4

CHRONOGENETICS

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CHRONOGENETICS
Its Foundations, Scope, and Impact

L. GEDDA, G. BRENCI
The Gregor Mendel Institute for Medical Genetics and Twin Studies, Rome, Italy

Many chronological correlations in different plant and animal species, in populations, in human families, and between cotwins, prove the existence of characteristic biological times. Some such times also tend to be related to cosmic time, in which they develop and from which they are induced, resulting in peculiar composite times, such as the daily, monthly, or annual rhythms, that are the object of study of chronobiology.
Beyond these examples of exogenous chronological induction, the existence of a hereditary biological time is postulated, as the basic phenomenon in the relationship between time and life. The newborn scientific branch of "chronogenetics" is devoted to the study of the fundamental, endogenous genetic time, with its theoretical and practical, normal and pathologic implications. To explain and interpret the mechanisms of the hereditary biological time, the authors have developed a model based on the concepts of "ergon" (i.e., stability of the gene) and "chronon" (i.e., lifespan of the information). This Ergon/Chronon System is related to the gene, bringing into focus the fourth dimension and the dynamic aspects of unit of inheritance.
The applications of chronogenetics extend to every expression of life, from the most primitive unicellular to the higher plants and animals. In the area of normal human traits, the study of the hereditary biological time contributes significantly to the interpretation of such phenomena as development, reproduction, homeostasis, and senescence. In the area of medicine, chronogenetics interpretes, unifies, and develops the temporal phenomena of inheritance. In a future perspective, chronogenetics appears to be fundamental for eugenics, preventive medicine, and prognosis.

A few years ago we discussed with our students an interesting case: two MZ twin sisters, at the age of ten years and ten months, experienced menarche in the same night, while asleep. The same physiological event may therefore take place in a synchronous, automatic way in two autonomous individuals.

Recently, a province magazine reported the death of two old-aged twins, as shown in Fig. 1: these are obviously MZ twins who have died at ten-days distance one from the other. According to the information we have gathered, they both died from circulatory troubles caused by senile diabetes.

Confronted with these two twin cases of physiological and pathological concordance, we may ask ourselves the two questions:

1. What is the probability that two women, born simultaneously, have menarche on the same day?

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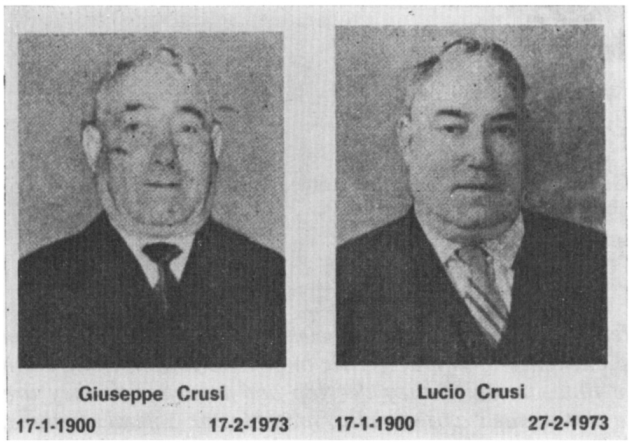

Fig. 1. These two MZ cotwins both died at 73 from cardiocirculatory complications of diabetes.

2. What is the probability that two men, born simultaneously, die from the same disease ten days one after the other?

In the case of the simultaneous menarche the random probability for this phenomenon taking place at age $10^{10}/_{12}$ corresponds to $0.0025 = 25 \times 10^{-4}$.

In the case of the old-aged twins, the probability of dying at age 73, at a ten-days distance, for two subjects born in 1900, being of 0.0008, and the probability of both dying from cardiocirculatory complications of diabetes being of 0.092, the random total probability of the event is of $0.0000736 = 736 \times 10^{-7}$. (Calculations based on Italian Vital Statistics, 1972).

While the probability that such events take place at random is almost nil, those who study twins are every day confronted with as many cases of physiological or pathological temporal concordance as are the MZ twin pairs they observe.

Whenever twins are said to be as like as two peas in a pod, they are by the same token, though unawares, defined as isochronic, in that they have developed the same traits at the same time. Two MZ twins are not just identical statues that remain such while time goes by: they are living beings, and therefore experience a process of continuous variation — a process that in their case is synchronous at every structural and functional level.

Identical twins are therefore the symbol and living example of the hereditary biological time, one and manifold, that they scan in parallel, as two violins play the same music keeping the time of the same metronome. Two MZ twins are isochronic to the point that, whenever a difference between them appears, one is led to infer that different environmental factors may have caused it.

Isochronic concordance being practically nil in random individuals of the same age, whereas it represents the rule in MZ twins, there must be a cause for that. Since MZ twins share a common heredity it may be safely assumed that the latter be responsible not only for the qualitative concordance but for the chronological one as well.

Our assumptions may therefore proceed as follows: (1) MZ twins are isochronic in that they are isogenic; (2) MZ twins show the existence of a hereditary, individual biological time; (3) the mechanism of this hereditary biological time is contained in the genome.

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Hereditary biological time is strangely ignored for two different and convergent reasons. First of all, the attention of research workers has been focused on the sideral or cosmic time, that accounts for the rhythm of hours, days, months, and years, because of the remarkable, continuous, and evident influence that cosmic rhythms exert on normal and pathologic functions of human beings. The study of these rhythms is the object of chronobiology.

