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RECENT CONCEPT

PERSPECTIVES OF GENETICS FOR MAN

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SUMMARY

The human species attained a high technological development, which enables it to induce important alterations in its environment and in the parameters of its own evolution. Genetics plays an important role in the study of such influences and in the solution of present problems of Mankind, as relates its future, genetic load and subsistence. The present objective of Genetics, as applied to the human being, is to understand what is inherited (and in what proportion). Hereditary diseases tend to occupy an important place among pathological entities and the physician's objective, saving his patients, increases the genetic load of the population, adding a new stress to the human genome, already under the influence of social and cultural transformations. To analyse this effect, more data on human social biology are needed, as well as on the results of new medical and biological technologies. Genetic engineering, the study of biochemical polymorphisms and their eventual selective value, cytogenetic analysis of malformative syndromes or sexual maldevelopment and genetic counselling, should be developed and extended to the general population. However, genetic counselling should preserve the freedom of choice of the individual or the couple in order to avoid its transformation into a mere kind of eugenics and to maintain both the personality of those being at risk and the population's genetic heteromorphism.

Science, taken as the human attempt to understand his environment and his own natural history, both fulfills the need for knowledge, which is one of the most peculiar characteristics of Man, and gives to our species some power upon the ecological factors which regulated it up to now.

A more limited and (in terms of evolution) less important power upon similar ecological factors was obtained unconsciously by other species which, through small changes in their immediate environment, were able to adapt themselves to better conditions of life; again, the *achievements* of some other species derive from a mere ecological equilibrium, obtained by means of selection.

In the case of Man, for the first time in the History of life one single species arises to a position of supremacy throughout the Earth and, by means of exploiting new sources of energy and developing more and more sophisticated instruments to use those sources, is able now to induce major changes in the environment and in the very rules of its own future.

Through technological application of scientific advances, Man now shapes his own immediate surroundings, uses (and abuses of) other species for his own benefit, and sets up conscious guidelines overriding the general rules of biological evolution in force until this moment. Such an achievement may itself be envisaged as the result of a further development in evolution: having reached the psycho-social level, Man is confronted with the problems posed by its own biology and tries to give a rational answer to them. Population density, disease, famine, and many other problems are

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not new in the history of all other species, which answered automatically through adaptation or extinction, but without resorting to the knowledge of biological phenomena underlying those problems and to the control of energy for a more correct and efficient answer.

In this context, Genetics appears as one of the key sciences for such an answer. Although its scientific basis is barely one hundred years old, Genetics is one of the oldest fields of knowledge in Mankind's history. Folklore includes many practical genetical rules, possibly derived from empirical reasoning; sanitary injunctions embodied into the discipline of some religions or mentioned in religious books reveal a quite correct knowledge of the hereditary transmission of a few diseases, although used as rules-of-thumb, and it may be assumed that the first geneticist was some unknown caveman who attributed to the deified forces of Nature the origin of a mutation appearing in his own child.

Again, Genetics is masked in the coarse attempts to adapt animals and plants for the benefit of Man since the agricultural revolution, mainly through empirical selection of breeders and seeds, as well as in the pathetic endeavour to analyze the mechanisms leading to the birth of a human being. Man always asked where he comes from and where he is going to — he now has a somewhat misty idea where he comes from, and he asks to Science where scientific technology is leading him to.

This is particularly true for Genetics, in special human genetics, and the impact of recent developments in this field is magnified by rash, uncautious communication mass media, often with untoward results.

The human organism, with its somatic and biochemical characteristics, its behaviour and specific types of reaction against environment and disease, is the result of a very complex interaction of hereditary and exogenous factors. It may be said that what a human being is in a given instant of his life is the consequence of hereditary/environment interaction: at birth some characteristics are already fixed or on the way of being fixed, while others are but virtual potentialities which will eventually become expressed according to the environmental influences affecting the organism. What Man is/has been is fulfilled at the moment of his death.

This means that the evolution of a human being is not complete when intrauterine development enables a new child to be born, or even after the 5-to-15-year period ascribed to extrauterine development. Such periods are currently defined as enabling the new organism to live independently (under the normal social conditions prevalent within each culture) or to reproduce himself (again under the rules of the culture he lives into or adheres to). However, we may assume that, as proposed by Fox, evolution moved from lower levels (atomic, molecular, macromolecular) through intermediate stages (cellular, genetic, multicellular, neural) to higher ones (mental, social) and even now is bound for a supra-social area, difficult for us to visualize since it is above our own present level.

If this is true for a species, a similar pattern may be proposed for each individual within a species, with mental and social evolutive processes going on in human beings until death puts an end to the individual's own evolution.

This concept of equal importance of what is inherited and what derives from environmental influences justifies the increasing interest in the study of human genetics, the science studying the way some characteristics are transmitted to the child being born. We must understand well what is inherited (and the proportion of this inheritance) before endeavouring to analyse the responsability of environment — and from there go back to the revision of genetical concepts and data. This paradox and the recent

progresses in Biology turn Genetics into an ever-changing, highly dynamic science, which must be recognized as such.

Genetics is not yet a proper science, at least when compared to an exact science such as Mathematics or Physics. Based upon observation data which are accumulated for long periods, spanning more than one lifetime, trying to study mechanisms and phenomena often expressed during brief stages of development, resorting to a probabilistic reasoning, Genetics will not entirely satisfy any mind in quest of exact truth. Maybe for this very reason, it elicits in geneticists a humble attitude towards life itself — or, as a compensation, a typical arrogance.

Basic information for human genetics comes from observation in animals and plants, and Genetics is contributing greatly for the concept of unity of living matter. Besides, experimentation is seldom performed in Man, either for ethical reasons or for practical ones: one given observer will be happy to examine four generations of human beings, with two or three scores of individuals, while Drosophila yields ten times more data for a thousandfold more generations during the same span of time; many data and their interpretation depend upon information given to the observer through an intermediary, often interested in not disclosing important facts, such as illegitimacy, and the use of exhaustive exams, as necropsy or total analysis of an organ, is not currently available. It may be easily understood why human genetics was considered until recently as the youngest, underdeveloped sister of other branches of Genetics.

