

THE ROLE OF CHRONOGENETICS AND OF GEMELLOLOGY IN THE PREVENTION OF GENETIC MORBIDITY *

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The prevention of hereditary diseases after birth is essentially based on the detection of these diseases at their preclinical level. This may be made possible through a careful pedigree examination and possible identification of a "genealogical alarm", as well as a detailed clinical examination of the subject and possible identification of preclinical signs of the pathogenesis, i.e., of a "clinical alarm". The respective roles of chronogenetics and of gemellology in this approach are reviewed.

The subject of our Conference hits one characteristic of Medical Genetics whereby the latter differentiates from Clinical Medicine, in that it may not merely deal with the diagnosis and treatment of hereditary diseases, but with its prevention as well.

Such a preventive action may be applied by Medical Genetics at three levels: (1) at the eugenic level, that is, before conception; (2) at the obstetric level, that is, between conception and birth; and (3) at the level of independent life. In my presentation today I will only consider the latter, that is, the preclinical stage of the hereditary disease at the level of independent life.

The preventive medicine of these hereditary diseases moves from their endogenous determinants, but leaves out chromosomal aberrations, their pathology being already expressed in the prenatal period. Moreover, the ratio between chromosomes and genes being of 1: 1500-2000, by far the largest part of hereditary pathology is determined at the gene level. Two are the fundamental concepts underlying the prevention of hereditary diseases, which may be realized through the results of a twofold alarm, as will now be made clear in the five points in which my presentation is subdivided: (1) Concept of gene stability, (2) Concept of duration of the gene's informatic action, (3) Exploration of the genealogical alarm, (4) Exploration of the clinical alarm, (5) Role of gemellology.

1. CONCEPT OF GENE STABILITY

The stability of the gene is a new concept underlying a dynamic genetics, that is, the study of the action of the gene on the temporal parameter that we call *Chronogenetics*. By stability of the gene we mean that the informatic power of the gene is limited in time: the gene possesses a fourth dimension that becomes apparent from the time of activation of the gene through

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to the time of extinction of its activity. Stability is a quantitative characteristic of the gene; it follows the Mendelian law of independence, may differ from one gene to the other, and reproduces the stability of the corresponding parental gene.

Gene stability results from the combined action of three molecular parameters: (A) the different number of hydrogen bonds that, as a result of the code degeneracy (or *Synonymy*), may be contained in DNA segments coding for one and the same information; (B) the number of repetitions of the same informatic sequence (or *Redundance*); and (C) the interaction between the structure of the informatic sequence and the repair system (or *Repair*).

As referred to, and as a product of these parameters — Synonymy, Redundance and Repair — the degree of stability of the single gene has been called *ergon*.

The *ergon* of a gene is the key of an original endogenous time we call genetic time. Two different times therefore act upon the human body and obviously on each living organism: the physical and the genetic time.

2. CONCEPT OF DURATION OF THE GENE'S INFORMATIC ACTION

The concept of duration of the gene's informatic action is dependent on the concept of gene stability; whereas stability is an actual measurement of the gene, the duration of its action is a potential measurement, because it is subject to environmental influences.

The duration of the informatic action is therefore an indirect measure of the *ergon*, though it may be defective. We have named it *chronon*.

Ergon and *chronon* build up a system whereby the chronogenetic profile of biological heredity may be represented at the level of the hereditary unit.

The concept of duration also comprises the principle of gene decay which is symmetrical and opposed to that of stability and determines the extinction of the informatic action. In most cases, gene decay goes hand in hand with a reduction in the amount of information and is conditioned by the organism's consumption. The decay may be anticipated when the mechanisms of heredity endow the phenotype with a gene possessing a lower *ergon* than the normal threshold. Then, the decay of the gene stability and the exhaustion of its informatic power result in the genetic disease.

In physiological conditions the *ergon/chronon* system of regulatory and structural genes controls the hereditary variability of times in the assembly line of the human organism from the zygote through to the adult organism.