Secondly, hereditary biological time is ignored because Mendelian genetics has entirely devoted its attention to the inheritance of qualitative and quantitative, normal and pathologic traits; and, similarly to cytogenetics and molecular genetics, has neither solved nor afforded the problem of the existence and the mechanism of the temporal parameter of the gene.

Chronobiology is by all means a deserving science, though it fails to exhaust the problem of the relation between time and life, inasmuch as it doesn't face the most important aspect of this relation, which concerns the time of internal, rather than external, origin.

Moreover, chronobiology has experimentally demonstrated that environmentally induced biological rhythms do also show hereditary characteristics, i.e., undergo a genetic control. Although true, this has eventually complicated the problem and masked the actually basic phenomenon. For instance, women living in the same environment, but belonging to different populations, in the average experience menarche at different times. Such phenomena show that the human organism's response to cosmic time has undergone an environmental selection of operative mechanism, although it remains evident that the primary nature of this time is exogenous.

Hereditary biological time, instead, is an originally continuous, i.e., nonrhythmic time, that has its starting point in the zygote and involves each of the genes; consequently, it is of an endogenous nature. It is therefore very important not to mix up chronobiology and chronogenetics.

The term, chronogenetics, was born in 1972 and announced in a lecture the senior author gave to the University of Tel Aviv (Gedda 1972). It had however been born *ante litteram* during the Second International Congress of Human Genetics (Rome 1961), when the same author referred to a " period of the gene " and to a " fourth dimension of the hereditary unit " (Gedda 1961).

The fourth dimension of the gene comes out at the right moment, when molecular genetics has discovered that the gene, as quality of information, corresponds to the DNA molecule, and describes the latter as a three-dimensional polypeptide. It becomes easier, therefore, to think of this molecule in terms of a fourth dimension as well, represented by its duration, indicated by the amount of time of which the gene disposes in order to express itself into the phenotype. To this time, i.e., to the average life established by the gene that supports its period of informatic activity, we have given the name *ergon.*

We have also transformed Beadle's aphorism, " one gene-one enzyme," into its chronogenetic equivalent, " one gene-one time," in order to stress that any primary gene-product has a limited, variable, and hereditary time of delivery. Moreover, since ergon and chronon are in a causal relation and directly proportional, we have worked out a model, the " Ergon/Chronon System," that correlates the two variables.

Since 1961, a number of authors have devoted their attention to the time of the phenotype depending on heredity — such as Strehler (1962, 1964), who sees the old age as a consequence of random somatic mutations; Burch (1968), who sees involutive diseases as autoaggressive phenomena due to somatic mutations in predisposed individuals; Medvedev (1966), who sees the old age as a disordered ontogenesis caused by alterations of operative genotypes. Other

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authors have directly referred to the chronon concept — such as Bartalos (1971), who has studied it at a cytogenetic level in neoplasia; Rainer (1971), who has studied it in mental diseases; or Halbrecht (1971), who has studied the population variability of menarche from a chronogenetic point of view.

On our part, we have tried to provide an experimental support to the phenomena shown (Gedda and Brenci 1971). Experimental work has been carried out on both drosophila and man. In drosophila, we found out that the duration of life differs in the wild and mutant types and that the crossing of different strains results in an intermediate duration of life in the hybrid. This shows that biological time is originally a product of the genotype. We have also shown that parental age in drosophila influences the duration of life in the offspring. This shows the ergon decay in the haploid condition, i.e., in the germinal phylum of gametes.

The twin test was used in man for cytogenetic and growth studies. At the cytogenetic level, temporal aspects of the genotype of mitosis have been examined. As an experimental parameter, the association frequency of acrocentries was chosen, i.e., a plate disposition of chromosomes indicating an inefficiency of information for euploid mitosis. A comparison of the caryograms of human twins aged 6 and 60 has shown a remarkable increase of these associations, which demonstrates the lack of information we had forecasted, i.e., the exhaustion of the Ergon/Chronon System in the diploid condition, as a result of age.

Twins were also used in a radiologic study of the development of dental buds and ossification nuclei, that has shown a significantly higher time concordance in MZ vs. DZ twins, both for the teeth and for hand bones. The twin test has thus shown the hereditary nature of the temporal phenomenon under study, i.e., the genetic origin of chronon.

As for the interpretation, we have suggested the following model.

Once noted that the concept of gene stability, or ergon, should be distinguished from the concept of DNA-molecule stability — the former being referred to the hereditary unit while the latter is limited to the physico-chemical structure of the double helix — we consider the ergon as a global formula that allows to include all stability factors responsible for the gene stability (i.e., the ergon):

1. *Redundancy*, i.e., the number of repetitions of the DNA molecule representing a given gene;
2. *Differential stability of the DNA molecule* as a function of the variability of the number of H bonds that, information being equal, synonimy permits;
3. *Repair*, i.e., the gene's ability to repair the damage caused by mutation through a battery of specific enzymes.

These three factors are a characteristic of the single genes and therefore easily account for the inheritance of the Ergon/Chronon System and, more generally, of biological time.

We think we have in this way demonstrated the existence of a fundamental biologic and hereditary time (i.e., the time of gene), and suggested a model for the interpretation and study of chronogenetics.

We should now like to pass from the fundamentals of chronogenetics on to its scope, both in the Greek sense of the word (*scopeo* = I see) and in the English one (area of competence).

The extension and competence of chronogenetics concerns life as a whole, for every

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living being, from virus to man, builds up itself and reproduces according to the times he has inherited and that he in turn scans and retransmits. Hereditary biological time characterizes the individual, establishing the timing of his life, i.e., of any function or disease of his organism, from mitosis and meiosis to the time and circumstances of natural death.