On the other hand, the human species has some advantages, regarding thorough study, over other species. Each physician may be (and should be) an attentive observer of hereditary phenomena; governments, foundations and international organizations will more readily promote projects directly related with the human species, because of their correlation with health problems of the populations, than with other species, unless these present an immediate economic interest. Also, although experimental models of behaviour analysis have been devised in animals, with good results, the best model is Man himself, in spite of the difficulties of test design, which often limits the freedom of the individual. But even in this field the skilled and shrewd researcher will eventually discover appropriate groups characterized by adequate historical and/or sociocultural parameters.

For the physician who attemps to recognize and treat disease, the knowledge of the field where a given disease develops is of utmost importance to understand its etiopathogeny and evaluate symptoms and therapy. The very early pathologists were aware of the variations in the effect due to the same morbid agent upon organisms of one species, and no physician would try to use the same therapeutic routine in all cases of one given disease. The fieldunder the influence of a morbid agent is defined first of all by what is inherited from the ancestors, progressively modified by environment or by other hereditary factors programmed to be expressed later in life or only under a given set of conditions.

Physicians feel the need to respect the uniqueness of the diseased individual and to study the reactions which are peculiar to each organism. In other instances — unfortunately too many — heredity or its mechanisms are directly responsible for disease, leading to death or incapability to adequate adaption to modern life.

Infections tend to loose the leading position in the list of death causes, as the development of therapeutic techniques and preventive measures is extended to more and more populations, and medical technology may eventually be efficient against cardiovascular disease, cancer and psychological disorders. At the same time, diseases due to genetic or chromosomal abnormalities acquire a greater importance, affecting about one in eighty newborns and many more products of conception which fail to develop

up to birth. A sound knowledge of these morbid patterns is needed, in order to achieve early diagnosis, treatment and prevention

A few generations ago, natural selection eliminated quite efficiently those afflicted by these diseases, but now the physician is in a better position to attempt saving them, thus maintaining defficient individuals, in need of constant care and help, within the population and increasing the probability of their reproduction. In this way genes which in old times would disappear are eventually transmitted to the next generation, increasing the genetic load of the population. The economic burden on the family may be alleviated by state or private programs or other measures, but no one will be able to reduce the psychological trauma to the parents of a defective child, who are affected in the most primitive instinct of a living being — reproduction, the survival of one's genes beyond death, onto the following generation.

This is one of the most complex problems of modern society and, when looking for a solution, it was at first logical to try the easiest (and oldest) way, eugenics. Used since the beginning of historical times by different sociocultural groups, where defective children were exposed in hidden places to die or thrown from cliffs, eugenics was embodied into well defined political contexts, and recently turned to genetical knowledge for help. However, geneticists in the end became aware that the available data were insufficient to ensure correct scientific basis for such help, and tried to analyse the long-range consequences of eugenic measures (both positive and negative).

There is not yet a satisfactory answer to this problem: transient, local measures may be adopted while the advancement of medical science does not come up with the correct therapy, and even then the geneticist must forecast the results of this attitude upon the genetic structure of the whole population and the incidence of genetic disease in areas where adequate treatment is available.

Simultaneously, modern technology is giving to Man a double-faced gift: the very means to obtain liberation from disease and better conditions of life have the side-effect of causing pollution of the environment and contamination by mutagens, which have increased both in efficiency and in dosage; more skilled techniques of animal and plant selection are useful as the economy of human populations goes thus far, but the risk exists that evolutive bottlenecks eventually appear, with lower viability and adaptability of new strains, while the original wild stocks are lost; the most recent development of molecular genetics, DNA recombination, is bound to prove itself one of the most important discoveries in the history of Science and a precious tool in Man's hold upon the environment, in corrective techniques of metabolic errors and in economic improvement of plants and animals, but some doubts were recently expressed regarding the possibility of becoming a danger to Man himself, through ecological imbalance (which is apparently a remote hypothesis).

Also, the biology of human populations is being changed throughout the world by current social and economical transformations and by a great improvement in travel facilities. An equilibrium of population numbers was in the past generally obtained by means of high birth rates (with small variations due to differences among regions and social levels), and high mortality rates due to famine and lack of efficient medical and sanitary conditions. As better conditions of life are obtained by populations, mortality decreases while the birth rate will also decrease (although at a slower pace, since previous socio-cultural injunctions will prevail until a conscious effort for birth control is integrated into the culture of each aggregate and modifies the existant pattern).

In the theory of demographic transition this process is divided into three stages, stage I corresponding to the *wild* situation (characterized by high death and birth rates), stage II, of *demographic explosion,* presenting an imbalance due to high birth rates and

low mortality, and stage III, the new, consciously-obtained equilibrium, with low birth and death rates, tending to a zero-growth situation.

The transition to stage III was exemplified with data from 19th-century Europe, where development, through changes in industrial and urban life, was a leading factor in modifying the structure and role of the family as a social and economic unit, reducing the pressure towards a high birth rate. A better knowledge of reproductive physiology and more effective contraception tecniques than the older ones speeded up the tendency for small, non-growing populations.

However, the European model shows some internal inconsistencies (high fertility variance, late marriage, high proportion of non-married people, pre-transition contraception, being four of the most important) when generalization of the theory to present developing countries is attempted. Besides, demographic patterns in these countries are not homogeneous, presenting wide variation of some parameters, while others — such as high fertility rates, tendency to migration, and steep declines in mortality — are almost constant.

More data, from recent years and from regions in different developmental levels and with different cultures will be needed for a reassessment of the transition theory, so that international organizations may possess a reasonably sound basis to propose scientifical advice on the crucial subject of population numbers and its correlation with economic development and conditions of life.

