FROM CHRONOGENETICS TO PHENOGENESIS*

LUIGI GEDDA
The Gregor Mendel Institute of Medical Genetics and Twin Studies, Rome, Italy

Allow me to start by observing that, in the word " reproduction ", the initial syllable, *Re*, has a remarkable importance, at least to the geneticist. In fact, when we say " reproduction ", we do not merely mean that a living being is produced, but we also mean that the production of such a living being implies the repetition of a model that is present in the species, in the population, in the family.

Moreover, the model that is reproduced is not only that of an embryo, of a fetus, of a neonate, but is also that of a child, of an adolescent, of an adult, of an old man.

Reproduction is therefore the repetition of a model that is not limited to the amphimixis, to gestation or birth, but that dominates throughout the entire cycle of life with a continuous variability, that is, through a dynamic and individualized phenogenesis. Such an extension of the concept of reproduction from the stage of conception to the standards of the successive ages, requires that a view based on immediate times be substituted with a view based on long times. This means, in other words, that a new parameter should be explicitly considered as part of the zygote's blueprint: the chronologic parameter.

Monozygotic twins have shown us the existence of a hereditary time, in that they scan simultaneously normal or pathologic times, thus making it clear that the biological fundamental time is controlled by their identical genotype. The examples are innumerable, and range from twin girls experiencing menarche during the same night, to twin brothers dying from infarction during the same night and in different places, and so on.

Going back to the extensive concept of reproduction, we may ask how can the two phenomena I have reported take place, that is: (1) the reproduction of a chronological model spanning the entire life, and (2) the variability of this model between populations, families, and individuals.

I start from the notion according to which each gene possesses its own lifespan. This temporal variability of the gene entails a variability in its time of information and a decay in its quantity of information. The Mendelian law of independence accounts for all possible combinations of temporality of the genotype, such as the variability among individuals, families and populations, that is to say, the horizontal chronological variability of hereditary time.

The longitudinal chronological variability is the one that concerns the informatic power of the gene in the successive stages of life. This informatic power undergoes operative variations during the age of development (such as, for instance, in the case of the block of the information concerning the thymus, or primary dentition). Moreover, the informatic power of the gene undergoes a physiological decay, that is due to the action of mutagenic agents reducing its informatic potential until it becomes exhausted. The gene's informatic power decays at every age, but in pathological cases it starts from a level that is already lower than normal. When the amount of available information becomes lower than the minimum amount needed by the organism, then the hereditary disease appears.

* Text of a lecture for the Second International Congress on Human Reproduction, Tel Aviv: 23-28 October 1977.

CODEN: AGMGAK 26 193 (1977) — ISSN: 0001-5660
Acta Genet. Med. Gemellol., 26: 193-196

Longitudinal decay is a typical phenomenon of both regulator and structural genes and its variability appears during the development of the ontogenetic model of the species.
Mendelian independent assortment, therefore, may account for the temporal variability in the life of the organism that originates from the zygote where the whole of its " programming " is present. This is also a notion that monozygotic twins have taught us, in that, without such a predetermination, it would unconceivable that identical individuals originate from a divided zygote. It is therefore logical to state that the Mendelian principle of the independence of characters also applies to those characteristics of the gene that control the lifespan of its information.
Since the times of reproduction are determined at the level of the gene, it must be admitted that the gene possesses, within the structure of its informatic mechanism, the possibility of a temporal dimension. We therefore have to indicate in what the temporal mechanism of the gene may consist.
The gene coding system that accounts for the synthesis and regulation of proteins through qualitative and quantitative pieces of information is sufficiently known. Less known is the fact that the same mechanism may be able to produce the temporal variability of one and the same information in different individuals, as well as the variability of an information in the same individual at different times.
For the sake of clearness and conciseness, we have termed *Chronogenetics* that branch of genetics that is devoted to the heredity of biological time. Three are the chronogenetic parameters of the hereditary information: (1) *Synonymy*, since the DNA molecules that code for one and the same information may be more or less stable according to the higher or lower number of hydrogen bonds, as determined by the different synonyms represented among the coding triplets, that is, changing A-T/G-C base pairs ratio; (2) *Redundancy*, that is, the number of repetitions of one and the same information, that clearly influences in a remarkable way the efficiency of the gene; (3) *Repair*, that is, the interaction between the structure of the information and the repair systems that restore a mutated DNA molecule.
The degree of stability of a gene determines the duration of its informatic action. The term, *Ergon*, indicates the degree of stability, whereas the term, *Chronon*, indicates the life expectancy of the gene information. Ergon and Chronon are directly proportional.
The molecular model of the gene's action in time having been thus defined, somatic mutations may be considered to affect the genotype by causing a decay in gene stability and thus progressively shortening the period of informatic action.
We have recently experimentally approached the problem of the definition of the temporal decay of the genotype through a study of the morphology and physiology of the human chromosomes at two age levels: 6-8 and 16-18 years. We found that this interval of ten years is responsible for a reduction of 5% in the blast index, a reduction that is reflected in an increase in both the mitotic and the association index. In other words, the lymphocyte response to phytohemoagglutinin appears to decrease with time. Moreover, the centromeric index of chromosomes 1, 9, and 16 shows a peculiar morphologic modification that allows to refer to a q— physiological modification of these chromosomes.
A direct estimate of a gene's ergon, and thus of its decay, is not yet possible, but may be deduced from the quantitative variation of the primary product of the gene that results from the corresponding reduction in the amount of information. Such a dosage is now practiced in geriatrics for a number of enzymes, for which a progressive decay is shown.
A problem arises with respect to reproduction, that is, the *zero-setting* of the zygote and of

mutagenic effects on the gametes in the case of sexual reproduction. How can it happen that the haploid set of the gametes remains untouched by the progressive decay that characterizes the diploid somatic cells, since the gametic line derives from diploid cells around the first month of intrauterine life?