The innumerable threads of hereditary biological time (one for each gene) mix up with the threads of cosmic time, that is rhythmic in nature and therefore transmits its own rhythms to the tissue of life.

With reference to the plant kingdom, we may take an example from Linnaeus, who was able to work out an individual " calendar " based on the month and day of bloom, and a " clock " based on the hours of the day at which the flowers open (Fig. 2).

The fact that the response of plant species to cosmic time be individually constant, demonstrates the existence of a biological time, strictly specific and hereditary, that interacts with cosmic time. The hereditary imprint that biological time transmits to « mixed » times as well, is illustrated by Kerner, who followed for twelve years, in the botanical gardens of Innsbruck, the bloom time of pure and hybrid willow-trees: with respect to pure parental varieties, hybrids exhibited intermediate bloom times (see Table).

The existence of a genetic biological time concerns all living beings, with progressively reduced variabilities of species, population, family, zygosity. The area covered by chronogenetics therefore extends to the entire realm of biology.

TABLE

BLOOM TIME OF WILLOW-TREES (*Salix*) IN INNSBRUCK'S BOTANICAL GARDEN
[*From Kerner*]

Parental species			Hybrid	Bloom time		
(1)	×	(2)	(3)	(1)	(2)	(3)
Cremsensis		*Caprea*	*daphnoides*	17 March	16 March	18 March
Mauternensis		*Caprea*	*purpurea*	23	16	7 April
attenuata		*Caprea*	*grandifolia*	25	16	27 March
Wimmeri		*daphnoides*	*incana*	26	18	17 April
Austriaca		*grandifolia*	*purpurea*	3 April	27	7
Seringeana		*Caprea*	*incana*	3	16	17
capnoides		*cinerea*	*incana*	5	10 April	17
intermedia		*grandifolia*	*incana*	6	27 March	17
rubra		*viminalis*	*purpurea*	6	3 April	7
Kerneri		*viminalis*	*incana*	10	3	17
Oenipontana		*purpurea*	*incana*	12	7	17
auritoides		*purpurea*	*aurita*	14	7	19
Fenzliana		*retusa*	*glabra*	21	21	21
retusoides		*retusa*	*Jaquiniana*	21	21	21
alpigena		*retusa*	*hastata*	23	21	27
excelsior		*fragilis*	*alba*	23	13	27
Ehrhartiana		*alba*	*pentadra*	23	27	6 May

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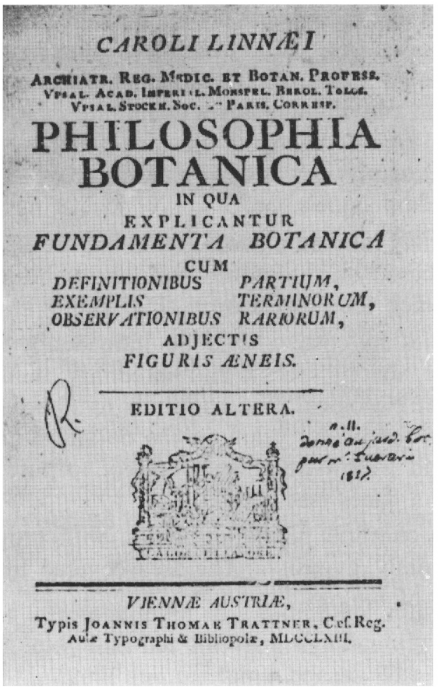

CAROLI LINNÆI

ARCHIATR. REG. MEDIC. ET BOTAN. PROFESS.
UPSAL. ACAD. IMPERIAL. MONSPEL. BEROL. TOLOS.
UPSAL. STOCKH. SOC. [illegible] PARIS. CORRESP.

PHILOSOPHIA BOTANICA

IN QUA

EXPLICANTUR

FUNDAMENTA BOTANICA

CUM

DEFINITIONIBUS PARTIUM,
EXEMPLIS TERMINORUM,
OBSERVATIONIBUS RARIORUM,

ADJECTIS

FIGURIS ÆNEIS.

EDITIO ALTERA.

VIENNÆ AUSTRIÆ,

Typis JOANNIS THOMAE TRATTNER, Cæs. Reg.
Aulæ Typographi & Bibliopolæ, MDCCLXIII.

276 ADUMBRATIONES.

33. Hemerocallis a. *fulva* 5 — —7. 8.
34. Convolvulus. 2. *sepium* 5 6. —
35. Malva 4. *helvola* 9.10.— —1.
36. Alyssum *Alyssoides* T. 6. 8.— —4.
37. Anthericum 267. *album* 7 — —3. 4.
38. Arenaria 376. *purpurea* 9.10.— —2. 3.
39. Anagallis 169. *rubra* 8.
40. — — — 1. *arvensis* 7. 8 —
41. Portulaca 1. *hortensis* 9.10.— 11. 12.
42. Dianthus 7. *prolifer* 8. — —1.
43. Mesembryant. 1. *barbatum* 7. 8.— —2.
44. — — 2. *crystallinum* 9.10.— —3. 4.
45. — — 10. *neapolitanum* 10.11.— —3.
46. — — 5. *linguiforme.* 7. 8.— —3.

☽. ☽: ☾.

Horologium Floræ ex sequenti tabula formandum postquam meteorici & emiculares flores exclusi sunt, de quibus alibi.