Together with the general increase of population, mainly in developing areas (a fact which may eventually prove itself a factor of imbalance in human ecology), a lower reproductive fitness of couples is being detected, as compared with previous generations. This is mainly due to a conscious or subconscious effort, both by the couple and by society: as a matter of fact, potential fitness is increased by better standards of life, medical care, sanitation, and knowledge of reproductive physiology, and men and women have now a longer fertility period than before, with lower menarch age and lower rates of disability after pregnancy.

This potential fitness is not expressed because other factors are at play: subconsciously, a couple knows that now children born will have a higher probability to survive until reproductive age, so that the compensation effect of child mortality rate is becoming restricted to those couples who see their progeny affected by hereditary disease; also, social factors such as housing facilities, working schedules, educational programs for children, and social security schemes, act as important subconscious motivators of a lower reproductive fitness.

This influence is potentiated by mass diffusion of birth control concepts: people hear nowadays that a small number of children is to be preferred, that contraception is easy and safe, without danger to the health of the members of those couples using it. Either as a cultural superstructure or a state-oriented planning, birth control became a parameter which should not be ignored in demography and in population genetics.

The questions raised by birth control in many fields are beyond our present scope: ethical problems, specially related with the forced generalization of contraceptive techniques; psychological analysis of couples who accept contraception; social effects of birth control and its influence upon social structures such as family, marriage, and the community couples belong to; cultural effects; pratical effectiveness of contraception techniques, which appear to be abandoned after a variable period, without any apparent reason sometimes, where such schemes have been extended to the population and scientifically analysed. These points are important and a global reassessment of the experience obtained in different countries ought to be done.

However, birth control also has some influence upon the genetic structure of the

population practicing it. It has been repeatedly said that a small number of children per couple is an important factor for natural selection: smaller sibships present higher phenotypic variance and thus a more ample set of phenotypic characteristics will come under the influence of selective forces, favouring the evolution of the human species.

This is easy to demonstrate, but such reasoning should be developed to include the analysis of phenotypic variance and its genotypic and environmental components Birth control, through smaller progenies, increases the genetic component, mainly the additive variance. Both genetic and environmental components may be subdivided into familial, regional, etc., subcomponents. If we analyze these two subcomponents, dividing the corresponding variances into two cells each (between families and within families, between regions and within regions), it may be deduced that the increase in variance due to differences between families is obtained at the cost of the within-families component, with higher dispersion of mean values between progenies and higher homogeneity within progenies. Similarly, the increase in the between-regions component corresponds to a diminution of the within-regions component.

If the influences of genetic/familial and genetic/regional interactions are included, a mathematical pattern is obtained of artificial introduction of factors which tend to aggravate the genetic distance between families and between regions. This tendency will be more intense in those regions or countries where the sociocultural environment does not favour identical conditions of life to all families who contribute to the next generation: if selective forces differ according to social strata as defined by family or region or country, birth control will increase the influence of environment upon the genetic structure of the populations who practice it.

This theoretical model calls for a sounder knowledge of human social biology. Data on the social pattern of reproduction and social influences upon selection processes are scanty and derived from a rather limited number of countries, mostly developed ones. Generalization to the human species upon that basis is risky, so a call for such studies should be made.

Evidence is also accumulating on the influence of environmental factors upon the incidence of congenital, non-hereditary disease in the human species. Some of these factors are infectious (mainly viruses) and both therapy and prevention will in the course of time reduce their importance; such is the case for rubella. However, the action of physical and chemical agents upon concepts will apparently develop into a major cause of disease, since higher technological levels in the general population mean a greater risk of exposure to such morbid factors. The list of carcinogenic chemicals widely distributed in the air, food and water is being periodically updated by the International Agency for Research on Cancer (IARC), and the work done points to a close correlation between carcinogenicity and mutagenicity. In fact, some of the most sensitive tests in use to define a chemical as carcinogen include its ability to induce mutation in well known models (Bacteria, HeLa cells, etc.).

Physical agents capable of mutagenic activity are also in constant contact with human beings: ultraviolet and both natural and artificial ionizing radiations are well known sources of mutation, either at gene or chromosomal level. Here again Man is confronted with a necessary technology he can not dispense with and which bears some danger to his own future. Radiation has always been an important factor in the induction of new mutations which were submitted to the test of evolution: radiation helped to shape Man, but the intensity and greater number of new sources and their wide use affect a larger number of individuals, and the pattern of technological development

makes it probable that this situation will be worse in the future — unless new, safer techniques are devised.

Radiation is indispensable in the study of some diseases, although physicians are well aware that mutation may occur after an X-Ray examination or a clearance test using a radioactive substance. Safeguards include the parsimonious use of these techniques (specially in a pregnant woman and then only when really necessary and no substitution method of exploration is available), and the resort to radioactive sources emitting low--energy, short-lived radiation. Even with such precautions, damage to germ cells may be eventually detected in the descendants of individuals submitted to radiation before a child is conceived — sometimes only in the second generation, through imbalance of the division mechanisms of cells or expression of new mutations in a favourable genome.

It appears easier to raise the point of danger to the species when discussing the usefulness of new technologies developed by Man, than to prove that they are safe. Events in the recent history of Science as applied to Man are currently recalled as proof that the means of developing a technology are more advanced than the means to assess its dangers, and sometimes damage already occured before a chemical is defined as mutagen.

Yet, an option should be made between the benefits of each individual technology and the risks it entails: this is true not only as regards the genetic assets of Man, although emotions are easier to be raised when risks to one's progeny are discussed. A well balanced information, timely released to the public, should be encouraged: at this moment, the printing of news on new data concerning drug risks for the conceptus almost obey the rules of epidemiology, scaring women into refraining from indispensable therapy.

It ought to be mentioned here that scientists are often the very source of this distrust: attention is called upon the discoverer of a new deleterious side-effect of a well known drug, which may be true for a small proportion of the population bearing a given genome or which was detected in experiments using models not readily adaptable to the human organism (in vitro conditions, animals with different metabolic pathways).

