Chronogenetics : the inheritance of biological time / by Luigi Gedda and Gianni Brenci.

CHRONOGENETICS

THE INHERITANCE OF BIOLOGICAL TIME

LUIGI GEDDA
GIANNI BRENCI


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By

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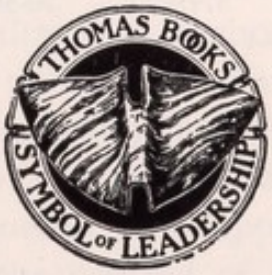

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Foreword

Professor Luigi Gedda's name has been familiar to me since my earliest days as a graduate student with the late Franz Kallmann, Professor Gedda's colleague and devoted friend, himself a pioneer in twin studies. At that time Professor Gedda was not well known in the United States, yet, to me, his name even then connoted one of the giants in the field of human twin studies. His founding of the Gregor Mendel Institute created a unique setting for the scientific study of twins and this Institute has devoted itself to the examination of normal and abnormal developments in twins throughout the life cycle, comparing twin partners both in health and in disease. It has remained unique in the world in terms of its facilities, the extensiveness of its investigations and the hundreds of twin pairs examined within its walls, whose total number by now is measured in four digits. Another monumental contribution of Professor Gedda's was the publication in 1951 of *Studio dei gemelli* which appeared 10 years later in translation, markedly abbreviated, as *Twins in History and Science,* and gives us insight into human fascination with twins since early historical times. Today, every student of medical genetics recognizes the name of Luigi Gedda as synonymous with twin studies.

In the course of his studies Professor Gedda became intrigued with the importance of time in medical genetics. Long before it became fashionable to talk about biological rhythms, Professor Gedda had the imagination to conceptualize and the courage to focus attention on time as a fourth dimension for the gene. He termed this temporal dimension the "chronon," hence the name chronogenetics. In 1961, when at the Second International Congress of Human Genetics, held appropriately in Rome, Professor Gedda proposed the concept of chronobiology, few members of the scientific community were prepared to keep in step with his advanced ideas. Today, we are all accustomed to think-

ing in terms of diurnal, circadian and ultradian rhythms. Thus, we exemplify change over the course of time.

Chronogenetics is devoted to an exposition of the thesis that authentic biological time is hereditary in nature and "that the mechanism capable of producing, maintaining and transmitting it, must be sought in the competence of genetics" (p. 39). Together with his collaborator, Dr. Gianni Brenci, Professor Gedda opens to us a world of times—cosmic, mathematic, astronomic, psychologic, as well as biologic. In giving us an opportunity to ponder these thoughts by means of an eminently readable translation, Dr. Louis Keith has rendered a real service to the English speaking world.

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and
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Introduction

At the Second International Congress of Human Genetics in Rome in 1961, I proposed the concept of "gene period," that is, the time during which the hereditary unit acts. I explained this concept by use of a metaphor, likening it to a birthday cake in which the number of lighted candles stood for the number of birthdays reached. In the case at hand, the ceremony takes place in another way in that each candle represents a gene in actual or potential action, and the candles at birth are of varying lengths. Each candle goes out by itself as it burns down; in other words in a time which is proportional to its length. The quantity of residual light which remains (the state of health and the life span) depends upon the number and importance of the candles which go out. The concept of "gene period" implies an inheritance of "time," and at that same genetics meeting, the importance of this viewpoint was outlined with regard to clinical genetics in order to prognosticate the date of onset, the course and the outcome of hereditary illnesses.

Before conceptualizing the gene period and the ensuing deduction that the gene must be recognized as having a fourth dimension, a "temporal" one, I had, as early as 1959, noted the phenomenon of coincident menarche in monozygotic (MZ) twins who had an equal hereditary patrimony. Subsequently, at the Human Genetics Seminar of the Council for International Organizations of Medical Sciences (CIOMS) held in Copenhagen in 1964, I described two MZ twins who had simultaneously been found to have pernicious anemia at the age of sixty-three, as well as another pair of twins, also MZ, who were found to have adenocarcinoma of the right breast at the age of sixty-four. On that occasion, I used the term "chronon" to indicate the temporal aspect of the hereditary unit and pointed out its medical applications. The same genes exist in the offspring as in the parents, but in a stage of earlier expression, that is, involved in a pheno-

typic action at a prior point in time: "As a consequence, we can, as we study the sick person, reconstruct their past through the children and forecast their future through the parents."

In the address I gave on August 2, 1965, on the occasion of receiving an Honorary Doctorate in Science from Villanova University in Pennsylvania in the United States, I formulated the concept of "a time for every gene" in relation to the degree of stability of the hereditary unit during the period of its informational activity. This concept of stability was given the name "ergon" in my presentation to the meeting of the Medical Academy of Rome, March 3, 1967. Then, at the Congress of the International Academy of Pathology held at Buenos Aires in 1969, on the basis of the research I had carried out together with my collaborator, G. Brenci, by means of cytogenetical and molecular genetics analyses, I proposed the "Ergon/Chronon (E/C) System" as an interpretative model of the inheritance of biological time.

Finally, on the occasion of the Fourth International Congress of Human Genetics which took place in 1971 in Paris, Brenci and I fully documented the results reached at a Round Table devoted to the "chronology of the gene," and other authors joined us to show the importance of the problem and to illustrate particular aspects of it. As frequently occurs when an interpretative model permits the delineation of a significant phenomenon, the subject of the inheritance of biological time awakened interest. This interest has continued to grow, making it possible to gather a great deal of objective data, clinical as well as experimental, concerning not only human genetics but the genetics of every living species, a fact which in itself has spurred the accumulation of extensive data dealing with the general ideas and phenomenology of biological time.

At the International Seminar on Human Reproduction held in Tel Aviv, I gave the name "Chronogenetics" (September 21, 1972) to the field of genetics which was forming in the manner indicated above and which suggested itself as a means of studying the inheritance of biological time in all living beings.

At the same time I accepted the invitation of the publishing

house of Mondadori in Milan to prepare a book on this subject, which Hermann of Paris published in French with an introduction by Prof. E. Wolff. I am now pleased to welcome the American edition which Charles C Thomas, Publisher of Springfield has prepared from the second revised Italian edition.

LUIGI GEDDA

The Mendel Institute, Rome

The subjects of research mentioned were published as follows: Gedda, L.: Genetica clinica. *Proceedings, Second International Congress on Human Genetics, Rome, 1961.* Rome, Istituto G. Mendel, 1963, vol. II, pp. 911-12; Fondamenti ereditari della sessualità (at First Italian Symposium of Sexology, Rome, 1959). *Stati Ipersessuali e Terapia.* Rome, Istituto G. Mendel, 1960, *pp. 1-12;* Application de la génétique à la pratique médicale. *Acta Geneticae Medicae et Gemellologiae (Roma), no. 1, 14:*1-12, 1965; From Gregor Mendel to Medical Genetics (at University of Villanova, Pa., USA). *Acta Geneticae Medicae et Gemellologiae (Roma), no. 3, 14:*216-218, 1965; Concetti e Problemi della Genetica Medica (at Academy of Medicine of Rome). *Acta Geneticae Medicae et Gemellologiae (Roma), no. 2, 16:*109-123, 1967; La Fisiologia del Gene (at Congress of the International Academy of Pathology, Buenos Aires, 1969). *Giornale di Batteriologia, Virologia e Immunologia (Torino),* vol. LXII, 11-12, 1969; Gedda, L., and Brenci, G.: Chronology of the gene. *Acta Geneticae Medicae et Gemellologiae (Roma), 20:*323-349, 1971; Gedda, L.: Twin studies in genetics. *Acta Geneticae Medicae et Gemellologiae, no. 3, 21:*265-269, 1972.

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CHRONOGENETICS

The Inheritance of Biological Time

Chapter I

The Scientific Study of Time

TIME IN INSTINCTIVE CONSCIOUSNESS

THE INSTINCTIVE CONSCIOUSNESS of time—that is, not reasoned or thought out—is peculiar to men as well as animals. Pigeons in the Piazza San Marco in Venice wait to be fed daily at nine in the morning and two in the afternoon, not guided by the sound of the clock's big bell, but because of an instinctive, though approximate, consciousness of time. There are thousands of these pigeons, and even admitting that a certain number of them might keep the "appointment" from a gregarious instinct, that is, an animal's tendency to copy the behavior of others of its own kind, the instinctive consciousness of those pigeons who lead the others comes from an internal feeling (cenesthesia) that informs them of their status, or else from particular sensations of hunger, fatigue, sleepiness, or from external stimuli such as light, sound, or odors which produce an automatic behavior which may signal "time" in various manners.

Even prior to that, that is, at the beginning of instinctive time consciousness or in its very mechanism, there are phenomena which occur in relation to time which are not sensed by the animal, phenomena which are rhythmic and automatic. This type of time even encompasses certain conditioned reflexes, beginning with the classic dog experiments of Pavlov. These animals, with their fistulized stomachs, became accustomed to being fed at a certain hour of the day. Because of an automatic correlation established between a functional endogenous time (secretion of digestive juices) and an exogenous time (food being given at a fixed hour) which set up rhythmic conditioning, these dogs secreted gastric juices at a precise hour even if they were not fed.

Functional rhythms of the type mentioned (Fig. 1), either spontaneous or conditioned, are present in all living beings. They can be of internal origin, that is, organismic, or of externally in-

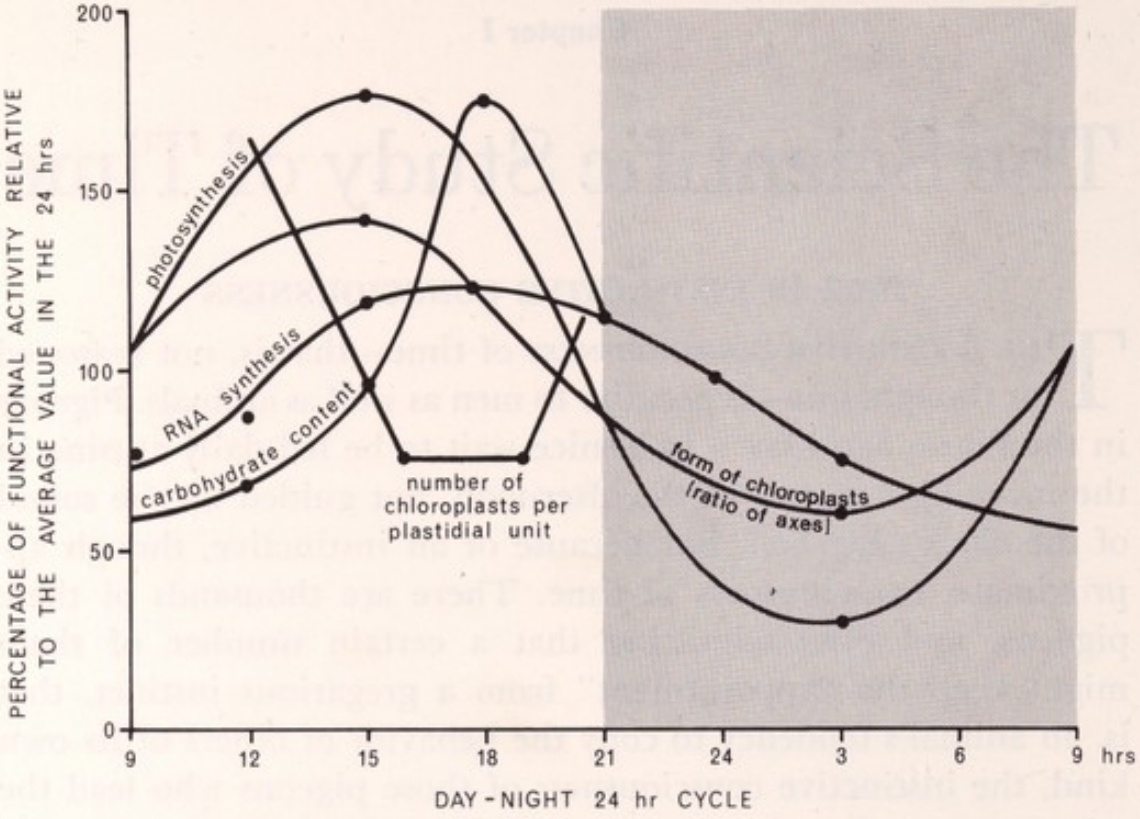

Figure 1. Temporal distribution of five functional activities of the chloroplasts of *Acetabularia mediterranea* cultivated in controlled conditions, in the light from 9:00 AM to 9:00 PM and in the dark from 9:00 PM to 9:00 AM the following morning. The curve relating to the number of chloroplasts per plastidial unit also shows the rhythm with which the chloroplasts themselves divide, the maximum occurring at 9:00 PM. (From T. Vanden Driessche, in *La Recherche, no. 10, 2*:257, 1971. Courtesy of publisher.)

duced origin, provoked by rhythms determined by cosmic time in the environment surrounding the organism.

Linneus created a clock whose hours were represented by the opening of certain flowers. For example, the lily of the field opens at three o'clock in the morning, the violet at nine, and the morning glory at six in the evening. This night-day rhythm is present in plants, represented by the majority of the leaves having one position for night and another for day, and in animals where it is correlated with the states of activity and rest. More obvious examples of induced rhythms are the migrations of various birds, mollusks and Annelida. A case in point is the *Eunice viridis,* an annelid living deep within the coral reefs of Polynesia. On the eighth to ninth day following the full moon in No-

vember, this animal divides into two parts: The posterior portion, composed of sexual elements, detaches from the asexual anterior part and rises to the surface where, floating, it produces a milky stratum called "palolo" by the native islanders who consider it a delicacy. The asexual part, on the other hand, remains on the bottom and regenerates the amputated segment. Within a year the phenomenon is repeated exactly on the same date.

The sensitivity of animals to music also forms a part of their instinctive consciousness of time: In fact, every musical composition is a formulated time in which the animal participates secondarily. The snake that uncoils to the notes of the Indian snake charmer's flute and the bear that dances to the sound of the tambourine both pick up the tempo of the music and reproduce it, revealing a sensitivity essentially tied in with rhythm. At certain times, animals are also able to create a musical variation on top of an unexpressed background rhythm. The song of a bird is precisely an instinctive musical composition linked with cenesthesic phenomena, the reproductive cycle, for example, or else to particular feelings such as those evoked by the light at sunrise or sunset.

Man, too, reveals an instinctive appreciation of time in rhythmic sequence when, without willing it and sometimes without realizing it, he moves a limb, his head or his whole body in time to music. His expression of rhythmic time becomes conscious, schematic and then even automatic when he keeps time by "beating" and "weaving" like a metronome, or when he dances. The most convincing expression of the instinctive consciousness of time on the part of man occurs during sleep. Even though the individual is not thinking, he awakens at a certain customary hour or, in the case of some individuals, by a sort of order or instruction given to his unconscious mind. Sleep itself, that is, the development of the most authentic representation of the subconscious, takes place according to a plan of chronologic nature, however paradoxical it may frequently seem.

RATIONAL CONSCIOUSNESS AND MEMORIZING OF TIME

Passing from the instinctive to the rational sphere, the consciousness of time in human language assumes the approximate

and summary definition which is often expressed by means of two adverbs: "before" and "after." The use of these or analogous words represents a mental elaboration which follows the awareness of a variation that has taken place between man and the external environment, or else between man and his internal environment. In other words, this results from the transformation of the subject's receptivity or the change of an external stimulus, or both.

The rational evaluation of time is a phenomenon of perception, in the sense that perception represents, according to experimental psychology, recognition of a sensation. In the case of time, perception comes from a change of the quality, quantity or speed of a sensation in progress, or from an equivalent phenomenon of thought, so that the individual notes the occurrence of a new event which follows a previous event, that is, of a "before" event followed by an "after" event. The perception of a "punctual time," which lasts beyond the threshold value, is transformed into the perception of a *continuum* or a "duration of time."

The threshold value that allows the distinction between punctual time and durational time is quite individual. In music, there are individuals who can distinguish the length of a thirty-second note from that of an eighth note and others who cannot; this chronological sensitivity is influenced by heredity and is one of the reasons why musical aptitude runs in families.

In connection with the perception of time, Bergson[1] observes that "there is a contradiction in assuming a perception which represents a progression and that, however, consists of a single and self-same instant." In reality, the concept of threshold, that is, of the minimum time interval from sensory variation necessary to catch temporal perception, clears up the objection, because once this threshold is reached, the stimulus is perceived as punctual time. However, if the temporal threshold is exceeded, the very same stimulus is perceived as durational time. The difficulty consists in distinguishing the specific effect that a given feel-

1. Bergson, H. L.: *Durée et Simultaneité*. Paris, Presses Universitaires de France, 1968.

ing produces (visual sensations, acoustical sensations, etc.) from the temporal effect that every sensation, taken as a whole, can produce.

Therefore, sensation, with its mechanism of intercepting specific external stimuli, also contains the fundamental moments of a uniform and generic background perception, that is, the perception of time. The conscious grasping of the order of entrance of sensations represents a typical phenomenon of perception of a time; it serves to build up a chronological order of events and also offers a model which analogically orders whatever does not come from the sensory system but rather from the imagination or thought.

In point of fact, there is a before and after, both of which are detached from external happenings concerning mental operations. It is also conceivable that the phenomena of thought leave traces, so far not well understood, in the nervous centers, permitting man to evaluate a variation, a subsequent time, or a duration of activities, as often happens for a sequence of sensations.

Starting from the instinctive consciousness of particular time and then from the summary evaluation of the before and after, man arrives at the rational consciousness of time. In other words, he not only lives it, as does the animal, but he is consciously aware of it. He compares it with previous and subsequent times in his life and uses it as the basis of his judgment. An additional advance consists of acquiring the "notion" and the "concept" of time. Man goes from the particular to the universal, paying no attention to the individual times which have occurred, but rather considering time generally, trying to grasp its characteristics and practical value (notion of time) in addition to its meaning and speculative value (concept of time). Both animals and men, to differing degrees, are able to register time lived or spent, as it were. The most characteristic functions of life are those which permit the conscious memorization of their occurrence by man. Prior to this, purely biological memory mechanisms occur for which the living being is not conscious, even though these events may be factual and proven. For example, in the immunological

sector, antibodies testify to the past presence or encounter with an infectious disease. This type of memory has no conscious aspect whatsoever and is therefore totally useless for studying the psychological phenomenon of time.

On the other hand, conscious memorization is the special human faculty of fixing certain events which succeed one another in time, diverse and successive with respect to the perception of time, but linked to it, not only because its content bears the imprint of a past time, but also because, broadly speaking, it is arranged in accordance with a temporal matrix. In other words, it conforms to the sequence of events that have happened. Thus man can reconstruct the chronological order of events by drawing upon his memory.

Memory has a life of its own, consisting of a time of fixation and a time of retention, the latter lasting until the recollection itself is erased by "oblivion." The relationships between rational memory and oblivion are greatly influenced by elapsed time and differ from individual to individual.

Psychophysiology is not yet able to pinpoint the biological mechanism that intervenes in the recording of recollections on the arc of memorized time. Two fixing phases seem to exist: a transitory phase and a permanent phase, both of which leave a trace on the molecular level. One school of thought believes that memory can be related to the nucleic acid composition of the nerve cell and, in particular, to the DNA/RNA relationship which varies in function according to age. In reality, it is well known that old people's memory, lucid and precise regarding distant events, weakens steadily when it comes to more recent occurrences; furthermore, research on amnesia resulting from electric shock, anoxia and anesthesia confirms the fact that the amnesia thus obtained involves only the transitory phase. The relationship between these two phases, that is, the exact point of intensity or duration when the second intervenes in the first, is not known; the only established point is that the permanent phase intervenes if the stimulus crosses a certain threshold or is "called back" in time. On the other hand, some researchers believe that memory can be related to the lipid components of the nervous system.

New points of departure for the study of memory start from the consideration that the nervous pathways conveying sensations to body centers are highly specialized. Other hypotheses hold that each afferent fiber is capable of producing a synthesis of specific substances determining both the sensation and the trace of the memory acquired. Ungar, Clark and Galvan[2] performed an experiment which aroused a fear of darkness in rats which usually are not afraid of this state but rather like it. The authors achieved this effect, which they call "scotophobia," by putting the experimental rats into darkened metallic cages and subjecting them to electric shock. They then removed the brains of the animals thus frightened and isolated an active substance, a peptide that they called scotophobine and succeeded in producing synthetically. When scotophobine is injected into other rats, and similarly into goldfish, it produces a fear of darkness which lasts for three or four days.

Ungar and his associates have also extracted a substance produced from rats' brains when they undergo prolonged acoustical stimuli and become used to them. In addition, Ungar as well as Domagk and Zippel,[3] have succeeded in imparting a preference for one color and an aversion for another to untreated goldfish by means of transferring substances from treated goldfish. These authors suggest that a comparison between the chemical structures of these substances of opposing action could be very instructive.

The existence of a macromolecular biochemical memory compound is the most probable hypothesis to explain these activities, difficult as it may be to distinguish the product of physicochemical activation of nerve fibers from that of specific proteins of the synaptic surfaces. As far as the duration which a recollection may be preserved is concerned, a phenomenon of transfer onto ribonucleic acid (RNA) could be postulated for short memory, whereas in the case of long memory, either the transfer and/or the translation into a specific polypeptide which is then preserved might be necessary. Evocability or recall, at a greater or lesser

2. Ungar, G., Clark, R. H., and Galvan, L.: In *Nature, 217*:1259, 1968.
3. Domagk, G. F., and Zippel, H. P.: In *Experientia, 25*:938, 1969.

distance from fixing, may be the result of either the intensity of the impulse or its repetition, or else—and perhaps more importantly—the operative capacity of the nucleic acid involved. Following cybernetic presuppositions, the physicist Wiener[4] postulates short-term memory to be the result of a series of impulses kept in motion in a closed circuit, at the same time considering long memory as additive impulses that determine degree of variable and proportionate permeabilities for the fixing phenomena, as well as those that eradicate recollection.

Experimental psychology allows us to establish other essential data. For example, the memory test developed by Gedda[5] permits us to conclude that the capacity of memorization, in permanent and retrievable form, is not congenital (present at birth), but rather is the result of psychic development which is in turn linked to man's somatic development. The reader can do this experiment, called "first recollection," by trying to establish the nature of his most distant recollection in time. In carrying out such research on a group of university students, the earliest recollection occurs most frequently in the third or fourth year of life with individual and family connotations. Its content is most likely marked by an emotional situation, either very pleasant or unpleasant.

Thus the study of this material permits us to conclude that, before the age of three or four years, the establishment of recollections subject to recall is weak, that is, such recollections do not remain for the entire life of the individual, and the validity of the first or earliest recollection is linked to the affective strength of the content. While it is true that the painter Salvador Dali begins his autobiography with memories of when he was a fetus, it is possible that this is due to imaginative transposition; at any rate, it has no experimental confirmation. On the contrary, Benvenuto Cellini had previously emphasized the pungent impact of emotion on memory in relating an incident that happened to him when he was about five years old:

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4. Wiener, N.: *Cybernetics: Control and Communication in the Animal and the Machine.* New York, Wiley, 1948.

5. Gedda, L.: Investigation of "first recollection." *Acta Genet Med Gemellol (Roma), 22:3,* 1973.

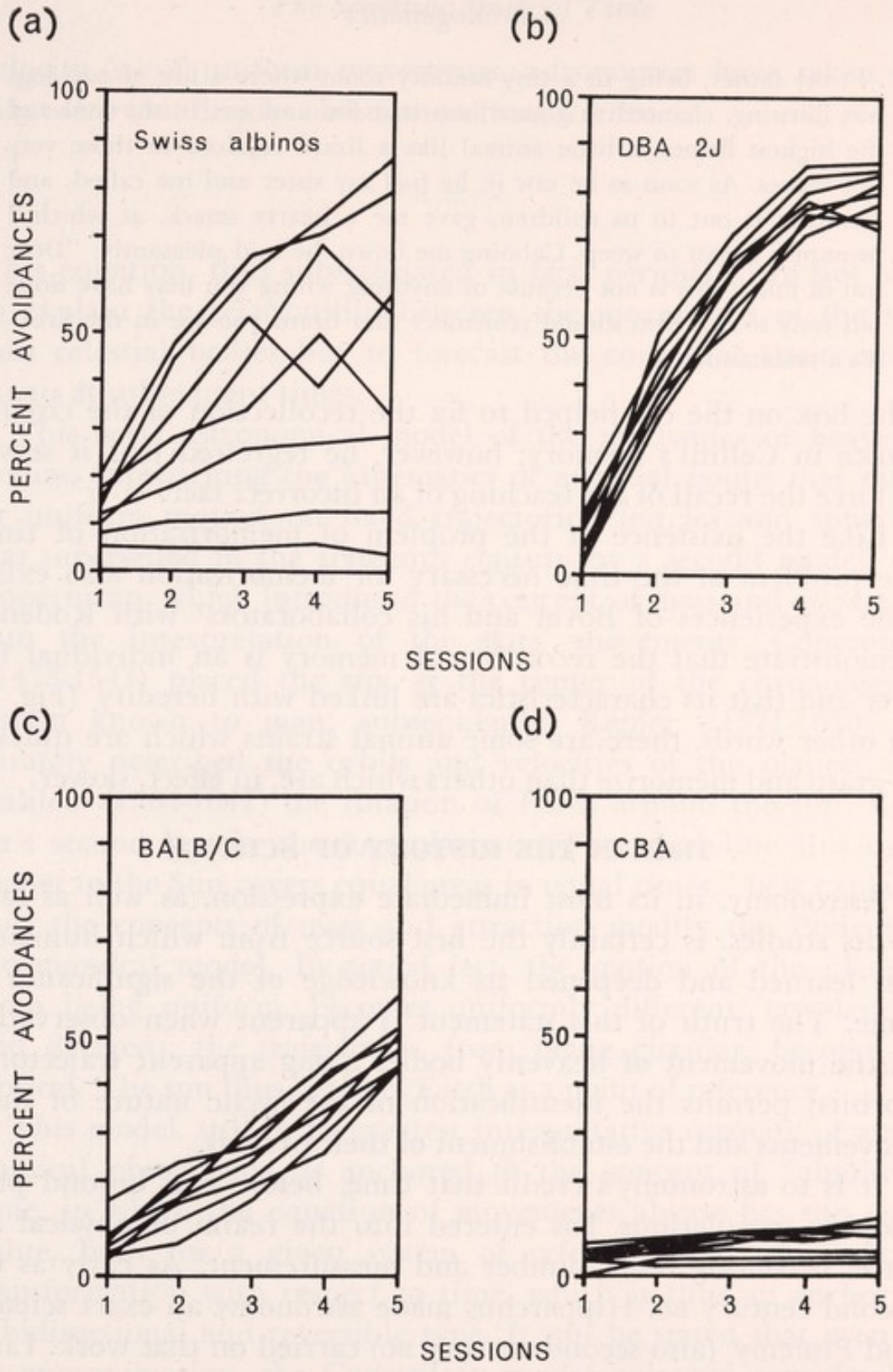

Figure 2. Genetic aspects of learning and memorization in rats. A heterogeneous population (*a,* Swiss albinos) has highly variable dodging or avoidance reactions. On the contrary, in pure strains (*b,* DBA/2J; *c,* BALB/C; and *d,* CBA) , many more homogeneous dodging or avoidance responses are noted. (From D. Bovet, F. Bovet-Nitti, and A. Oliverio, in *Science, 162*:139, 1969. Courtesy of publisher.)

> . . . my father, being in a tiny laundry room where a fire of oak logs was burning, chanced to glance into that fire and see, in the midst of the highest flames, a little animal like a lizard rejoiced in those very hot flames. As soon as he saw it, he had my sister and me called, and pointing it out to us children, gave me a hearty smack, at which I promptly began to weep. Calming me down, he said pleasantly: "Dear son of mine, this is not because of anything wrong you may have done but only so that you should remember that lizard you see in the fire—it's a salamander."[6]

The box on the ear helped to fix the recollection of the circumstance in Cellini's memory; however, he regretted that it served to force the recall of the teaching of an incorrect fact.

Like the existence of the problem of memorization of time, the problem of the time necessary for memorization also exists. The experiences of Bovet and his collaborators[7] with Rodentia demonstrate that the recording of memory is an individual faculty and that its characteristics are linked with heredity (Fig. 2). In other words, there are some animal strains which are quicker to grasp and memorize than others which are, in effect, slower.

TIME IN THE HISTORY OF SCIENCE

Astronomy, in its most immediate expression, as well as later in its studies, is certainly the first source from which humanity has learned and deepened its knowledge of the significance of time. The truth of this statement is apparent when observation of the movement of heavenly bodies along apparent trajectories (orbits) permits the identification of the cyclic nature of these movements and the establishment of their periods.

It is to astronomy's credit that time, before and beyond philosophic speculations, has entered into the realm of physical science, becoming both number and measurement. As early as the second century BC, Hipparchus made astronomy an exact science, and Ptolemy (also second century BC) carried on that work. Linking the two observational parameters, the trajectory *(s)* and the time *(t)* employed in traveling it, by means of the concept of the

6. Cellini, B.: *The Life of Benvenuto di M°. Giovanni Cellini, Florentine. Written by Himself at Florence.* Florence, Sanjoni 1923, *12-13.*

7. Bovet, D., Bovet-Nitti, F., and Oliverio, A.: In *Science, 162:*139, 1969.

velocity (v) of uniform movements, astronomers have taken the giant step that divides observation from science:

$$v = \frac{s}{t}$$

This equation, thus substantiated in fact, permits them not only to explain the relationship between the movements of the various celestial bodies but to forecast the course of their movements at subsequent times.

This early astronomical model of the mechanics of heavenly bodies, approaching the kinematics of material points that move in uniform motion on fixed trajectories (circles and spheres), was superseded in the sixteenth century by a second model, the Copernican, which introduced the concept of mass and attraction into the interpretation of the stars' movements. Copernicus (1473-1543) placed the sun at the center of the chronological system known to man; subsequently, Kepler (1571-1630) accurately described the orbits and velocities of the planets and Galileo (1564-1642) the rotation of Earth around the sun. Kepler's second law in the formulation, "The ideal line linking a planet to the Sun covers equal areas in equal times," best explains how the concepts of mass and attraction modify the Ptolemaic astronomical model. In actual fact, the motion of the planets, from being uniform, becomes uniformly different (accelerated and delayed); the trajectories, from being circular, become elliptical. The sun thus replaces Earth as a point of reference.