☽ ☾

8. — Tragopogon *luteum* 22.
4. — Leontodon *Taraxonoid.* 2.
4-5 — Picris *augus* 13.
— Cichoreum *scariosum* 28.
— Crepis *tectorum* 12.
6. — Scorzonera *tingitana* 21.
5. — Sonchus *levis* 17.
— Leontodon *Taraxacum* 1.
— Crepis *alpina* 3.
— Tragopogon *Columnæ* 23.
— Lapsana *Rhagadiolus* 25.
— — *glutinosa* 27.
— Convolvulus *sepium* 34.
6. — Hypochœris *pratensis* 4.
— Hieracium *fruticosum* 9.
— — *Fulmonaria* 8.
— Crepis *rubra* 14.
— Sonchus *arvensis* 16.
7. — — *helgicus* 19.
7. — Leontodon *Chondrilloides* 3
— Hieracium latifolium 10
— Sonchus *lapponicus* 18.

— Lactuca *sativa* 20.
— Calendula *officinalis* 31.
— Nymphæa *alba* 29.
— Anthericum *album* 37.
8— Hypochœris *hispida* 5.
— Lapsana *Rhagadiolus* 26.
— Mesembryant. *barbatum* 48
9.— Hieracium *Pilosella* 7.
— Anagallis *rubra* 39.
— Dianthus *prolifer* 42.
—8.9. Leontodon *Taraxacum* 1.
9— Hypochœris *Chondrilloid.* 6.
10— Malva *helvola* 35.
— Arenaria *purpurea* 38.
— Mesembr. *crystallinum* 44.
— 10 Lapsana *glutinosa* 27.
— Lactuca *sativa* 20.
— Scorzonera *tingitana* 21.
10.11. Mesembr. *neapolit.* 45.
— 11. Crepis *alpina* 13.
— Tragopogon *Columnæ* 23.
—12. Sonchus *levis* 17.
—12. — *lapponicus* 18.

S 2 Hypo-

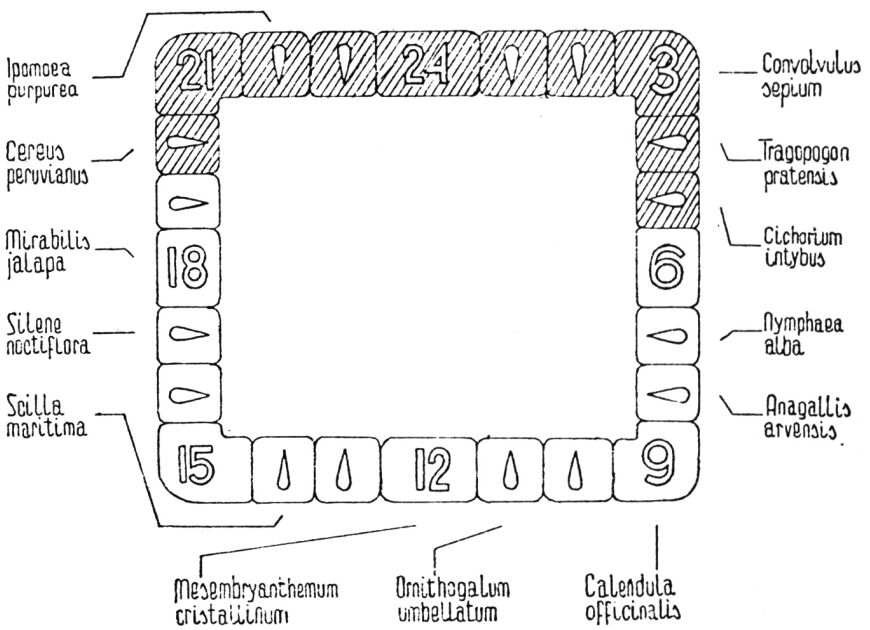

Fig. 2. Linnaeus's flowers "clock".

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Wherever life exists, hereditary units, or genes, exist as well; and wherever a gene exists, this possesses an energy charge proportional to the time of its informatic action. The life of the gene is represented by a cycle of decaying energy, that expresses itself through the time phene, i.e., through the duration of the individual hereditary trait.

At this point, we may ask ourselves: what is the impact of chronogenetics on human and medical genetics? To human genetics, chronogenetics gives the formula to study the normal times of the gene; to medical genetics, it gives the interpretation and prospection of pathologic times.

With reference to normal times, Fig. 3 shows the ontogenetic times of stature development in children from three populations: Italian (lower), American Negro (faster), and White-Negro mulattoes (even faster). This is a temporal phenomenon that should be better examined and that seems to correspond, on the dynamic plane, to the phenomenon that, on the static plane, Mendelian genetics calls heterosis (Gedda et al. 1960).