Nevertheless, the danger deriving from a society which will not easily abstain from using the fruits of its own scientific advances creates a complex situation which may be leading to rupture, either by ecological imbalance or by genetic overload. Man has to answer this new crisis — and will probably do so, aided by his scientific knowledge. He now tries to forecast the consequences of the use of the tools he himself made, and Science gives him the way to reason a way out. This is where Genetics acquires a relevant role in the near future, together with social biology.

The genetical parameters in this answer include recent developments in so diverse fields as molecular genetics, biochemical genetics, population genetics and clinical genetics, which may be applied either directly to Man or to the species which are economically valuable to him. The effect of these developments upon Mankind largely exceeds the mere scope of demography and the health science: changes already under way, and others eventually induced in Man's environment, will influence more efficiently the prevalence of disease and famine than mortality and birth rates would do.

The rearrangement of genes or parts of genes in vitro constitutes one of the most far-reaching discoveries in human history and provides a general technology which, at this moment, is still at the level of prokarionts, namely bacteriophages and plasmids, but is rapidly advancing towards eukariont level.

This rearrangement, sometimes called genetic engineering or molecular cloning,

permits the isolation of a given part of the genome of a species and its implantation into the DNA of replicating Bacteria, where it may eventually express itself by the appearance of the product of its activity. As regards scientific theory, the point is already made of the unity of living beings, since material from a species far apart from the bacteria used as vector is accepted by it and replicated jointly with the bacterial DNA.

However, recombinant DNA still has to fulfill more promises in the field of applied genetics: DNA corresponding to a gene lacking in the patients of a hereditary metabolic disease may be isolated or built and then introduced into a bacteria or virus, but the expression of this particular DNA is not yet readily regulated as it should be in a human being. When such a technique is developed, it will be possible to use bacteria as sources of gene products, either to be transferred to the cells of the patient or to obtain large, cheap quantities of substances difficult to synthetize by chemical methods.

In recent years, this field was subject to strong criticisms on account of the dangers lurking in bacteria and viruses which would be *new*, since their genomes were altered, and thence not yet submitted to the trial by evolution. The possibility of a *total* pandemy due to a new infectious agent was elaborated with fiction tones, not taking into account that vectors are limited, as all infectious agents, by definite metabolic and infective requirements.

The use of bacteria which present some mutations leading to its dependency from an artificial laboratory medium for culture constitutes a good barrier and a safeguard against any accidental dissemination into the environment: under normal conditions, such bacteria would not resist the competitive growth of wild strains, less squeamish as regards nutrients. Again, such bacteria would include in their genome material for substances which are currently antigenic to the human organism, thus eliciting the immune response against an eventual infection. Also the limitation of recombinant research to those institutions and laboratories who accept to adhere to stringent rules of security against the unintentional spread of experimental bacteria is an important safeguard: if a lethal mutation should ever appear in a bacteria that would prove itself lethal for Man or for the species he depends economically on, sanitary conditions and medical surveillance, as existing in those institutions, would provide a better environment to prepare therapy and prevention than anywhere in nature.

The transfer of DNA sequences is also attempted in experimental designs such as the injection of whole nuclei into enucleated cells, the fusion of cells from different species, and the transformation of cultured cells by viral DNA, but only DNA recombination permits the recovery of DNA or the amplification of its function, since DNA segments become coupled with genes responsible for autonomous replication. This is why other techniques have not elicited so prompt an interest — but it remains a fact that the new properties given to engineered genomes may change the pattern of evolution: present forms of life are the result of a very delicate evolutive balance, with new genes being developed in new species. The most important effect of recombination techniques will probably be upon the ecology of altered plants and animals, and the development of such strains (such as nitrogen-fixing plants) should end by a careful analysis of their influence upon the environment before distribution is contemplated.

Biochemical genetics, as applied to the human species, began by the study of some clearly defined diseases, the so-called inborn errors of metabolism. This denomination stemmed from the old concept that morphological and biochemical characteristics were not as correlated as we see them now. The truth is that all morphologically-defined hereditary disease are due to the biochemical action of a gene (or genes) during the development of the patient, either in embryonic life or after birth.

Extensive analysis of the data from different countries on hereditary disease shows that two factors influence the prevalence of this group: the lack of good registries, where data may be confidently taken from (this raises the problem of correct medical assistance), and the presence of local environmental agents which inhibit or potentiate the activity of morbid genes.

An important conclusion from biochemical genetics is the existence of different genomes within populations which were previously considered as homogeneous: such polymorphisms are present in varying proportions in almost every population examined, and the question may be raised whether genetic disease is not in itself a polymorphism balanced by evolution through selection, or corresponds to transient polymorphism bound to disappear.

A patient with a hereditary disease is himself at selective disadvantage: if the illness does not cause directly infertility, by the mere fact of its existence reduces the probability of the patient getting married and having children. Sometimes hereditary disease acts both way, as in achondroplasia. This selective pressure is sure-acting and relentless, exception being made for some instances where cultural injunctions may favour marriage with a patient or a person known to bear the gene.

This model does not explain satisfactorily the relatively high incidence of some diseases which would have had similar incidences many generations ago. In general, this paradox is attributed to a compensation effect of the birth of a defective child — leading to more pregnancies to substitute for the *wrong* one —, a large mutation rate which should in some cases be absurdly high, and the conservation of the gene either by genetic drift, admixture of populations or overdominance of heterozygotes. Overdominance of heterozygotes is more elegant as a model and was proved in a few instances of hereditary disease, such as drepanocytic anemia. However, to accept it as a logical explanation, the mode of selection against the homozygote for the allele must be demonstrated, as again was the case of drepanocytic anemia: homozygotes for hemoglobin S die from anemia, homozygotes for (normal) hemoglobin A are more susceptible to Plamodium infestation wherever paludism is endemic.