This model, still in its greatest interpretative capacity of astronomical phenomena, is anchored to the concept of "absolute" time, in which the equation of movements always has the same value, both for a given system of reference and its negative transformation with respect to time, which is thus an anchor of a bidirectional and reversible type. It can be stated that even in its approximation, the Copernican model enlarged considerably the field of knowledge.

The broadest and most felicitous synthesis of knowledge made possible by the Copernican model was that of Isaac Newton. His gravitational astronomy set forth the relationship between a

planet's distance from the sun and the force of attraction to which it is subject, hence his statement, "every particle of material attracts every other one with a force proportional to the product of the masses and inversely to the square of the distance separating them." Newton's idea of the structure and functioning of the universe prevailed until the theory of relativity was developed.

A great achievement in the knowledge and prediction of time, in actuality a fundamental discovery in the astronomical sector, was marked by Halley (1656-1742) who, on the basis of Newton's universal theory of gravity, calculated that the great comet of 1682 which had previously appeared in 1531 and 1607 would reappear in 1758, as in fact it did. In the nineteenth century, the *Mécanique celèste* of de Laplace (1749-1827) represented the most notable text of the branch of astronomy studying the movements and times of heavenly bodies.

At the beginning of the nineteenth century, physics was enriched by the work of Rumford (1753-1814), Carnot (1796-1832) and Joule (1818-1889) on heat. Thermodynamics, in which time is eminently irreversible, made its appearance with these scientists. Even though at the beginning this science paralleled Newtonian dynamics, without specific contacts, the theory of the conservation of energy and the subsequent statistical demonstration of Carnot's principle of degradation of energy have reduced thermodynamics and Newtonian dynamics to two aspects of a single body of knowledge, the statistical aspect and the causal one.

The twentieth century saw the introduction of the present concept of time, which by now considers astronomy as astrophysical and every physical phenomenon as a meteorological phenomenon, or simply stated, a phenomenon that can be statistically defined only for a given moment and in a given place.

One of the most modern aspects of the study of time is that of its directionality. The reversible time of physics, in which nothing new occurs, becomes, especially with Bergson (1859-1941), the unidirectional irreversible time of galactic expansion, geophysical modifications and biological evolution. Within this,

the species is directed from the past towards the future, and the individual is like an arrow pointed in a single direction in time. This concept of time leads to "chronology," now understood as a science in itself.

Bergson's idea is characterized by the fundamental dualism that places or sets the origin of matter, which follows a gradual decay or decline, against the origin of life, which follows a gradual line of enrichment or progression. On the premise that the time of which he speaks is not mathematical time, because mathematical time is nothing but a particular form of space, Bergson maintains that space and time are profoundly dissimilar in that the former is a characteristic of matter and the latter an essential characteristic of life.

"Everywhere something lives," says Bergson, "there exists somewhere an open register in which time is being entered."[8] Bergson gives the name of "length" to this time register which is a combination both of the past and the present. The "length" form is the one our conscious states take when our ego lets them live, when it permits the separation of its present state from its past states. According to Bergson, "problems concerning the subject and the object, their destruction and their union, should be put in terms of time rather than space."

The past is thus integrated in an absolutely new present. This is fundamental not only because Bergson's philosophy is dualistic and consists of the conflict between life which rises toward the top (higher planes) and matter which falls toward the bottom (lower planes), but also because, Bergson claims, the most plausible explanation of evolution is not environmental adaptability but Nature's creativity, like the work of an artist.

In 1905, with the word "chronotope" establishing in subtle mathematical terms the concept outlined a long time before by Gioberti (1801-1852), Albert Einstein introduced the relativistic model (restricted relativity) founded on the concept of space-time, in which only those systems of reference in which one moves with respect to the other in a uniform rectilinear motion are considered. Within the scope of this theory, Einstein arrived

8. *Op. cit.*

at the formulation of the principle of the equality between mass and energy ($e = mc^2$). Generalizing the equations of transformation to the point of including any movement whatsoever of every system of reference, in 1916 Einstein[9] formulated the theory of general relativity, in which gravitational phenomena are also included via the principle of equivalence. Subsequent attempts to create a unified field theory embracing the totality of physical phenomena were unsuccessful and remained uncompleted upon Einstein's death.

An intuitive example of the tetradimensional properties of space-time is that of Langevin's paradox of the clocks and the traveler. This traveler, who moves away from Earth at a velocity close to that of light and returns after having lived a period corresponding to a year of terrestrial life, would not find his contemporaries greeting him but rather his great-grandchildren. In Langevin's hypothesis this happens because velocity, hence the kinetic energy possessed by the traveler, makes him use up time at a proportionately slower rate. The time of the system in which the traveler journeys with the velocity of light and in which he is living for the duration of his travels and the terrestrial time of his separated family and contemporaries have different values and a different effect upon life span. Thus, a portion of the traveler's life would be equivalent to several times the average life of terrestrial man, since the biological value of time, that is, life span, is directly proportional to the value of energy possessed: the more energy, the more life and vice versa.

The relativistic model does not seem to lead very far from what contemporary philosophical definitions state regarding time, for example, Bergson's unidirectional time. In reality, the two concepts are closer than they may seem at first glance. Einstein himself, at the end of his life, considered that owing to the probabilistic character of the quantum theory, physicists had come to be convinced that they should give up trying to arrive at a complete causal description of reality. Einstein believed it necessary instead to revive the existence of a continuous and eternal

9. Einstein, A.: *The Meaning of Relativity*. Princeton, Princeton U Pr, 1922.

flow in which phenomena upheld by causality take place.[10] The concept of temporal flow as a series or succession of before and after events, identifiable in their causes and effects, is in practice capable of being superimposed on the concept of unidirectional time of philosophic origin. This time, relative to the inertial system of reference, is the time that enters into the relativity theory as the fourth dimension. As such, the concept of time loses its own individuality in order to be intimately bound up with that of space.

MEASUREMENT OF TIME

In every era man has tried to acquaint himself with the meaning and nature of the importance of time as it pertains to his life. More broadly and especially for practical reasons, man has tried to measure time, utilizing whatever possibilities the state of general knowledge and specific scientific techniques of his day placed at his disposal.

From the earliest efforts of astronomy onward to the present day, time has been measured utilizing the movement which strikes human beings the most—the apparent motion of the sun. From the precisely calculated orientation of the Pyramid of Chefren, which symbolizes ancient Egyptian knowledge with respect to the sun, to the making of sundials, the reference is always the same: the utilization of an astral model as a more immediate and certain mimetic mechanism of time. The sundial makes use of the progression of the shadow of objects, determined by the sun's light, and the mechanism of observation becomes more and more refined so that the slant of the pointer (gnomon) also serves to identify the place where the sundial is located.

Another mimetic mechanism concerns a knowledge of the time necessary to cover a spatial interval, reproducing this space in miniature, and utilizing gravity as a force determining movement. This principle encourages the study and creation of sand and water hourglasses. From the measurements obtained by the use of sundials or hourglasses, which passively reproduce the

10. Frank, P.: *Einstein: His Life and Time.* New York, Knopf, 1947.

passing of time, we arrive at clocks, which represent a measurement based on the active mimicry of astronomical time, that is to say, on the reproduction of the astronomical system on a reduced but illustrative scale. The hands, in fact, show the position of Earth with respect to the sun. The Renaissance brings modern horology with it, which by setting up intermediate mechanisms, profits greatly from the discovery of the isochronism of the pendulum as determined by Galileo. Following the discovery of the pendulum, the isochronism necessary for the measurement of time has been achieved by the use of special constant properties of both solid bodies and certain forms of energy. Thus it has progressed from the constant elastic properties of particular solid bodies to the constant properties of the electrical characteristics of a quartz monocrystal and the constant velocity issuing from electromagnetic waves in vacuum.

The nineteenth century saw the perfection of horology, especially with regard to miniaturization and chronological information, thus allowing substantial progress in the measurement of time, freeing it from active or passive motion as a reference to mimic time. Finally, thermodynamics, which introduced the concept of "time interval" as "change interval," makes possible the solution of the problem of dating. Scientific observation is presently in a position to mark the times of the universe with atomic spectrums, the times of the Earth with geological eras and the times of life itself with paleontological parameters and the decay of radioactive isotopes. From the state and the type of rock containing the evidence, and from the site of the survey, it is possible to date the era and geologic period, and hence the evidence as well. For example, the fish *Dyplomistus,* shown in Figure 3, is enclosed in a rock in Wyoming (United States) which dates back 20 million years and is therefore of that epoch.

The study and classification of natural radioactive elements has permitted the use of radioactive isotopes as a mechanism which best reproduces the phenomena of transformation and hence best identifies the times of the transformation itself. Today's precision clocks are based on this fact, using the radiation

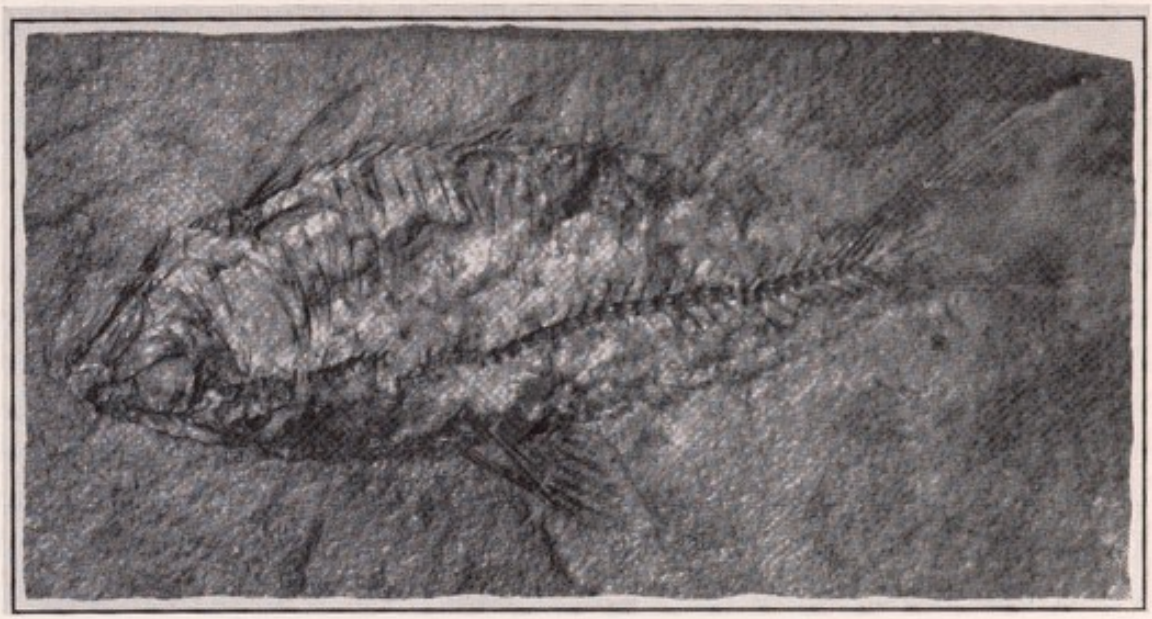

Figure 3. *Dyplomistus,* a fossilized fish found in a rock sample in Wyoming (United States), belonging to a presently extinct species which goes back about 20 million years on the basis of dating the stratum in which it was enclosed. The petrified deposits are those that best preserve with singular details the imprints of examples of aquatic life.

periods through which an atom has passed from one fundamental state to another.

Besides the choice and construction of the mimetic or reproductive mechanism in order to render the concept of time operative on the physical level, it was necessary to resolve a second difficulty, that of the definition and choice of the unit of measurement. In the period of empirical observation, the alternation between periods of light and dark led to the definition of day as that interval of time between two successive periods of illumination. This definition, though correct for the "average day" because of variations in the periods of illumination related to different seasons, is still valid today. After astronomical observations began, however, the study of the lunar and astral cycles allowed placement of the day into relationship with the month (lunar period) and the year (astral period).

Only when the era of navigation began did the necessity for identifying routes through astronomical points lead to the definition of hour, first minute and second minute. These time inter-

vals are, in fact, defined as taking place in distances intervening between the moments of maximum illumination (noon) of two points a known distance apart. The second minute, so defined, coincides with the time elapsing between the moments of maximum illumination of two points on the Equator placed apart by the distance of a nautical mile (1.853 km). Inasmuch as for practical purposes the utilization of these measurement units has remained constant up to fairly recent times, there have been attempts to obviate their approximation by means of conventions which limit their narrowness; in other words, with definitions that are more rigorous and more in keeping with new scientific knowledge, like the one defining the second as a fraction (1/31 556 925.9797) of the tropical year 1900. The present international convention (October 1967) defines the second as corresponding to 9.192 631 770 periods of the radiation emitted in the transition between two hyperfine levels of the fundamental status $^{2}S_{½}$ of ^{133}Cs, undisturbed by external fields.

The devices invented for recording time and the measurement units adopted for expressing it both serve to emphasize the presence of individual initial systems that assign to each measuring mechanism a certain validity limited to the sensitivity of the measurement of time necessary for the practical problem it must solve. This problem can be as simple as the cooking time of an egg, solvable by the kitchen hourglass, or as complex as the period of a particular electromagnetic wave which requires a determination based on its atomic structure for its definition. These diverse necessities of measurement and the corresponding measuring instruments stress, in practice, the relativity of scientific models applied to time.

It is evident from the above, especially with regard to the measurement systems that, in synthesis, represent the knowledge man has progressively acquired, that time is not only a reference of life, but a foundation qualifying life and at the same moment conferring upon it a relative value in time and space. Hence, it is reasonable that modern biological sciences—and particularly medical genetics—realize this, setting against this background the entire life of man in that he is a part of the phenomenon of time.

Chapter II

A Time in the Time

COSMIC TIME

TIME THAT IS UNDERSTOOD as a train of events, that is, as a parameter included within the train of these events, involves the universe which, from its very origin to the present, has marked and still marks an uninterrupted chain of phenomena described and studied by cosmology. This time is called "cosmic" or "physical" time. Cosmic time includes astronomic time that reaches us but also antedates astronomic time because the cosmos has observed times before the stars existed with their solar systems from which the closest times are marked.

The origin of the cosmos is deduced on the basis of an empirical law, Hubble's law, which makes a connection between celestial objects and their relative velocity, and can therefore be interpreted as a sign of the general expansion of the universe, begun about 10 billion years ago. This expansion obviously causes a diminution in the density of energy, at least if one does not postulate, as some do, a continuous creation of matter which replaces matter that is lost.

Hence, the universe must have begun its present phase of expansion about 10 billion years ago. The approximation of experimental evidence, however, more than an average piece of data to be sure, advises the indication of a period which can be extended from $5 \times 10^9 \times 5 \times 10^{10}$ years ago. In this interval of time it is possible to place the zero time of mathematical functions (cosmological models) which best interprets the data of the changes as they occur, as, for example, the removal of the red lines in the spectrum of the stars contained in the galaxies according to their distance.

The conjecture that the present phase of expansion was preceded by a phase of contraction cannot be advanced as a scientific hypothesis, because the beginning of the phase of expansion would represent so radical a modification of the phenomenon of

contraction as to render the deductions of its previous phases unreliable based on present observational possibilities. Therefore, the available experimental data do not permit going back to zero time, but do allow the admission of a punctual origin of the cosmos.

The limitation of the universe in space and time, and hence the existence of its origin, is a concept which is accepted by the great majority of present-day cosmologists. In terms of probability, and according to Einstein's formulation,

> an infinite universe is possible only if the average density of matter therein contained is zero. Although this hypothesis may appear to be logically possible, it is in fact less probable than the hypothesis that there is an average finite density in the universe.[1]

Today the origin of the cosmos is identified with a stage corresponding to a body of very high energy density. The existence of universal radiation with the temperature of 3K, observed for the first time in 1965, furnishes the earliest experimental confirmation of the theory that the universe evolved from an initial state of very high density and very high temperature (big bang theory) subsequently cooling off during expansion. Radiation of 3K would represent the fossil of the primordial fireball, and its temperature agrees to a considerable degree with theoretical expectations. The law linking radiation temperature to the passage of time is the following: $T = K/t^{½}$, in which T represents thermal energy measured in megaelectronvolts (MeV) or in Kelvin degrees, t being time in seconds and K a proportionality constant related to the unit of measurement adopted. In this manner, not only is the dating of the cosmos' origin possible, but the evaluation of the quantity of initial thermal energy is calculable at 15×10^9K. Such energy, in its process of decay at a temperature level of 5×10^9K, could have produced elementary particles such as electrons, neutrons and protons. At the temperature level of 300×10^6K, the aggregation of the particles could have formed

1. Einstein, A.: *The Meaning of Relativity*. Princeton, Princeton U Pr, 1922.

TABLE 1

EVOLUTION OF THE UNIVERSE ACCORDING TO GAMOW'S MODEL*

Time	*Temperature of Thermic Energy*	*Density*	*Period*	*Particles Present in Thermic Irradiation*
				γ, υ e^+, e^-
0	∞	∞	Hadronic	π^+, π^-, π° p, n, $\bar{p}$, $\bar{n}$,
10^{-4} S	100 MeV			Strange particles The π are the last hadrones to disappear
			Leptonic	γ, υ e^+, e^-
1 S	1 MeV			The electrons and positrons disappear
			Radio-active	γ, υ
5000 years	5000K			End of thermic equilibrium; the radiation photons cool, because of expansion
			Stellar	
10^{10} years	3K	10^{-31} g/cm^3		Present situation

* From R. Omnes, in *La Recherche, no. 23, 3*:462, 1972. Courtesy of publisher.

the first nuclei, while at a level of 40×10^6K they could have organized more complex structures.

For a duration of time which lasted millions of years, radiant energy represented the greatest part of physical reality. As the density of energy became progressively lower, the universe passed through progressively longer periods, to which Gamow gave the names of hadronic, leptonic, radiative and stellar (Table I). It is interesting to note here that equilibrium of energy-mass having been reached, clouds composed of energy and particles were formed through condensation, clouds which today are called "galaxies." These clouds, through further condensation, brought about the formation of the individual stars grouped into galaxies. The galaxies continued the process of expansion of the

universe and of lowering of energy. As they progressively cooled, in some cases they formed the planets.*

The formation of the various stellar systems and the degradation of energy marked by the continuous expansion of the universe introduced new times into cosmic times, times which appear as periodic, that is, astral and planetary movements which approximate uniform circular movements, or movements uniformly accelerated or delayed due to gravitational forces. In reality, the lowering of energy also has an influence on these cyclical times and progressively slows them down. However, granted the relative times of life and astral movements, these latter unite with us and act as if they were regularly cyclical with respect to us.

From the time of the stellar phase onward, the study of cosmic time must be localized to the planet on which we dwell and thus becomes, more properly, geologic time (Fig. 4). The origin of this planet goes back 4.5 to 4.6 $\times$ 10^9 years and hence, from that period on, the terrestrial focalization of cosmic time can begin. This dating of cosmic time is a much better approximation than that of the origin of the universe, in that an almost exact dating of the Earth's birth is obtained by calculating the velocity of transformation of the radioactive elements in its rocks.

The particular interval of cosmic time that directly involves man, the one scanned by geologic time, continues with the consolidation of the Earth's crust which took place about 3.6 $\times$ 10^9 years ago, while the formation of the ocean masses with a dislo-

* In conversations concerning the origin of the solar system among specialists in celestial mechanics, astrophysicists, mineralogists and nuclear physicists, held in Nice in April 1972 under the auspices of the Centre National de la Recherche Scientifique, the origin of the solar system, that is, the condensation of the protoplanets from interstellar dust and gas of the primitive nebula, was hypothesized on the basis of the observations resulting from examination of aggregations of lunar dust. The recent datings of meteorites and lunar rocks show that the most ancient objects of the solar system condensed in a relatively brief time, 4.6 $\times$ 10^9 years ago. New analyses of meteorites, lunar soil samplings and eventually the soil of Mars, as well as astronomic observations of interstellar dust under infrared rays and of interstellar molecules in millimetric waves, will permit a deeper knowledge of this chain of transformations, which, however, to date can be interpreted in their various phases as the result of a sequential mechanism of lowering of energy.

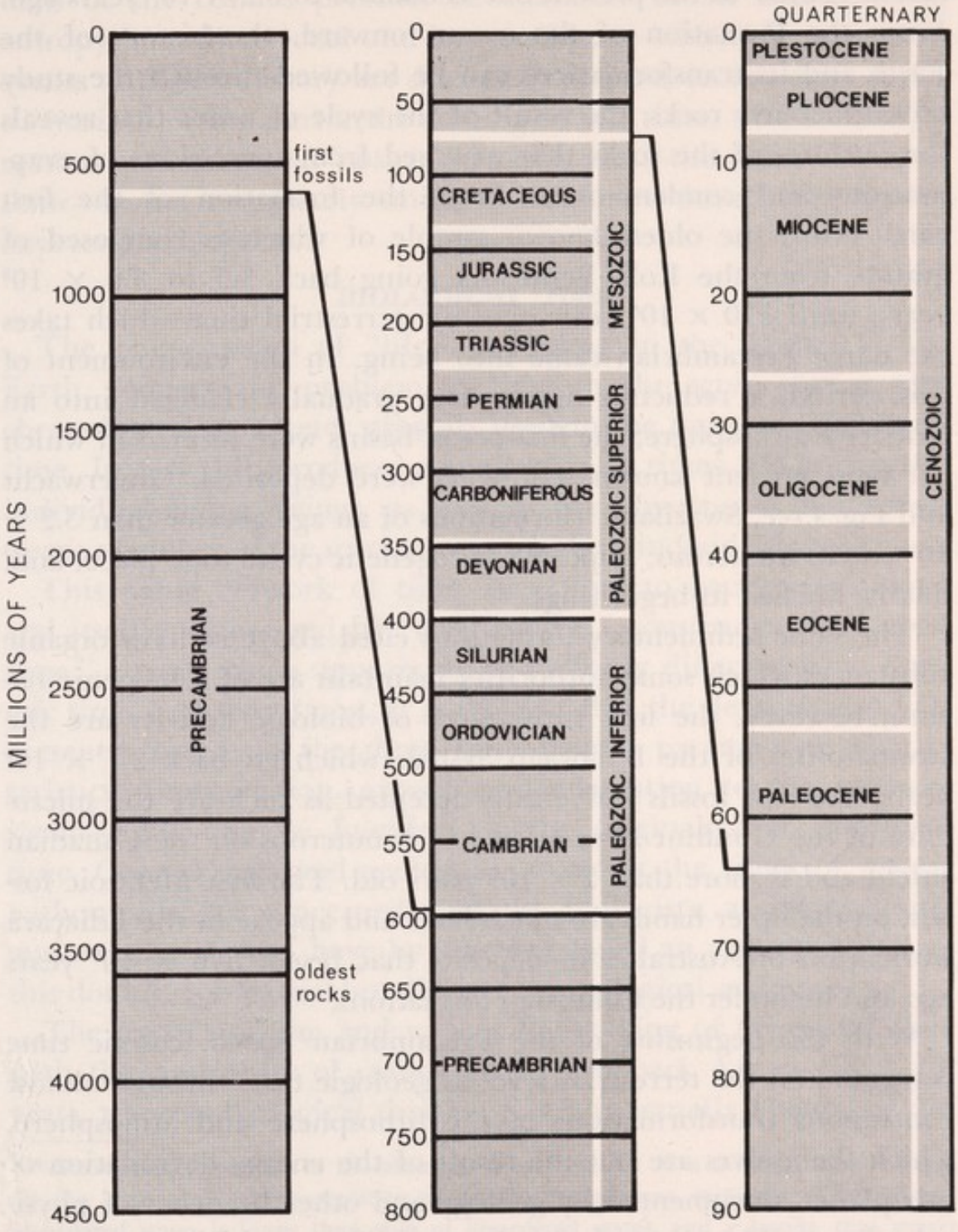

Figure 4. Chronology of the Earth to the present epoch beginning from its origin, going back to about 4.6 billion years ago. The geologic time scale is subdivided into eras (Precambrian, Paleozoic, Mesozoic, Cenozoic and Quaternary) and these into periods. (Modified from J. Lancelot, and J.-C. Rossignol, in *La Récherche, no. 27, 3*:847, 1972. Courtesy of publisher.)

cation similar to the present one is datable to 3.2×10^9 years ago. From the formation of the oceans onward, the history of the Earth and its transformations can be followed through the study of sedimentary rocks, the result of the cycle of water that reveals the outlines of the rocks that emerged from successions of evaporations and condensations. From the formation of the first earth crust, the oldest known sample of which is composed of granite from the Kola Peninsula going back 3.5 to 3.6×10^9 years, until 570×10^6 years ago, the terrestrial time which takes the name Precambrian came into being. In the environment of this period, a reductive atmosphere gradually changed into an oxidative atmosphere; the first ocean basins were formed in which the most ancient known sediments were deposited, Onverwacht and Fig Tree, Swaziland (formations of an age greater than 3.2×10^9 years); numerous, imposing horogenetic cycles took place; and, finally, life had its beginnings.

The same sedimentary formations cited above contain organic substances which some authorities maintain are of a biogenic nature; however, the first sure traces of biologic activity are the stromatolites of the Bulawago System which go back 2.7×10^9 years; the first fossils universally accepted as such are the microflora of the Gunflint Formation which outcrops on the Canadian shield and is more than 2×10^9 years old. The first Metazoic fossils, on the other hand, are much later and appear in the Ediacara Formation of Australia, in deposits that began 570×10^6 years ago and lie under the Cambrian formations.

With the beginning of the Precambrian epoch, cosmic time continues on the terrestrial level as geologic time through almost continuous transformations of the lithosphere and atmosphere, which themselves are but the result of the energy degradation of our planet, documented by geology and other branches of physical science. They exceed the times of life, to which we will devote ourselves, to so great an extent that it is pointless to speak of them here.

The sequences of cosmic time to which we have alluded are interpreted, on the causal plane, to be the result of the total phenomenon called "degradation." For this reason, the energy sys-

tems of the cosmos present the character of an impregnating entropy,* unidirectional and irreversible, to which the successive events of cosmic history are due, as is likewise, on the most limited horizon of the Earth, the coming of our time, which—for the reasons indicated and notwithstanding what the clocks seem to show—is not completely uniform but slows down, that is, the days tend to lengthen.†

BIOLOGICAL TIME

The phenomenon of "life," appearing in the history of the Earth, reopens the problem of time in the sense that a new chronological parameter presents itself in the universe, biological time. In fact, life produces a multitude of times which concern individual living beings, as well as the appearance and subsequent existence of the species to which these individuals belong.

This dense network of time, stretching to background times and itself encompassed by "cosmic time," constitutes "biological time," a time which appears to be radically different from "cosmic time." At the utmost, it is thought that the definition of life, presently based on the three fundamental parametrical characteristics—reproduction, growth and adaptation to the environment—must also be founded on the originality of biological time. Cosmologists and geologists, as far as the times of matter without life are concerned, and the biologists, as far as living matter is concerned, have by now developed an understanding of this double, contextual but distinct chronological sequence.

The Earth's origin, and with it the coming of terrestrial time with the continuity of cosmic time, goes back 4.5 to 4.6 $\times$ 10^9 years, whereas biological time on Earth is actually about 3 $\times$ 10^9

* Entropy is a measure of the amount of information in a message that is based on the logarithm of the number of possible equivalent messages. The entropy of ordered states is lower than that of disordered states, and a system that moves from an ordered to a disordered state increases its entropy.

† The Bureau International de l'Heure, with headquarters in Paris, has the task of regulating time marked by atomic clocks (international atomic time, TAI) as compared with the rotation of the Earth, which undergoes an almost imperceptible variation, and of indicating the universal coordinate time (TUC). The most recent correction occurred on December 31, 1972, a day which was officially lengthened by 1 second.

years old. It can therefore be said that biological time is "a time within the time," geological time predating biological time and representing a temporal niche in which life manifests and repeats itself.

At present much research and discussion is taking place as to whether other planets have ecological conditions so as to permit the existence of forms of life like those on Earth. It must be noted, however, that the existence of ecological situations analogous to those of the terrestrial environment is a condition that is necessary but insufficient for conceding the existence of life on other celestial bodies. Even the beginning of life, based on the most recent researches, confirms the ancient axiom *omnis vita e vita,* for which reason there is no valid experimental proof to date to infer the spontaneous generation of life in a favorable environment.

Hence, life on Earth manifests itself as an original phenomenon in the Precambrian period and, placing the sequence of its times side by side with those of cosmic time, shows its originality because of the following characters:

1. *pseudonegative entropy,* in that the utilization of external energy permits life to take a course characterized by more and more complex forms which follow one another, both on the species level (from protozoa to man) and on the individual level (from the zygote to the individual);

2. *subdivision,* in that life comes about through individual units that unite, wear out and die after having generated other units of the species, each one being characterized by an individual chronological variability exactly opposite to the characteristic monophasic continuity of cosmic time;

3. *repeatability,* in that all the individual units of life start from one type, the "ontogenetic zero," and repeat the chronological program of autosynthesis of the species, unlike the times marked by cosmic expansion, which are unrepeatable;

4. *adaptation,* in that biological times, manifesting themselves in the context of cosmic times, receive dynamic impressions from them which can be reflected in anatomic and functional stigmata;

5. *heredity,* in that the variability of primary biological time is dependent on the genotype, that is, it is transmitted from one generation to another through the mechanisms of genetics.

Because of these characteristics, and perhaps because of others as well, biological time cannot be considered as an epiphenomenon of cosmic time, even if an ecological adaptation from the first to the second takes place, an adaptation which, through the phenomena of selection, may manifest itself as being hereditary. The originality of biological time, based on the five characteristics listed above, must naturally be stated on the condition that the existence of a characteristic generating mechanism of its own be proved.

As there already exists a history of cosmic time, to which brief reference has previously been made, it can also be said that a history of biological time exists, traced out by the order of appearance of the extinct or extant vegetal or animal species endowed with characteristic times. In general, these times present increasing complexity, beginning from the times of subcellular organisms and, with the human species, reaching living beings endowed with superior psychic functions.

As was noted above, the story of biological time opens about 3×10^9 years ago in the Precambrian period with lower forms of aquatic life for which physical reconstruction is not possible because they did not possess skeletal parts and hence did not give rise to fossils. The existence of these forms of life is indirectly proved by the existence of ferrous and carboniferous rocks going back to that period whose origins are not magmatic but certainly organic (*see again* Fig. 4).