With reference to senescence, chronogenetics may contribute to the solution of the etiologic problem. The different theories suggested are overcome by the observation that the diagram

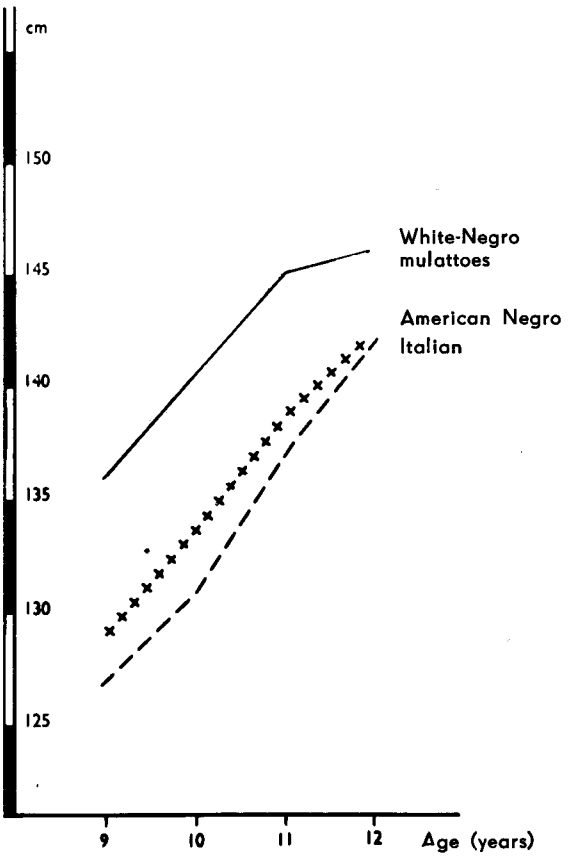

Fig. 3. Stature development in different populations.
[*Modified after Gedda et al. 1960*].

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of senescence presents significant repetitions in members of the same family, and is concordant in twins, as is also shown by our research studies on teeth loss and white hairs in twins (Gedda and Brenci 1971). Chronogenetics explains senescence observing that gene stability decreases in the third age and that the duration of the information ends in a different way from one gene to the other in the same individual. This corresponds to the Mendelian principle of independence, and therefore takes place in a completely different way from one individual to the other, though with a reduced variability within the same family and identically in MZ twins.

With regard to medical genetics, chronogenetics represents the common denominator of hereditary pathology, because — in contrast with senescence, that is uniform, since the genome decay is chronic and global — in hereditary diseases the lack of information is sporadic and anticipating. The so-called morbid genotype has a negative meaning (*ex-vacuo*), i.e., it corresponds to the silence of one or more genes that fail to produce the information anymore, their ergon being practically exhausted and their chronon having ended. This gap of information may be filled, either supplying from the outside a natural or artificial gene or a by-product of the missing substance, or by stimulating redundancy, repair, or substitutive genotypes. But it is too early to give therapeutic conclusions.

We should now make some use of chronogenetics in order to better study genetic diseases. We have tried to afford an elementary screening based on McKusick's very good catalog of Mendelian inheritance in man (1966). Looking for any possible temporal parameter in this catalog, we were able to gather a general view of the situation, which is definitely incomplete, since the author had not the same objective as we had, but, for the very same reason, full of significance.

McKusick's catalog includes approximately 1500 hereditary diseases, divided in dominant, recessive, and sex-linked. The basic chronogenetic parameter is represented by the age of onset of the disease. This is traditionally given in the medical literature, the description of any disease including, as a rule, etiology, symptomatology, course, prognosis, and treatment. Age of onset is given within the description of the course, and this detail acquires a particular importance in the hands of the geneticist.

To start with, 10% of the diseases catalogued by McKusick give, more or less precisely, the age of onset. It should be added, however, that another 30% are congenital, since fetal-life onset is also a true chronogenetic parameter. We may therefore consider that the age of onset is already known for at least 40% of hereditary diseases.

In the chronogenetic perspective, the age of onset corresponds to the time at which the responsible gene stops supplying the normal information; therefore, the onset of the disease marks the end of the responsible gene's chronon. The geneticist may then verify the behavior of the same gene's chronon in family relatives. Other chronogenetic phenomena may be considered, such as the within-family correlation of chronon; its sex-linkage; its anticipation, postponement, or end; the chronogenetic typing of the disease; the influence of parental age and of birth rank.

We shall now try to give a few examples of these parameters making use of literature data, other than those cited by McKusick.

Let us start with the pedigree of sex-linked or sex-modified cataract (Fraser and Friedmann 1967: Fig. 4). Actually, cataract is not strictly sex-linked, the same symptons being

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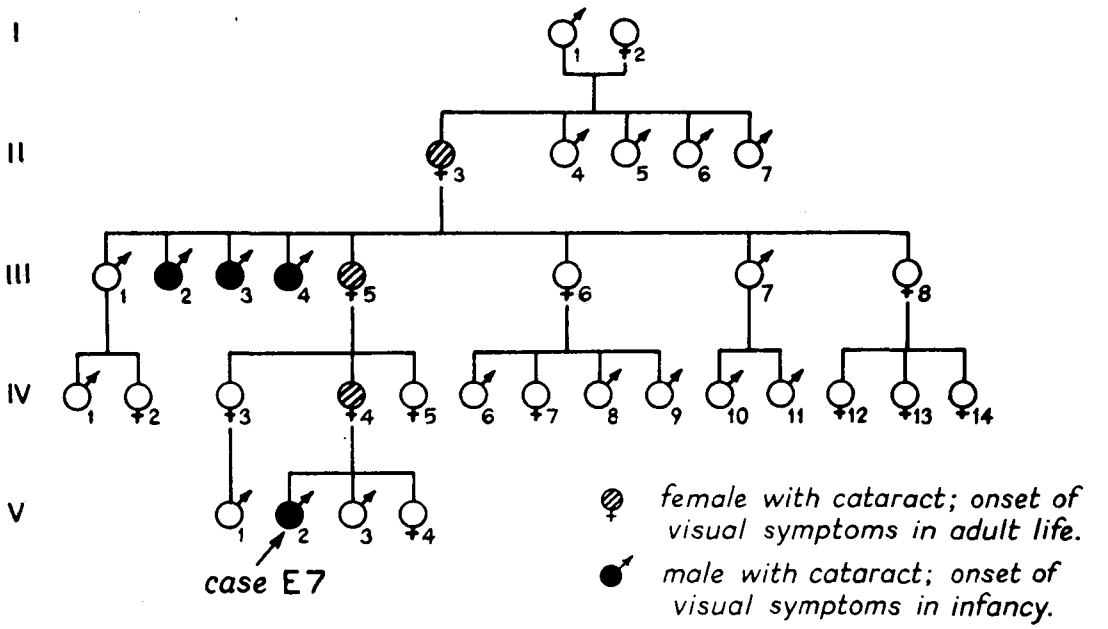