This stage, also called the auxologic stage, is followed by the stage of homeostasis: this represents the management of the genotypes coacting, according to the endogenous chronogenetic characteristics, in turn influenced by the stimuli of the physical time. Homeostasis is then followed by senescence — the stage characterized by a general decay of the *ergon/chronon* system of the genotypes coacting according to a hereditary model of the aging process (at the family and population level). When this decay eliminates "sine qua non" genotypes, responsible for essential functions, death supervenes, and this at an age that is also under chronogenetic control.

3. EXPLORATION OF THE GENEALOGICAL ALARM

Almost all genetic diseases are inherited and may therefore be detected in the pedigree. The ratio between inherited genetic diseases and genetic diseases originated by fresh mutations is in fact of about 100 : 1.

The medical geneticist is therefore able to detect a significant alarm in the pedigree, which gives the advantage to isolate the likely disease or diseases from the very broad area of possible hereditary pathology and/or disposition to exogenous causes of disease.

When drawing the pedigree, however, chronogenetic data should also be incorporated, such as the age of onset of any hereditary disease or disposition, as well as the most significant ages in the course of the disease and the age of death of single family members.

The study of a pedigree may thus lead to define, not only the disease's mode of inheritance and its risk of occurrence in the propositus and in the sibship, but also the likely age of onset. For instance, progressive muscular dystrophy shows a clinical onset age characteristic for the family (see Fig. 1).

The study of the repetition of the clinical damage at a given age has just started (e.g., in diabetes, epilepsy, heart disease), but should now be extended and referred to the inheritance of gonosomal or autosomal, simple or polygenic, quantitative traits. As far as we are concerned, we have already recorded the phenomenon of anticipation in the sibship according to birth rank, both in cases studied by us and from the literature, as can be seen from the pedigree shown in Fig. 2.

The anticipation in the age of onset of a hereditary disease in the same sibship may also find a possible interpretation in the observation by Mørch (1941) who, in a study of 175 cases

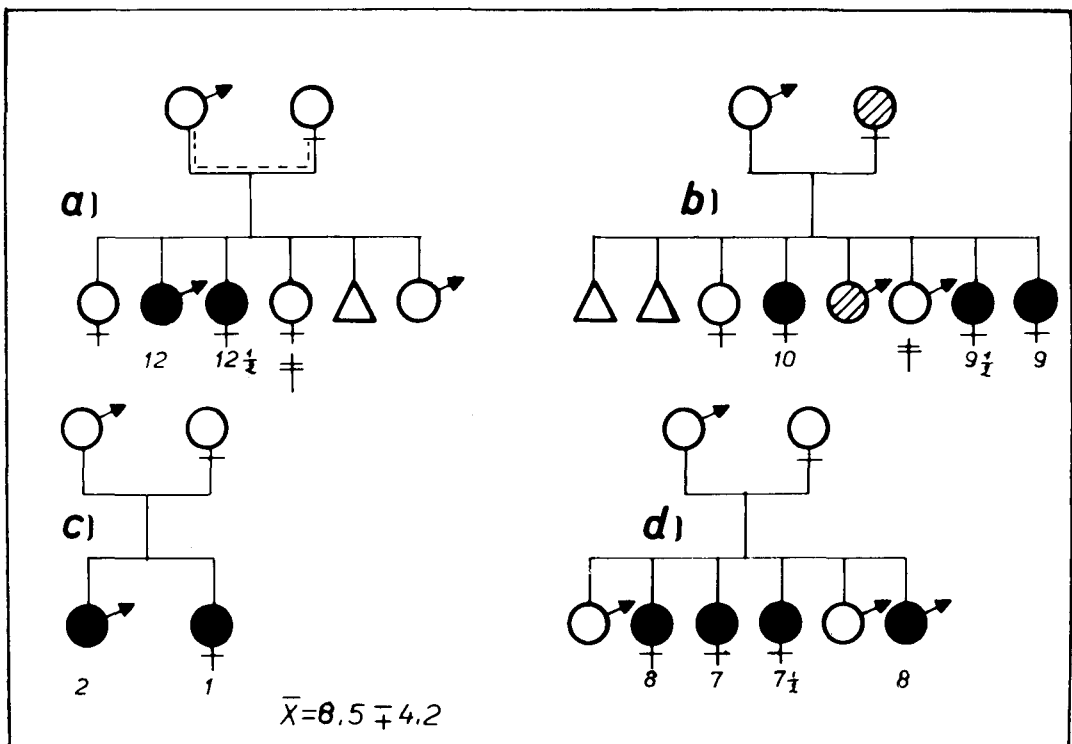


Fig. 1. Juvenile progressive muscular dystrophy showing family-characteristic age of onset: 1-2 years in family c, 7-8 years in family d, 9-10 years in family b, and 12 years in family a.

of chondrodystrophy, has shown the mutation rate, and therefore the instability of the gene, to increase with paternal age. A similar observation has been reported by Blank (1960) concerning paternal age in Apert's syndrome.