After about 2.5×10^9 years, the Precambrian period was followed by the Cambrian, the period represented on the biological plane by Algae, Arthropoda, and Mollusca. With this began, 570×10^6 years ago, the primary or Paleozoic era, which also includes the Ordovician, the period which saw the appearance of the agnatic Vertebrata, and the Silurian, in which Pisces appeared. Still in the primary era, there followed the Devonian, with the first specimens of terrestrial flora and fauna, the Carboniferous, and finally the Permian with the Echinodermata. The secondary

or Mesozoic era opened 225 million years ago with the Triassic period, in which life was enriched with the appearance of the Mammalia. The Aves appeared in the Jurassic period that followed, while the Sauria arose and spread over the land areas emerging from the waters in the Cretaceous period. Their fossilized remains have greatly captured the imagination of man. The speciation of the great Reptilia in the various ecological niches belongs to this period. Fossils of Ichthyosauria, Dinosauria and Pterosauria have been found, which adapted to life respectively in the waters, on terra firma and in airborne flight. The decline and disappearance of the various groups of Sauria was totally complete before the end of the Cretaceous period.

The ecological changes which took place at that time are so strongly reflected in the fauna and flora that geologists and paleontologists agree in considering these events as marking the end of the secondary era.

Other forms of vegetal and animal life appeared in the Tertiary or Cenozoic era, which began 65 million years ago and is subdivided into the Paleocene, Eocene, Oligocene, Miocene and Pliocene periods which are particularly distinguished by the rise of the Mammalia.

In the Quaternary era, whose beginning is placed between 1.8 and 3 million years ago, and more precisely in the Pleistocene period, the history of life presents the first fossilized evidence of *Homo sapiens*. From that time onward, biological time continues to make history through the variations of the extant species. The appearance of present-day man in the Quaternary era is datable at between 30,000 and 60,000 years ago.

CHRONOBIOLOGY

Cosmic time, the first to appear and the typical coefficient of the ecological niche in which life appears, even though different and clearly distinguishable from biological time, establishes a dynamic, unidirectional relationship with biological time, a relationship which consists of the capacity to change biological times, adapting them to their own characteristics.

This phenomenon of reflection of exogenous time on living

organisms was recognized in ancient times; it has so far masked the existence of an original biological time in its own right, by relating to cosmic time every chronological aspect of life, the times of which are generally considered as a "participated" time in the life of cosmic environment in which the event takes place, or as "induced" time.

In this sense, a branch of biology has recently developed which is dedicated to the study of the biological rhythms deriving from cosmic time. This branch has been given the name "chronobiology," clearly redundant because it deals with only one part of that which its name tends to signify. In general, it is useful to know the meaning, methods and outcome of chronobiology, repeating, at the same time, that the synchrony of some functions of life with cosmic time is not the only aspect of the relationships between time and life. Furthermore, it is not the primary relationship, its fundamental aspect being that of the time that life itself produces, on the basis of which, and only secondarily, the rhythms of cosmic time establish a relationship with life.

In the following chapters, biological time will deal broadly with cosmic time, in and by itself, its mechanisms and its outermost limits. Chronobiology is presently mentioned in the context of this term as defined by usage.

The adaptation of the human species to the characteristics of the ecological niche surrounding it has taken about 30,000 generations. In man, as in every other species, these adaptive modifications did not come about by chance, but rather followed the continuous and cyclical variations of environmental forces, producing a hereditary selection of forms and functions related to these demands.

In this sense, actions of fundamental importance are played by the forces bound up with cosmic time, such as variations of light, temperature, barometric pressure, gravity and electromagnetic field. In the course of successive generations, cosmic time, rather than the basic diet, various conditions of exogenous disease or other environmental coefficients, has operated as a mutagenic or selective factor of the first order, producing a selection of the species with respect to certain aspects of cosmic time, that

is, a synchronization which has been not phenotypical, but rather genotypical as well and hence inherited.

The phenomenon of the induction of the times and the concomitant genetic participation of biological times in cosmic times does not change the nature of biological time as such; biological time remains substantially distinct and different from cosmic time. Synchronization of biological time with cosmic time is thought to come about in living beings because of the presence of receptive and reproductive mechanisms of cosmic times which life itself has been able to prepare, by means of protracted selection brought about by environmental forces, as previously stated. In molecular genetic terms, these mechanisms could correspond to different responsible operators of groups of structural genes, those gene complexes termed "operons" having different qualitative and quantitative abilities of specific syntheses. Theoretically, the term "synchronizators" could be adapted to these mechanisms. It cannot be used, however, since it has been chosen by chronobiologists to indicate the environmental phenomenon which acts upon the times of living organisms.

To avoid confusion, the following terminology will be adopted: *inductive time* is cosmic time that produces the rhythm shared by the living organism; *induced time* is biological time which shares in the rhythm of cosmic time; and *inductor* is the mechanism which enables the living organism to be synchronized with the inductive phenomenon.

Chronobiology has stressed that the rhythms regulating the functions of organisms are subordinate to the rhythms of the environmental phenomena. For this reason, both in the case of inductive cosmic time and in the case of induced biological time, chronobiology deals with periodic phenomena that can be described by a system of coordinates with a diagram of the typical sinusoidal movement in which it is possible to distinguish an amplitude *(A)* and a period *(T)*. Frequency, on the other hand, is understood to be the number of the periods in the unit of time: This is indicated by 1/T. In comparing inductive cosmic times and induced biological times, movements that present the same amplitude at the same time are defined as being "in phase," while

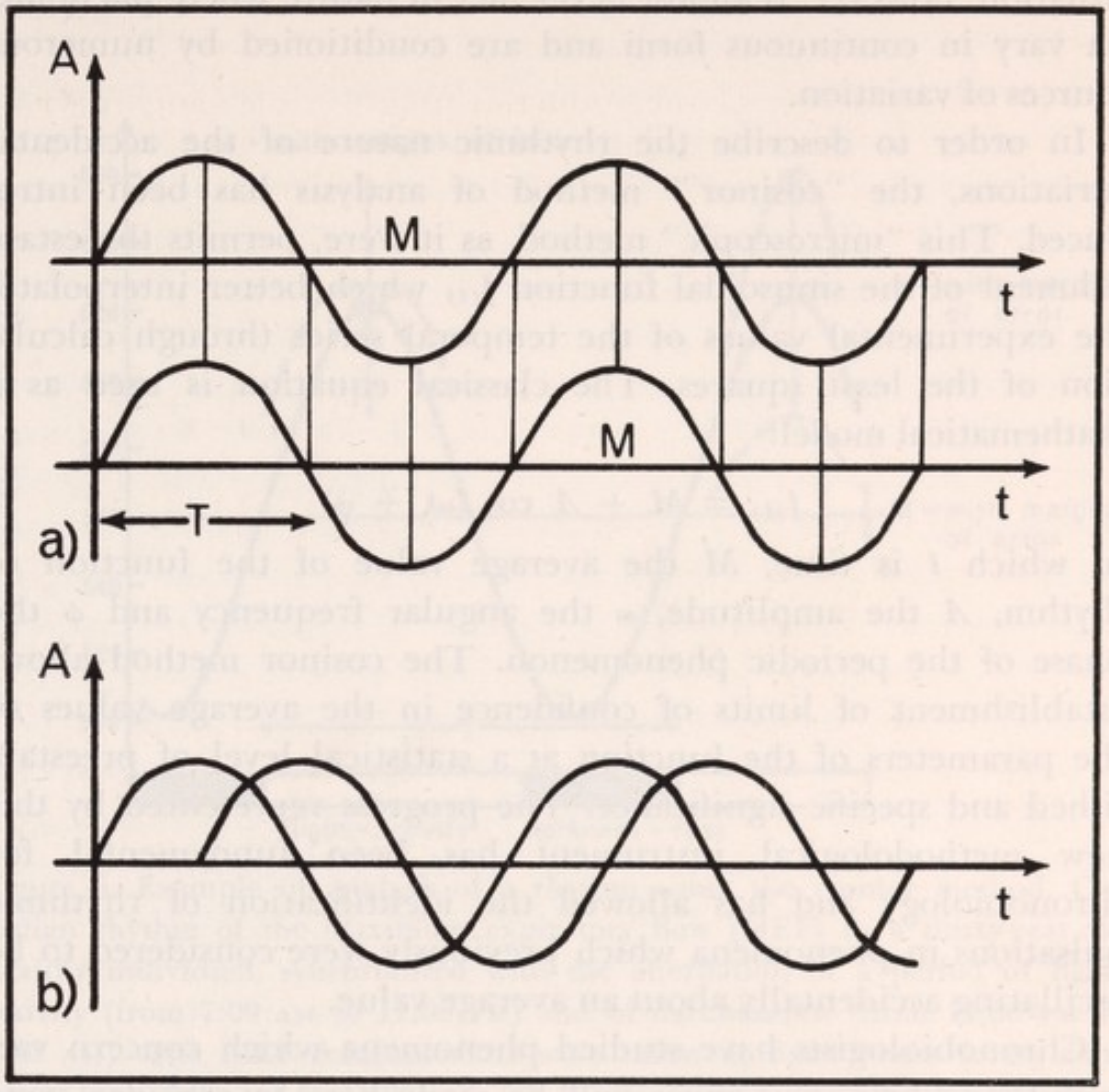

Figure 5. The rhythms regulating the functions of an organism may be subordinate to the rhythms of environmental phenomena. In a system of Cartesian coordinates, the course of these rhythms takes on a typical sinusoidal aspect and the two progressions can be "in phase" *(a)* or "out of phase" *(b)*. *A,* amplitude; *M,* average value of the functions of the rhythm; *T,* period; and *t,* time.

movements presenting the same amplitude at different times are defined as being "out of phase" (Fig. 5).

Until a few years ago, direct evaluation of the parameters of the sinusoidal function was the only possible method of studying rhythmic variations. This method, called "macroscopic," is only operative when individual values can be well delineated and made to correspond to the modalities of a temporal series. This

situation, however, is almost never met in nature where phenomena vary in continuous form and are conditioned by numerous sources of variation.

In order to describe the rhythmic nature of the accidental variations, the "cosinor"[2] method of analysis has been introduced. This "microscopic" method, as it were, permits the establishment of the sinusoidal function $f_{(t)}$ which better interpolates the experimental values of the temporal series through calculation of the least squares. The classical equation is used as a mathematical model:

$$f_{(t)} = M + A \cos (\omega t + \phi)$$

in which t is time, M the average value of the function of rhythm, A the amplitude, ω the angular frequency and ϕ the phase of the periodic phenomenon. The cosinor method allows establishment of limits of confidence in the average values of the parameters of the function at a statistical level of preestablished and specific significance. The progress represented by this new methodological instrument has been fundamental for chronobiology and has allowed the identification of rhythmic pulsations in phenomena which previously were considered to be oscillating accidentally about an average value.

Chronobiologists have studied phenomena which concern various living beings; a pause will be made here to consider some examples which concern man.

The biological times that reflect the rhythm of cosmic time can be classified according to the characteristics of inductive cosmic time in the following manner:

1. *Circadian rhythms* (from *dies,* day), which reflect the times of the Earth's rotation on itself and the variations of light, temperature, electromagnetic fields, etc., that this rotation carries with it. For example: circadian rhythms of sleep, of body temperature, of maximum expiratory flow (Fig. 6), of the number of white corpuscles in peripheral blood, of the circulatory rate

2. Halberg, F., Tong, Y. L., and Johnson, E. A.: Circadian system phase, an aspect of temporal morphology procedure and illustrative examples. In *The Cellular Aspects of Biorhythms, Symposium on Rhythmic Research.* Proceedings International Congress of Anatomists. Berlin, Springer Verlag. 1967, pp. 20-48.

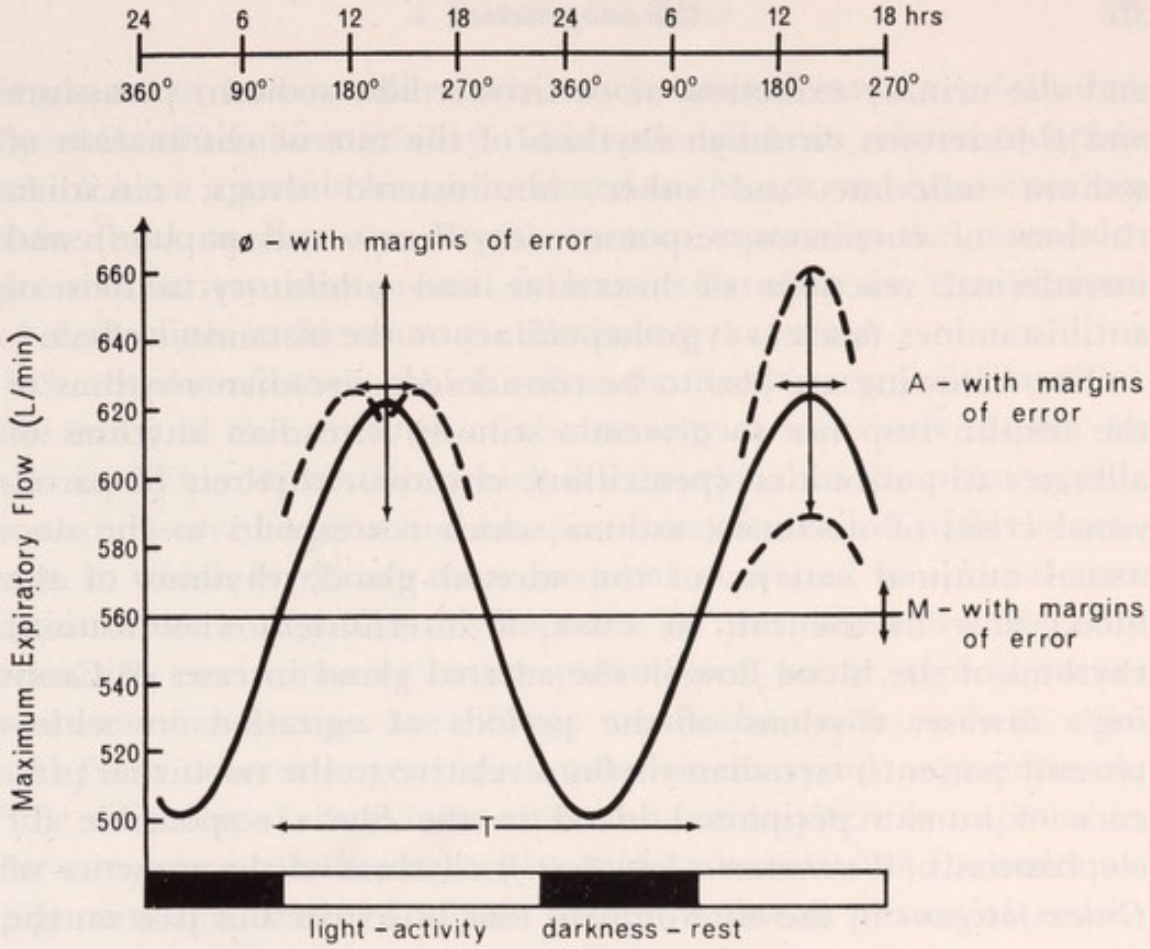

Figure 6. Example of analysis of a rhythm using the cosinor method. Circadian rhythm of the maximum expiratory flow (MEF) in a thirty-year-old healthy individual, synchronized with the alternation of a period of light-activity (from 7:00 AM to 11:00 PM) and of darkness-rest (from 11:00 PM to 7:00 AM). The MEF measurements were taken at fixed hours (every four hours from 7:00 AM to 11:00 PM) for 10 consecutive days. By the minimum squares method, the sinusoidal function was obtained as shown, which comes closer to the experimental values. The rhythm under examination can be characterized from the statistical evaluation of several parameters, apart from the T period, which is calibrated from the experimental conditions on 24 hours. Each of these parameters is expressed as a quadratic average of the margin of error. The acrophase ϕ corresponding to the maximum of function is distinguished; its value is expressed in hours or in degrees (24 h equals 360°), with a reference phase of midnight; the acrophase ϕ of the subject under examination occurs at 1:20 PM (in practice from 11:25 AM to 3:15 PM); the amplitude A corresponds to the variations of function with respect to the average value of the function of rhythm M; the M of the maximum expiratory flow of the subject under consideration is 560.2 ± 4.2 l/min, its amplitude A is 63.6 (from 28.8 to 98.4), which means that the circadian rhythm under study varies, on the average, between 496.6 and 623.8 l/min. (From A. Reinberg and collaborators, in *Presse Medicale, 78:*1817, 1970. Courtesy of publisher.)

and the urinary excretion of corticosteroids, sodium, potassium and aldosterone; circadian rhythms of the rate of elimination of sodium salicylate and other administered drugs; circadian rhythms of cutaneous responses (erythemas and papules) and intradermal reactions of histamine and inhibitory actions of antihistamines (such as cyproheptadine) on the histaminic effect.

The following are also to be considered: circadian rhythms of the insulin response to glycemic stimuli; circadian rhythms of allergies to antibiotics (penicillin); circadian rhythms of paroxysmal crises of nocturnal asthma which correspond to the nocturnal minimal activity of the adrenal gland; rhythms of the blood flow in the calf in cases of intermittent claudication; rhythms of the blood flow in the adrenal gland in cases of Cushing's disease; rhythms of the periods of agitation in schizophrenic patients; circadian rhythms relative to the nocturnal presence of human peripheral blood in the filaria responsible for elephantiasis *(Wuchereria bancrofti);* rhythms of the presence of *Culex fatigans* in the environment that bite man and pass on the disease, and so on. On the cellular level, it is possible to demonstrate a circadian rhythm of mitosis in the adult cutis that reaches its maximum between 12:00 PM and 4:00 AM. DNA and RNA syntheses in the hepatic cells of man present a circadian rhythm correlated with light. Most of these activities take place between 12:00 PM and 5:00 AM of the following day. In most cases, renal colic also begins between 4:00 and 5:00 AM.

2. *Catamenial rhythms* (from *mensis,* month), that reflect the times of the moon's revolutions about the Earth. For example, woman's menstrual rhythm (follicular phase from 0 to 12 to 16 days, luteal phase from 12 to 16 days to 28 days) and the rhythm of the inherent hormonal phases have an influence on the blood level of cortisone and, through this, on the activity of the central nervous system and its behavior as well as on the relationships of the electrolytes in the blood and on calcium metabolism. Another example is represented by the monthly cycle of ketosteroids in women, which presents a maximum on day 18 and a minimum at the beginning of the cycle.

In the pathological sector, periodic catatonia is classical; there

is a more or less monthly cycle, where normal states are followed by states of semi-immobility. This cycle has been related to lipids which have a metabolic cycle related to the adrenal hormones via a feedback mechanism. Psychoses, too, especially the manic-depressive variety, may present cycles correlated to the equilibrium of electrolytes in the nervous cells during the month.

3. *Annual rhythms,* which reflect the Earth's revolution around the sun and the shiftings of the terrestrial axis with respect to the sun. This correlation, which is exceptional in the plant world, is also observed in the human species in connection with the seasons in which births are more frequent as related to optimal conditions for embryonic development as furnished by the surrounding environment. In the pathological sector, typical recurrent seasonal diseases are allergic manifestations from heat, cold and from other allergens (urticaria, eczemas and angioedemas). The variation of ultraviolet rays in the atmosphere is responsible for cutaneous conditions such as hydroa aestivale and xeroderma pigmentosum, both of which present seasonal phases of remission and activity.

Chronobiology is therefore a borderline science that studies the reciprocal reactions between cosmic times and biological times, recognizing and analyzing times which are the result of this interrelation, that is to say, "mixed times."

The study of mixed times is important because of the practical conclusions to which they may lead: in a positive sense, for example, by utilizing biological rhythms for a more efficacious administration of medicines, as in the case of cortisones which must be administered in a single dose in the morning; or for a more intense action of antimitotic substances, as in the case of the control of tumoral cells; or else, in the negative sense, to avoid the acute protracted desynchronization which could be harmful for flight crews, especially in transmeridian flights from east to west. Many interpretations and conclusions of this type have been gathered by chronobiologists.

Concerning the underlying problem which recurs in chronobiological themes—the meaning of the rhythm that takes part in living matter and its biological time, which is not rhythmic but

continuous and hereditary—chronobiology has the following to say through the words of one of its most notable representatives, A. Reinberg:

> Rhythmic activity is a fundamental property of living matter; its manifestations, on all levels of organization, whether vegetable or animal, have a hereditary character. It is not going too far to admit that we are born with a given temporal structure, just as we are born with a given anatomy or spatial structure. Why? The question is often put to me, and I have to recognize that I am incapable of answering in a satisfactory way, that is, without having recourse to an avalanche of hypotheses.[3]

Apart from the fact that rhythm is not time, but a way of being *a part of time,* we think that rhythm is not a property of living matter but a phenomenon that living matter derives from cosmic time, that is, a phenomenon shared, reproduced, or obtained. With regard to the temporal structure of each living organism, we speak of a "temporal phenotype," and maintain that this phenotype can be of an inherited nature in two aspects: one which regards the selection of the inductor mechanisms of cosmic times, and the other which regards the time of action that every hereditary unit possesses, having been endowed with it by the previous generation.

CHRONOGENETICS

The causal vacuum reported by Reinberg should be filled. In order to formulate the problem in such a way as to facilitate its solution, the following questions may be helpful:

1. Since the rhythms of cosmic time, which induce many important rhythms of the temporal phenotype belonging to living beings, are permanent, why do the rhythms so induced become distorted and die during the life of these organisms?
2. Why are the variations of the induced rhythms repeated in succeeding generations according to genetic laws?
3. Why does the rhythm prompted by cosmic time obey a

3. Reinberg, A.: In *La Recherche, no. 10, 2:*241, 1971. *See also,* Biological rhythms. In *Encyclopedia of Science and Technique,* 5th ed. Milan, Mondadori, 1953.

different endogenous time from that possessed by the living organism?

4. What is the nature of this basic biological time that can reflect cosmic time but also can condition and limit it?

The reply to these questions makes it possible to find the end of the string so that the knot can be unraveled. It is easier to start with the last question, that is, from a demonstration of the nature of biological time that acts as an intermediary agent in the impact of cosmic time on the living being.

In the first place, every single species is maintained in cosmic time because it (the species) preserves not only its quali- and quantitative characters, but also the times of appearance, duration and regression of these characters which are transmitted from one generation to the other, or which are, in simple terms, inherited.

In the second place, monozygotic (MZ) organisms, that is, twins resulting from the same zygote that splits before the starting of ontogenesis and thus having an identical heredity, have concordant ontogenetic times, and the times of the recession of characters and the onset of hereditary diseases are likewise equal. Dizygotic twins (DZ), on the other hand, furnish verification of the hereditary motivation of the synchrony of biological times in MZ twins, in that they present a coefficient—50 percent—of chronological concordance equal only to that of nontwin siblings.

In the third place, biological times properly identified, studied in the environment of a homogeneous population, present a coefficient of concordance proportionate to the coefficient of genetic affinity; that is, they obey the fundamental canon of the genetics of population concerning the genealogical relationship of hereditary characters.

It can therefore be stated that authentic biological time is of a hereditary nature, and that the mechanism capable of producing, maintaining and transmitting it must be sought in the competence of genetics. The fact that times infused by cosmic time exist in living beings, and that they too are transmitted according to the laws of Mendelian genetics (the perennial times of the

development of flowers studied by Vanden Driessche[4]), does not contradict the existence of an inheritance, primitive and different, of biological times precisely so named, that is, quite autonomous with respect to cosmic time in that they do not contradict the existence of a genotypic-dependent temporal variability not dictated by cosmic time. The rhythms arising from cosmic time in living beings can sometimes simulate a direct genotypic heredity, but in reality they are the result of an indirect heredity which goes through the selection of hereditary variability. Such a mechanism, which takes place by favoring the reproduction of the most adapted genotypes in the ecological profile and, especially by new genotypes which are made available with mutations, as is explained by the presence of races and subraces, can thus explain the presence of inducing mechanisms of particular cosmic times in the individual heredity. Selection is certainly the genetic mechanism that presides over or directs the "production" of mixed times by means of the fixation of operative genotypical mechanisms in the species, mechanisms which are more adapted to the different induced rhythms; however, this action of selection must be kept clearly separated from the one that selection has exercised and exerts on the length of the informational action of the genes in original biological times.

There thus exists an inheritance or heredity of biological time, authentic and autonomous, primitively produced by the genotype and secondarily reflecting characteristics of cosmic time as well. Given the specific hereditary nature of biological time, the science with which it concerns itself should first of all be genetics, in the context of which there can be singled out a specific branch that deals with the inheritance of biological time. We maintain that the genetics of hereditary time can properly be called "chronogenetics" to differentiate it from chronobiology which has been mentioned before.

The differentiation of chronogenetics seems necessary and real to us because until now, the science of heredity did not sufficiently and specifically concern itself with the inheritance of time.

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4. Vanden Driessche, T.: Les rythmes circadiens, mécanisme de régulation cellulaire. *La Recherche, no. 10, 2*:255, 1971.

In its recent, spectacular expansion, genetics has passed through two methodological phases. The first phase, termed Mendelian, was dominated by the statisticomathematical analysis of the evidence. In this phase, the problem of time was not considered in and by itself, since the field of research was dominated by the quality of the character and study of the transmission of the qualitative relationship. In the Mendelian period, time tended to show itself only indirectly through the polymerical phenomenon by means of the quantity of the character. The second phase of genetics was characterized by the specific study of the genotype through cytological and biochemical methods which now permit this. Here, too, time was seen through the quantity of information, but the problem of inheritance of time was not resolved or even formulated.

It now seems necessary to face the problem of the genetics of biological time precisely stated, a problem which is not one of detail but basic, with many notable fundamental implications and practices which concern all sectors of genetics, and especially medical genetics, of which chronogenetics is bound to be an animating principle.

Chapter III

Biological Time and the Genetic Code

FROM GENE TO CODE

IN ORDER TO STUDY biological time, going beyond the approximations and superstructures which have hidden it until now, and in order to create a theory of chronogenetics, it is necessary to recount the history of genetics and describe how the concept of the gene evolved. For this reason, we will discuss the progression that has led from the statisticomathematical concept of the hereditary unit to the biochemical, and thence to the genetic code.

The fundamental discovery of Gregor Mendel was the hereditary unit. Stated in more detail, it was the fact that individual inheritance was not undifferentiated, but rather made up of a large number of characters which behaved independently at the time of their transmission, as if by drawing lots from parental generation (P) to filial generation (f) or the offspring. The study of the distribution of physical characters in succeeding generations led Mendel from the plane of appearance to the causal plane, or, as is said today, from the phenotypic plane to the genotypic plane which, like the good mathematician that he was, Mendel interpreted using binomial distribution as a theoretical model and admitting that every hereditary character resulted from one paternal and one maternal factor.

The Mendelian model is still valid, and its conclusions are now considered "laws." The hereditary unit called "factor" by Mendel was subsequently named the "gene," and the gene as a whole was given the name of "genome" or "genotype," whereas the science of heredity received the name "genetics."

In Mendel's thought, time did not manifest itself as such, though it was implicit in the relationship between subsequent

generations, and therefore passed unobserved. However, Mendel's conclusions were fundamental for chronogenetics in that, as biological time is admitted to have a hereditary nature, there follows the hypothesis of its derivation from the gene as a temporal dimension that the gene itself possesses with respect to the temporal character that it determines.

In the body of Mendelian genetics, time is observed through quantitative genetics, as studied by Fisher[1] and others, which underscores the relationship between polymery and intensity of the genetic effect. Here the concept of time is implicit in the sense that a greater phenotypic expression for the unit of time often corresponds to a greater number of genes. On this theoretical premise, research on the problem of time has been carried out by such scholars of the genetics of population as Haldane, who published a study entitled "The Times of Action of Genes, and Its Bearing on some Evolutionary Problems."[2] The time of action of genes, as investigated by Haldane, involves genetics on the level of the species. In actual terms, this deals with operative times that can become hereditary by means of natural selection, and not times originally inherited which express the temporal essence of the gene.

The flow of studies concerning the cell meanwhile crosses the flow of genetics, bringing to the latter important knowledge which refers to the chromosomal components of the nucleus, so that the nucleus itself is considered the cytologic correspondent of the genome. These studies, carried forward in collaboration with cytology and genetics, represent an approach to the study of the gene through microscopic observation, and have yielded a flourishing branch of genetics, cytogenetics. In this vein, the problem of biological time can be seen by means of the study of mitotic and meiotic phases as well as by means of the experiments of synchronization of cells through the action of blockage of a stathmokinetic, for example, by vincristine. Thus it has been shown that the temporal phases of mitosis render it more

1. Fisher, R. A.: In *Transactions, Royal Society, 52*:399, 1918.

2. Haldane, J. B. S.: The times of action of genes, and its bearing on some evolutional problems. *The American Naturalist, 66*:5, 1932.

or less receptive to the effect of chemical substances.* This is an interesting phenomenon, but it falls within phenotypic times on the cellular level.

Genetics had a more important development around the 1950s because of work done by the biochemists in the study of macromolecules of nucleic acids. With the discovery by Watson, Crick and Wilkins of the structure of deoxyribonucleic acid (DNA),[3, 4] research concerning the gene passed from the plane of mathematical analysis and cytological approximation to that of the direct study of the hereditary unit by means of chemicophysical methods. On this plane, genetics has represented the DNA molecule as the equivalent of the gene. While the structure and functioning of the gene-molecule will be described in detail later in connection with biological time, at this point it is important to continue with the development of the cognitive process by which the concept of the hereditary unit, understood by Mendelian genetics as gene function, is at one and the same time confirmed and surpassed in that, on one hand, the hereditary unit in function can include more than a single DNA molecule, whereas on the other, submolecular hereditary units are identified as the unit of recombination (recon) and the unit of mutation (muton).

This cannot be done without recognizing that, in the climate of scientific research a quarter of a century ago, genetics encountered a singular methodology. The informatics serving it offered terms and models which, studied for other reasons and cognitions, become useful for deciphering the inner mechanism of heredity. Above all, informatics gave to genetics the term "infor-

* Stathmokinetics are substances capable of arresting cellular division at the level of metaphase. The most common mechanism of action is the inactivation or destruction of the spindle apparatus. For example, colchicine can be considered an authentic mitotic poison in that it destroys such apparati. Vincristine and vinblastine, two alkaloids extracted from *Catharanthus roseus,* on the other hand, are temporary stathmokinetics that limit their action to a reversible inhibition. This characteristic permits the achievement of a cellular synchronization by means of blocking the inhibition in a given time. (Gedda, L., and Cardinali, G.: In *Acta Genet Med Gemellol (Roma), 17:*185, 1968).