Fig. 4. Differential onset of cataract in the two sexes. [*After Fraser and Friedmann 1967*].

present in the two sexes; however, the sex modifies the chronon of the disease, the onset being in infancy for males, but in the adult life for females. Chronon is therefore sex-linked, and the fact that it is longer in females makes us think that chronon, just as the gene itself, may be linked to the X-chromosome, that is double in females, accounting for a double ergon in the mutant gene, whereas it is single in males.

The family correlation of chronon may be well shown by a pedigree collected in our Institute and shown in Fig. 5. There are five cases of intestinal polyposis with carcinomatous transformation and three cases of death probably caused by the same disease. In all the cases the onset is before 30 and the correlation consists in this young-age onset.

An example of correlation in the adult life is shown by a pedigree presented by Anderson (1970) and shown in Fig. 6. A woman aged 43 and eight relatives are affected by uterus and colon adenocarcinoma. Onset was always in the adult age, between 34 and 51; at the time the pedigree was drawn, the fourth generation, still in the young age, was healthy.

These examples of family correlation of chronon may be easily explained if time is considered as a phene, so that, in Mendelian terms, one may speak of a family correlation of the trait chronon.

A typical Mendelian behavior of chronon may be found in a pedigree presented by Denden and Franceschetti (1968), showing a woman affected by Fabry's diseases (cornea verticillata and angiokeratoma), transmitting the disease to each of the two sons conceived with two different husbands (Fig. 7). In both cases the onset was at 16. This agrees with the model of X-linkage and with our interpretation that the maternal allele repeats in the two sons its temporal dimension.

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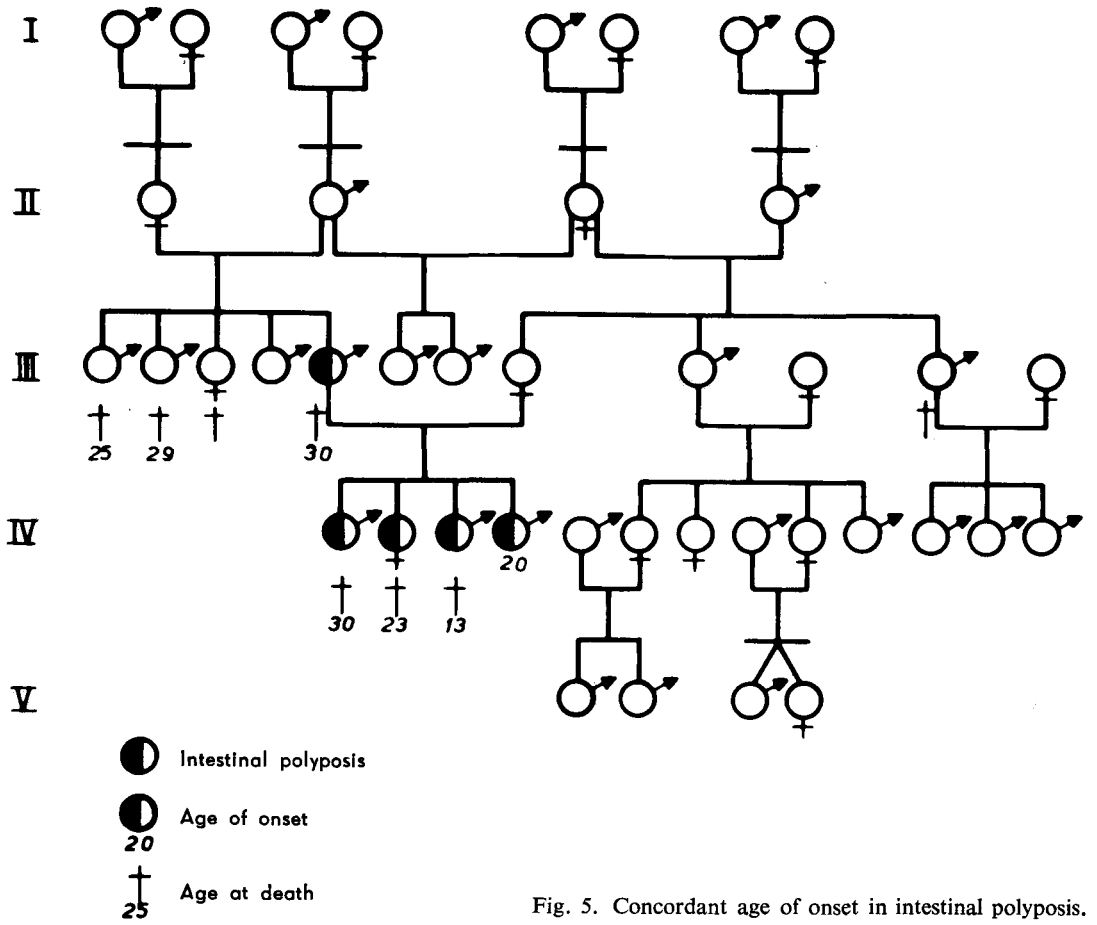

Fig. 5. Concordant age of onset in intestinal polyposis.