At the same time, other polymorphisms considered until now as neutral under a selective point of view, began to show their importance in ecogenetics, reducing the viability of some organisms confronted with new drugs (either by a greater susceptibility to usual drug dosage or by a quicker inactivation), polluants, food constituents, etc. Also a few correlations between specific diseases and gene systems were found significative (ABO blood group and ulcus, as an example) in some reports.

The discussion of neutral versus non-neutral mutations as elements for evolution did not yet end and is an interesting subject of general Genetics. In the human, the situation is still more complex since it deals with a species characterized by a small progeny, where genetic drift plays havoc with the mathematical models assayed thus far. However, it is not a mere speculation to admit that, unless proved, a polymorphism may be another instance of heterozygote overdominance. This calls for a more extensive survey of populations regarding such genetic systems, which would also be rewarding in terms of health care: mass screening will detect people at risk, enabling adequate measures to be taken for prevention, and data for a correct analysis of eventual selective pressures will be available. Indeed, if a polymorphism is proved to be balanced by selection against homozygotes, genetic counselling will have to take this into account, since the presence of a gene causing disease may be necessary to the population.

At least, while an expensive mass screening system is not organized, conditions for the study of individuals at risk (relatives of patients, people working with com-

pounds which may be eventually harmful) should be set up. Although less accurate, this scheme is cheaper and constitutes an acceptable ascertainment technique.

When adequate and reliable data exists on polymorphic characteristics in populations, the calculated gene frequencies may be used to test for deviations from the expected distribution of genotype frequencies, according to the Hardy-Weinberg law, as corrected for endogamy and mutation. The influence of mutation upon the Hardy--Weinberg mathematical model is easy to evaluate: mutation rates computed for different loci are in the $10^{-4} - 10^{-6}$ range, and reverse mutation rates may be assumed to be one tenth of those values.

Correction for endogamy is more difficult: in the human species prohibition of crosses between closely-related people was integrated in the cultural complex of the majority of populations — mainly between parents and children, between brother and sister, and in some cases between first degree cousins and between uncle and niece (or aunt and nephew). Social codes may also phohibit crosses without any genetic significance, between people related to each other by social connections.

Nevertheless, crosses between members of the same family, in the sense that they bear at least one common gene inherited from the same ancestor, are quite frequent: it was calculated that, if one single individual possessed a private genealogy, without any relation to other families and without endogamic crosses, he would have 2^n private ancestors at the nth generation — this menas about 10^{12} ancestors ten centuries ago. The absurdity of this number and the historical knowledge of bottlenecks, such as war, famine, plague, drastically reducing populations to small aggregates, often isolated for some time, lead us to accept the alternative concept, that unknown consanguinity is quite high.

The mean endogamy coefficient is calculated adding the frequencies of each known type of consanguineous crosses in the population, corrected by the corresponding inbreeding factor. The ascertainment of such crosses is not accurate: the real number is greater than that obtained in marriage registries, important crosses are not disclosed because of the incest taboo, and far-related crosses will not be included in the investigation. Another technique uses the frequency of identity of family names, in those populations where the cultural pattern confers significance to that identity, as in Japan.

If reliable endogamy coefficients are available for the populations under study, then any departures from the Hardy-Weinberg distribution of genotype frequencies may be attributed to genetic drift (depending on the mean sibship size), generation overlap, and mostly to the effect of selective forces. Mathematical development of the Hardy-Weinberg law, taking into account the mentioned parameters (at least), is needed to support the effort of analysis of the population polymorphic structure.

Most of the polymorphisms under current study demand elaborate and expensive techniques, so that international support for setting up the necessary registry laboratories should be encouraged. Health systems of the contributing countries would be compensated by the knowledge of the expected numbers of patients with a given disease or at risk when submitted to a given therapy or other environmental influences.

In cytogenetics, development on human data was important in the last twenty years, after half a century of stagnation in comparison with non-human species. Cytogenetics was responsible for some valuable discoveries which helped develop techniques for obtaining new strains of animals, and specially plants, which proved very useful to the economy of populations. The so-called Green Revolution owes much to cytogenetical methodology, and still more is to be expected in this field.

As regards the human species, technical difficulties retarded the study of chro-

mosomal abnormalities, which were demonstrated to be responsible for a set of definite morbid situations. Scientific basis for the mechanism of appearance of syndromes affecting the newborn is now available and may be used in genetic counselling. Diseases such as the Down syndrome are defined by a chromosomal imbalance (variation in the number of chromosomes or chromosomal segments, or translocation of normally active segments to inactive segments, thus leading to inactivation), but there is still insufficient information on what genes are responsible for the disease. New, elaborate techniques of identification of chromosome segments are being developed, while the attribution of loci to such segments was made easier by methods such as somatic hybridization. More data are now available on gene localization in the human species than in most of those species which were previously used in the laboratory for such purpose.

Cytogenetics is now a reliable source of information for the physician, helping him to obtain a diagnosis in polymalformative congenital diseases and in cases of error of sex development. Also, reports point to a rather high incidence of chromosome abnormality in mental defficiency, congenital heart disease, and leukemia. At the same time, extensive work is been done on the frequency of chromosomal polymorphisms in the general population, including those situations of balanced abnormalities which are not expressed in the phenotype but may reveal themselves in the progeny. Most of these polymorphisms are not responsible for disease, corresponding to heteropyknotic, silent segments, but even in these cases meiotic impairment may be discurbed and gross abnormality of the conceptus may follow.

The analysis of products of spontaneous abortion shows that a high proportion of them is due to chromosomal alterations: it may be assumed that chromosome abnormality impairs viability of the conceptus and only minor variations of the karyotype allow the embryo to develop up to birth. Selection in utero is very efficient, and women with a history of repeated spontaneous abortions should be examined, together with her husband, for balanced chromosome polymorphisms.