3. Watson, J. D., and Crick, F. H. C.: In *Nature, 171:*737, 1953.
4. Wilkins, M. H. F. et al.: In *Nature, 171:*738, 1953.

mation" to indicate the message the gene recorded and transmitted for the construction of a particular protein. This name, by a curious return to its etymological origin *(in-formatio),* means exactly the construction of a message by means of the "juxtaposition of symbols of which certain groupings characterize objects or ideas."[5]

In the case of molecular genetics, the information consists of the juxtaposition of symbols (A, T, G and C) that represent the four nitrogen bases (adenine, thymine, guanine and cytosine, respectively) aligned in the DNA molecule. The succession of bases constituting the information is "read" on the level of another nucleic acid, that is, ribonucleic acid (RNA), during the process of codification or deciphering of the code by means of reading units formed by three bases or triplets, codons. Here it is of interest to underscore:

1. that the triplet represents the unit of subgenic reading to which a certain amino acid corresponds and which, together with the other triplets of the gene to which it belongs, is read in order to synthesize the one protein among the thousands present in the organism, which is dependent on that certain gene;
2. that the system of correspondence between triplets and amino acids constitutes the genetic code.* This is seen more clearly by means of the linguistic comparison frequently used in which the triplet (corresponding to one amino acid) is considered analogous to a letter of the alphabet, the sequence of the triplets in the RNA molecule (corresponding to a protein) analogous to a word and a succession of RNA molecules analogous to a sentence.

Since, in our case, we wish to single out the placing of time into the genetic code, we too have recourse to a comparison. The gene molecule is similar to a day of the calendar, and the individual having it is similar to a season of the calendar itself. Just as the days of the calendar do not have the same number of "sun

5. Fages, J. B., and Pagano, C.: *Dictionnaire des Media.* Tours, Mame, 1971.

* In general informatics, the "code" represents a group of rules or conventions assuring the functioning of a language (Fages, and Pagano, *op. cit.*)

hours" because light varies with the seasons, so the genes of two individuals, even though identical with respect to the product for which they are responsible, can have a duration differing from their own information. In other words, some genes that represent the very same protein in two living organisms may have a different number of "sun hours," that is, an informatic time differing in length.

Turning now to the history of the gene, it must be recognized how this finally has been approached directly, and how, from the theoretical concept of the hereditary unit, genetics has passed to the concept of the molecular hereditary unit in which minor reading units can be singled out on the submolecular level with the possibility of deciphering the hereditary message. The ardent creativity of the geneticist does not stop here. Placed on this path, referring to the fact that the complex of individual genes repeats itself on the level of the nucleus in every cell of the organism, he stresses the resemblance of the informatic system of biological heredity to that of a gigantic organizer which functions in an autonomous way so as to carry out the program built into the individual genome.

Furthermore, the cycle of life consists of innumerable single times through which the cycle is completed and of which molecular and informatic genetics until now have given neither the interpretation nor the code. Therefore, knowledge of the structure of information must be integrated with the knowledge of the time at the disposition of the single gene, the focal point for knowledge of the mechanism that can be called "the individual clock of life."

THE MOLECULAR STRUCTURE OF THE GENE

What then is the relationship between the genetic code and biological time? The question arises when, on one hand, one thinks that biological time, properly stated, is of a hereditary nature, and on the other, that the hereditary program of living beings is written in codified terms in the double DNA strands. Up to now, the code has permitted the decodification of qualitative parameters of information, but it can be presumed, at least

as a working hypothesis, that it also contains the key of the temporal parameters of the gene and of character. How?

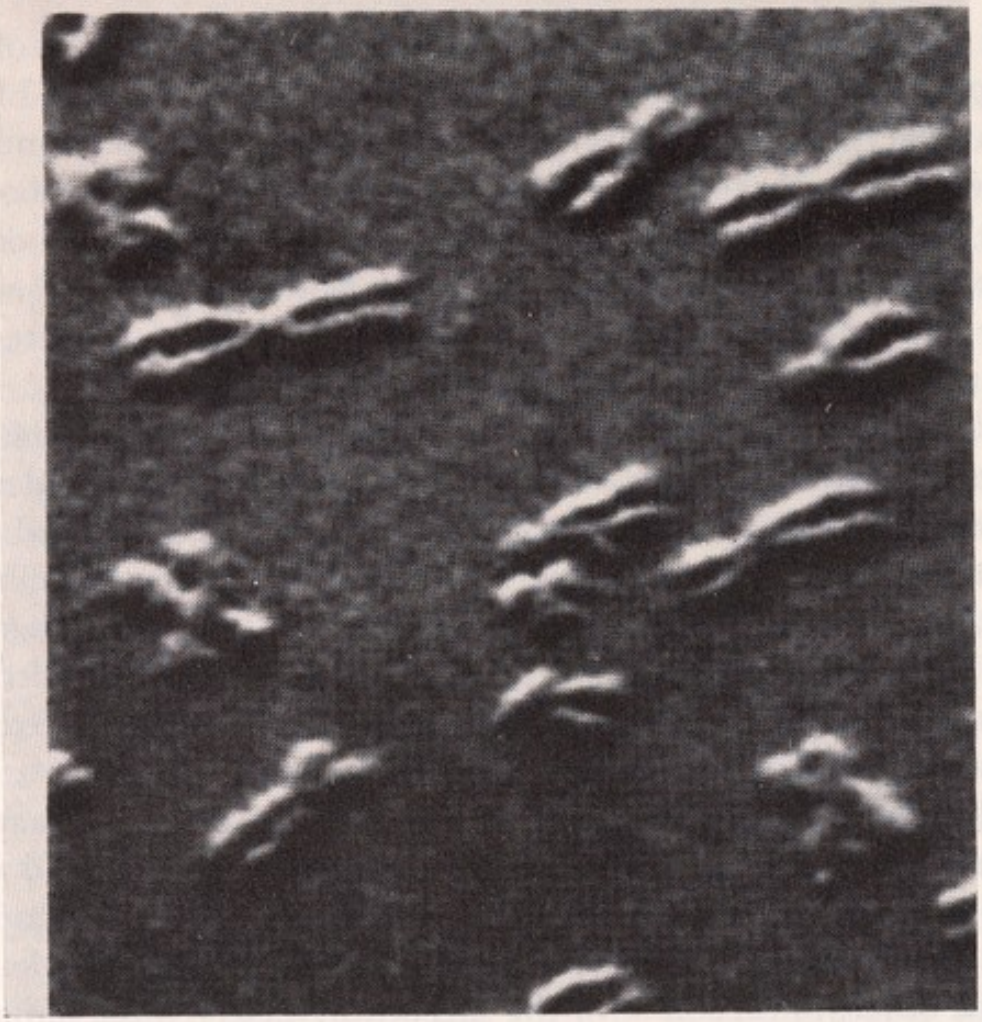
In order to answer this latter question, and consequently to place the genetic code in a position to also read the "sun hours," that is, the informatic time at the possible disposition of the genes, it is necessary to pass from the historic evolution of the gene concept to a more detailed analysis of the structure and function of the gene-molecule, that is, DNA.

The DNA molecule (Fig. 7) is a large, highly polymerized molecule, distinguished from other nucleic acid molecules because of its inherent structure—a double filament wound in a spiral around a single axis—and its ability to replicate itself during the unwinding of this "double strand." It is precisely because of this capacity of replicability that the DNA molecule constitutes the gene's support and succeeds in transmitting hereditary characters from one generation to another.

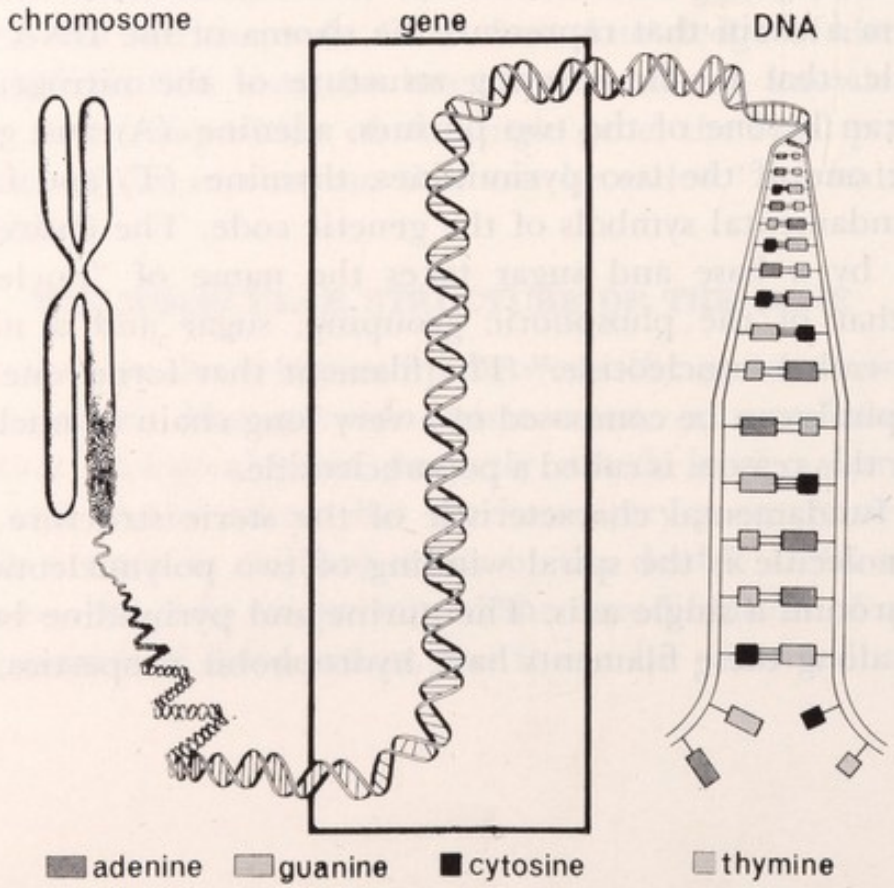
The filaments of the double strand are formed by a pentose sugar, a phosphoric grouping and nitrogen bases. The sugar is always deoxyribose, just as the orthophosphoric acid that binds itself, on one hand, to carbon 3′ of one deoxyribose molecule and, on the other, to carbon 5′ of the succeeding deoxyribose molecule is also constant. The sugar and phosphoric groupings, by means of alternating one molecule of the former with one of the latter, form a chain that represents the stroma of the DNA macromolecule, that is, the carrying structure of the nitrogen bases which can be one of the two purines, adenine (A) and guanine (G), or one of the two pyrimidines, thymine (T) and cytosine (C), fundamental symbols of the genetic code. The entire group formed by a base and sugar takes the name of "nucleoside," while that of the phosphoric grouping, sugar and a nitrogen base, is called "nucleotide." The filament that forms one of the DNA spirals can be composed of a very long chain of nucleotides and, for this reason, is called a polynucleotide.

The fundamental characteristic of the steric structure of the DNA molecule is the spiral winding of two polynucleotide filaments around a single axis. The purine and pyrimidine bases arranged along these filaments have hydrophobic properties, differ-

a)



b)



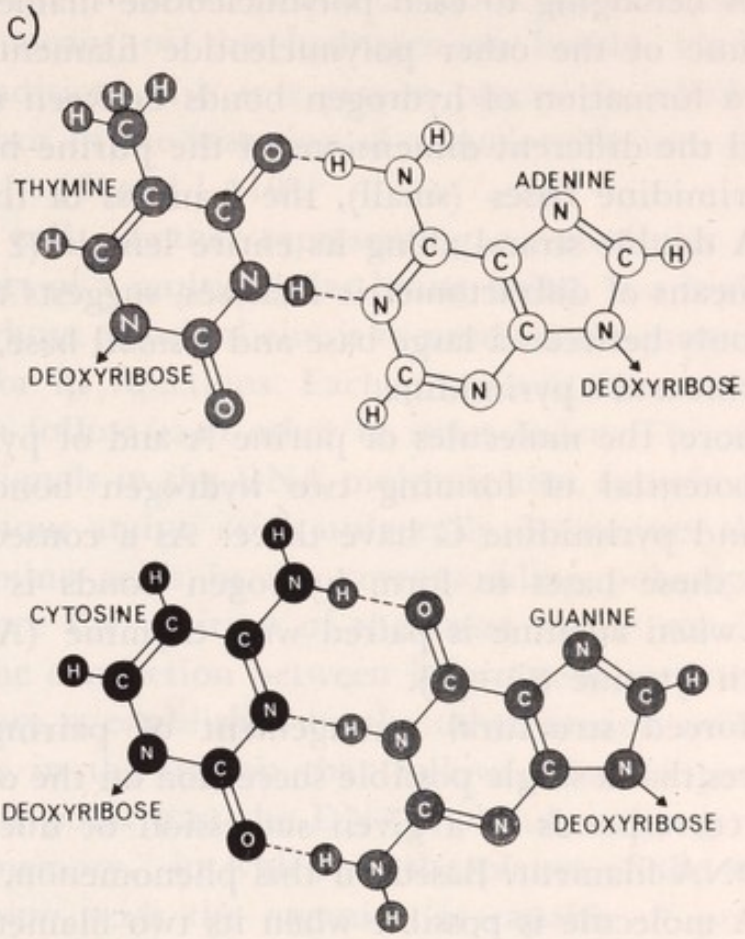


Figure 7. Relationship between chromosomes, genes and DNA. *a*) Some human chromosomes in the scanning electron microscope (×40,000); *b*) From the left, a single chromosome. Note the tangled grouping that assumes the double-stranded structure of the DNA, clearer at the center, where a segment of it appears that constitutes a gene, while to the right a detail of the DNA molecule is carried over with the pairing of the bases (rectangles of different shading, consolidated by the presence of hydrogen bonds; *c*) The two pyrimidine bases (thymine and cytosine) paired with the two purine bases (adenine and guanine respectively). The double hydrogen bond in the case of the thymine-adenine couple and the triple hydrogen bond in the case of the cytosine-guanine couple are pointed out. (Photo Dienst aus Deutschland, Hamburg, 1968; diagram by D. E. Comings, Chromosome Replication, *Topics in the Study of Life,* 1971. Courtesy of Harper & Row Publishers, New York.)

ent from the residues of the sugars and the phosphoric groupings that make up the various nucleotides; therefore, they protrude towards the inside of the DNA double strand, thus remaining better isolated from the external aqueous environment.

The bases belonging to each polynucleotide filament are thus opposite those of the other polynucleotide filaments and they pair off in a formation of hydrogen bonds between them. Bearing in mind the different dimensions of the purine bases (large) and the pyrimidine bases (small), the firmness of the diameter of the DNA double strand along its entire length (2 nm), as revealed by means of diffractometric analyses, suggests that pairing is possible only between a large base and a small base, that is, between a purine and a pyrimidine.

Furthermore, the molecules of purine A and of pyrimidine T have the potential of forming two hydrogen bonds, whereas purine G and pyrimidine C have three: As a consequence, the capacity of these bases to form hydrogen bonds is completely satisfactory when adenine is paired with thymine (A – T) and guanine with cytosine (G – C).

This enforced structural arrangement of pairings between bases requires that a single possible succession on the one filament necessarily corresponds to a given succession of nucleotides on the other DNA filament. Based on this phenomenon, replication of the DNA molecule is possible when its two filaments separate and move away; then, free nucleotides join each of the two filaments of the mother molecule through the complementary bases, giving rise, according to the criteria of affinity described above, to two daughter molecules, each an identical copy of the mother molecule.

Replication is achieved through the separation of the two complementary filaments of the molecule; however, these do not separate completely before the synthesis of the new spiral. For this reason, duplication or replication is interwoven with their separation. The monomeric precursors of DNA synthesis are the deoxyribonucleotides that unite into a single spiral filament through the action of the enzyme, DNA-polymerase. Besides the polymerase, other enzymes come into play: ligase which binds an alcoholic function of sugar in position 3′ with a phosphoric grouping belonging to an adjacent nucleotide on the same strand, and nuclease which is responsible for the inhibition of the synthesis.

The correct selection of nucleotides for incorporation into the

hemimolecule which serves as a mould is achieved on the basis of union by means of the hydrogenous bonds. Under average-normal conditions, this is a precise process in which the probability of error in the insertion of a nucleotide into the sequence is between $1 : 10^8$ and $1 : 10^9$.[6]

A living cell, whether representing a unicellular organism or forming part of a multicellular living being, is a highly complex structure whose principal aim is to produce the protein molecules necessary for its functions. Each protein is formed from amino acids which follow each other in strict order. The succession of groups of signals in the DNA molecule that contain information for the various amino acids univocally determines the sequence of these amino acids in the corresponding polypeptidic chain, and therefore the position of the same in the structure of the protein. The connection between information structure and protein structure is established by the other nucleic acids which we will discuss in the section that follows. Here a pause may be made on the point that the DNA molecules of a genome represent the "memory," in which all the planes of the sequences of protein amino acids the organism is capable of producing are preserved.

DNA, besides having the ability to record information and to replicate itself, is capable of "changing" its own information by the action of environmental forces, through the modification of its own chemical structure and, in particular, by the modification of the number and order of the bases. This is a purely temporal aspect of information, both in that it has been adopted, together with selection, as an explanatory model of interspecific and intraspecific variation—that is, as a model of the adaptation of life to changes in the environment—and in that each gene, under the same conditions of the external environment (that is, of mutagenic conditions) has its own rate of mutation per unit of cosmic time.

THE MOLECULAR PHYSIOLOGY OF THE GENE

The discussion of the molecular structure of the gene has served to set up some premises to justify the possible existence of

6. Watson, J. D. and Crick, F. H. C., *op. cit.*

a variability in the gene's stability conditions, thus explaining the temporal variability of its information. This subject is now resumed on the level of the physiology of the gene which, in this section, means the itinerary of the hereditary information as it passes from the gene to the character.

The information contained in the nuclear DNA is reproduced and transformed in the corresponding protein through operative sequences in which certain acids and enzymes take part. Included are the nucleic acids of the RNA series, the amino acids which are the elements necessary for the biochemical structures that must be constructed, and the enzymes which catalyze the synthesis. The succession of operations necessary to carry out the phenogenesis of the information contained in the DNA can be represented in the manner indicated in Figure 8.

Transcription is a process similar to that of replication. It brings about the disjunction of the two DNA hemimolecules with the difference that, in transcription, the complementary filament is not a DNA hemimolecule, but the filament of another nucleic acid, ribonucleic acid (RNA), which arranges its steric structure in such a way as to become the reverse side of the DNA, that is, to contain the bases complementary to those present in the DNA chain. Structurally, the DNA and the RNA are very similar; however, the RNA differs in that it is composed of a single polynucleotide filament, in which deoxyribose is replaced by ribose and thymine by another pyrimidinic base, uracil.

The enzyme RNA-polymerase is responsible for the moulding operation of the RNA filament on the DNA hemimolecule. This first phase of protein synthesis, called "transcription," is carried out in the cell nucleus. From there the synthesized RNA migrates towards the cytoplasm, receiving the name "messenger" for this reason. In the cytoplasm, the second phase of protein synthesis occurs. The name of "translation" is given to this, in that one goes from an alphabet of nucleotides or triplets to an alphabet of amino acids. Besides the RNA messenger (m-RNA), two other nucleic acids also participate in translation—the transport RNA (t-RNA) and the ribosomal RNA (r-RNA).

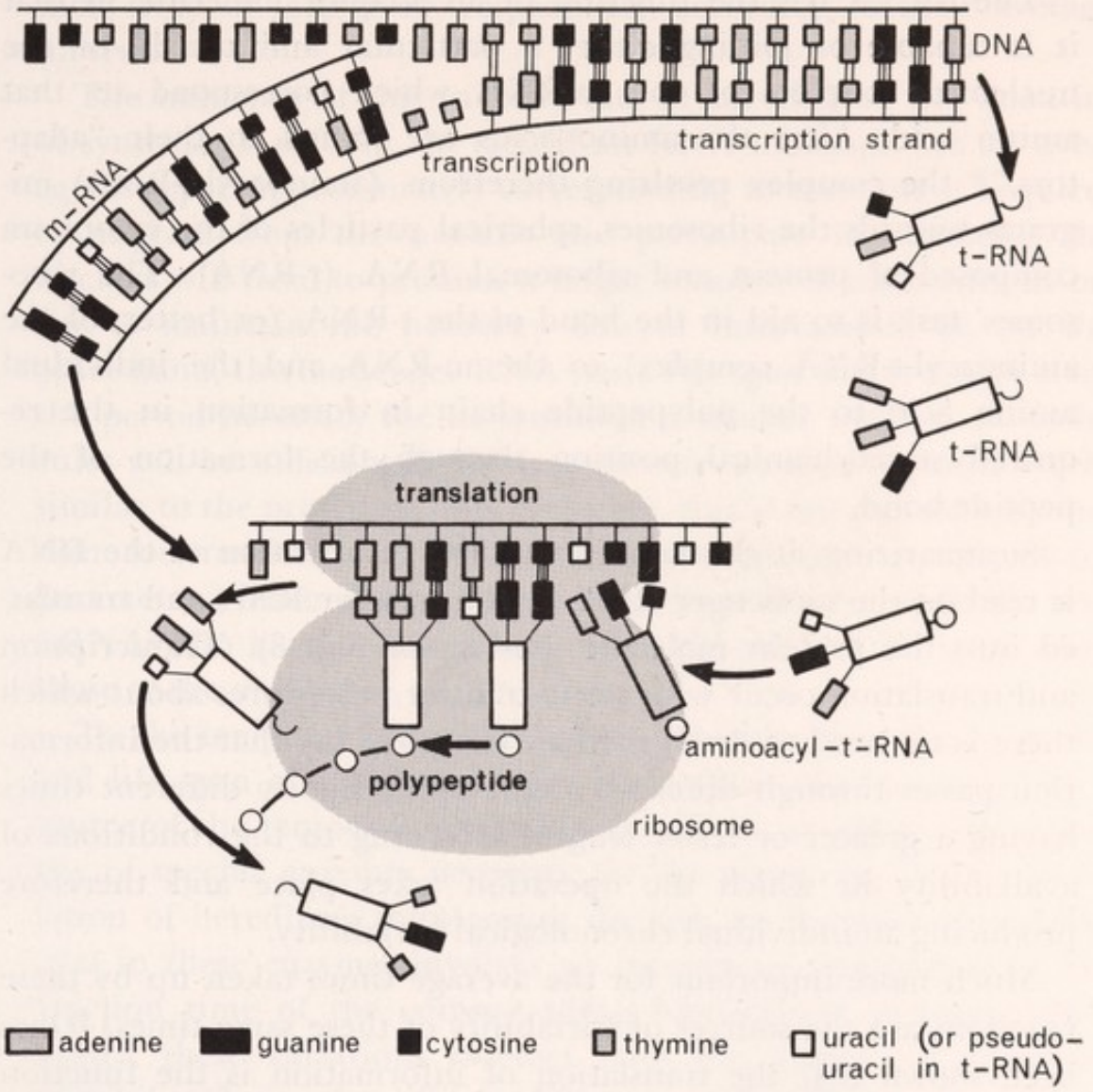


Figure 8. Various phases of the synthesis of a polypeptide (primary structure of a protein) starting from the genetic information contained in the DNA molecule. One of the two filaments of the DNA (*see* Fig. 7) is the transcription strand that functions as a mould for the synthesis of the messenger RNA (m-RNA). When the transcription of the genetic information on RNA occurs, the latter spreads out on the ribosome, where it is joined by the transfer RNAs (t-RNA), also synthesized at the level of DNA. The t-RNAs previously joined in the cytoplasm, each to a specific amino acid, forming an aminoacyl-t-RNA which goes to place itself opposite a specific triplet of m-RNA. The "reading" in succession of the various triplets of m-RNA by the various aminoacyl-t-RNAs leads to an alignment of the individual amino acids in a sequence which will constitute the polypeptide, once the amino acids, by enzymatic action, become chemically bound among themselves. This is the translation phase of the genetic message in the structure that will subsequently give rise to the protein.

The t-RNA has the function of an adaptor molecule in that it is capable of joining either a particular amino acid or the nucleotide triplets of the m-RNA which correspond to that amino acid. After the amino acids are joined to their "adaptors,"* the complex resulting therefrom (aminoacyl-t-RNA) migrates towards the ribosomes, spherical particles of the cytoplasm composed of protein and ribosomal RNA (r-RNA). The ribosomes' task is to aid in the bond of the t-RNA (or better, of the aminoacyl-t-RNA complex) to the m-RNA and the individual amino acid to the polypeptide chain in formation in the required stereochemical position through the formation of the peptide bond.

Summarizing, it can be said that the information of the DNA is read on the messenger RNA by the transfer RNA and translated into the protein molecule (*see again* Fig. 8). Transcription and translation occur with steric transfer procedures about which there is no need to dwell further, except to say that the information passes through different stages which signify different times having a greater or lesser length, according to the conditions of availability in which the operation takes place and therefore producing an individual chronological variability.

Much more important for the average times taken up by these reactions are the sources of variability of these same times. It has been shown that the translation of information is the function of the transcription time of the information itself, in the sense that a minimum variable period of synthesis of messenger RNA exists, a period that is required for the translation of the corresponding information to take place.

It is now known that this minimum period corresponds to the number of molecules of messenger RNA required to initiate translation. This correlates the quantity of information in molecules of m-RNA with the time necessary to produce them. This variability comes about because of the different rate of survival of the m-RNA molecules for which reason they are classified as

* This process is activated by a specific enzyme, the aminoacyl-t-RNA-synthetase.

short-lived or long-lived, respectively, according to their average survival.†

The influence of this variable rate of survival on the quantity of synthesis is evident. In fact, if an RNA molecule has an average life span approximately corresponding to the time it requires to migrate from the nucleus and participate in synthesis, the nucleus will need to produce a larger number of molecules in order to maintain the necessary flow of information. If, on the other hand, the messenger RNA has a life span much longer than the period necessary for its synthesis, a smaller number of molecules will be sufficient to obtain a protein synthesis quantitatively similar to the preceding one. However, this is not the only mechanism for translation of information entailing time as a necessary parameter, inasmuch as the other two RNAs (t-RNA and r-RNA) also have definite life spans, although much longer than those of the m-RNA.

To the temporal variability which depends upon the structure and life span of RNA molecules there must also be added, as a source of the temporal variability in protein synthesis, the quantity of specific enzymes necessary for the transcription and translation of hereditary information. In fact, an increase or diminution in these enzymes involves an increase or diminution of the reaction time of the corresponding biochemical processes. Naturally, these variations interact with the sources of temporal variability due to the different life spans of the RNAs.

It is extremely important to individualize the existence of these times as sources of variability on the level of the genetic code. It is also necessary to recall the existence of fundamental time which corresponds to the duration of the informatic action

† The existence of different survival times (or length) of the RNA was demonstrated by R. B. Scott and E. Bell (in *Science, 145*:711, 1964) through the study of the protein syntheses carried out at a specific moment in the development of a chicken embryo. Administering actinomycin D and blocking RNA synthesis in this manner, these authors were able to show the persistence of RNAs, even considerably after blockage. Furthermore, by examining the distribution in the tissues, they were able to establish that these RNAs involved only the synthesis of specific proteins. In other words, they demonstrated that a specific survival time for the RNA molecule exists for each synthesis.

exercised by the DNA molecule carried out through the minuscule time intervals operative in this regard.

THE TIMES OF THE PHENOTYPE

Every cell of the organism is endowed with a hereditary patrimony enclosed within its nucleus and distributed in the genes. All the information necessary for the organism to produce the proteins it requires is present in a potential state in every cell as it leaves the zygote. However, its actual availability is divided into a series of sequential groups according to a precise calendar of impact.

Phenogenesis, that is, the building of the organism, occurs through a succession of events during which the cell becomes differentiated and specialized, and so, gradually passes from the totipotency of the zygote to the structure adapted for definitive specialized function.

The progressive and selective mobilization of the genome requires a precise programming of the informatic activity in a progression and serial sequence of time-related events. Similarly, when development occurs, the maintenance of the organism in a state of equilibrium with respect to the environment requires the integration of numerable biological times which are linked together. The phenotype is therefore imbued with times and events, from those that are repeated in every cell to those that concern the organism in its entirety within the framework of the species.

As previously mentioned, Mendelian genetics highlighted the action time of the gene, with Haldane[7] interpreting this to be the mechanism at the service of evolutionary selection. He arrived at this conclusion after a comparative study of numerous vegetable and animal species; of these, he analyzed some times that were found in the phenotype which he generically attributed to genes intervening in successive periods of development.

Molecular genetics, in its turn, has dealt implicitly with the problem of phenotypic time, singling out some mechanisms that transform potential information to actual information, that is,

7. *Op. cit.*

mechanisms that regulate the transcription and translation periods of the information. Monod and Jacob[8] were able to demonstrate in *Escherichia coli* that these mechanisms act by means of a repression and induction system analogous to the adaptive system of the enzymes. Schematically, the mechanism regulating genic activity, according to these authors, functions through a battery of genes having different attributes.

A first gene, or "regulator" gene, synthesizes a substance which has been given the name of "repressor." This blocks the activity of the "operator," a segment of DNA capable of bringing about the transcription of a battery of genes that are called "structural genes." The repressor goes into action combining with specific DNA sites of the operator, thus preventing the formation of messenger RNA. In this type of system, the repressor's function is that of a relay, in that the production of a derepressor (inductor), whether on the part of the organism as a final product of other batteries of genes or directly or indirectly on the part of the environment, releases the entire system, setting off the transcription of a battery of linked structural genes and the consequent translation of their transcribed message. The combination of the operator and the structural genes which it regulates is called "operon." This mechanism makes it possible to explain the automatism of ontogenesis, homeostasis and all the processes of the organism's vital cycle, that is, the programming and carrying out of the sequence of events these processes require in the phenotype.

The same phenotypic mechanism that transforms potential information into the corresponding protein at a specified instant permits identification of the characteristics of the times connected with it, times which are clearly mixed because they represent, in the phenotype, the result of the interaction between a hereditary mechanism and a stimulus from the internal or external environment.

The times of action of the operon, as has already been forecast by Haldane, are hereditary in the sense that natural selection

8. Monod, J., and Jacob, F.: In *Cold Spring Harbor Symp Quant Biol, 26:*389, 1961.

between possible mechanisms can have selected and imposed those times which involve the activity of the structural genes most adapted for a certain environment. The times of occurrence of male and female puberty and the menstrual periods of the different human races and subraces offer substantiating examples of the chronological variability connected with operative mechanisms fixed by natural selection.