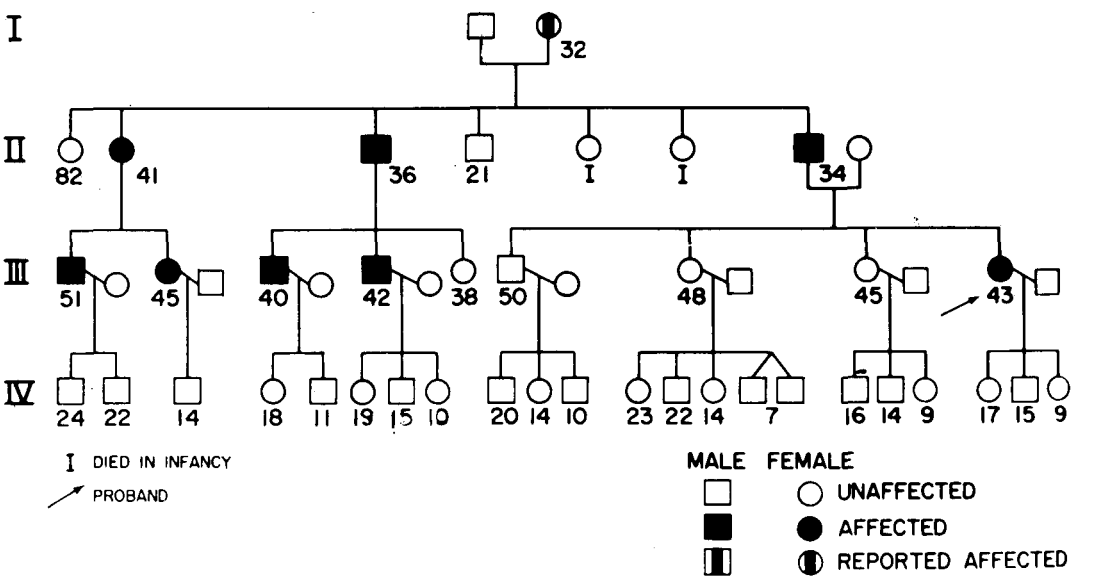

Fig. 6. Concordant age of onset in uterus and colon adenocarcinoma. [*After Anderson 1970*].

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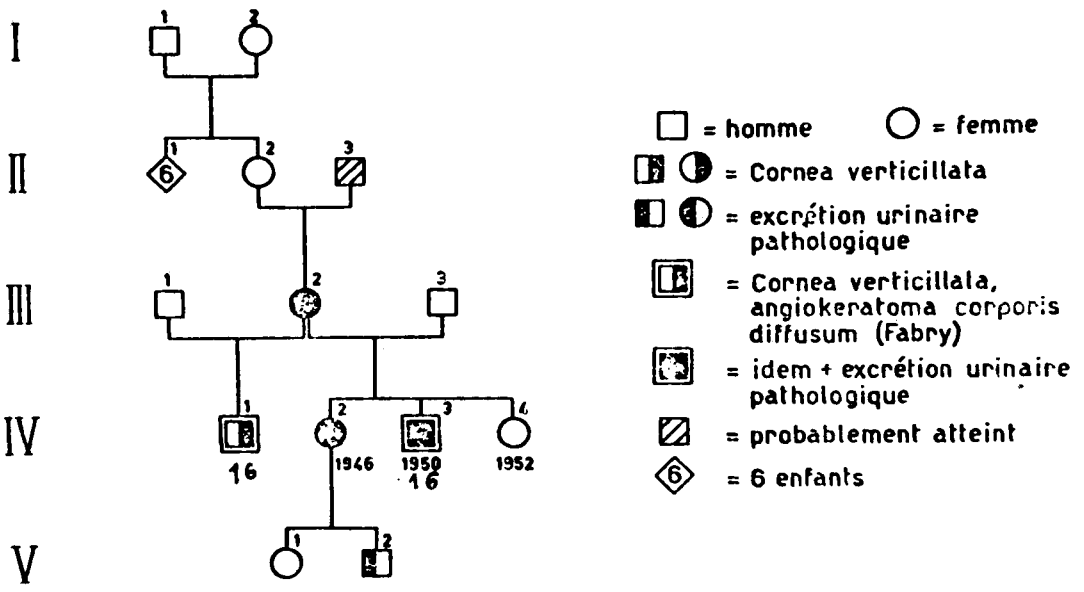

Fig. 7. Concordant age of onset in Fabry's disease. [*After Denden and Franceschetti 1968*].

When different conceptions are distributed over a longer period of time, another chronogenetic phenomenon may become apparent, as shown by a pedigree (Fig. 8) collected by Gruber (1946) and completed by Franceschetti (1967), where a female carrier of Fabry's disease has a total of fourteen conceptions, with symptoms of the disease in at least nine of these. When we pass to examine the age of onset, we find the following progression: no. 7, age 20; no. 14, age 12; no. 15, age 11; no. 16, age 9; no. 19, age 5. This is a very clear example showing the progressive decay of chronon in the haploid set of the maternal gamete and the corresponding reduction of chronon in the offsprings' specific genotype.