Also parents to a child where inheritable chromosomal abnormalities are detected (such as in the case of translocation Down syndrome) should be studied, and cytogenetical methodology should be available whenever possible, since it constitutes sound scientific basis for genetic advice regarding the opportunity of a new conception.

One of the chromosomes presenting higher incidence of polymorphism is the Y, which is also responsible for the orientation of the embryo towards a male phenotype through its action during the early days of development. Few, if any, other genes have been ascribed to it, but some reports mentioned a higher incidence of cases with double Y or Y + in inmates of high security prisons. This was not confirmed by other researchers, but raised a long argument regarding the predisposition of people possessing a XYY or XY+ karyotype for aggressivity: such a karyotype would then be a legal basis for declaring its bearers as irresponsible, the presence of material from two Y chromosomes being an extenuating circumstance. Until more is known about the biochemistry of such individuals (the existence of a gene regulating an endocrine mechanism may be put forward as a working hypothesis), this conclusion is not warranted by the data at hand.

Both in diseases due to abnormality of chromosomes and in those induced by the presence of morbid genes, the examination of amnictic fluid enables the physician to search for a particular cytogenetic or biochemical alteration and thus define the embryo as abnormal. This is an answer to those couples who abstain from having another child because an abnormal one was born unto them. People known to be at risk of fathering a child with a given disease may try a new conception, and interrupt the pregnancy if the embryo is proven to be affected.

It should be stressed that for practical reasons the number of tests to be performed is very limited: aside from the karyotype, biochemical analysis is usually circumscribed to the screening for the disease which prompted the investigation, and the normalcy of the embryo will be eventually declared regarding that disease alone. In some cases mass screening techniques may however be developed, as in anencephalia and spina bifida, through the presence of alpha-fetoprotein, in large quantities, in the mother's blood.

Examination of the amniotic fluid is an elaborate technique and it should be resorted to only after the couple accepts to have an abortion if the embryo is affected. It presents two potential risks (aside from death to the embryo or the mother, which are very small in the reports from experienced groups), namely the definition of what the child is wanted to be, and the result of generalized amniocentesis upon the general population.

In the first case, the risk exists that a couple may consider a mere bearer of a morbid gene or of a balanced chromosome abnormality as abnormal (although he will have a normal phenotype), and demand an abortion: they may want their child to be free from the risk of having diseased children himself, or they may go further and prefer a child of a given sex. Rules for abortion after amniocentesis should envisage this situation, which may disturb important balances such as the sex ratio.

The second consequence is the increase of the frequency of the morbid gene or chromosome abnormality — if only embryos presenting the disease are aborted —, due to a renewed fertility of couples which would otherwise resort to contraception after an affected child was born. It is true that such increase will be small, correlated with the availability of amniocentesis, but quite definite and may play an important role in populations with high incidence of the disease under study.

All the developments in human genetics, together with those in general medicine, helped to organize a sounder basis to genetic counselling. In the past, advice to couples at risk was practically empirical, based upon the experience of the counsellor or the data published on the incidence of a second case of disease in sibs of a patient (this is still the current practice for abnormalities where environmental influences are known to exist but not yet defined or where a multifactorial model is assumed). In a small number of cases, Mendelean rules were at play, but the definition of heterozygotes for recessive genes, for instance, was almost always done through the analysis of the family tree, and variations in expression or lack of penetrance were not readily explained or were simply ignored.

The advances in biochemical genetics now enables the physician to define such heterozygotes by means of the dosage effect, and data on clinical genetics is increasing rapidly.

Also a better knowledge of environmental agents and their responsibility regarding the damage to the conceptus is being acquired, and early detection of some diseases (for which mass screening should be performed, since the technique is easy and quite inexpensive) will help to prevent the most significant symptoms through adequate measures, as a phenylalanine-poor diet in phenylketonuria or the graft of bone marrow in combined immunodefficiency, or even the *graft* of enzymes protected by semipermeable chambers or polymerized plastics. It is here that molecular cloning may also have an important role in the future, if our expectations are not deceived.

Besides, medical technology is helping more efficiently those handicapped children, either by surgery or prosthetics, and the care and education of mentally retarded patients begins now to be considered a duty of the society and to have a scientific basis.

Nevertheless, these are desperate measures, and it should be stressed again that a couple at risk of having a deffective child has the right to demand help for their decision of trying a new conception. Thus, genetics must furnish to this counselling a scientific basis.

Prevention of congenital malformations and chromosomal or genic disease may be obtained through two different ways: the betterment of life conditions, reducing environmental morbid factors which are known to affect the genetic material or the development of the embryo (ionizing radiations, radiomimetic substances eventually employed in therapy, etc., food imbalance, food additives...), and the help to those individuals at risk of having children which will be diseased because they have a given gene or a chromosomal abnormality — this is genetic counselling. This concept of genetic counselling as a kind of help, of service, is fundamental in the definition of its aims and techniques.

Essentially, what genetic counselling can do is to give an advice based upon the probability of a defective child being born, calculated with the data at hand. The geneticist must not attempt to cover every field of medical knowledge, but try a synthesis on the basis of the interpretations from other medical specialties for a given case.

The genetic counsellor usually has a preliminary work to perform: to explain the situation, so as to reduce the state of psychological tension and specially the feeling of guilt which frequently affects the couple or the individual resorting to him. The high frequency of hereditary diseases and congenital malformations should be mentioned, as well as their accidental or deterministic character (according to their respective pathogeny).

Another point to be made is the aim of marriage: the discussion of the values in marriage (aside of procreation) opens perspectives which are indispensable to prepare the field for the information which will eventually be given, namely the personal interrelationship and the concept of responsible paternity.

These aspects are essential to the genetic counselling and should be embodied into its theory. Most of the problems raised to the geneticist appear plurifaceted and a single parameter (the genetical for instance) will not be enough to arrive to the solution for each individual case. The information regarding the probability of having a deffective child has to be translated to the couple in a way that it will be left free to take its own decision, and the geneticist must take care not to force an orientation neither to permit that the capacity (and the duty) to decide be transferred to him.