For all that, Monod and Jacob did not explicitly tackle the problem of time; it is clear that their study concerned time in a manner different from that employed by Haldane but in the same direction, which is that of phenotypic times dealt with on the molecular level. The operon, in fact, is an excellent model for explaining the impact of competent genes intended to supply the organism with the necessary proteins at the time of need. This impact is fostered by a derepressor, which is also a product of phenotypic nature. The origin of the derepression, in its turn, leads to phenomena connected with the internal or external environment.

However, whoever studies the operative times of the phenotype realizes that while they can and do explain the entrance and the suspension of the informatic action of the gene into the phenotype with mechanisms of impact, they do not explain the absolute duration of the information coming from the gene, a length that can differ from individual to individual and, in the same individual, according to age. In this sense, these mechanisms do not clarify the innermost essence of endogenous time, which should explain how the gene has access to a certain informatic time subject to individual variation and how this is transmitted to succeeding generations as a temporal character.

In order to be able to reach a focalization of the mechanism that presides over hereditary biological time, it is necessary to go beyond the level of phenotypic times so as to arrive at the point of discussing hereditary time at the level of the genetic code, integrating all those cognitions that genetics has at its disposal.

Chapter IV

Stability of the Gene: The Ergon

THE CONCEPT OF STABILITY

BIOINFORMATIC LANGUAGE affords chronogenetics the necessary approach to hereditary time, that is, the average life of genetic information. This approach finds some clarification in the genetic code, but above all in a very important concept developed by general informatics—that of the *stability* of information, and hence the average life of information which represents the result of stability for a given environment.

In the first place, the stability of genetic information signifies the capacity of information to maintain its own integrity (because of the stability of the gene which initially codifies the information), against which is set the causal action of sporadic agents that cause its decay. In general, just as the degree of mutability is an index of the degree of stability, so the different spontaneous and experimental mutability of the individual genes reciprocally demonstrates their different stability, *coeteris paribus*.

Numerous data testify to the differential mutability of the gene. As for the spontaneous mutability, Table II demonstrates

TABLE II

MUTATION FREQUENCY IN NUMBER OF MUTANT GENES PER MILLION GAMETES IN ANIMALS AND VEGETATION*

Species	*Genes*	*Mutation Frequency in M 0/00000*
Escherichia coli (bacterium)	st^8 st^7	0.001
	lac^- lac^+	0.200
	His^+ His^-	2.000
	His^- His^+	0.040
Chlamydomonas (alga)	st^8 st^7	1.000

* From C. Petit, and G. Provost, *Genetics and Evolution*, Arnoldo Mondadori, Editor, 1971. Courtesy of Mondadori Publishing Company, Milan.

TABLE III

MUTATION FREQUENCY INDUCED BY X RAYS OF SIX DIFFERENT GENES IN ZEA MAIZE. MUTATION FREQUENCIES ARE EXPRESSED IN THE NUMBER OF MUTANTS PER MILLION GAMETES*

Genes	*Number of Gametes Studied*	*Number of Mutations*	*Mutation Frequency in 0/00000*
R	554,786	273	492
J	256,391	28	106
Pr	647,102	7	11
Su	1,678,736	4	2.4
Y	1,745,280	4	2.2
Sh	2,496,285	3	1.2

* From L. J. Stadler, The Frequency of Mutation of Specific Genes in Maize, *Anatomical Record, xxx:*47, 1930. Courtesy of publisher.

the different mutation rates of the genes of a bacterium *(Escherichia coli)* and an alga *(Chlamydomonas).*

Experimental mutability demonstrates that the same mutagenic agents determine a spectrum of frequency of diverse mutations according to the gene. In Table III, the different number of mutations induced by equal doses of ionizing radiation upon different *Zea mays* genes are shown.

TABLE IV

MUTATION FREQUENCY OF SOME HUMAN GENES EVALUATED IN MILLIONS OF GAMETES*

	Disease or Abnormality	*Frequency*
Dominant autosomes	Epiloia (tuberous sclerosis)	10
	Acondroplasia	42
	Pelger's (nuclear) anomaly	80
	Aniridia	5
	Retinoblastoma	23
Recessive autosomes	Microphthalmia	15
	Albinism	28
	Color blindness (total)	28
	Amaurotic familial idiocy	11
	Ichthyosis	11
Recessive connected with sex	Hemophilia	32

* From J. V. Neel, and W. J. Schull, *Human Heredity,* 1954. Courtesy of University of Chicago Press, Chicago, Illinois.

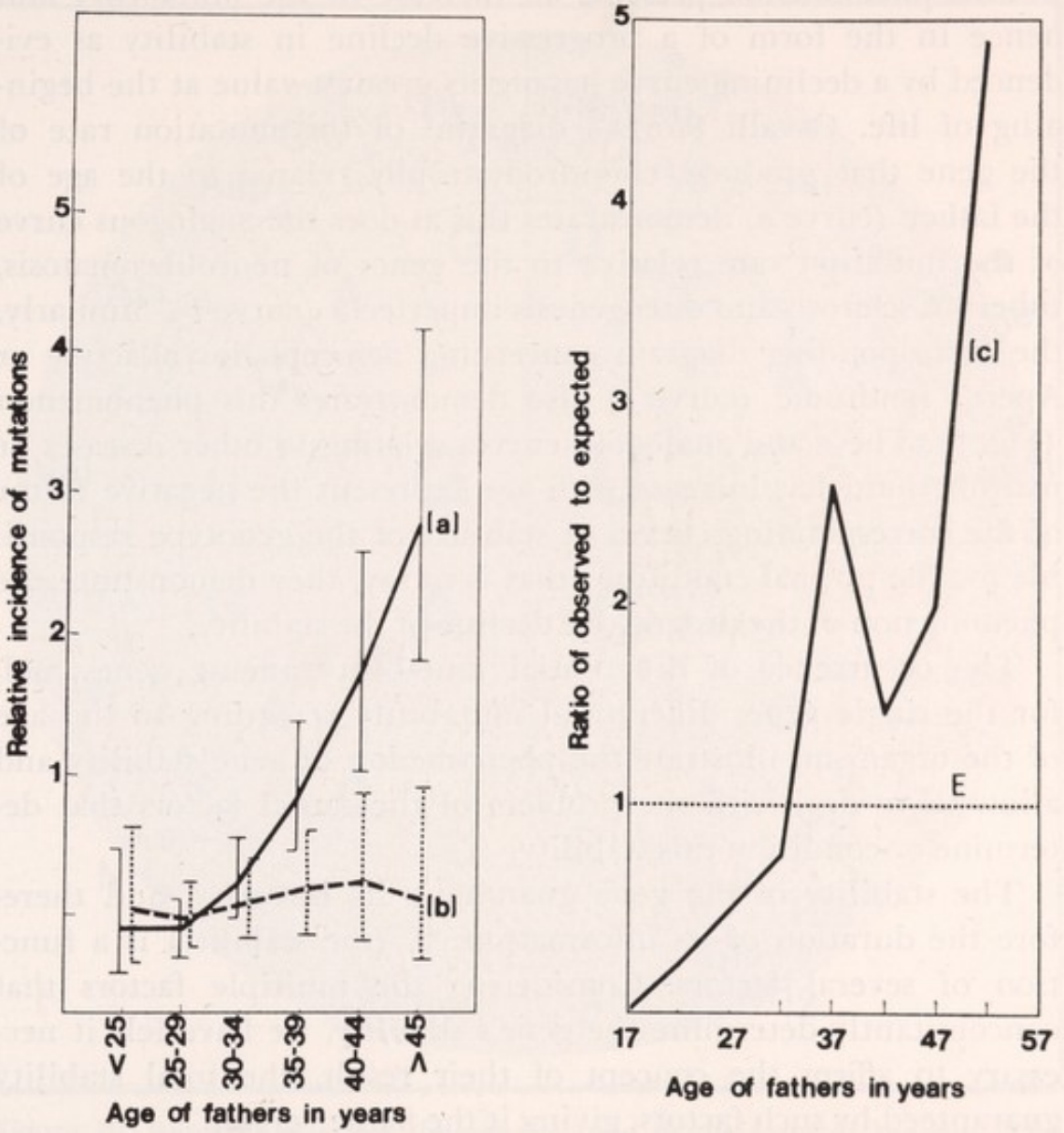


Figure 9. Relative incidence of dominant mutations among individuals grouped according to their fathers' ages (at birth of offspring) is *(a)* chondrodystrophy, *(b)* osteogenesis imperfecta and *(c)* acrocephalosyndactyly. (From L. L. Cavalli Sforza, and F. W. Bodmer, *The Genetics of Human Populations,* 1971. Courtesy of W. H. Freeman and Company, Publisher, San Francisco, California.)

As regards man, Table IV demonstrates the different mutation rates noted among genes responsible for different diseases.

The mutability of the gene is variable, not only according to the gene under consideration, but also for the same gene depending on the age of the individual to whom the gene belongs.

This phenomenon presents an increase in the *mutability* and hence in the form of a progressive decline in stability as evidenced by a declining curve having its greatest value at the beginning of life. Cavalli Sforza's diagram[1] of the mutation rate of the gene that produces chondrodystrophy related to the age of the father (curve *a*) demonstrates this as does the analogous curve of the mutation rate relative to the genes of neurofibromatosis, tuberous sclerosis and osteogenesis imperfecta (curve *b*). Similarly, the corresponding diagram concerning acrocephalosyndactyly or Apert's syndrome (curve *c*) also demonstrates this phenomenon (Fig. 9). These and analogous curves relating to other diseases or malfunctions that increase with age represent the negative factor of the corresponding curves of stability of the genotype responsible for the normal condition; that is to say, they demonstrate the phenomenon of the progressive decline of the stability.

The occurrence of differential mutability among genes and, for the single gene, differential mutability according to the age of the organism, illustrate the phenomenon of gene stability and allow us to deal with the problem of the causal factors that determine or condition this stability.

The stability of the gene guarantees its integrity, and therefore the duration of its information; it (the stability) is a function of several factors. Considering the multiple factors that concomitantly determine the gene's stability, we have felt it necessary to affirm the concept of their result, the total stability guaranteed by such factors, giving it the name "ergon."

The various aspects of the ergon will now be analyzed according to the type of stability they guarantee, considering separately physicochemical stability (synonymy), informatic stability (redundance) and repair stability ("repair").

PHYSICOCHEMICAL STABILITY (SYNONYMY)

Biological information has as a vector the DNA molecule, hence this molecule is the prime object of study for ascertaining the possible existence of causal factors of the differential stability of information within it.

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1. Cavalli Sforza, L. L., and Bodmer, F. W.: *The Genetics of Human Populations.* San Francisco, W. H. Freeman and Company, 1971.

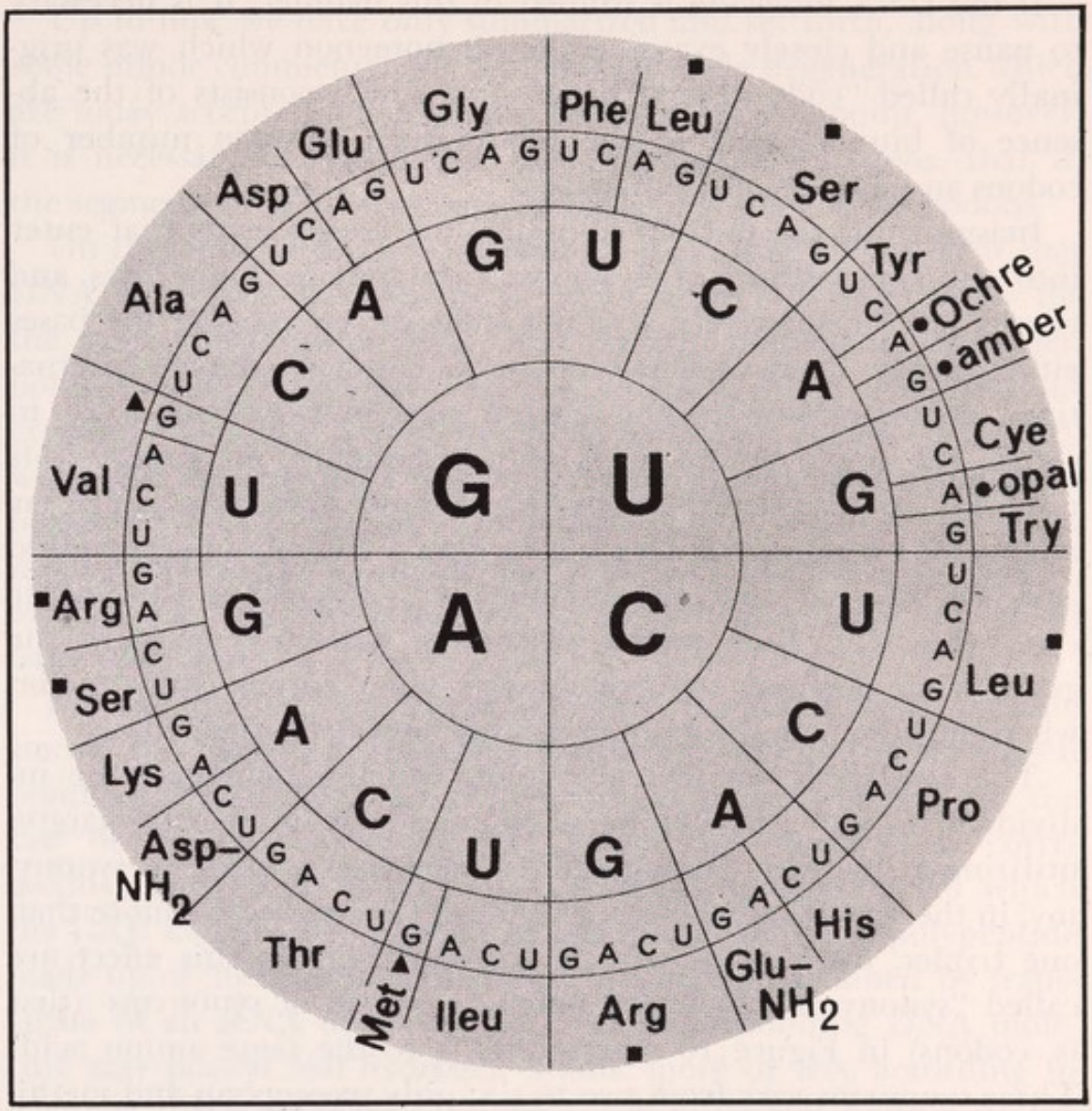

Figure 10. Representation of the genetic code in the form of the sun. The sequences of three bases (triplets), corresponding to the codons of the messenger RNA which codify for the amino acids, are read from the center towards the periphery. The amino acid abbreviations are set out along the periphery of the circle: *Ala,* alanine; *Arg,* arginine: *Asp,* aspartic acid; *Asp-NH₂,* asparagine; *Cys,* cystine; *Glu,* glutamic acid; *Glu-NH₂,* glutamine; *Gly,* glycine; *His,* histone; *Ileu,* Iso-leucine; *Leu,* leucine; *Met,* methionine; *Phe,* phenylalanine; *Pro,* proline; *Ser,* serine; *Thr,* threonine; *Try,* tryptophan; *Tyt,* tyrosine; *Val,* valine. Ochre, amber and opal are three codons to which no amino acid corresponds: They are the terminators of the chain (●). The mark ▲ indicates the initiating codons of the chain while ■ indicates amino acids that appear twice, being codified by several triplets which differ for the first base. (From C. Bresch, and R. Hausmann, *Klassische und Molekular Genetik*. Courtesy of Springer, Publisher, Berlin, 1972.)

If the DNA molecule is studied in this manner, it is necessary to pause and closely examine the phenomenon which was originally called "code degeneration" and which consists of the absence of biunivocality in the relationship between number of codons and number of amino acids.

Inasmuch as the nucleic acids and the amino acids that enter into the composition of a polypeptide contain four bases and twenty bases respectively, it is not sufficient to consider the bases either singly (four alternatives) or in couples (sixteen alternatives, corresponding to the sixteen permutations) in order to codify the single amino acids of the sequence. In reality it is necessary to consider them by threes, thus obtaining sixty-four alternatives represented by as many base "triplets." Every amino acid has, on an average, three triplets at its disposal in the genetic code (Fig. 10). Each triplet places the molecule (that is, the gene) in a position to produce the same correct information when the other conditions of normality have been satisfied.

The availability of several triplets which characterize the individual amino acid has been enhanced by informatic jargon utilizing a linguistic analogy. Thus reference is made to synonymy, in the sense that when an amino acid is codified by more than one triplet, the various triplets corresponding to this effect are called "synonyms." Note the different groups of synonyms (that is, codons) in Figure 10 corresponding to the same amino acid: These synonyms vary from two to six; only tryptophan and methionine have no synonyms. Suppose, for example, that there are two or four of them; in this case, the first two bases of triplets are equal, and the difference between the synonyms is found in the third base. For example, the synonymous codons that read proline *(Pro)* are CCG, CCA, CCC and CCU, while those reading histidine *(His)* are CAC and CAU. Carefully observing the cases of synonymy, we see that the alternative to the third bases C and G are still represented respectively by the bases U and A. The qualitatively corrected information that each synonym is able to produce is, therefore, the same; yet the duration of the information differs according to the synonymous combinations, the reason for which will soon be seen.

Up to now we have only summarized and set forth, along with some minor comments, the principles of code degeneration which are today accepted by molecular genetics. At this point, however, it is necessary to return our attention to the codogens, that is, the segments of DNA that correspond to the single RNA codons.

On the basis of the genetic code, it is possible to establish that DNA molecules or segments of DNA molecules that codify for the same information may differ by the number of hydrogen bonds.* Suffice it to say that the complementary guanine and cytosine bases are united by three hydrogen bonds (G ≡ C), while the adenine and thymine bases are united by two hydrogen bonds (A = T). Similar information may be codified by DNA molecules that have a nucleotide with G or indifferently with A, or else with C or indifferently with T, corresponding to the third bases of codons.

For example, in the case of histidine, the alternatives possible among the codogens determine a different number of hydrogen bonds in the DNA—greater (hence with greater stability) in the case of the GTG codogen (to which the codon CAC corresponds), and lesser in the case of the GTA codogen (to which the CAU codon corresponds). As a result, assuming a polypeptide made up of 500 amino acids whose synthesis is obtained by translation of an RNA of 500 codons, the corresponding DNA molecule may possess 500 hydrogen bonds, more or less, according to whether there are bases of type G or C (+500 bonds) in the third position of the triplet or else of type A or T (−500 bonds).†

If one now considers that in the same average information, 1500 bases are present corresponding to the 500 codons already mentioned, and if one accepts an average makeup of the molecule given by an equal number of A or T bases and G or C bases,

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* A "hydrogen bond" is defined as one in which the hydrogen atom acts as a bridge between two electronegative atoms, having a covalent bond (donor) with one of them and a purely electrostatic bond (acceptor) with the other. The latter has an energy of about 5 kcal/mol while the covalent bonds have energies of 50 to 100 kcal/mol.

† The average gene contains about 1500 couples of nucleotides, hence 600 codogens (Watson, J. D.: *Molecular Biology of the Gene*, 2nd ed. Bologna, Zanichelli, 1972, p. 279.)

it is possible to calculate the total number of hydrogen bonds of the average molecule. The number of hydrogen bonds present in the entire molecule can be arrived at by multiplying 1500 as far as the contribution of the A or T bases is concerned, and $3 \times 1/2 \times 1500$ as far as the contribution of the G or C bases is concerned; that is, it will total $(2 + 3)1/2 \times 1500 = 3750$. The average number of hydrogen bonds per molecule estimated in this manner emphasizes the importance of the 500 hydrogen bonds on the molecule's stability in a greater or lesser way, in that they represent an inclusive value of between one seventh (15%) and one eighth (12.5%) of all the hydrogen bonds of the DNA molecule. The phenomenon becomes still more remarkable when one considers the case of the amino acids (such as leucine) codified by six synonyms in which the alternatives involve not only the third base but also the others. For example, the synonym between the codogen AAT (to which the codon UUA corresponds) and the codogen GAG (to which the codon CUC corresponds) involves a difference of two bonds per triplet, even codifying the two codons by leucine.

These considerations concerning synonymy permit us to state that the hydrogen bonds which unite the bases in the double strand have the significance not only of acting as signals which are necessary for the synthesis of a second DNA filament, as in the case of duplication, or of one RNA filament as in case of transcription, but inasmuch as they accomplish the task of guaranteeing cohesion between the two hemimolecules, they represent a coefficient of stability of the DNA molecule.* Therefore, the variability of the number of hydrogen bonds, on a par with the information recorded, is reflected in a greater or lesser stability of the molecule and, as a result, of the information contained therein. In other words, synonymy takes on a differential significance with respect to stability on the DNA level.

* On this subject it is appropriate to quote V. M. Ingram: "The original DNA is a very long, very fine and yet rigid molecule. . . . This molecule is rigid because it is composed of two polynucleotidic chains wound one on the other in a double strand; the cohesion of this structure is assured by the hydrogen bonds between complementary bases of the two chains." (In *Biosynthesis of Macromolecules*. New York, W. A. Benjamin, 1970.)

If one now considers that the DNA molecule is "written" in accordance with a given sequence which utilizes given nucleotides in the mould of one of the parental DNAs, it follows that variability in the DNA molecule's stability and the information contained therein is a hereditary fact. In other words, the synonyms present in an individual for a given information are the same as were contained in the DNA corresponding to the parents' gametes.

At the moment of amphimixis, the combination of the different stabilities of the genes contained in the parental gametes gives rise to a filial genotypic variability of stability analogous to the one achieved for the qualitative characters of the information. Thus a hereditary variability in the degree of stability of the single DNA molecule takes place due to the different number of hydrogen bonds present therein. However, since any DNA molecule is subject to decay, that is, a probability of deterioration in time, the result is that the existence of a different initial stability for the molecules carrying a given piece of information is reflected in a different average life of the gene.

In our hypothesis, and because of the reasons set forth above, we believe that the combination of synonyms in information is not accidental but is a cause and an index of the degree of stability of the gene. The different stability resulting from this warrants the different informatic power the same gene can have in two individuals and/or at two distinct ages in the same individual. This entire phenomenon—the differential stability resulting from the possible hereditary combinations of synonyms in the DNA molecule—represents one of the most obvious causal factors to explain the variability of inter- and intraindividual biological time.

In 1965 Watson had already considered the phenomenon of synonymy and precisely the relationship of A + T over G + C which is different in different species. This is the authoritative quotation:

> Higher plants and animals all have an excess of A + T over G + C in their DNA, while among viruses and bacteria and lower plants there is much variation, and both (A + T)-rich and (G + C)-rich species oc-

> cur. These variations, however, are not purely random, and the base ratios of taxonomically related organisms are quite similar. No one yet knows the reason for the wide base-ratio spread. It may be a consequence of but certainly not a prerequisite for extensive evolution. Witness extreme differences between higher plants and animals despite roughly similar percentages of the four main bases.[2]

Without excluding the possibility that code degeneration may have a significance linked with phylogenesis, we advance the hypothesis that synonymy has a significance which is linked with individual biological time: That is, it represents the causal phenomenon for stability on the level of the DNA molecule and, therefore, the genetic code cipher as far as biological time is concerned.

Experimental evidence supporting our opinion about the chronogenetic significance of synonymy is provided by J. Koch's researches on the different stability of DNA bases according to their reciprocal position, i.e. according to which are their neighboring bases. This position effect obviously produces a different stability of synonymous codons, the corresponding triplets differing for at least the third base.[2a]

Turning to the number of hydrogen bonds as a stability factor of the double strand molecule of DNA is not an abstract hypothesis, but rather the result of a correct and univocal interpretation of much experimental data, in part given to the literature by various authors, in part drawn up by us.

As has already been stated, the concept of ergon considers the gene as a holder of a degree of stability which allows the repetition of information for a time that varies according to the greater or lesser stability of the gene itself. Therefore, the experimental proofs which show that hereditary matter or DNA can present different degrees of stability pertain to the concept of ergon and the correlated concepts of stability and decay.

From this point of view it appears necessary to mention the research concerning the denaturation of DNA and the correspon-

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2. Watson, J. D.: *Molecular Biology of the Gene,* 2nd ed. Bologna, Zanichelli, 1972, p. 236.

2a. Koch, J.: The Influence of Neighboring Base Pairs Upon Base Pair Substitution Mutation Rates. *Proc Nat Acad Sci, USA 68:*773-776, 1971.

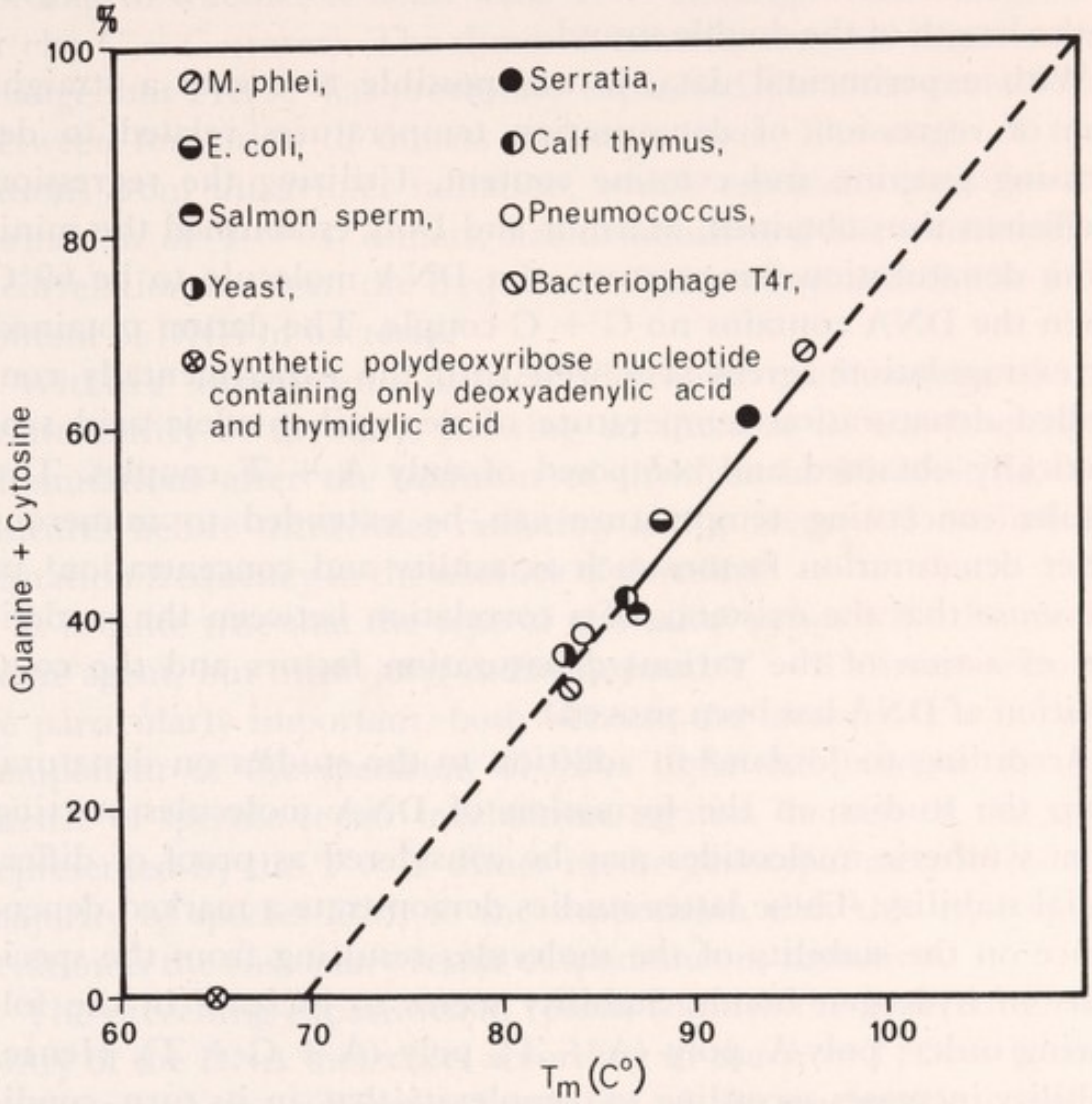

Figure 11. Dependence of the denaturation temperature T_m on the guanine-cytosine content of various samples of deoxyribonucleic acid. (From J. Marmur, and P. Doty, in *Nature 183*:1428, 1959. Courtesy of publisher.)

dence between the energy applied or required for denaturation and that contained in nitrogenous bases (Fig. 11). J. Marmur and P. Doty[3] proved that the temperature at which denaturation takes place varies according to the organism and the tissue from which the DNA has been extracted, and that this variation can be related to the guanine and cytosine content of the different DNA molecules. According to the experiments of these investigators, the denaturation temperature turns out to be a function

3. Marmur, J., and Doty, P.: In *Nature, 183*:1428, 1959.

of the number of hydrogen bonds between hemimolecules equal to the length of the double strand.

With experimental data, it was possible to create a straight line of regression of denaturation temperatures related to decreasing guanine and cytosine content. Utilizing the regression coefficient thus obtained, Marmur and Doty established the minimum denaturation temperature of a DNA molecule to be 69°C when the DNA contains no G + C couple. The datum obtained by extrapolation agrees very well with the experimentally controlled denaturation temperature of deoxyribonucleic acid synthetically obtained and composed of only A + T couples. The results concerning temperature can be extended to numerous other denaturation factors such as acidity and concentration[4] in the sense that the existence of a correlation between the modalities of action of the various denaturation factors and the composition of DNA has been proved.

According to Jordan,[5] in addition to the studies on denaturation, the studies on the formation of DNA molecules starting from synthetic nucleotides may be considered as proof of differential stability. These latter studies demonstrate a marked dependence on the stability of the molecules resulting from the specificity of hydrogen bonds. Stability seems to increase in the following order: poly-A, poly-(A + T), poly-(A + G + T). Hence, stability increases according to complexity that, in its turn, conditions specificity.

Besides the direct proofs of the differential stability of DNA molecules according to their content in A + T/G + C, a considerable number of indirect proofs exists in this direction. The indirect proofs are based on the opposite concept of stability—that is, the concept of instability. Considering the most frequent changes that can occur in a DNA molecule, such as the formation of anomalous bonds between the bases, it is possible to show that the rate of change is different in the nucleotide pairs A + T and G + C.

