Department of Genetics, Federal University of Paraná, Curitiba, Paraná

Genetics, Medicine and Public Health

From the Geography of Diseases to the Phenotypic Spectrum of Malformation Syndromes [1]

Newton Freire-Maia

SUMMARY

The following problems are briefly mentioned and discussed in this paper: (1) the role of genetics in public health, both in developed and in developing countries; (2) genetic aspects of the differential geographical distribution of diseases; (3) clinical and etiological aspects of malformation syndromes; (4) nosological complexity and phenotypic spectrum of these syndromes, with special reference to ectodermal dysplasias; (5) some problems of modern human communities.

Human genetics is a rapidly expanding field with increasing importance in medicine. At the rate that public health problems arising from malnutrition, as well as infectious and parasitic diseases, are being solved through the improvement of the socio-economic and sanitary levels of populations, other problems, for which the genetic approach proves to be essential, turn out to be of overall importance. These problems include congenital malformations, mental disturbances and the so-called degenerative diseases, such as diabetes, cancer, atherosclerosis, etc. To the primary concern as regards infancy, existing in developing countries, developed ones have to add an increasing interest for the social and bio-medical problems of old age. While, however, pediatric problems in public health have an ample but very simple strategy in developing countries, being mostly attacked with food, antibiotics and rudimentary hygienic measures, in developed countries they generally pose a high level scientific challenge primarily asking for research. Let us cite only two situations to exemplify the two constellations of problems: in developing countries, umbilical tetanus is known as an important cause of death for the neonate, and, if the most simple and elementary hygienic measures were performed by the midwife and the mother, the prevalence of umbilical tetanus would practically fall to zero; in developed countries, considerable efforts are applied in the investigations of the

[1] This paper is based on a lecture delivered at the World Health Organization in 1970, when the author was a member of the staff.

Rec. 15. V. 1971

Acta Genet. Med. Gemellol. (1971), **20**: 237 244

clinical and cytogenetical aspects of the chromosome diseases, the biochemical pathways of the genetic disturbances, the detection of carriers of detrimental " recessive " genes, the clinical delineation of birth defects in general, etc.

Public Health and Development

A classical definition states that public health is a science as well as an art aimed at preventing diseases, extending life and promoting health through organized efforts for the community as a whole. Naturally these efforts have to be concentrated on the most important problems among those found in a list of priorities, in such a way that a given disease or even a group of related abnormalities that would be put at the first place in one population may appear as the tenth in another. Only public health officers well acquainted with the sanitary situation of a country and inspired by a realistic policy of welfare for the whole population may decide which problems deserve the most urgent attack and which ones may wait a decade or more to be conveniently handled. Single genetic diseases, such as mucoviscidosis, haemophilia and the Duchenne form of progressive muscular dystrophies, for instance, may be severe problems for population A, whereas, at the same time, these conditions are simply unimportant for population B, as compared with communicable diseases such as tuberculosis, leprosy, malaria, schistosomiasis, and Chagas' disease, and the deficiency diseases, such as protein-caloric malnutrition, avitaminoses, anaemias and endemic goitre.

With regard to purely genetic abnormalities, different populations may also have completely different problems. For example, the high prevalence of sickle-cell anaemia, beta-thalassaemia and G6PD deficiency in extensive and specific areas, and their practical absence in others. In areas of high prevalence, public health services have to face these problems (and some of them really do) under priority terms. Genetic counselling, generally made on a personal or familial level in other areas, has to be performed here on a population level, as far as those conditions are concerned.

Genetics and Public Health

The duration of a disease, together with its severity and frequency, form the triad of elements on the basis of which we may judge its relevance to public health purposes. A rare, lethal genetic disease (such as the Chédiak-Higashi syndrome) or a severely handicapping, but also rare, congenital malformation (such as acheiropodia) certainly does not deserve investment for preventive measures at the population level. The genetic load of our species is, however, largely due to the summation of a tremendously large number of abnormalities, each one of which has a very low prevalence. Therefore, genetic diseases as a whole and congenital malformations in general are being considered important enough to deserve special attention in developed countries.