The considerations we have made so far only concern the age of onset, whereas the temporal parameters that may be found in the literature are various and meaningful, such as the age of exitus (that sometimes, although more rarely, may mean recovery) and its factors of anticipation and postponement, the times of expression that represent the hereditary component of a larger picture that medicine calls course.

Special Pathology may foresee and set up a chronogenetic control of every disease, and may lead to finding out that chronogenetic variability has made different names be given to the same disease.

For instance, according to a classification of some lipid storage diseases, Tay-Sachs disease corresponds to the infantile form of amaurotic idiocy, whereas Bielschowsky-Jansky disease corresponds to the late infantile one, Batten-Vogt-Spielmeyer's disease to the juvenile form, and Kufs disease to the adult form (Berman 1973).

Chronogenetics may unify what the clinical picture seems to divide.

From an individual point of view, chronogenetics has a definite impact at three levels: eugenics, preventive medicine, and clinical medicine.

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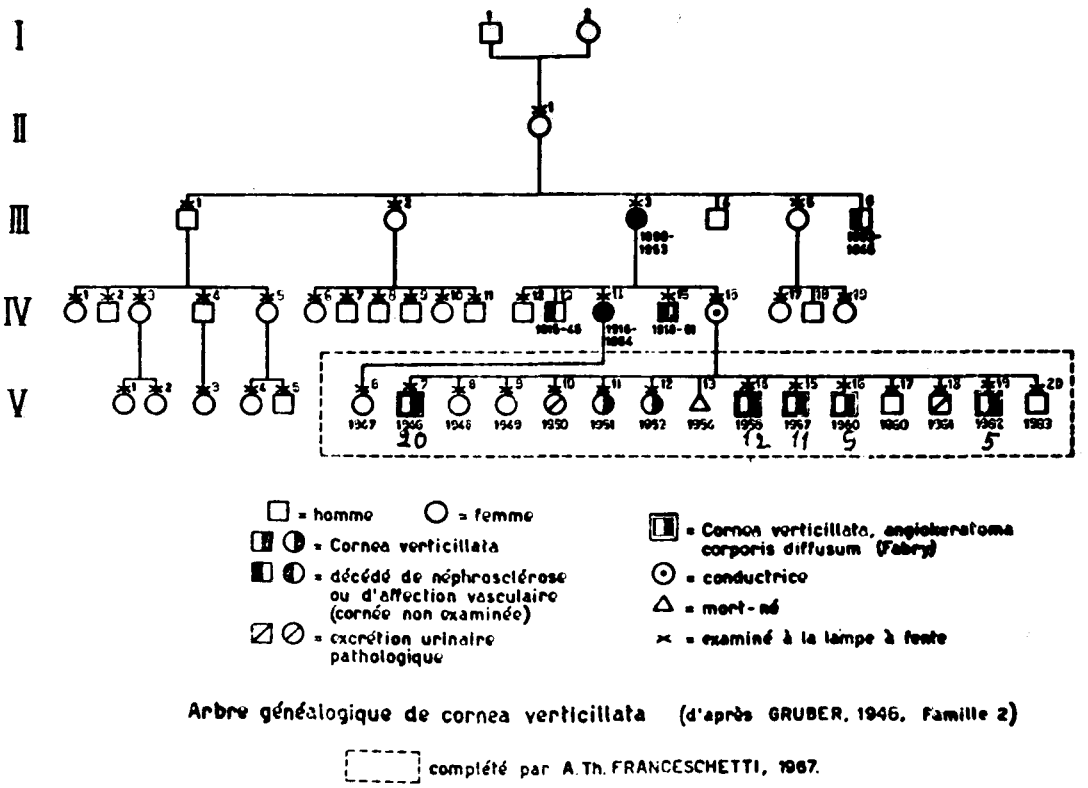

Fig. 8. Progressively anticipating age of onset in Fabry's disease. [*After Franceschetti 1967*].

In this Congress, one section is devoted to eugenics, under Prof. Klein's chairmanship. Therefore, we have a special occasion to say that the eugenic forecast should not only be qualitative, i.e., referred to the hereditary diseases presented by the family branches, but chronologic as well, in that the risk to the couple also concerns the age of onset. This is important, because, on the one hand, the risk may thus be better evaluated; while, on the other hand, after the marriage has been celebrated, the risk itself may disappear when the calculated age of onset is passed.

Chronogenetics may help preventive medicine by finding out the age of danger and setting up measures to detect and correct the disease before its clinical manifestation.

After the manifestation of the disease, chronogenetics may give a doctrinal and practical basis to prognosis; the latter may be considered as a chronogenetics *ante litteram* practiced since the times of Hippocrates.

We should finally like to observe that chronogenetics marks the passage from a static to a dynamic view. Obviously, Mendelian genetics, as well as cytogenetics and molecular genetics, have all afforded the study of the sequence of hereditary phenomena: this is, however, a study of discontinuous stages, where the *continuum* of a dynamic action is lacking. The difference is similar to that existing between describing a phenomenon through a series of

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slides and describing it through a moving picture. Chronogenetics has this kind of efficiency because it follows the *continuum* of the information in the time, its incidence, its variability, and the different consequences of its action in the different times of life.

With chronogenetics, a dynamic view is realized through which every genetic phenomenon appears to be the effect of the various presence or absence of a flux of information distributed all over any autonomous individual and any part of it capable of autonomous life.

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Prof. Luigi Gedda, Istituto di Genetica Medica e Gemellologia Gregorio Mendel, Piazza Galeno 5, 00161 Roma, Italy.

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