For example, the formation of pyrimidine dimers differs ac-

4. Jordan, D. O., and Inman, R. B.: In *Biochem Biophys, 37:*162, 1960.
5. Jordan, D. O.: *The Chemistry of Nucleic Acids.* London, Butterworths, 1960.

cording to whether it deals with T − T (much more frequent) or else C − C (rarer). The dimer is actually only an inactivating change, but Freese[6] has previously explained the close correlation between formation of dimers and mutations. The study of mutations from ultraviolet radiation, which especially provoke the formation of T − T dimers, has demonstrated the existence of a correlation between the frequency of mutations and the A + T content of DNA in bacteria.[7]

Witkin's[8] experiments provide additional confirmation of the vulnerability of thymine, showing an increase in the frequency of mutations after the addition of thymine in *Escherichia coli* cultures before ultraviolet radiation and a reciprocal decline in mutation frequency in the absence of thymine.

It is quite true that the type of alteration varies with the mutagenic agent, but ultraviolet radiations and T = T dimers seem to be particularly important, both because the former are a normal component of the spectrum of solar light and because the existence of specific repair mechanisms against damage of the type represented by the T = T dimer in the genotypic memory of the majority of species leads to the supposition that this type of alteration is the customary result of spontaneous mutation.

The preceding experimental results confirm the differential stability of the DNA molecules according to the A = T/G ≡ C content through the differential stability of the nucleotide couples. The significance of this characteristic, deriving from experiments on molecular stability (that is, in terms of the E/C system, the value of the ergon as the degree of stability of a molecule), is underscored by Jordan, in the conclusions of his book *The Chemistry of Nucleic Acids,* with these words:

> The variations in stability of nucleic acids according to their composition in nitrogen bases, as has been proved by the temperature at which

6. Freese, E.: Molecular mechanism of mutations. In Hollaender, A. (ed.): *Chemical Mutagens.* New York, Plenum Pub, 1971.

7. Kaplan, H. S., and Zavarine, R.: In *Biochem Biophys Res Commun, 8:*432, 1962.

8. Witkin, E. M.: "Dark repair" of mutations induced in *Escherichia coli* by ultraviolet light. In Sobels, F. H. (ed.): *Repair from Genetic Radiation Damage.* Long Island City, Pergamon, 1963.

> denaturation is achieved, add an additional parameter to the list of differences between nucleic acids to which differences in genetic behavior can be attributed. It is well known that the differences between nucleic acids may come from diversity in molecular composition, sequence and weight. To these differences we must now add stability, even though this is not a completely independent variable in that it may be correlated and partially conditioned to all the others.[9]

STABILITY AND REDUNDANCE

In the language of molecular genetics, "redundance" indicates repetition of the same piece of information. General genetics has faced this problem *ante litteram* by means of the polymeric model: the additive polymery signify redundant repeats of what today is considered the matrix of one and the same piece of information.

The first studies on the existence and origin of genetic redundance go back to the discovery of genetic duplication. While studying the alignment of genes, Bridges noted that similar or sometimes identical functions often were found located on chromosomes in genic elements very close to each other. In order to explain the origin of this phenomenon, he hypothesized that these elements were the result of asymmetrical chromosomic rearrangements during cell divisions.[10] Experimental studies have confirmed this interpretation—or rather, have suggested its extension by introducing the concept of multiple duplications or repeats. Duplications and repeats have thus given a concrete, chromosomic base to the polymeric models, resolving the problem of almost continuous quantitative hereditary characters in a theoretical manner.

In addition, a particular form of duplication of entire chromosomes can take place by means of genomic mutations of the polyploid or polysomic type. In this case also, the result is an increased number of genes for each function with the further result of an increase both in the possible genetic variability and the stability of the function in its entirety.

Molecular genetics has confirmed and amplified this concept in

9. *Op. cit.*

10. Bridges, C. B.: In *Genetics, 1*:1, 107, 1916.

considering the phenomenon of redundance. A first confirmation occurred at the level of the entire genome. In fact, the evaluation of the number of genes present in a human genome, conducted by biological methods (rearrangement, number and length of the chromosomes), has ascertained the presence of about 60,000 genes, while the evaluation of the number of DNA sequences present in the same genome has given a count of 1,200,000 sequences. The relationship between these two figures leads to the logical conclusion that many informational sequences are repeated.

This proof, at the level of the entire genome, has been supported recently by experimental researches conducted on specific cistrons (genic functional units). Ritossa and Spiegelman[11] were able to show that, in the haploid state of *Drosophila melanogaster,* information concerning fractions 18 and 28 of ribosomal RNA is repeated 130 times; Brown and Weber[12] discovered that the same information in *Xenopus laevis* was repeated 450 times; Britten and Kohne[13] demonstrated that most of the genomes of higher organisms are composed of considerably redundant information. Analogous results were also obtained concerning the transport RNA that is repeated 13 times on the average in *Drosophila melanogaster.*

In this same direction, Wimber and Steffensen[14] studied the phenomenon of redundance by means of the hybridization of chromosomic DNA with specific RNA marked with tritium ($^3_1$H). The autoradiograph of nuclei so treated has allowed these authors not only to identify the chromosomic DNA segment involved, but also to calculate the number of repeated pieces of information utilizing the values of the specific radioactivity.

Through ioduration and bromuration of nucleic acids, an experimental method for localizing and identifying sequences repeated only 10 or 20 times is presently available. The variability of redundance, that is, of the number of repeats of the same se-

11. Ritossa, F. M., and Spiegelman, S.: In *Proc Natl Acad Sci USA, 53:*737, 1965.
12. Brown, D. D., and Weber, C. S.: In *J Mol Biol, 34:*661, 1968.
13. Britten, R. M., and Kohne, D.: In *Carnegie Inst Wash Yearbook, 65:*87, 1966.
14. Wimber, D. E., and Steffensen, D. M.: In *Science, 170:*639, 1970.

quence in the individual genome, is in agreement with the existence of a different individual stability of information, postulated by our interpretative model.

While molecular biologists were experimentally working with the problem of redundance, ascertaining the existence of repeated sequences in the DNA molecule by means of hybridization, the students of bioinformatics were confronting and probing the concept of redundance in a theoretical manner, considering the gene on the standard of an ordinary piece of information and the bases of the single nucleotide as a signal, in terms of classic informatics.

Gatlin[15] made the first experimental approach to the problem. He calculated the quantity of "recorded information" in the DNA of numerous animal and plant species. The quantity thus defined is none other than the product of Shannon's[15a] "redundance," in this case referring to the four bases A, T, G and C. Since the quantity of Gatlin's "recorded information" is the product of a constant (that is, of the quantity of maximum information of the symbols multiplied by a redundance), it is obviously a measure of redundance. Gatlin was able to subdivide "recorded information" into two fundamental components, of which the first (D_1) directly reflects the composition of nucleic acid in bases and the second (D_2) being calculated on the basis of the conditioning of one base apart from the preceding or successive base. The quantity of "recorded information" thus represents a "measurement of order" and in practice coincides with the measurement of the "quantity of organisation" of classic informatics suggested by Rothstein.[16]

Measurement of the quantity of recorded information is doubly useful in that it permits the calculation of the value of different organisms, starting from experimental data concerning DNA and subsequently verifying if these values are correlated

15. Gatlin, L. L.: The information content of DNA II. *J Theor Biol, 18:*181-194, 1968.

15a. Shannon, C. E.: A mathetical theory of communication. *Bell Syst Tech J, 27:*379-423, 1948.

16. Rothstein, J.: Information and organisation as the operational viewpoint. *The Philosophy of Science, No. 4, 29:*406-411, 1962.

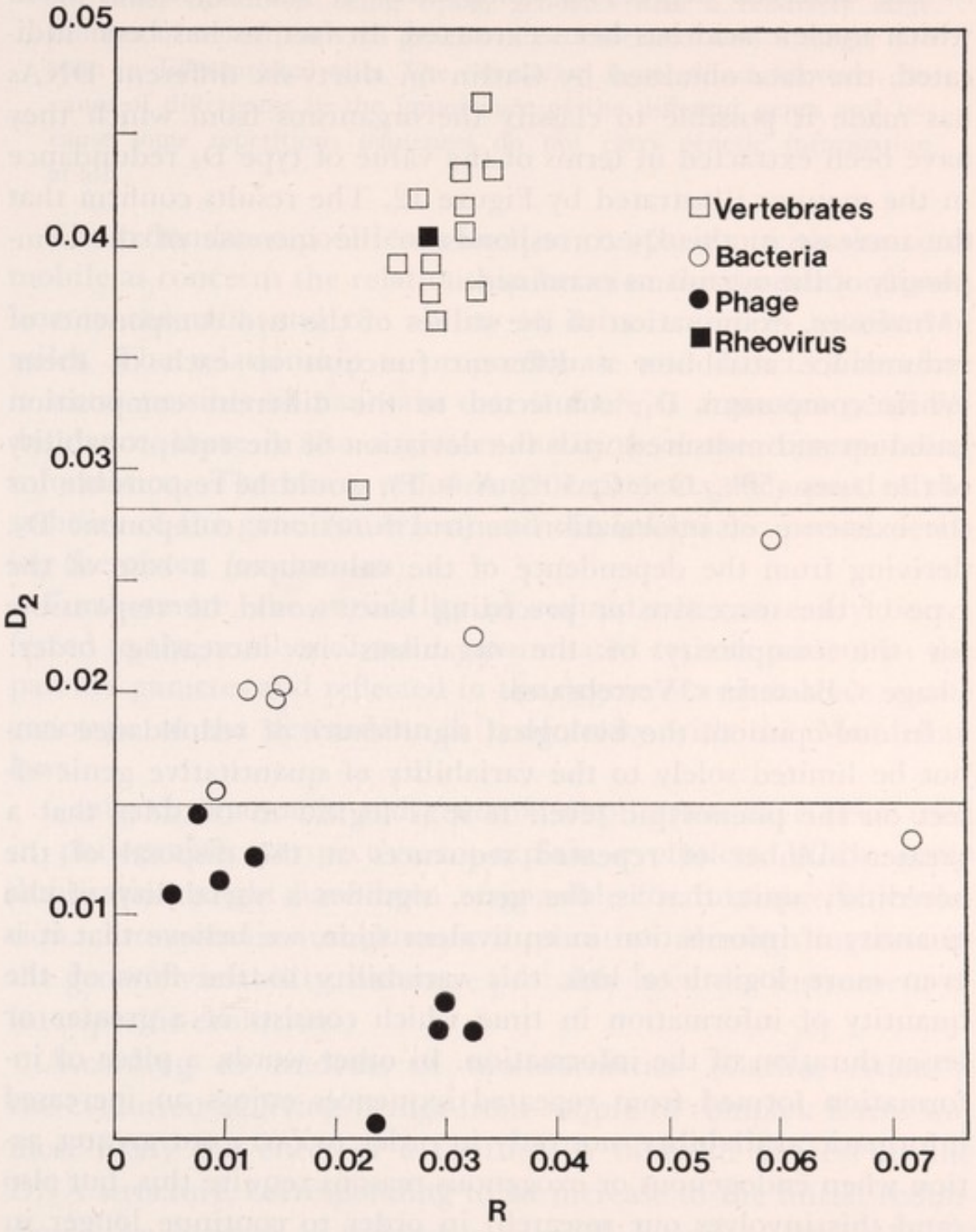

Figure 12. Diagram of D_2 values in terms of R. The separate areas correspond to the DNA of Vertebrates, Bacteria and Phage for decreasing values of D_2. (From L. L. Gatlin, The Information Content of DNA II, *Journal of Theoretical Biology, 18*:181, 1968. Courtesy of publisher.)

to the different degrees of complexity of the organisms from which nucleic acid has been extracted. In fact, as has been indicated, the data obtained by Gatlin on thirty-six different DNAs has made it possible to classify the organisms from which they have been extracted in terms of the value of type D_2 redundance in the manner illustrated by Figure 12. The results confirm that the increase in the D_2 corresponds to the increase of the complexity of the organisms examined.

Moreover, examination of the values of the two components of redundance attributes a different function to each of them. While component D_1, connected to the different composition based on and measured with the deviation of the equiprobability of the bases (50% G + C; 50% A + T), would be responsible for the existence of information control functions, component D_2, deriving from the dependence of the value upon a base of the type of the successive or preceding base, would be responsible for the complexity of the organisms in increasing order: Phage < Bacteria < Vertebrates.

In our opinion, the biological significance of redundance cannot be limited solely to the variability of quantitative genic effect on the phenotypic level. If it is logical to consider that a greater number of repeated sequences at the disposal of the hereditary unit, that is, the gene, signifies a variability of the quantity of information in equivalent time, we believe that it is even more logical to link this variability to the flow of the quantity of information in time which consists of a greater or lesser duration of the information. In other words, a piece of information formed from repeated sequences enjoys an increased informatic availability, not only in order to carry out greater action when endogenous or exogenous reasons require this, but also (and this involves our research) in order to continue longer in the time of informatic activity itself.

The significance of redundance with respect to the lifespan of information (i.e. from our viewpoint, as a chronogenetic causal factor) has also been noted by Zh. A. Medvedev with the following considerations:[16a]

16a. Medvedev, Zh. A.: Possible role of repeated nucleotide sequences in DNA in the evolution of life spans of differentiated cells. *Nature, 237*:453, 1972.

All other conditions being equal, genomes with a relatively large number of repetitious vital genes will be associated with a longer life span in differentiated cells. The correlation is not direct, however, because of differences in the importance of the different genes and because some repetitious sequences do not carry genetic information at all.

The redundance pool lends itself to comparison with the automobile as concerns the relationship between the quantity of gasoline in the tank and the ability to drive a certain number of miles. The relationship is proportionate and direct. Therefore it seems possible to maintain that if there is a greater genic redundance, there is also a greater duration of the corresponding information. Therefore, redundance represents an aspect of the stability of the gene (or ergon) and the informatic period deriving therefrom (or chronon).

Furthermore, the variability of redundance can easily be referred to the number of valid, nonmutated repeats present in the parents' gametes and reflected in the degree of redundance in the genotype of the descendent in conformity with the Mendelian laws.

Genic, chromosomic and genomic duplication have been used in philogenetic perspective to explain evolution. While genic duplication might have been responsible for intraspecific evolution, chromosomic and genomic duplication, through increase in the genetic variability, has more probably been the instrument of interspecific evolution.

According to students of bioinformatics (Gatlin, Atlan[17]), the evolution of living beings from simple to complex forms was most likely the effect of a continuous inherent process in the DNA structure, corresponding to an increase in the initial redundance. An increase in redundance would guarantee the "reliability" of a living organism against casual factors of disturbance in the environment (mutagenes) through an increase of complexity and differentiation. In other words, initial redundance would guarantee the quantity of information necessary for cor-

17. Atlan, H.: *L'organisation Biologique et la Théorie de L'information*. Paris, Herman, 1972.

rect development of individual ontogenetic processes. Consequently, selection would stabilize both the value of redundance necessary for a gene in terms of ontogenetic processes and the progressive exhaustion of redundance resulting from the action of casual factors of aggression peculiar to the environment.

From the chronogenetic viewpoint, redundance plays a role of great importance because, in addition to the physicochemical stability of the gene it serves, in its turn it lends a diverse, characteristic value to the ergon of specific individual information.

STABILITY AND REPAIR

General genetics had already recognized the need for formulating hypotheses regarding the vulnerability of the gene in terms of particular genomic characteristics. This was accomplished by studying the effect of mutagenic agents. For example, Demerec[18] and Timofeev-Resovsky[19] have shown that, mutagenic agents being equal, different strains of Drosophila vary in their rate of production of mutants. General genetics has demonstrated the existence of differential stabilities of the genome, depending on the mechanisms that are inherited by identifying, among the genetic modifiers of mutability, those which are responsible for this phenomenon.

More pointedly, molecular genetics has isolated and identified these mechanisms. This discipline defines a peculiar phenomenon of DNA molecules as "repair"; i.e. the capacity of replacing incorrect information with correct information at the moment of duplication. This mechanism obviously acts only upon certain types of errors, in particular upon incongruous signals that cannot exist in a normal DNA molecule. The well-known classical example of this is the formation of pyridiminic dimers. In a DNA molecule, ultraviolet radiation may lead to the breaking of the double hydrogen bond between adenine and thymine and to the formation of a new bond between two thymine residues when one of the latter is near the other along the same DNA

18. Demerec, M.: In *Genetics, 22:*469, 1937.
19. Timofeev-Resovsky, N. V.: In *Z Ind Abst Vererb, 66:*319, 1934.

hemimolecule. This bond between two thymine residues, which exactly determines the pyrimidinic dimer, evidently changes the significance of the entire information and prevents both the duplication of the DNA molecule as well as its transcription.

Ultraviolet radiation is a normal component of the solar spectrum and the probability of two thymine residues occurring is very great: Therefore, the necessity for a specific mechanism to prevent this type of damage from occurring in the course of philogenesis is understandable. Such a mechanism is composed of a "battery" of specific enzymes capable of reading the error, excising the incorrect DNA hemimolecule, and restoring the correct information. The first group of three enzymes is responsible for the splitting of the dimer: An endonuclease, so called because it is able to act directly on the interior of the DNA helices, "recognizes" the dimer and cuts the filament to which the dimer belongs; the tip of the DNA filament so freed bears a phosphoric grouping that is eliminated by a specific phosphomonoesterase; finally, a hexonuclease fastens the DNA filaments together at their free ends and eliminates the dimer. The repair of information is thus achieved through the participation of two enzymes: a polymerase which synthesizes the complementary DNA segment that sets itself against the breach performed by the excision, and a ligase which assures the union of this new stump to the repaired filament.

Inasmuch as each of the enzymes participating in this mechanism is genetically determined, just as the quantity of information contained therein is hereditarily determined, the result is that the greater or lesser capacity for repair is also genetically conditioned.

Even more important than the genetic conditioning of the repair mechanism is the fact that each gene has its own probability of forming pyrimidinic dimers according to its own A + T content. It is, in fact, evident that the efficiency of the repair system will vary according to the varying number of dimers that it has to eliminate. What is especially interesting, however, is the conclusion that the capacity of repair enters into the gene's stability;

that is, in the quantity of ergon of that particular gene which has, as an equivalent, a proportionate duration of its information in time.

Proof that the excision-repair mechanisms of genic damage do not act only on the unicellular level but also on the mammalian level is given by one of the hereditary skin diseases in man, xeroderma pigmentosum. Families stricken with this disease show a high incidence of skin cancer that may be easily triggered by the weak ultraviolet content of sunlight. The transmission of this disease is of a recessive nature. In 1969 Cleaver[20] studied the skin cells of ten people stricken with xeroderma pigmentosum and was able to prove that the rate of repair of errors for each repetition of DNA was reduced to 25 percent of the repair rate occurring in the cells of normal individuals. The classical example of xeroderma pigmentosum, and the more recent examples of Bloom's syndrome, Fanconi's anemia, and Louis-Bar syndrome (German,[21] Rutten et al.[22]) as well as Nordén and Pero's[23] research on the population of Dalby, besides confirming the importance of repair on the stability of information, prove how a defect in DNA repair may provoke an increase in the frequency of carcinogenesis.

The quali- and quantitative variability of the coefficients of molecular repair represents a variability factor of biological time which joins up with synonymy and redundance in producing stability of information and the time of its informatic function. Therefore, in our model, repair capacity is a factor of the ergon and becomes part of the mechanisms upon which the values of the chronon of hereditary information depend.

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20. Cleaver, J. E.: *Proc Natl Acad Sci USA, 63:*428, 1969.

21. German III, J. L.: Chromosome instability and defective repair. *Excerpta Medica, International Congress Series, No. 16:*397, 1976.

22. Rutten, F. Y., Ter Haar, B. G. A., Hustiax, T. W. J., and Scheres, J. M. J. C.: Bloom's syndrome in the Netherlands. *Ibid., No. 245.*

23. Nordén, A., and Pero, R. W.: Carcinogen induced DNA repair synthesis as a clinical parameter. *Ibid., No. 96.*

Chapter V

Duration of Information: The Chronon

DETAILS OF THE CHRONON

HAVING INDICATED in the title of this chapter that when the word "chronon" is used, it means the duration or length of information, we must mention at the outset what information we are talking about. Specifically, it deals with the hereditary message of the gene, a message which, between its formula written in code on the DNA molecule and translated in the corresponding polypeptide, is subjected to some procedures by which it subsequently becomes codified on the genic DNA, transcribed on the messenger RNA, read and translated on the transport and ribosomal RNA and expressed in the polypeptide.

There is a reason to call each of these phases "information." Their duration depends on the times of the corresponding DNA and RNA molecules, on their availability and life span, that is to say, on the information's operative times. However, it is not the duration of the RNA molecules to which we refer, but rather to the original duration that the DNA, in simple or redundant form, is able to guarantee to the organism as a time during which it is possible to transfer its writing through the short and long times of life of the RNA molecules mobilized by the translation of the genic message into a polypeptide.

The genetic imprint of mixed times or their hereditary characteristic comes about not only from their chronological typization but also from the experience of crossing, such as the one studied by Kerner[1] with regard to the blooming time of willow trees (Salix) which differs according to the variety, and which is transmitted to hybrids according to the Mendelian model of interme-

1. Kerner, M. A. von: *Pflanzenleben*. Leipzig, Verlag des Bibliographischen Instituts, Vol. 1, p. 563, 1887.

diate heredity (Table V). The information about which we are speaking is therefore codified in the DNA molecule and remains available until the death or mutation of the molecule itself. The more stable the molecule and hence the more available it is for informatic activity, the longer the RNA molecule remains available.

While the ergon is present in the gene as a degree of stability, the chronon, which mirrors the ergon in the temporal value of the information's duration, is present in the gene as an average probability of the life of the information borne by the gene and fulfilled in the phene, that is, in the somatic character controlled by the gene as a time of its duration. Hence, the chronon has two aspects: that of "potential chronon" in the genotype and that of "actual chronon" in the phenotype. Both of these are expressions of the gene or, as may also be stated, representatives of its fourth dimension. On the level of the gene the chronon represents the potential of the informatic activity during the

TABLE V

BLOOM TIME OF WILLOW TREES (Salix) IN INNSBRUCK'S BOTANICAL GARDEN*

Parental Species		*Hybrid*	*Bloom Time*		
(1)	*(2)*	*(3)*	*(1)*	*(2)*	*(3)*
Cremsensis	Caprea	Daphnoides	16 March	18 March	17 March
Mauternensis	Caprea	Purpurea	16 March	7 April	23 March
Attenuata	Caprea	Grandifolia	16 March	27 March	25 March
Wimmeri	Daphnoides	Incana	18 March	17 April	26 March
Austriaca	Grandifolia	Purpurea	27 March	7 April	3 April
Seringeana	Caprea	Incana	16 March	17 April	3 April
Capnoides	Cinerea	Incana	10 April	17 April	5 April
Intermedia	Grandifolia	Incana	27 March	17 April	6 April
Rubra	Viminalis	Purpurea	3 April	7 April	6 April
Kerneri	Viminalis	Incana	3 April	17 April	10 April
Oenipontana	Purpurea	Incana	7 April	17 April	12 April
Auritoides	Purpurea	Aurita	7 April	19 April	14 April
Fenzliana	Retusa	Glabra	21 April	21 April	21 April
Retusoides	Retusa	Jaquiniana	21 April	21 April	21 April
Alpigena	Retusa	Hastata	21 April	27 April	23 April
Excelsior	Fragilis	Alba	13 April	27 April	23 April
Ehrhartiana	Alba	Pendatra	27 April	6 May	23 April

* From M. A. von Kerner, *Pflanzenleben,* Vol. 1, 1887. Courtesy of Verlag des Bibliographischen, Leipzig, East Germany.

time of the gene; on the level of the phene, the chronon represents an actual, measureable value of the length of the informatic activity of the same gene. For the sake of convenience, we will also call this "phenotime."

The potential chronon can either coincide or not coincide with the actual chronon; in other words, the former may be longer or shorter than the latter. For example, it is longer when the environment acts upon the mechanisms that regulate the transmission of information, diminishing or cancelling the actual chronon. Reciprocally, the potential chronon may be shorter than the actual chronon when, during transcription, the phenomenon known as genic "amplification" takes place. Since amplifiers exist autonomously, it may come about even after the exhaustion of the potential chronon. However, as will be stated later on, a relationship between the potential chronon and the actual chronon does exist.

The actual chronon, or the duration of the phene, or phenotime, is the empirical datum upon which chronogenetics is based and is the objective point of departure for showing the original and hereditary nature of biological time. In fact, the actual chronon, being the effect of information possessed and distributed by the gene, permits regression to the fundamental biological time of the gene, which expresses the extraordinary ability of living matter to produce a time of its own, a time which is distinguished from physical time but which lives in this time and interacts with it, thereby producing secondary or mixed biological time.

The existence and original nature of fundamental biological time springs to mind when one considers that physical time itself, contingent on solar system time, is accounted for in different manners by the different species and, in each species, by different organisms living in the same environment. The genetic nature of biological time is likewise evident when one considers that its variability is circumscribed and repeated in the sphere of the species to which a certain living thing belongs.

A philogenesis of the chronon exists, just as does a philogenesis of quali- and quantitative hereditary characters. This philogene-

TABLE VI
AVERAGE LIFE SPAN OF PLANTS, SEEDS, AND POLLENS*

Plants	*Life Span in Years*	*Seeds*	*Life Span in Years*	*Pollens*	*Life Span in Days*
Sequoia gigantea	2000-3000	*Nelumbium nelumbo*	150	*Malus pumila*	1465
Quercus alba	300-600	*Trifolium pratense*	100	*Prunus domestica*	1278
Fagus grandifolia	300-400	*Triticum aestivum*	10	*Lycopersicon esculentem*	1095
Magnolia grandiflora	80-120	*Zea mays*	9	*Cucumis melo*	30
Salix nigra	50-125	*Lycopsersicon esculentem*	312 days	*Betula lutea*	30

* From P. L. Atlman, and D. S. Dittmer, *Biology Data Book,* 1964. Courtesy of Federation of American Sciences for Experimental Biology, Publisher, Washington, D.C.

TABLE VII

TEMPORAL VARIATIONS IN THE DEVELOPMENT STAGES OF A NUMBER OF SPECIES*

Stage	*Man*	*Macacus Rhesus*	*Sheep*	*Rabbit*	*Rat*	*Cock*
Morula of 4 cells (hours)	48	36	34	11	48	3
Beginning of implantation (days)	6.5	9	10	7	6	—
Stage of somites (days)	27	25	17	9	10.5	3
End of embryonic period (days)	36	28	21	10	12.5	5
Open eyelids (days)	140	—	84	42	38	21
Birth (days)	260	164	150	32	22	22
Life span (years)	70	30	20	—	3	—

* From P. L. Altman, and D. S. Dittmer, *Biology Data Book*, 1964. Courtesy of Federation of American Sciences for Experimental Biology, Publisher, Washington, D.C.

sis may possibly be described and outlined in future, but we can exemplify it from the experimental data[1a] presented as average values of the life of plants, seeds and fowl in taxonomically different species (Table VI).

The average life span of living organisms that differ greatly among themselves gives a convincing panorama of the chronological variability of phenotypes differentiated according to species. Observing the phenomenon of the sequence of biological times shown by every species at various levels of ontogenetic development, there is confirmation of the exact and differentiated "timing" to which all living organisms are subject with a limited variability contained within the frame of the species itself (Table VII).

In the physical time that envelops and imbues the functions and structures of every living being, the multiplicity of ways by which different organisms living in the same environment react to the same rhythms scanned by solar time and accept them is the best proof that exogenous time must filter through a very thick and specific mesh network, represented by the genetic specific mechanisms that control fundamental biological time.

1a. Altman, P., and Dittmer, D. A.: *Biology Data Book*. Washington, Federation of American Sciences for Experimental Biology, 1964.

EXPERIMENTS AND RESEARCH

A first group of experiments which shows the duration of variability of genic action was performed by us by means of an experimental determination of life span in pure and hybrid strains of Drosophila which differed from each other because of the presence of certain mutant genes. Numerous authors previously had studied the average life span of *Drosophila melanogaster,* but their experimental methods did not permit the isolation of important parameters (for example, the age and generative experience of the parents) which must also be considered as subexperimental factors capable of interacting on the mechanism determining life span. As a consequence, we paid particular attention to the standardization and equalization of (1) the genotypic environment; (2) the parental genetic environment; (3) the experimental environment; (4) the circumstances of generative experience; and (5) maternal effects.

With the methods described, an arrangement was achieved that allowed the attribution of the differences in the average life of the strains studied to the sole differences of the experimental modalities. We calculated the average life of eleven Drosophila strains as indicated in Figure 13.[2] The result, shown in the drawing as the number of days of average life span of each strain, puts into perspective (1) a considerable difference in the life span of the parental strains; (2) a length intermediate to that of the parental strains in the sample of the first-generation hybrids (F_1); and (3) an average life variability correlated with the number and type of mutants in the homozygotic strains with one, two, three mutants.