This zero-setting problem is very important in human chronogenetics, since here is the starting line of any new individual, and this is especially evident in monozygotic twins who, from then on, will progress in parallel. And, even before that, this zero-setting phenomenon is important in that it differentiates living from nonliving matter: in fact, it only takes place in the former, as opposed to the linear decay that chracterizes nonliving matter, that is, entropy.

What is then the mechanism that keeps at zero, or near zero, the mutagenic damage to gene stability at each conception?

This question is also justified from a medical viewpoint, since genetic analysis has shown many times an effect of parental age on the offspring's genetic blueprint, at least with respect to the maternal gamete. Down's syndrome represents the most obvious, but certainly not the only example. Also the expression of normal hereditary traits may be affected by maternal age, such as in the case of twinning, or in the case of quantitative traits, as shown by Lints, from the University of Louvain, and Parisi, from the Mendel Institute, on the total finger ridge count in man, and as already shown on sternopleural cheta number in *Drosophila* and on caudal fin rays in a fish, *Lebistes reticulatus*. The heritability estimates of these, and possibly other quantitative traits are significantly affected by maternal, and partly by paternal, age at conception.

Human chronogenetics has gone farther, as we, as well as other authors, have shown that, for given diseases, in later members of affected sibships, a relation is found between increasing parental age at conception and earlier manifestation of the hereditary damage in the offspring. This has been found in cases of Fabry's disease, intestinal polyposis, colon adenocarcinoma, cancer of the kidney, Alport's syndrome, and in other cases.

A hypothesis to explain the zero-setting of the exogenous decay in the genes of the zygote is based on the condition of stability concerning the genes of gametes. In the case of the male gamete, one may refer to the selection of sperms in the environment of the female genital system, whereby only one out of million sperms, the fastest and most efficient, gets over the immunitary barrier and fertilizes the ovum.

In the case of the female gamete, one may refer to the selection taking place in the tetrad, whereby three elements become polar bodies and only one, possibly the most efficient, is used as the ovum. Moreover, the deutoplasm of the ovum may also play a relevant role: although it is usually considered at the operative and episomic level, it may also be considered as a shield or as a buffer contrasting mutagenic agents.

In any case, the problem of the zero-setting remains to be explained, because it also takes place in asexual species and in unicellular organisms during mitosis.

From a pratical viewpoint, the most important problem consists in managing to dose the ergon of an individual gene, in order to predict the time for its informatic extinction. When lymphocytes may be used to set up specific cultures whereby the gene activity may be stimulated and dosed, similarly to what is presently done with chromosomes, then preventive medicine will have found the key to the study of the pathologic future of the individual subject, thus moving from an indefinite ground toward a specific knowledge and an early treatment, before the gene information becomes exhausted and the disease appears.

In this land, where the word of the Bible intensely resounds, allow me to conclude with a quotation from Psalm 127:

As arrows in the hand of a mighty man,
So are the children of one's youth

With these words, the efficiency is stressed of the offspring conceived when the parents are still young, and a biological principle is stated that is typical of Chronogenetics.
Thank you.

REFERENCES

Denden A., Franceschetti A.T. 1969. Cornea Verticillata: Ein Symptom des Morbus Fabry-Anderson. Ber. Dtsch. Ophthalmol. Ges., 69: 145-148.

Gedda L. 1963. Genetica clinica. In: Proc. 2nd Int. Congr. Hum. Genet. [pp. 911-919]
Rome 6-12 September 1961. Rome: Istituto G. Mendel Publisher.

Gedda L., Brenci G. 1969. Biology of the gene: The ergon chronon system. Acta Genet. Med. Gemellol., 18: 327.

Gedda L., Brenci G. 1971. Chronology of the gene. Acta Genet. Med. Gemellol., 20: 323-349.

Gedda L., Brenci G. 1973. Chronogenetics - Its foundations, scope, and impact. Acta Genet. Med. Gemellol., 22: 3-17.

Gedda L., Brenci G. 1977. Chronogenetics - The Inheritance of Biological Time. Springfield, Illinois: C.C. Thomas Publisher.

Lints F.A., Parisi P. 1977. Heritability and parental age. A twin study on finger ridge counts. In: Abstracts of Second International Congress on Twin Studies [No. 91], Washington.

Valleteau de Moulliac, Ganansia R., Hors J., Letexier A., Moris M. 1974. Cancer du rein familial et system HLA. Quatre cancers du rein gauche dans une fratrie. La Nouvelle Presse Médicale. Paris, Masson et Cie., p. 24.

Prof. Luigi Gedda, Istituto Mendel, Piazza Galeno 5, 00161 Roma, Italy.