The reasoning used to obtain the revelant probability is based on Mendelean laws, the rules governing the segregation of unbalanced haplotypes in gametes from individuals heterozygotic for chromosomal polymorphisms, and empyrical data for polygenic or partially-environmental diseases. Endogamy is a frequent cause for fear and, in many cases of patients affected by conditions derived from a homozigotic situation, will in fact be responsible, if the morbid gene presents a low frequency in the general population.

On the assumption that couples will follow the geneticist's advice, and that genetic counselling is made available to the general population, the consequences of this pratice must be analysed.

By his very profession, the physician fights natural selection, saving from certain death individuals with hereditary diseases or prolonging life so that procreation may eventually ensue. Each time the adequate therapy is given to a young diabetic or to a phenylketonuric, genes which would disappear from the general pool will be saved and transmitted to the next generation — in terms of population genetics, this means that the selection coefficient was reduced by medical interference.

This influence is extremely low but its effect will be constant and proportional to the ability of cure and the number of patients who access to therapy. For example, phenylketonuria is almost lethal under the genetic point of view (s=.975) and presents an incidence of about 1 in 10 000 newborns, corresponding to a gene frequency of .01; heterozygotes are present in the population with a frequency of .02. If we assume that the loss of genes in the patients was, until this moment, compensated by new mutations, the mutation rate may be calculated as 10^{-4} and will not be expected to change. An efficient and generalized therapy, reducing selection against the gene for phenylketonuria to zero, will increase the frequency of this gene until a new equilibrium point is reached, to .91: then the incidence of phenylketonuria will be about .83 in the population — and the disease will be a normal condition at that time (which is certainly very far away). Such an increase is very slow: in the beginning, near 2 p. 100 of the present gene frequency per generation, so that 2800 generations would be needed to increase the frequency fourfold.

This slowness gives a false feeling of security: the effects upon the population are too insidious, and even then a constancy of the conditions enabling patients to be efficiently treated has to be assumed. However, if the same reasoning is applied to diseases with higher present incidences, a noticeable increase in the gene frequency will be obtained within few generations, thereby increasing the number of patients in need of therapy.

Genetic counselling induces a decrease in the frequency of a morbid gene through advice to couples or individuals at risk, in most cases regarding recessive genes. In mathematical terms, this means the extension of selection against a recessive homozygote to selection against the heterozygote, which will be proportional to the effectiveness of the advice, and the increase of the selection coefficient against a dominant or codominant gene. This will be obtained only if couples or individuals accept the information and do not procreate: genes and chromosome polymorphisms will then act as lethals as regards their ability to be transmitted to the next generation.

In general, it may be calculated that the result of genetic counselling, in retrospective prevention (relative to recurrence in affected sibships) is not higher than 15 p. 100 of the present cases of diseases due to autosomal recessive genes. The situation is better for prospective prevention, where individuals bearing a gene are identified by analysis of the whole family tree; the proportion of recurrences which may be avoided is equal to the reproductive fitness of patients for autosomal dominant or codominant genes, from two to three times the frequency of the gene for autosomal recessive genes, and almost 80 p. 100 for recessive X-linked genes with reproductive fitness equal to 1.

However, genetic counselling may induce instead an increase of the frequency of autosomal recessive genes if the couple divorces, or breaks plans for marriage, and its members marry again within the general population, probably with homozygotes for the allele gene: their children will have a 50 p. 100 probability of being heterozygotes, free from selective influences.

The knowledge that selection constitutes an important mechanism for the improvement of plants and animals, and the attempt to apply it consciouly to the human species is prior to the discovery of the rules of hereditary transmisson and of the intimate structure of the complex biological pattern of heredity.

Eugenics was practiced already in pre-historical times, and was accepted in the last centuries as a concept embodied into pholosophical and political doctrines. To Condorcet, the betterment of our own natural organization would depend upon the transmission of physical characteristics, such as strength, sagacity and sharpness of the senses.

Malthus considered impossible that some of the children would possess the desirable qualities of their parents to a higher degree and, although he admitted the possibility of betterment of the human species through oriented crosses, concluded that it was not probable that orientation of breeding would be generalized since the human race can not be ameliorated without condemning bad speciments to celibacy.

After Spencer and Darwin, the basis of the malthusian thesis was inverted, and struggle for life became a test, not for moral survival, but for physical fitness. Although this concept was in accordance with the sociological pattern of that time, it was quickly understood that conditions of life were now very different from those prevailing during the period of evolution to modern Man. A conscious effort would be a good substitute for previous selection forces, and the interest of eugenics should be centered on the exceptional specimen, the genius. Even those who then advocated the need for an eugenic methodology reacted to this concept — as Ward did, considering the galtonian version of social darwinism as the most complete example of an oligocentric conception of the which was then prevailing in the higher classes of the society and would center the attention upon a very small fraction of the human species, ignoring everybody else.

The comparison of biological and sociological processes was a temptation, and the apparent similarity of natural selection in Biology and artificial selection in Sociology led to concepts where colective, even national experience, was substituted for the individual. After a period of discredit following the consequences of the application of such theories, the hypothesis of eugenic orientation of human evolution is again being put forward by some geneticists and sociologists.

Two main categories of eugenic measures have been proposed: negative eugenics, through prohibition of marriage or procreation of those individuals with characteristics considered undesirable (using more or less subtle techniques which go from compulsive sterilization to psychological coercion or sociological degradation), and positive eugenics, which would be more attractive, as it includes amelioration of life conditions to *normal* people or to individuals presenting a favourable phenotype. It was even said that, while negative eugenics was to be condemned, positive eugenics might and should be practiced, since its rules were beneficial to those it selected.

This distinction is artificial: the resort to positive eugenics means to increase the intensity of positive selection favouring one group, and, by a basic formula in population genetics, the intensity of negative selection against those outside that group is proportionally increased.