These data demonstrate the specific purview of the single mutant genes in the average life span and also show that this diminishes in proportion to the increase in number of mutant genes in the homozygotic genotype. Further, the diminution varies with the type of mutant. The effect of mutation upon the gene studied through its life span is therefore manifested by a specific diminution of the temporal dimension of the gene itself. In

2. Gedda, L., and Brenci, G.: In *Acta Genet Med Gemellol (Roma) 20:*323, 1971.

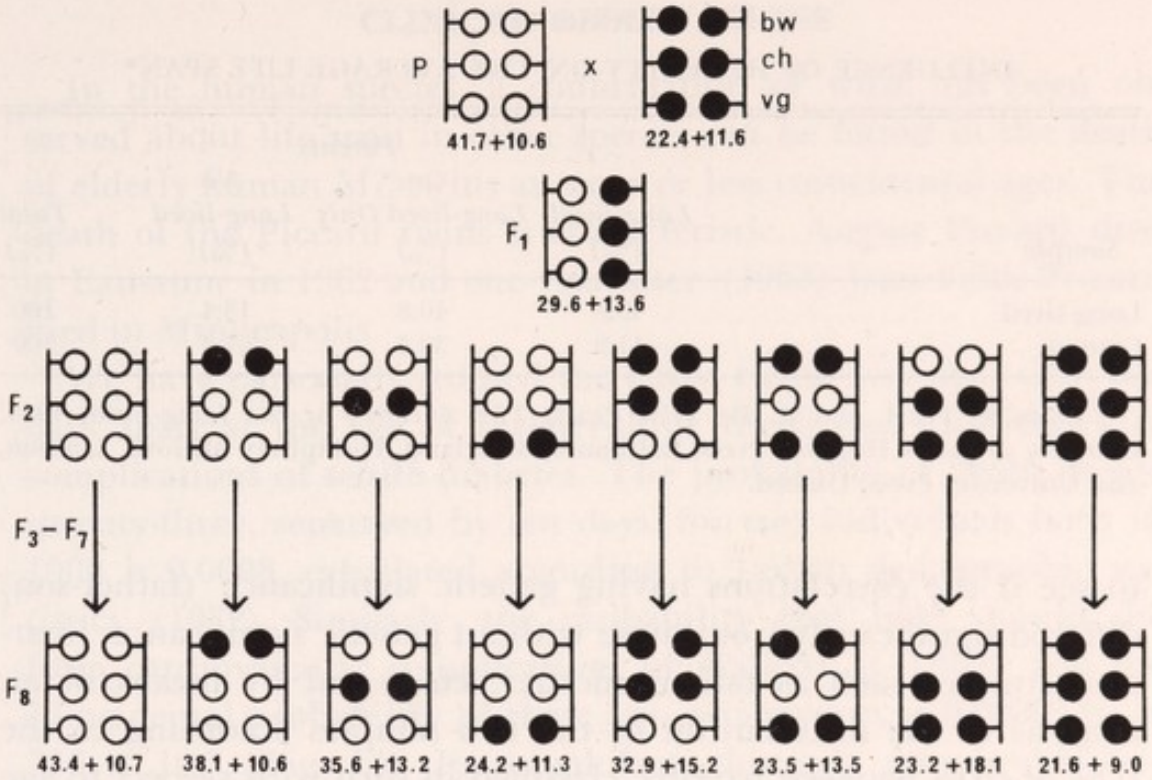

Figure 13. *Drosophila melanogaster.* Average life span in parental strains (Oregon and bw, ch, vg) and in their offspring strains (Oregon; bw, +, +; +, ch, +; +, +, vg; bw, ch, +; bw, +, vg; +, ch, vg; bw, ch, vg).

other words, the primitive gene and the mutant genes differ because of the corresponding temporal dimension.

On the human level, a confirmation of the results we obtained in Drosophila is found in the research of Pearl and De Witt Pearl[3] on the family spaces of the long-lived. These authors, comparing family spaces of two groups of persons with differing life spans, were able to prove the influence of heredity on the determination of average life span. The two experimental groups were formed, one of persons who were more than ninety (83.8%) and one hundred (16.2%) years of age and in good health, and one of members of the same family selected at random as far as longevity was concerned. For both groups the authors also considered the age of death of the parents and the four grandparents. The data were analyzed by means of correlation indices

3. Pearl, R., and De Witt Pearl, R.: *The Ancestry of the Long-lived.* Baltimore, Johns Hopkins, 1934; London, Humphrey Milford; University Press, Oxford, 1934.

TABLE VIII

INFLUENCE OF HEREDITY ON THE AVERAGE LIFE SPAN*

Sample	*Parents* *Long-lived* (%)	*One Long-lived Only* (%)	*No Long-lived* (%)	*Total* (%)
Long-lived	45.8	40.8	13.4	100
Control	11.9	30.8	57.3	100

* From R. Pearl, and R. De Witt Pearl, *The Ancestry of the Long-lived,* 1934. Courtesy of Johns Hopkins Press, Baltimore, Maryland, Humphrey Milford, London, and University Press, Oxford.

to see if the correlations having genetic significance (father-son) differed significantly from those without genetic significance (married couples such as father, mother, etc.), and by means of an analysis of the distribution of the two samples according to the type of cross between parents, classified in turn with respect to age as "long-lived" and "not long-lived" depending on whether or not they had passed ninety years of age. The results are reported in Table VIII. It is evident that about half of those over ninety came from crosses between parents both of whom were long-lived; in the control sample, on the other hand, only one-eighth came from a similar cross. On the basis of such results, Russel[4] states: "The critical problem of heredity is the problem of the cause, that is, the problem of its material or physical bases and of the maintenance, on the somatic level, of the specificity contained on the gametic level." This statement indicates that the genetic schools of biometric origin had already seen the necessity for a dynamic concept of the hereditary unit which we understand today as information which repeats itself, decays and is limited in time. This is proven by the existence of differential times of the length of genetic information on the level of Drosophila and of human gametes, that is, the existence of the average life of genes which differ among themselves but which are dependent on the stability of the genes in question.

4. Russel, E. S.: *The Interpretation of Development and Heredity—A Study in Biological Method.* Oxford, Clarendon Press, 1930.

CLINICAL OBSERVATIONS

In the human species, a confirmation of what has been observed about life span in other species can be found in the death of elderly human MZ twins at more or less coincidental ages. The death of the Piccard twins is characteristic. August Piccard died at Lausanne in 1962 and one year later (1963) Jean Felix Piccard died in Minneapolis.

We have personally studied the Crusi twins who died only ten days apart at the age of seventy-three. Both had cardiovascular complications of senile diabetes. The probability of death at age seventy-three, separated by ten days, for two individuals born in 1900 is 0.0008, calculated according to Italian demographic statistics (1972). Similarly, the probability that both should die from cardiovascular complications of diabetes is 0.0092 and the coincidental probability of these two occurrences is 0.0000736 or 736×10^{-7} (Fig. 14). In actual fact, this is a zero probability which supports the hypothesis of the concordant presence of an equivalent pathological genotype and also, because of the length

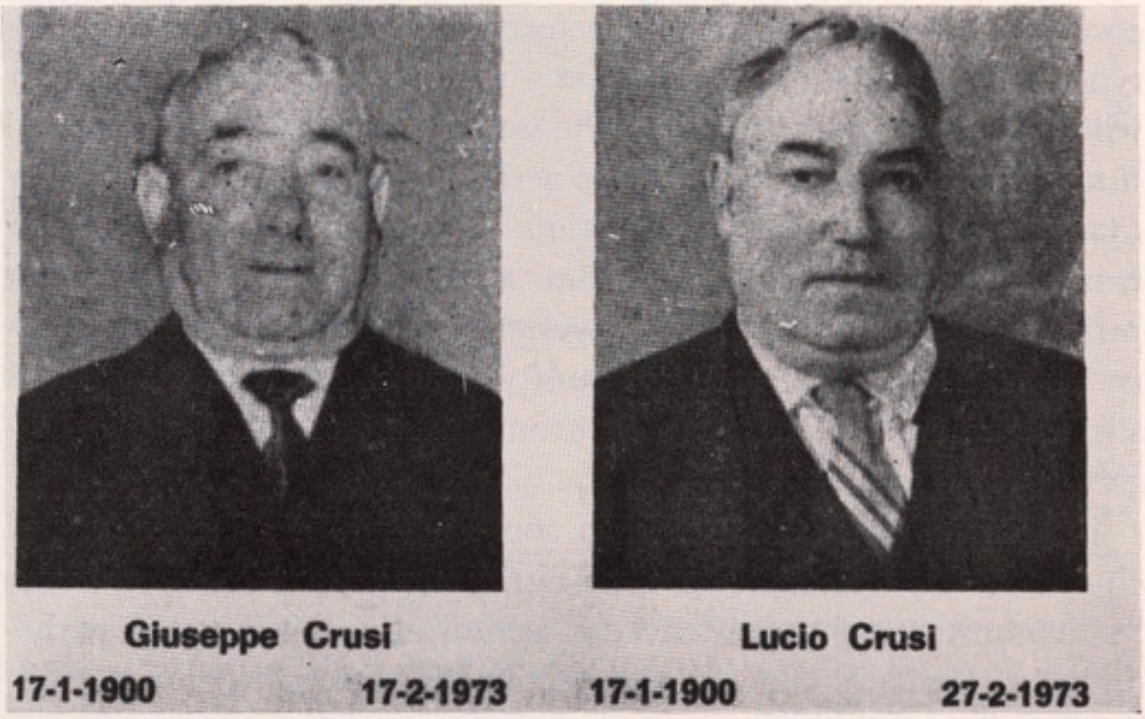

Figure 14. MZ cotwins both died at seventy-three from cardiocirculatory complications of diabetes.

of the chronon, of a *quoad vitam* information as the cause of death of two MZ twins separated by a very brief distance in time.

An even more significant synchrony is the one reported by Reuter News Service in London on 22 May, 1975:

> John and Arthur Mowforth, identical twins who shared the same interests and lived lives more or less parallel, met death on the same night, each of them after a heart attack. Mrs. Edith Taylor, their sister, said, "Since they were boys they did everything together; what happened to one usually happened to the other, too. . . ." Sixty-six-year-old twins, they were career members of the British Air Force, each attaining the rank of Air Squadron Leader. John Mowforth died in a Bristol hospital and Arthur in the hospital in Windsor west of London.

The existence of length of genetic information, that is, of a chronon of the gene, is implicit in the observations concerning family variability of human life span and the eventual contemporaneity of the death of MZ twins. It proves to be true even if the responsible genotype is not defined or is only defined in an approximate way. In terms of the temporal variability of the corresponding information, the specificity of the deficient genotype becomes obvious in the vast field of hereditary pathology where the disease arises when the genotype guaranteeing normal function suspends its informatic action because of an instability that brings it to an early exhaustion. The damage resulting either from hereditary means or from actions of the environment proves that it not only possesses genetic characteristics or an ability for coherent repeats in the family environment, but that it is also capable of differentiating from family to family with regard to the same pathology.

In Chapter VIII we refer to some examples of pathological chronons that demonstrate clear familial characteristics. In order to demonstrate the existence of genetically conditioned pathological informatic times, we now cite the observation of Burch[5]

5. Burch, P. R. J.: *An Inquiry Concerning: Growth, Disease and Ageing*. Edinburgh, Oliver & Boyd, 1968.

concerning cases of myasthenia gravis (Fig. 15). This work demonstrated the existence of genotypes which, while determining the very same hereditary disease, differed among themselves in that they produced the disease at different ages. Analyzing the distribution of the onset of the hereditary diseases by age and sex, Burch explains the variation of such distribution while admitting that alleles responsible for the same disease differ among themselves only because of the temporal modality of their actions. The interpretative model suggested by Burch is based on the accumulation of one or more mutations of one or more somatic cells in a fraction of the population composed of "genetically predisposed" indi-

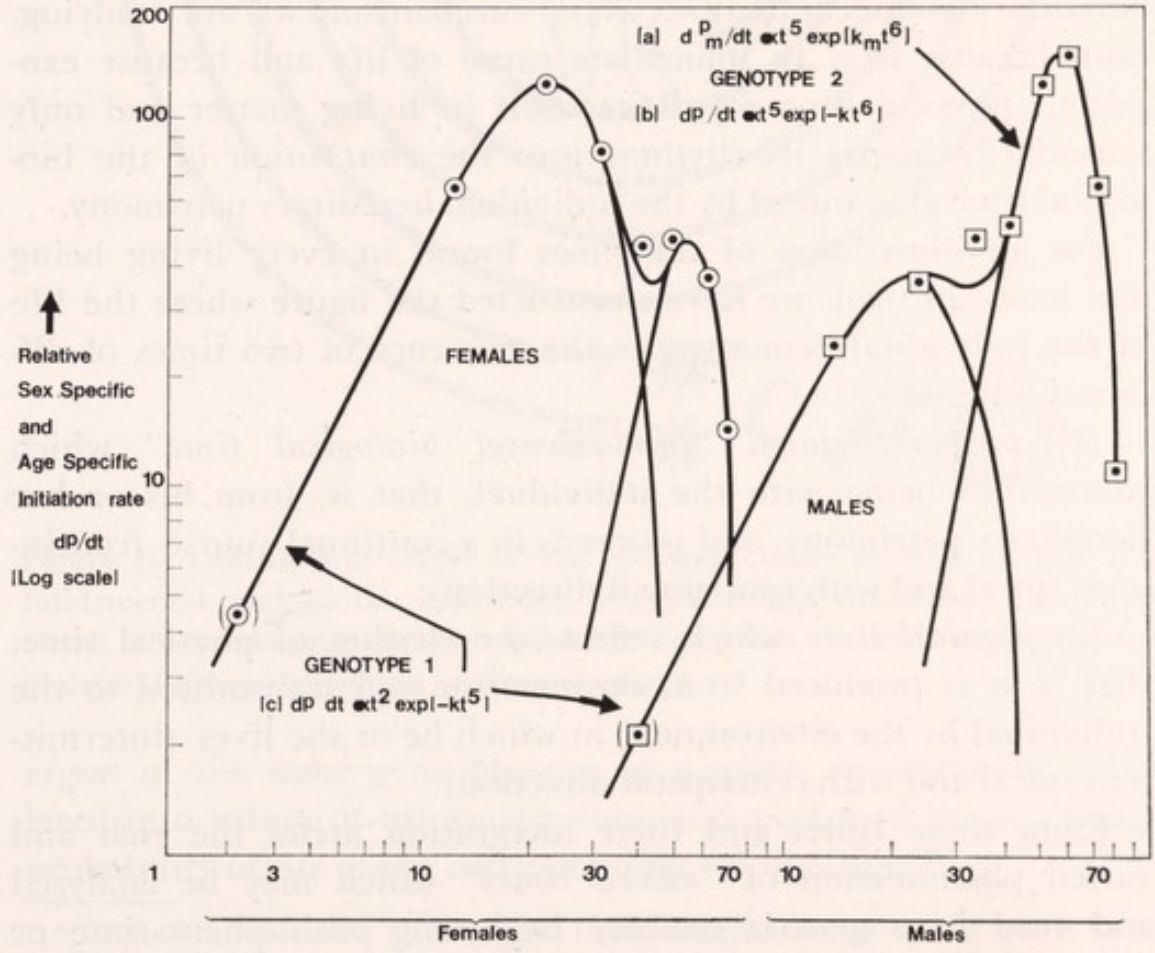

Figure 15. Age of onset of myasthenia gravis. The existence of two genotypes is shown producing the same disease at different ages, i.e. earlier in females and later in males. (Data of Howard, Silverstein and Mülder, elaborated by J. R. Burch, *An Inquiry Concerning: Growth, Disease and Ageing,* 1968. Courtesy of Oliver & Boyd, Publisher, Edinburgh.)

viduals, but it does not specify the endogenous factors determining this predisposition.

CLASSIFICATION OF BIOLOGICAL TIMES

The fundamental fact that emerges from the study of the duration of information, or *chronon,* on the interspecific and intraspecific level, as well as through experiences of crosses, is the existence of an endogenous time that does not depend on physical or exogenous time however much it exists with it, producing mixed times where the imprint of one and the other time is found.

We have given the name of "fundamental biological time" to hereditary endogenous time whose mechanisms we are studying, both because it is an immediate cause of life and because exogenous physical time manifests itself in living matter and only secondarily inserts its rhythms into the *continuum* of the biological time guaranteed by the individual hereditary patrimony.

For an illustration of the times found in every living being and hence in man, we have constructed the figure where the life of the individual demonstrates the existence of two times of different origins:

(1) *properly stated "fundamental biological time"* which comes into being with the individual, that is, from his or her hereditary patrimony, and proceeds in a continual course (continuous spiral and with centrifugal direction);

(2) *physical time* which reflects the rhythm of physical time, that is, it is produced from the exterior and transmitted to the individual by the environment in which he or she lives (intermittent spiral and with centripetal direction).

From these times and their integration arises the rich and varied phenomenon of *"mixed times"* which may be analyzed and read in a genetic manner beginning with pheno-time or chronon, that is, from the phenomenon of the appearance and duration of hereditary information, and from the latter going back to fundamental biological time with which the gene is endowed (Fig. 16).

Therefore, the chronon may be defined in a more complete form, as follows: The *chronon* of a gene is the equivalent of the

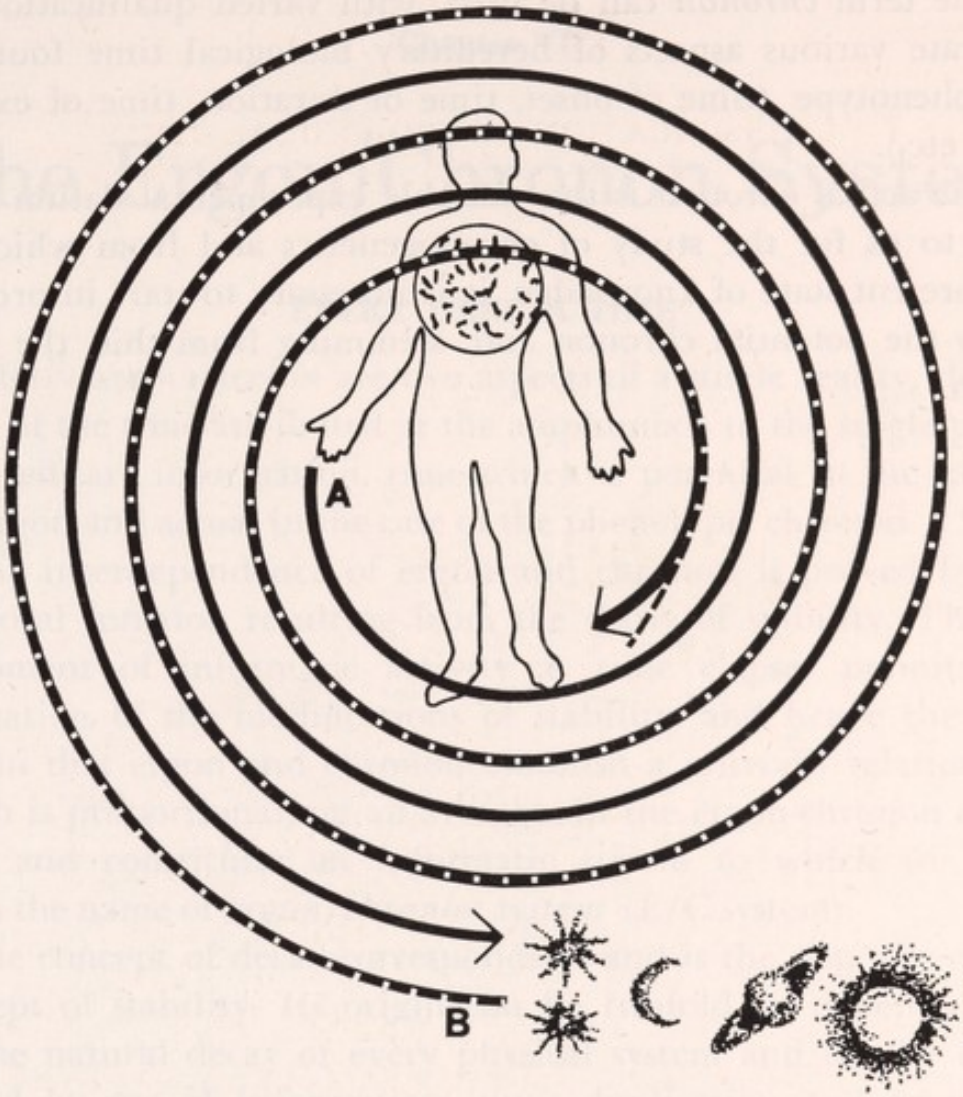

Figure 16. Outline and origin of the biological times present in man; *(A)* fundamental, endogenous, hereditary and potentially continuous times (the object of chronogenetics); *(B)* reflected, exogenous, selected and rhythmic biological times (the subject of chronobiology).

ergon of the same gene because of a given environment translated into values of informatic time and expressed as an average probability of life of the corresponding information.*

* We found it necessary to emphasize in *Lancet* (*14*:1455, 1974) and feel it necessary to repeat here that the use of the term *chronon* made by Ehret and Trucco (*J Theoret Biol, 15*:240-262, 1967) is improper, both because they apply it to a mixed phenotypic time relative to transcription of information and because they do not take into account that three years before they used this term, we had invented this term (CIOMS Copenhagen, 1964, *Acta Genet Med Gemellol (Roma), No. 1, 14*:1, 1965). We have clearly intended it to single out a purely endogenous time, that is, the period of the gene, or the potential duration of the informatic action of a hereditary unit.

The term *chronon* can be used, with varied qualifications, to indicate various aspects of hereditary biological time found in the phenotype (time of onset, time of duration, time of exhaustion, etc.).

The actual chronon is the valuable experimental datum available to us for the study of chronogenetics and from which, in the present state of knowledge, it is necessary to start in order to study the potential chronon and, stemming from this, the genic ergon.

Chapter VI

The Ergon/Chronon System

EVERY GENE A TIME

ERGON AND CHRONON are two aspects of a single reality, that is, of the time attributed at the amphimixis to the single pieces of hereditary information, time which is potential in the case of the ergon and actual in the case of the phenotypic chronon.

The interdependence of ergon and chronon is proved by the temporal function resulting from the decay of stability. The development of informatic activity as time elapses permits the evaluation of the modifications of stability, and hence the realization that ergon and chronon establish a univocal relationship which is proportional, on an average, in the ergon-chronon direction, and constitutes an informatic system to which we have given the name of *ergon/chronon system* (E/C system).

The concept of decay corresponds to and is the opposite of the concept of stability. Its origin can be twofold. It depends both on the natural decay of every physical system and on the decay caused by use of information, since duplication and transcription both decrease the stability of information. The gradient of the decay is therefore the criterion with which the E/C system is formulated and may be studied.

In the history of genetics, the quali- and quantitative variability of hereditary information precedes the notion of temporal variability which today reabsorbs the former as an epiphenomenon of the stability of information.

The study of both ergon and chronon, referred to information, give evidence of temporal variability as they put each other in perspective, showing that hereditary information has a limit in time, and that the fourth dimension is characteristic of every specific information and, therefore, differs from one piece of information to another in the same organism and from organism

to organism in the same species. Paraphrasing Beadle's[1] aphorism regarding the enzymes considered as a primary effect of the gene, one can say: "for every gene, a time," and this can be stated with even greater emphasis because time is not an effect but a property of the gene.

The nonreproducibility of a living being that has been affirmed thus far on the basis of the possible qualitative combinations of characters is, therefore, at a minimum redoubled because temporal variability is added to quali- and quantitative variability.

On the basis of observations of correspondence and reciprocity, ergon and chronon are integrated in composing a new system to recognize the hereditary unit in which information can be represented solely in terms of stability energy (amphimictic ergon), or solely in terms of time (chronon of information) by means of surveying its life span in case of a total exhaustion, or else in mixed terms of the two parameters (stability and time) if the information is still functioning.

The chronogenetic formulation renders dynamic both the frame of information considered and the aggregate hereditary patrimony. The latter can no longer be considered to have been sufficiently described, simply in terms of the static framework of qualitative information, but requires an evaluation of the energy stability of individual pieces of information.

POPULATION PERSPECTIVE

Chronogenetic variability can be investigated and studied in a population of cells or individuals which function normally or are pathological.

Gedda and Brenci[2] carried out intense longitudinal research to ascertain the quantitative movement of a gene's primary product on *Drosophila melanogaster* pupae of pure and hybrid strains. This work was concerned with alkaline phosphatase, an enzyme which is a normal component of the insect's hemolymph and is

1. Beadle, G. W., and Tatum, E. L.: Genetic control of biochemical reactions in Neurospora. *Proc Nat Acad Sci, Vol. 27*:429-506, 1941.

2. Gedda, L., and Brenci, G.: Chronology of the gene. *Acta Genet Med Gemellol, 20*:323-340, 1971.

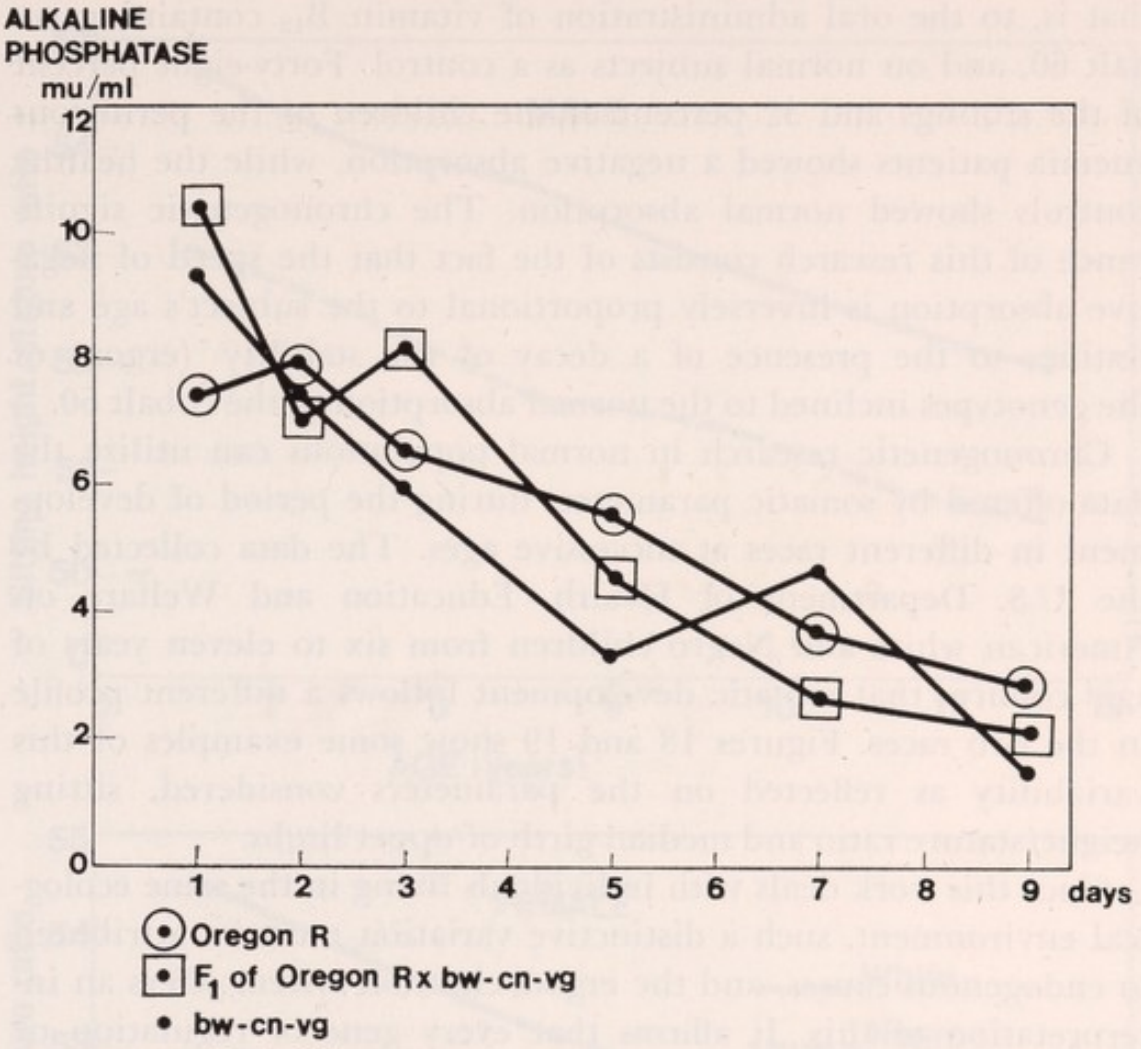

Figure 17. Decreasing activity of alkaline phosphatase in Drosophila larvae and pupae of pure and hybrid strains.

controlled by three alleles located in the third chromosome. The results of these experiments (Fig. 17) show that the volume of material decreases linearly as life proceeds and represents the chronon of information. The quantity of alkaline phosphatase produced is an index of the informatic energy available at every temporal level, that is, of the progressive decay of stability in accordance with the theory of the E/C system.

Ante litteram chronogenetic research was conducted by McIntyre and coworkers[3] on the relatives of thirty-four patients with pernicious anemia who were subjected to the Schilling test,

3. McIntyre, P. A., Hahn, R., Conley, C. L., and Glass, B.: Genetic factors in predisposition to pernicious anemia. *Bulletin Johns Hopkins Hospital, 104*:6, 1959.

that is, to the oral administration of vitamin B_{12} containing cobalt 60, and on normal subjects as a control. Forty-eight percent of the siblings and 32 percent of the children of the pernicious anemia patients showed a negative absorption, while the healthy controls showed normal absorption. The chronogenetic significance of this research consists of the fact that the speed of negative absorption is inversely proportional to the subject's age and testifies to the presence of a decay of the stability (ergon) of the genotypes inclined to the normal absorption of the cobalt 60.

Chronogenetic research in normal populations can utilize the data offered by somatic parameters during the period of development in different races at successive ages. The data collected by the U.S. Department of Health, Education and Welfare on American white and Negro children from six to eleven years of age[4] confirm that somatic development follows a different profile in the two races. Figures 18 and 19 show some examples of this variability as reflected on the parameters considered, sitting height/stature ratio and median girth of upper limbs.

Since this work deals with individuals living in the same ecological environment, such a distinctive variation must be attributed to endogenous causes, and the ergon/chronon system offers an interpretation of this. It affirms that every gene of regulation or structure involved in growth presents an ergon, that is, a characteristic informatic potential that liberates and conditions the sequence of the information according to the hereditary times of the race under study. As will be mentioned subsequently, we ourselves have verified the hereditary character of the times of ontogenesis, establishing that the auxological curves of mulattoes take an intermediate course between the curves of white subjects and those of the Negro race. In this case also, the cross furnishes verification of the chronogenetic nature of auxological development, that is, of the existence of hereditary biological time.

In order to show proof of the E/C system, the gathering of data on heterogeneous biological times in people living in the

4. Body Dimensions and Proportions, White and Negro Children 6-11 Years, United States. *Data from the National Health Survey*, U.S. Department of Health, Education and Welfare, Series 11, No. 143, Bethesda, 1974.