We therefore assume that the germinal line, which differentiates in the first weeks of life and may receive diseases originally present in the zygote, though better isolated and protected than somatic cells, may undergo a decay in the ergon of the affected genes that is in turn reflected in an anticipated age of onset of the genetic pathology, in inverse proportion with birth rank.

The importance of parental age in the manifestation of hereditary traits is, on the other hand, well known from a number of examples. Such are the increased frequency of Down's syndrome with maternal age (referred to, in this Conference, by Matsunaga), and previously and repeatedly, for the same and other conditions, by Penrose, or — as recently shown by Lints and Parisi for quantitative traits both in *Drosophila* (sternopleural chetae

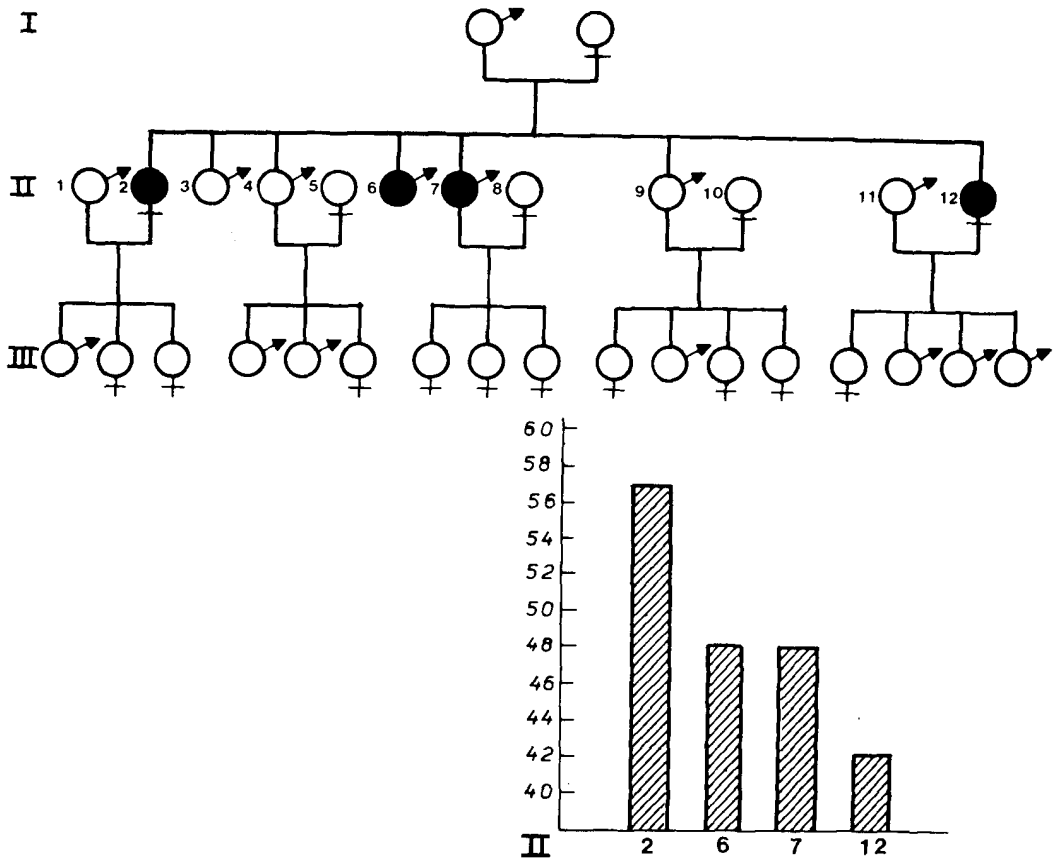


Fig. 2. Pedigree showing recurrence of cancer of the kidney in various members of one sibship. A trend toward anticipation in the age of onset clearly appears from the histogram, the first-born, patient no. 2, having become affected at the age of 57 years, patients no. 6 and 7 at the age of 48, and the last-born, patient no. 9, at the age of 42.

number) and in man (total finger ridge count) — the increase of heritability estimates with maternal (and, to a lower extent, paternal) age, Though not overlapping in nature, these and other phenomena show many analogies.