On the other hand, generalization of genetic couselling and effective medical orientation may have serious consequences to the population structure, increasing the genetic load; it may also mean negative eugenics if it is applied to a population without relatively homogeneous life conditions.

Before defining in a global scale which are the undesirable genotypes, the effect of genes usually considered as harmful should be studied under different environmental conditions. The human mind, used to command a technology which serves it, abhors to submit to mechanisms of natural selection which it does not entirely understand and which it can not dominate.

When substituting himself for the natural selection, Man must forecast the consequences and, if this substitution may be questioned, the opposition to the negative selection effect of a hereditay disease is mandatory to the medical profession. The consequences of this opposition were already summarized, under the assumption of total, efficient coverage of the population by a health system and the embodiment of obedience to genetic advice into the cultural pattern.

Aside from ethical and legal aspects of eugenics, the result of restrictive measures should be evaluated, since a few are being proposed — and this when communication mass media develop their social impact.

Marriage prohibition because of a morbid gene will usually affect genes with frequencies decreased by natural selection or, alternatively, genes which are convenient to heterozygotes, through overdominance. In the second instance, it may be said that hereditary disease is the price the population must pay for the presence of genes which may be essential to its survival. Sometimes, the presence of a recessive gene, which is harmful in homozygosity, has some significance under the environmental conditions prevalent until now, through mechanisms which are still ignored.

The presence of a dominant or codominant gene is easy to detect (unless penetrance is low or expression is variable), so those bearing it would be readily referenced and the gene eliminated through non-procreation; in the next generations, the disease would decrease to the level of the corresponding mutation rate.

When the gene is recessive, the gene reservatory in heterozygotes must be taken into account, and the mere prohibition of marriage of homozygotes does not eliminate the occurrence of the disease in the next generations (nor even reduces it to the level of the mutation rate). This would be obtained only if heterozygotes were also included in the prohibition, but then a proportion of individuals slightly larger than double the frequency of the gene would be barred from procreation: the frequency of heterozygotes is quite high for some common diseases due to autosomal recessive genes.

Besides, the introduction of artificial selection, as proposed by eugenics, may hurt the equilibrium of genetic homeostasy, through the conflict between the necessity of endogamy (to obtain the fixation of the desired characteristic) and the heterozygosity indispensable to maintain the biological fitness of the population, as pointed out by Lerner. The artificial elimination of those who derivate from the *norm* (the standard pattern which is defined by men, at the same time object and subject of this artificial selection) will increase the stabilizing component of natural selection, with increasing tendency to hypermorphosis and subsequent loss of the organism plasticity.

So, genetics also raises some objections to eugenic measures. The future of medical genetics remains in the development of therapy directed to the gene, through a technology which molecular genetics is now trying to evolve. Never the frontiers between pure and applied research were so illusory.

RESUMO

A espécie humana atingiu um grau de tecnologia que lhe permite determinar alterações importantes no ambiente e nos parâmetros do seu próprio futuro. Neste contexto, a Genética desempenha importante papel na análise das linhas prováveis de evolução da espécie e pode contribuir decisivamente para a solução de problemas actuais de subsistência do Homem.

Não se deverá esquecer que se trata de uma ciência baseada em dados acumulados durante longos períodos, que tenta estudar mecanismos e fenómenos que muitas vezes se exprimem em curtos momentos do desenvolvimento do indivíduo, e recorre a um raciocínio probabilístico. O seu objectivo actual é compreender o que é herdado (e em que proporção), antes de tentar analisar a responsabilidade do ambiente no desenvolvimento duma característica fenotípica. Neste aspecto, a Genética humana apresenta algumas vantagens, que se sobrepõem aos clássicos inconvenientes da impossibilidade de experimentação, reduzido número de observações, etc.: em especial, o reflexo directo

das investigações no bem-estar das populações constitui factor de relevo a favor do estudo mais aprofundado do Homem no ponto de vista genético, que permitirá ao médico dispor de dados mais correctos para a protecção da população que lhe está confiada.

As doenças hereditárias tendem a assumir um lugar importante entre os factores de doença, e a missão do médico, no sentido de salvar os seus pacientes terá como consequência o incremento da carga genética da população, sobretudo no momento actual, em que a biologia da espécie humana se modifica por transformações sociais e culturais. Todavia, são mal conhecidos os dados de biologia social relativos a cada população que interessariam para uma análise mais correcta da genética de populações quando aplicada a um grupo humano determinado. Estão neste caso o aumento geral das populações e a diminuição da aptidão reprodutiva dos casais, sobretudo pelo planeamento familiar, que tem reflexos sérios sobre a estrutura genética da população que o pratica.

Acumulam-se os dados sobre a influência de factores ambienciais na incidência de doenças congénitas, não-herdadas (mas herdáveis), e o aumento desses factores, em qualidade e quantidade, torna imperiosa a opção entre os riscos e os benefícios de uma dada tecnologia — e o que diz respeito à progénie excita mais facilmente as emoções que qualquer outro risco.

O perigo de uma sociedade que se não abstém facilmente do uso dos seus avanços científicos cria uma situação complexa que pode conduzir a uma rotura, quer por desequilíbrio ecológico, quer por sobrecarga genética. O Homem deverá responder a esta nova crise, e provavelmente fá-lo-á, na base dos seus conhecimentos científicos. É aqui que a Genética adquire um papel relevante, através da engenharia genética, do estudo extensivo dos polimorfismos bioquímicos e seu eventual valor selectivo, da análise citogenética nas situações de plurimalformação ou vício de desenvolvimento sexual, e, em especial, do aconselhamento genético, o qual deve manter preservada a liberdade de opção do indivíduo ou do casal que o busca, ao mesmo tempo que será posto à disposição daqueles que o necessitam. Apenas desta forma se conseguirá evitar a sua conversão numa simples forma de eugenia e, simultaneamente, manter a personalidade dos indivíduos em risco e a riqueza genética da população.

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