It may occur, however, that a specific genetic anomaly, rare in the majority of

the world population, may attain a high frequency in a given isolate, due to a purely random process (genetic drift). Three examples will illustrate the phenomenon: (*a*) high frequencies of cleft palate (1:75), of Sjögren-Larsson's disease (1:160) and of hereditary benign intraepithelial dyskeratosis (2%) have been verified in an American isolate; (*b*) about 50 patients with the Quelce-Salgado's and Grebe's syndrome (a polymicrodactylous dwarfism) were born in a very small and inbred Brazilian region, encompassing only two townships, whereas only 4 or 5 equally affected patients have been sofar described in the rest of the world; (*c*) almost as many patients with the Ellis-van Creveld syndrome (52) were found in an inbred religious isolate — the old order Amish — in USA, as had previously been reported in the whole medical literature.

Other examples of geographic concentration of diseases either due to simple mechanisms of inheritance, or only having some genetic component, or already suspected of being " genetic " in some way, may be cited: (1) one form of amyloidosis (the Andrade or Portuguese type) in the population of the area of Povoa de Varzim, in the Northern coast of Portugal, and among their descendants in Brazil, Africa, Germany, United States and other regions of Portugal; (2) amyotrophic lateral sclerosis (ALS) among the Chamorros of Mariana Islands; (3) diabetes among a tribe of American Indians, the Pima of Arizona; (4) multiple sclerosis (MS), whose prevalence shows a negative correlation with sunshine intensity in different parts of the world, i. e., it decreases as one approaches the equator from either direction. It is to be noted, however, that both geographical concentration and familial aggregation, although suggestive of an at least partial genetic etiology, are not, *per se*, a proof of it. They may simply be a consequence of common exposures to an exogenous agent. Kuru, for instance, was thought during some time to be a genetic entity, whereas human and experimental data have firmly established it, in recent years, as a viral disease. As a matter of fact, besides kuru, some other chronic central-nervous-system degenerative diseases, previously listed as " idiopathic ", have also been shown to be virus infections. Maybe ALS and MS are to be added to this group.

Public health officers should be aware of such cases of " rare " diseases and syndromes becoming " common " in certain populations. A genetic counselling programme, at the population level, should not be out of purpose in such cases.

Another interesting aspect of the geography of the diseases is the exceeding rarity of some of them in certain areas as compared with their prevalence in the majority of the world population. For instance, the low incidence of mother-child antigenic incompatibility in Asiatic populations in comparison with the levels verified in Europe and in European descendants in the Americas.

The same may be said as regards consanguineous marriages, that show " negligible " or " very low " frequencies in many parts of the world but that are common events in a number of areas. Investigations have established with different degrees of accuracy, or merely suggested with different amounts of data, a relationship between consanguineous marriages and some variables such as precocious mortality (both prenatal and infant-juvenile), morbidity (including both physical and mental

disturbances, congenital malformations, idiopathic anomalies and infectious diseases), low I. Q., poor school performance, decreased fertility, sterility, disability, hematocrit, blood pressure, anthropometric data, growth and development. In areas with a high inbreeding level, consanguineous marriages may attain the importance of a problem deserving a community approach through some sort of genetic counselling at the population level.

For the determination of the position that a given entity or a group of clinically related abnormalities will occupy in the list of priorities for a given region, two sectors of human genetics are of basic importance: *clinical genetics* (for diagnosis and prognosis) and *population genetics* (for estimating its parameters at the population level). Clinical genetics will use all the possible tools (biochemical analysis, electroencephalography, electrocardiography, radiographs, psychological tests, dermatoglyphic investigations, etc.) to attain a clear picture of the problem. Population genetics, based on mathematical models and aided by demography, will determine the main parameters defining the genetic structure of the population (gene frequencies, genotypic frequencies, sex distribution, mating patterns, migration, population number, etc.).

