*, USP), inherited hemostasis defects (*Instituto de Biociências*, UFRGS), ectodermal dysplasias (*Setor de Ciências Biológicas, Universidade Federal do Paraná*) among other examples which could be mentioned.

In the public institutions, another factor that contributes to prevent the majority of medical professionals (with the usual exceptions) from achieving a leading role in research on important themes of Medical Genetics is overwork in clinical assistance, which deprives them of the necessary conditions to dedicate themselves to scientific investigation. In the whole country there exists only about forty Medical Genetic centers in public institutions, half of which in the State of São Paulo, which provide care for tens of thousands of families per year that seek for genetic counseling for the risks of occurrence and recurrence of genetic diseases. In these centers there are working about one hundred clinicians specialized in Medical Genetics, and a slightly larger number of other professionals (biologists, psychologists, nurses, social workers and technicians). This lack of perspective is contributing to the growing number of private clinics (usually with better infrastructure than the public institutions) in the largest Brazilian cities. These clinics are mainly oriented towards prenatal diagnosis of chromosome abnormalities and inherited diseases, and to carry out complementary tests. Due to these reasons that even when these medical professionals are able to draw out topics for investigation from their loaded routine, these matters usually tend to focus on case-reports of diseases previously described in pertinent literature, attempts to characterize syndromes, statistical surveys of limited value, or the application of technologies that are most likely not innovative.

The naked truth is that the lack of Departments of Medical Genetics in the medical schools are harmful to the reformulation of Genetics in medical practice. In the present state of knowledge in which there are about 7,000 well-documented inherited Mendelian disorders, about 1,000 chromosomal abnormalities, and an unknown number of multifactorial diseases, it is impossible to graduate medical professionals with experience in all of these disorders, besides having the ability to decide if a congenital malformation has genetic or environmental origin. What appears feasible is to have dermatologists specialized in genodermatoses, ophtalmologists specialized in ophtalmologic inherited diseases, orthopedists specialized in genetic bone changes, and so forth. In a medical school such specialists should be part of a Department of Medical Genetics, since it is not enough

that patients with inherited or chromosomal defects receive an accurate diagnosis and, eventually, therapeutic support, which can also be provided by ordinary clinics. In clinics dedicated to genetic diseases one should look beyond the individual, since it is necessary to study his ancestors, descendants and other relatives among whom the pre-clinical stage of these diseases should be investigated, offering them all the necessary genetic counseling. The organization of such departments should facilitate the creation of a network of Applied Molecular Biology, through which Brazil can really enter the era of the molecular diagnosis of inherited diseases. With such a structure and the incentive of the funding research agencies, Brazilian Human Genetics will certainly return to its important rank in the international scientific community, since creativity and the will to work even in adverse conditions have never lacked in Brazilian research.

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RESUMO

O presente trabalho pretende ser uma curta análise histórica das condições para o desenvolvimento da Genética Humana e Médica no Brasil.

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