4. EXPLORATION OF THE CLINICAL ALARM

For preventive medicine to follow its course, the genealogical alarm must be followed by a clinical alarm.

The clinical alarm serves the purpose of establishing whether the genealogical alarm involves the propositus. To this end, the possible hereditary damage has to be identified in the phenotype looking for the preclinical signs of the pathogenesis and possibly for the deficit of the primary product (usually an enzyme) of the decaying gene, or of the metabolite that marks the deficit, tracing back as much as possible.

The dosage of these substances is not sufficient, even if the values appear to be within normal limits. Two ways may be followed.

The first way consists in the effectuation of a new dosage after some time, say, one year. Because of the occurring gene decay, the values will show a modification, both in the case of a primary product of the gene and in the case of a metabolite that the gene should have controlled. In both cases, if the variation is significant, by extrapolation from the curve of decay or of accumulation it will be possible to calculate the time within which the genetic risk produces clinical damage, unless a substitutive treatment is undertaken and the damage caused by the corresponding genotype's extinction is avoided.

The second way consists in a load test with a substance that should be metabolized under the control of the specific genotype. The responses to the load, such as the peak of the curve and the time of return to normal, may indicate the subclinical deficit and the likely time of onset of the disease.

5. ROLE OF GEMELLOLOGY

Postnatal preventive medicine, individualized and based on the chronogenetic parameters, is a recent branch of genetics applied to human health and requires the close cooperation of general geneticists and medical geneticists.

The theoretical and practical implications of this research represent a path that our joint endeavour should transform into a model for future medicine.

A very useful research area where the hypotheses, the methods and the limits of the prevention of hereditary diseases may be verified, is represented by Gemellology, that is, by the study of twins, monozygotic (MZ) and dizygotic (DZ).

This is an *in vivo* method, of clinical use to the twins and of scientific use to all, in that it can provide the evidence supporting the genetic and chronogenetic phenomena we have considered.

The usefulness of gemellology for chronogenetics derives from a number of possible applications:

(1) Demonstration of the temporal potentiality possessed by the gene and expressed through the lifespan of its informatic power. Such a demonstration is provided by MZ twin pairs, in that a continued synchronism is presented by the two MZ twin partners in their auxologic, homeostatic, and aging processes. The researcher is faced with two clocks that start operating

at the same time and then proceed independently but synchronously. The twin test thus provides experimental evidence for the existence of a genetic time, that is, of a "clock of life".

(2) Demonstration of the possible influence that environmental and operative variations may have on the genetic time, when MZ twin partners happen to be separated and live in different environmental conditions, characterized by different rhythms.

(3) Demonstration of the genetic value of a phenotypic finding on the basis of the comparison of MZ vs. DZ twin partners.

(4) Verification of the genetic significance of a chronologic phenomenon or phenotypic trait on the basis of the corresponding finding in twins of MZ pairs, of the same sex and of the same age class.

In closing, I should like to note that twin research is also made easier by a number of practical circumstances. First of all, twins are more frequent than one is usually inclined to believe. Generally speaking, in fact, the average for the world population is of one twin delivery every eighty deliveries, which comes to say that one out of forty subjects may be expected to be a twin.

In the last few years twin research, twin data collection and methods of analysis have been considerably implemented also on account of the promotional activity of the International Society for Twin Studies. After a First International Congress in Rome in 1974 and a Second in Washington in 1977, the Society will hold its Third International Congress in Jerusalem in 1980.

It is in Jerusalem, in fact, that an institute devoted to the study of twins, similar to the Mendel Institute in Rome, is about to be opened for the benefit of research and of the twins of the various countries of the South-Eastern Mediterranean.

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