Malformation Syndromes

In a certain proportion of cases (i. e., when the entity under investigation appears clear cut and easily distinguishable from all the others), the task of the geneticist may appear relatively simple, even when (as in the case of some malformation syndromes, for instance) it is not possible to give, from the beginning of the investigations, a complete clinical description of it.

In collaboration with some colleagues, we had the opportunity to evaluate a situation of this type last year. From an apparently nonconsanguineous normal couple, 4 (3 boys and 1 girl) out of 8 children were born with a series of abnormalities. Only 2 (1 boy and 1 girl) of the affected sibs were still alive and have been examined. Both shared at least seven defects: (1) hypotrichosis; (2) abnormal dentition (hypodontia and microdontia, with persistence of some deciduous teeth); (3) hypohidrosis; (4) hypoplastic areolae and nipples; (5) large, thin, protruding and deformed auricles; (6) abnormalities of the tyrosine and/or tryptophane metabolism; and (7) extensive deficiencies of the four limbs with associated dermatoglyphic abnormalities. In addition, the boy showed (8) hypoplastic nails (the girl did not have any fingers or toes); (9) growth retardation; (10) incomplete, unilateral cleft lip; and (11) EEG abnormalities. The only additional findings in the girl were ECG abnormalities.

Observations on many other similarly affected patients are required before it will become clear whether all these defects are common components of the syndrome or whether some of them are purely coincidental findings (for instance, the cleft lip, only present in one of the four affected sibs). The hypotrichosis, the abnormal dentition, the onychodysplasia, the hypohidrosis, etc., clearly show that this syndrome (that we called " odontotricomelic hypohidrotic dysplasia ") represents a type of ectodermal dysplasia.

More than 30 apparently different " forms " of ectodermal dysplasias have been described before by other investigators. Some of these conditions are accompanied by euhidrosis, others by hypohidrosis and still others by hyperhidrosis. They are characterized by somewhat overlapping constellations of other clinical signs, such as mental deficiency, short stature, hearing loss, characteristic facies with saddle nose, cleft lip and palate, ocular abnormalities, malformations of limbs and of internal organs, atrophic rhinitis, deformed auricles, disturbances of the pigmentation of the skin, palmar and plantar hyperkeratosis, disturbances of the oral mucosa, etc. However, there is not only a large clinical heterogeneity among these ectodermal dysplasias, but also genetic heterogeneity, since cases of autosomal dominant, autosomal recessive and sex-linked inheritance have been described. Some of the conditions have, however, an unknown etiology. The ectodermal dysplasia we studied seems to be different from all the others. We postulated the action of a rare autosomal recessive gene to explain its etiology.

Phenotypic Spectrum

In many cases, the situation appears more confused, because there may be a considerable clinical overlapping among a group of syndromes having either the same pattern of inheritance or an unknown etiology; in such cases, it is extremely difficult to clearly delineate the limits of each entity. Patients with the same syndrome may be described as having different syndromes, and a group of different, but very similar, syndromes may be thought to represent a single complex entity. In this context, expressions such as " spectrum " or " continuum " of diseases and " nosologic spectrum " are loosely used to define a series of similar overlapping conditions going from the simplest or mildest to the most complex or severe situation, without any consideration to etiological aspects. These expressions may represent, however, a pure over-simplification of the problem, because what is said to be a " spectrum " or " continuum " may either be a series of clinical variants of the same disease (i.e., they all have the same etiology) or a group of similar, from the phenotypic point of view, but really different diseases (i.e., having different etiologies). Expressions such as " incomplete syndromes ", " formes de passage ", " hereditary chain of diseases ", etc., are also sources of imprecision and should be avoided.

It is our impression, however, that we should accept the expression " phenotypic spectrum " to encompass the different clinical " forms " and " variants " of the *same* disease. This concept is to be applied, however, only to the situations in which it is really known that the various clinical variants are merely different expressions of the same basic etiologic factor. For instance, the thalidomide syndrome. Depending on the period of action of the drug in the embryo, different constellations of signs may be produced. Ingestion of the drug early in pregnancy may produce anomalies of the ears and thumbs, followed by bone aplasias and hypoplasias of the upper limbs and those of the lower limbs, and finally by gastrointestinal and cardiac malformations. The whole sensitive period is between the 34th and the 50th day after the

beginning of the last menstrual period. Reduction deformities of the limbs, however, will only appear when the drug is taken between the 39th and the 48th day, the first six days representing the sensitive period for upper limbs and the five last days that for lower limbs. We think, therefore, that it may be safely said that thalidomide absorption by the embryo produces a phenotypic spectrum.

When, in a given family, it is shown that the same gene is causing abnormalities with different degrees of severity, we may also apply the concept of phenotypic spectrum. In a large family we studied some years ago, with a great number of persons showing the mild expression of brachymesophalangy of the Wriedt-Mohr type, it was possible to verify that two of the carriers of this autosomal dominant gene had rather severely malformed hands. In another family, we could also verify that the same autosomal recessive gene could produce both radius aplasias and complete absence of an upper limb. In another family, the same autosomal dominant gene was causing, in some patients, split-hand associated with severe malformations of the lower limbs, whereas, in others, only isolated unilateral defects of the lower limbs. Many other examples could be cited. In cases of mendelian inheritance, they simply illustrate the well known phenomenon of the variable expressivity of genes. But, as we mentioned, " exogenous factors " may also have a wide spectrum of manifestation. Experimental teratology and clinical observations have abundant examples showing that the genetic background of the individuals and the period of action of the teratogenic factor are very important to decide on the type or types of malformation to be produced, or in other words, which band of the phenotypic spectrum will be seen.

The great difficulties found in the study of the malformation syndromes stem from four different sources: large number, etiological heterogeneity, nosological complexity (due to variable similarity between etiologically distinct entities, to inadequacies of diagnostic methods, etc.), and phenotypic variability of the same entity in different individuals. We would like to comment on the last two items. Malformation syndromes are characterized, many times, by a large number of nonpathognomonic clinical signs, some of which may be either absent in some patients and/or present with variable degree of severity in others. They are, therefore, complex constellations of disturbances, many of which are commonly found in a number of syndromes. Some of these disturbances are, for instance, congenital heart disease, hypotrichosis, low set ears, cleft lip and palate, growth retardation, strabismus, hypertelorism, micrognathia, deformed ears, limb deformities (such as polydactyly, syndactyly and bone aplasias and hypoplasias), highly arched palate, mental retardation, etc. Considerable clinical overlap is, therefore, the rule, clinical similarities verified among patients being not a criterium for considering them as having the same syndrome. Naturally, patients with the same syndrome share at least some clinical findings in common, but the inverse reasoning may not be always true, i.e., patients with similar combinations of clinical findings may have different syndromes.

Conclusion

A considerable amount of research is still needed for us to fully understand the impact of genetic factors even on gross parameters such as " precocious mortality " and " general morbidity ". These are, however, the first steps along a long road leading to a more refined analysis of the adaptive value of human populations. This is a parameter for whose knowledge we will have to evaluate not only the fitness of the grossly abnormal individuals but also the fitness of the so called " normal " individuals.

It is well known that man is not only a polytypic species (by virtue of his geographic races) but also a polymorphic one (through the genetic variation within the same population). What is the impact of this polymorphism on the adaptive capacity of man? What effects do the so-called " recessive " abnormal genes exert on the " normal " individuals carrying them? How is the genetic make-up of man being influenced by the conditions of the modern way of life? These are questions of the utmost importance for the understanding of the structure and evolution of the human populations. We still do not have good answers for them.

It is widely mentioned that the environments in which " modern " human populations now live and present day " primitive " ones will be living in the future are extremely different from those in which man evolved and differentiated into a number of geographical races. The tremendous concentration of people and industries in large metropolitan areas has created serious and pressing environmental problems so far unknown to man. Food additives, drugs, pollutants and man-made sources of ionizing radiation are normal components of modern life. We know very little about the damage all these elements may produce in man, both on the " somatic " and " genetic " level. One of these effects is through mutagenesis, including the somatic cell level. It was discovered that a number of widely used agents (ionizing radiation and chemicals) are potent inducers of gene and chromosome mutations. Since a large proportion of the induced deleterious point mutations are recessive or slightly semi-dominant, they may accumulate for a long time in human populations before being noticed. The increased mutational load will therefore be discovered only when it will manifest in a much larger proportion of persons than in previous generations. Then, there will be no remedy any more. Recessives are like icebergs: the concealed part is much larger than that disclosed in every generation.

The development of huge human communities created, as mentioned, new ways of life in which new forms of physical and mental stresses arose. They introduced, therefore, substantial changes in the long range trends of natural selection, relaxing its pressure in some cases and creating new pressures in others. It is well-known, for instance, that selection pressure has been relaxed for a number of genetic diseases and malformations, since through social assistance and medical care, many affected individuals that would die early are now able to survive and reproduce. Increased mutation rate and decreased selection pressure act, therefore, in the same direction, increasing the frequency of the genetically determined abnormalities, i.e., increasing the weight of " our load of mutations ".

Another aspect of modern life is that the development of transportation facilities helped the displacement of large amounts of people from their original populations to other areas, where race admixture created new gene pools in which gene frequencies are far from the equilibrium state. The consideration of these problems shows that modern man, having the direction of his evolution in his own hands, changed it in several aspects. Two different steps may be visualized along the tasks facing man as regards the problem of deciding his own future as a species. The first is represented by the tremendous task of understanding the biological processes related to human evolution. It is a purely scientific endeavour. The second refers to the application of our knowledge for the welfare of mankind as a whole. It is an essentially ethical task. It is hoped that we shall have as much wisdom and sense of humanity in the last as we have intelligence and creative power in the first.

ACKNOWLEDGMENT. I thank Dr. John M. Opitz for reading the manuscript and proposing suggestions for improvement.

Our researches mentioned in the text are parts of projects sponsored by the National Research Council of Brazil, WHO, the Rockefeller Foundation, the Calouste Gulbenkian Foundation and the Research Council of our University.

RIASSUNTO

Vengono brevemente passati in rassegna e discussi i seguenti problemi: (1) il ruolo della genetica nella salute pubblica, nei paesi sia evoluti che in via di sviluppo; (2) gli aspetti genetici della diversa distribuzione geografica delle malattie; (3) gli aspetti clinici ed eziologici delle sindromi malformative; (4) la complessità nosologica e lo spettro fenotipico di queste sindromi, con particolare riferimento alla displasia ectodermica; (5) alcuni problemi delle comunità umane moderne.

RÉSUMÉ

Les problèmes suivants sont brièvement discutés par l'auteur: (1) le rôle de la génétique dans la santé publique, dans les pays développés ou en cours de développement; (2) les aspects génétiques de la différente distribution géographique des maladies; (3) les aspects cliniques et étiologiques des syndromes malformatifs; (4) la complexité nosologique et la manifestation phénotypique de ces syndromes, particulièrement en ce qui concerne les dysplasies ectodermiques; (5) quelques problèmes concernant les communautés humaines d'aujourd'hui.

ZUSAMMENFASSUNG

Kurze Übersicht und Erörterung folgender Probleme: (1) Genetik und Volksgesundheit bei kultivierten und unterentwickelten Völkern; (2) die genetischen Aspekte der verschiedenen geographischen Distribution der Krankheiten; (3) klinische und äthiologische Aspekte der missbildenden Syndrome; (4) die verschiedenen Krankheitssymptome und das phänotypische Spektrum dieser Syndrome unter besonderer Bezugnahme auf die Dysplasia ectodermica; (5) einige Probleme der modernen menschlichen Gemeinschaften.

Prof. N. FREIRE-MAIA, Department of Genetics, Federal University of Paraná, P.O. Box 756, Curitiba, Paraná, Brazil.