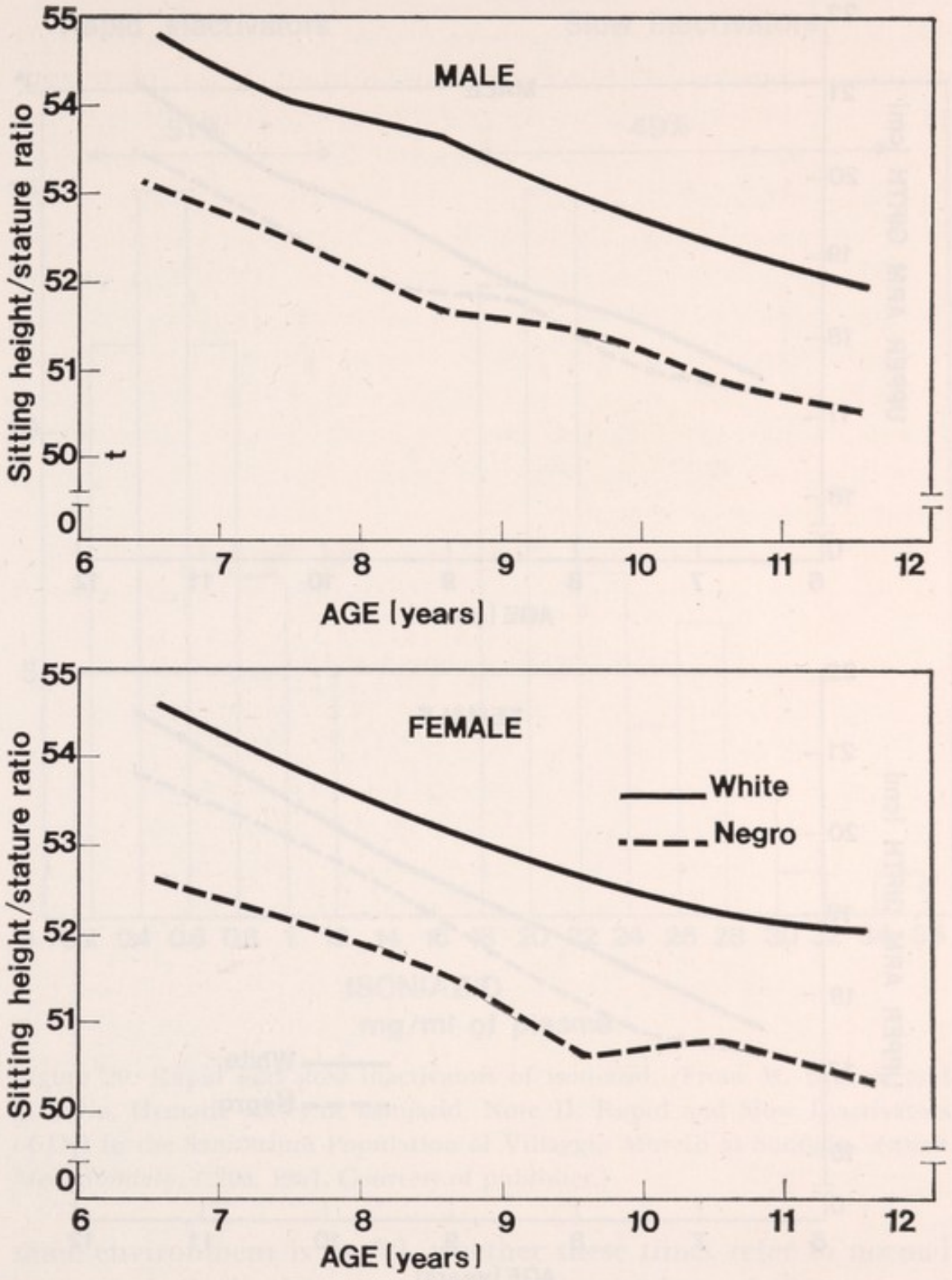

Figure 18. Mean sitting height/stature ratio of White and Negro children by sex and age.

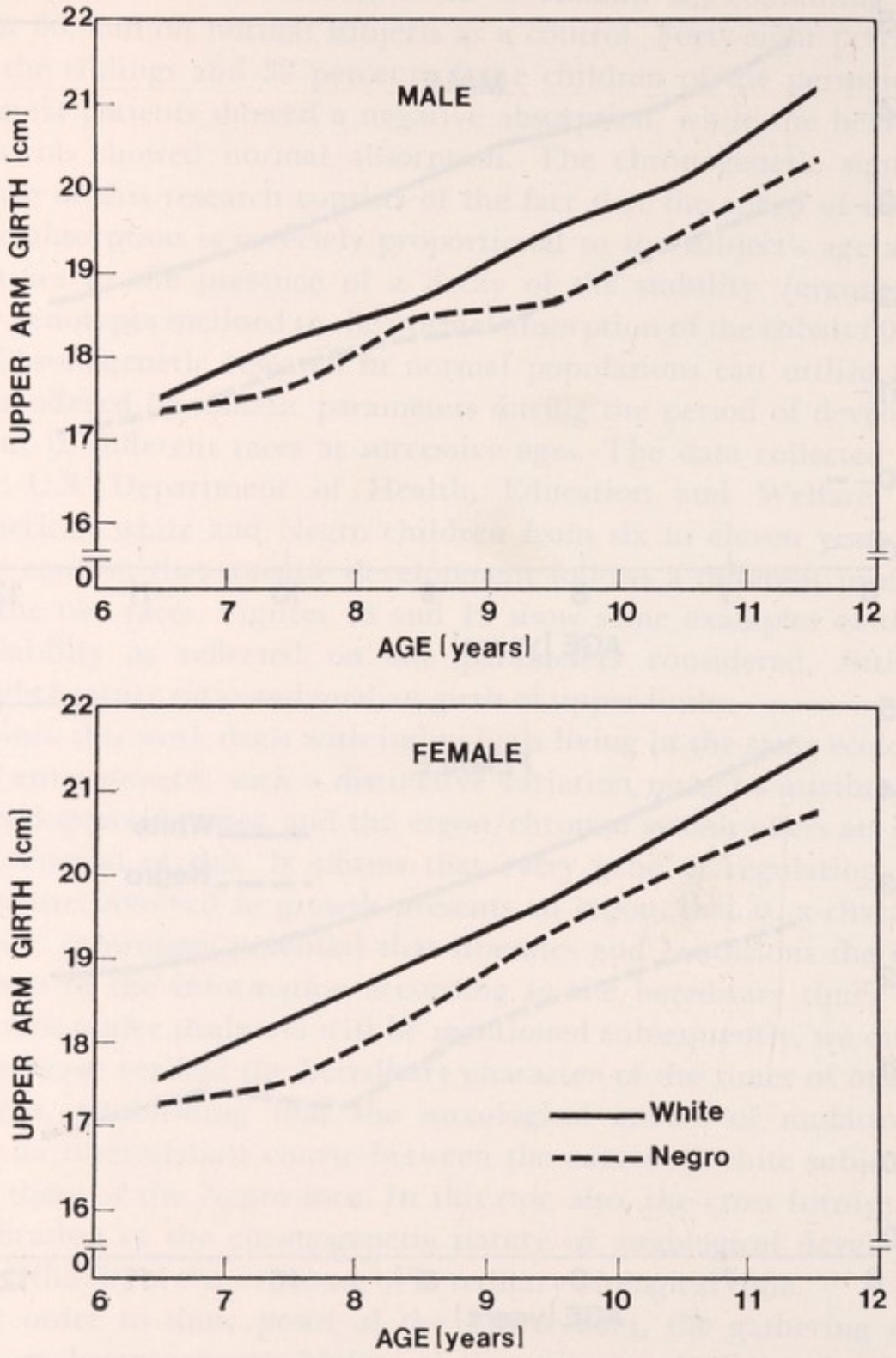

Figure 19. Median upper arm girth of White and Negro children by sex and age.

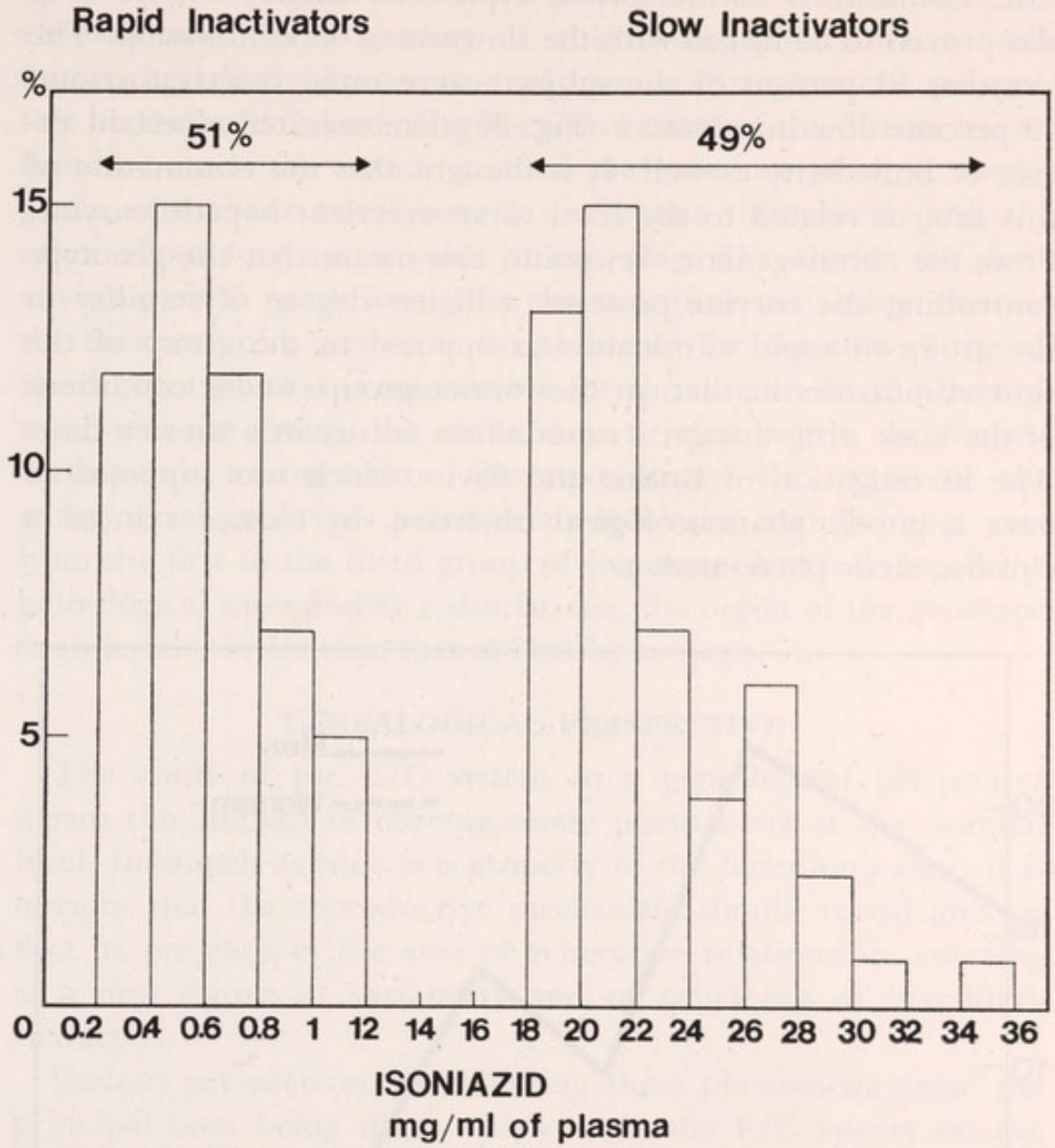

Figure 20. Rapid and slow inactivators of isoniazid. (From M. Bracco, and E. Savio, Hematic Rates of Isoniazid. Note II. Rapid and Slow Inactivators of INI in the Sanitarium Population of Villaggio Morelli at Sondalo, *Annali Med. Sondalo, 4*:206, 1961. Courtesy of publisher.)

same environment is useful, whether these times refer to normal or pathological phenomena. The observation of Bracco and Savio[5] in regard to the inactivation of an antitubercular medi-

5. Bracco, M., and Savio, E.: Hematic rates of isoniazid. Note II. Rapid and slow inactivators of INI in the sanitarium population of Villaggio Morelli at Sondalo. *Annali Med Sondalo, 4*:206, 1961.

cine, isoniazid, is of the former type. The efficacy of this drug was proven to be linked with the slowness of its elimination. The fact that 51 percent of the subjects were rapid inactivators and 49 percent slow inactivators (Fig. 20) demonstrated a certain degree of bimodality as well. It is thought that the elimination of this drug is related to the level of an acetylant hepatic enzyme. From the chronogenetic viewpoint, this means that the genotype controlling the enzyme possesses a higher degree of stability in the group of rapid eliminators as opposed to the group of the slow eliminators in that, in the former group, under conditions of the same drug dosage, its catabolism occurs in a shorter time. The investigation of Bracco and Savio, which was supposed to have a purely pharmacological objective, by chance evinced a chronogenetic phenomenon.

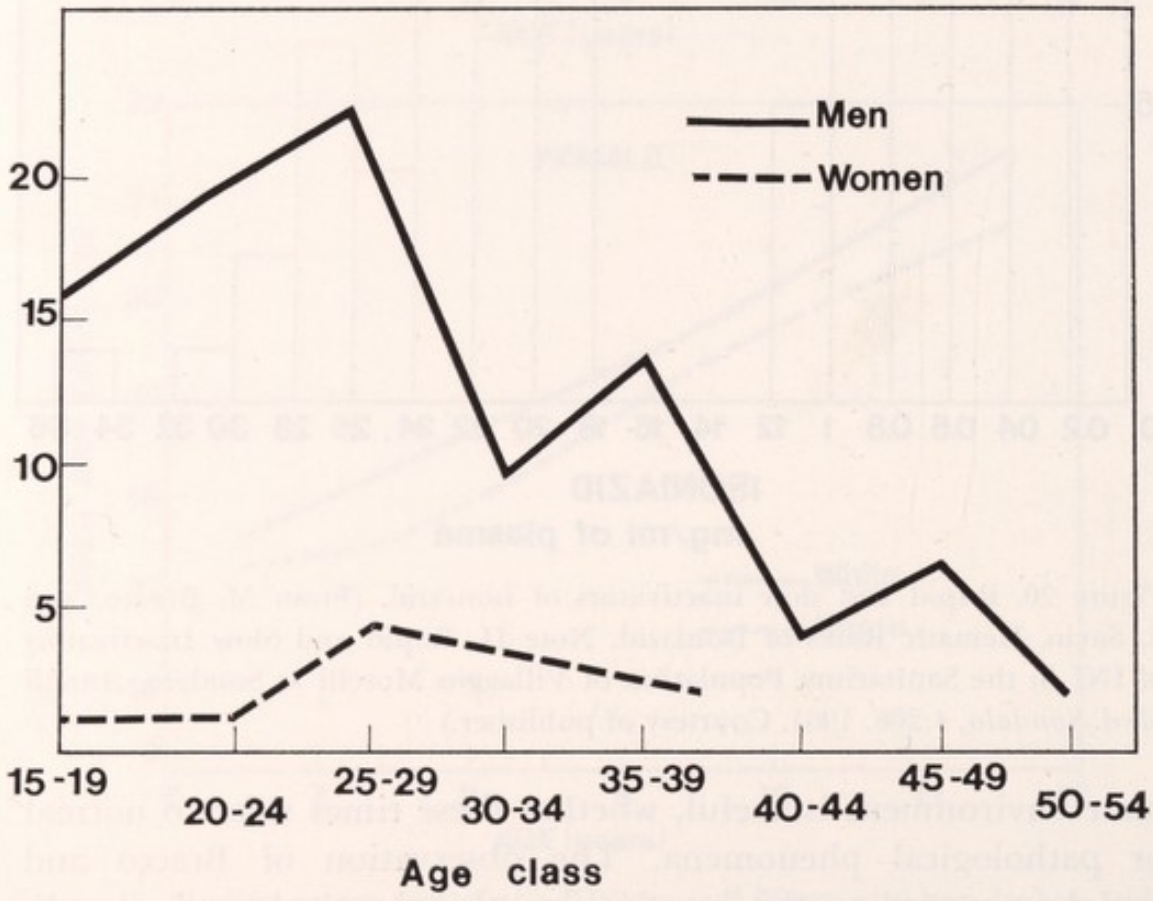

Figure 21. Distribution of the age of onset of ankylosing spondylitis in one hundred cases of both sexes. (From L. Ondrasik and S. Sitaj: Biological time in Ankylosing Spondylitis. *Acta Med Auxol, 8:*121-124, 1977.)

In the pathological sector, this proof can be exemplified by the chronogenetic heterogeneity of ankylosing spondylitis, a well-known hereditary disease studied from a chronogenetic perspective by Ondrasik.[6] Analyzing the age of onset of the disease in one hundred cases, the author verified the existence of three modal peaks, one about twenty-seven, one about thirty-seven and the other about forty-seven years of age (Fig. 21). Under the same environmental conditions, this chronological variability denotes the existence of a genotypic variability of the chronon of the altered genotype that is responsible for the disease. In the twenty-seven-year-old group, the chronon is briefest, while the longest corresponds to normality. Correspondingly, the ergon of the pathological genotypes possesses an increasing stability that goes from the first to the third group of the cases observed. In all the pathological cases and at a similar age, the ergon of the genotype considered is lower than that of healthy subjects.

GENEALOGICAL PERSPECTIVE

The study of the E/C system in a genealogical perspective means the analysis of chronogenetic phenomena at the familial level. Inasmuch as time is a property of the hereditary unit, it is obvious that the reproductive mechanism should reveal and reflect its presence in the area of generative relationship, entering as a new source of variability and of coherence of hereditary characters.

Various perspectives for analyzing these phenomena exist, the principal ones being those which study the E/C system on the diploid (organismic) level and on the haploid (gametic) level. For this reason we will treat them separately.

Diploid Situation

The study of the E/C system on the diploid level can involve all the cases of hereditary disease when one or more temporal parameters are kept in mind. When dealing with sufficiently numerous family data, the patterns resulting therefrom can be sub-

6. Ondrasik, M., and Sitaj, S.: Biological time in ankylosing spondylitis. *Acta Med Auxol, 8:*121-124, 1977.

TABLE IX

AGE OF ONSET OF PSORIASIS: CORRELATION IN RELATIVES

*Values of Covariance**	*Theoretical*	*Experimental*	*Expectations†*
Brother-brother	½ V_A + ¼ V_D	.69	.70
Parents-children‡	½ V_A	.70	.70
Uncles-nephews	¼ V_A	.35	.35

* In the hypothesis of a diallelic monomeric character.

† Taking as fundamental relationship the parents-children value in the hypothesis of absence of dominance.

‡ Relative to only the parent-daughter relationship.

jected to statistical analysis to verify their conformity with the formal models of Mendelian heredity.

This method was applied in connection with the onset age of psoriasis by Cavalieri et al. of the Mendel Institue.[7] They studied the family trees of two hundred probands for a total of three hundred and twelve blood relatives. From this family sampling, the following blood-related pairs were singled out: eighty-three parent-child pairs; ninety-four brother-brother pairs; and forty-eight uncle-nephew pairs. Table IX indicates the values of the experimental covariations and those expected on the basis of the hypothesis of a diallelic monomeric character in the absence of dominance. The results clearly prove that the "age of onset" of psoriasis represents a quantitative mendelian character.

Thomas, Calne and Stewart[8] arrived at an analogous result in connection with Roussy-Lévy disease, a motor and sensory polyneuropathy called musculoperoneal atrophy. The authors' material concerns seventeen families and sixty-four probands studied from the point of view of the age of onset of the disease. By means of calculating the correlation index *(r)* between pairs of blood relations, the following results were obtained:

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7. Cavalieri, R., Orsi, G., Zecca, S., and Romano, M.: *A Chronogenetic Approach to Psoriasis.* First International Congress of Twin Studies. Rome, October 28-November 2, 1974.

8. Thomas, P. K., Calne, D. B., and Stewart, G.: Hereditary motor and sensory polyneuropathy (peroneal muscular atrophy) . *Ann Hum Genet, 38:2,* 1974.

	r
Brother-brother	0.460
Parent-child	0.527
First cousins	0.363

These figures prove the clear connection of Mendelian relationships and hence the hereditary nature of the "age of onset" of Roussy-Lévy disease.

Kondo[9] has recently shown that the population distribution of the age of onset of Parkinson's disease, a multifactorial hereditary disease, can be mathematically interpreted only assuming each allele to possess a lifespan of its own.

Analysis of individual genealogical trees often provides the ability to survey family trees where the presence of dynamic chronogenetics is evident and whose interpretation is permitted by the E/C model. For example, in the tree worked out by Cardinali and Pace[10] of the Mendel Institute (Fig. 22) concerning a family whose members were stricken five times by intestinal polyposis, the onset of the disease is exclusively in subjects below thirty years of age. Contrariwise, in Anderson's tree[11] (Fig. 23) concerning a family distribution of adenocarcinoma of the colon and uterus, the age of onset is always beyond thirty years, so that the fourth generation was totally free of it when the tree was designed. The familial nature of the diseases described and the considerable variation in the age of onset as reported in the literature give a specific genetic significance to the evidence of the circumscribed chronological family variability in that the hereditary component turns out to be not only a causal factor of

9. Kondo, K.: Patterns of familial clustering and age onset in multifactorial adult disease, computer simulation and survey of Parkinson's disease. *Excerpta Medica, International Congress Series, No. 488:*397, 1976.

10. Cardinali, G. G., and Pace, D. P.: In Gedda, L., and Brenci, G.: Chronogenetics, its foundations, scope and impact. *Acta Genet Med Gemellol (Roma) 22:*3-17, 1973.

11. Anderson, D. E.: Genetic varieties of neoplasia. In *Genetic Concepts and Neoplasia.* A collection of papers presented at the Twenty-third Annual Symposium on Fundamental Cancer Research, The University of Texas, M. D. Anderson Hospital and Tumor Institute of Houston, 1969. Baltimore, Williams & Wilkins, 1970, pp. 85-109.

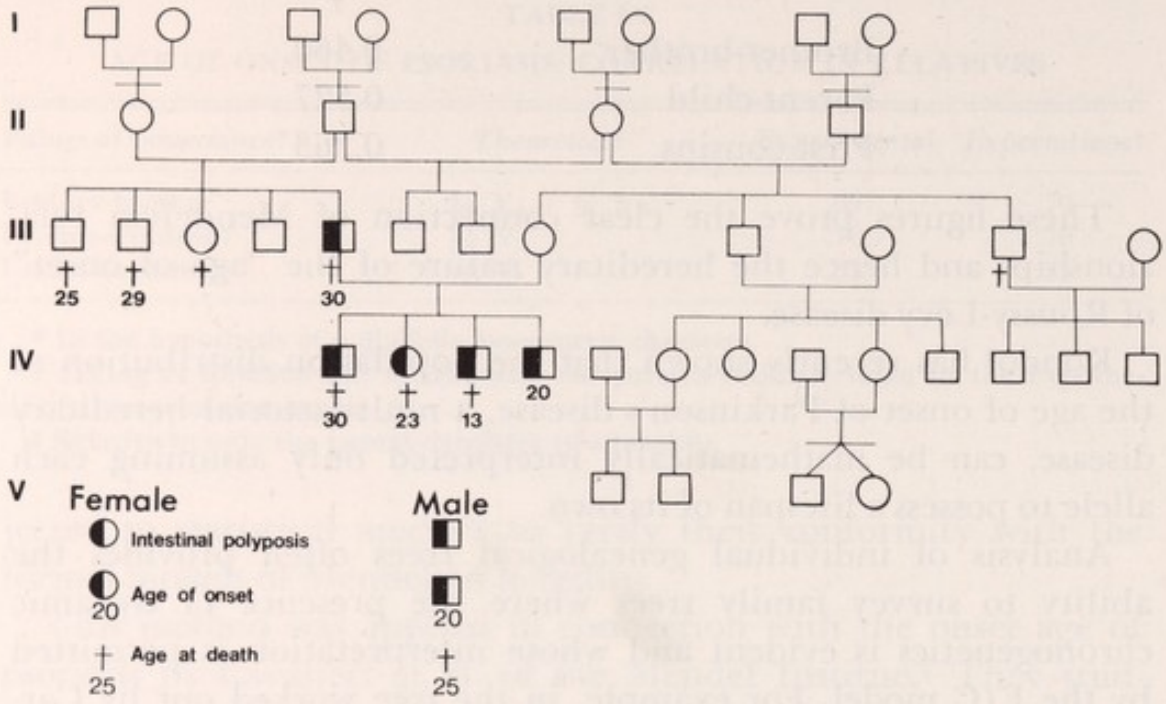


Figure 22. Concordant age of onset in intestinal polyposis.

such diseases, but also of the age of their onset. The responsible genotype proves to have an ergon and a chronon relatively and proportionately more reduced, in the case of the family with polyposis, and less so, on the other hand, in the case of the family with adenocarcinoma.

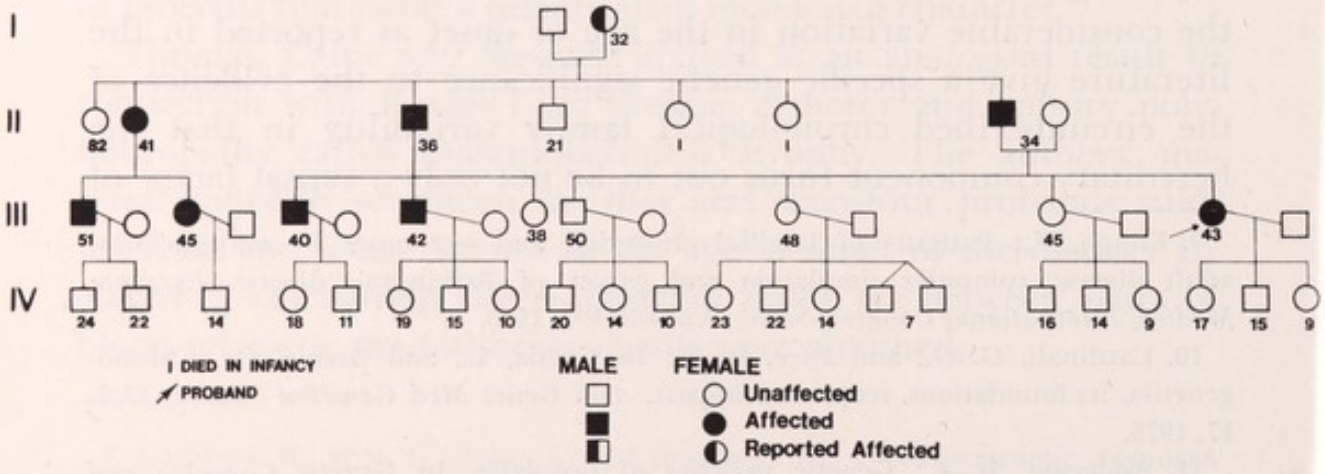


Figure 23. Concordant age of onset in uterus and colon adenocarcinoma. (From D. E. Anderson, Genetic Varieties of Neoplasia, in *Genetic Concepts and Neoplasia,* 1970. Courtesy of Williams & Wilkins Company, Publisher, Baltimore, Maryland.)

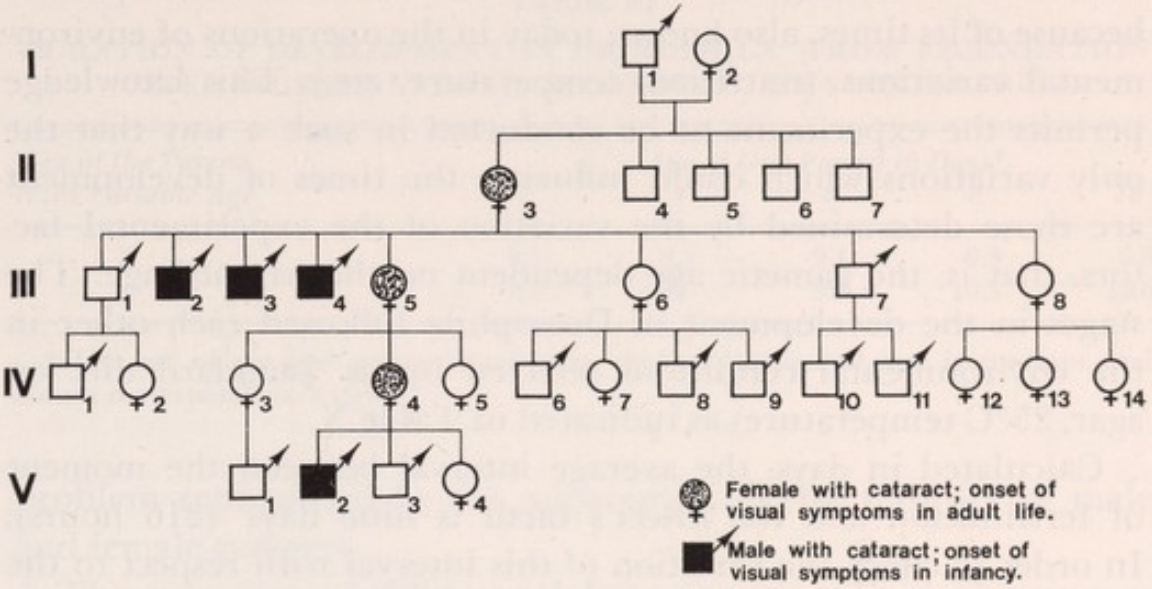


Figure 24. Differential onset of cataract in the two sexes. (From G. A. Fraser, and A. I. Friedmann, *The Causes of Blindness in Childhood,* 1967. Courtesy of Johns Hopkins Press, Publisher, Baltimore, Maryland.)

Typical is the case of a tree constructed by Fraser and Friedmann[12] concerning juvenile cataract (Fig. 24) in which the stricken subjects present an age of onset which differs according to the sex of the patient. In the males, the cataract manifests itself in infancy, while in the females, it appears at an adult age. This leads one to think that damage to a genotype located in the X gonosome, being double in the female genome, allows for a greater availability of specific informatic energy in female patients.

Haploid Situation

The possibility of a decay of information according to the E/C model was approached by us experimentally through the study of the development times of *Drosophila melanogaster.*

This type of study was possible because the genetic research on Drosophila, carried out in the course of seventy years, has provided an extensive knowledge of the biological nature of this in-

12. Fraser, G. A., and Friedmann, A. I.: *The Causes of Blindness in Childhood, A Study of 776 Children with Severe Visual Handicaps.* Baltimore, Johns Hopkins Press, 1967, pp. 57-69.

sect. The embryology of Drosophila also enters into the picture because of its times, also known today in the operations of environmental variations (nutrition, temperature, etc.). This knowledge permits the experiment to be conducted in such a way that the only variations which could influence the times of development are those determined by the variation of the experimental factors, that is, the gametic age dependent on the parents' age. The stages in the development of Drosophila followed each other in the environmental conditions selected by us (standard diet on agar, 25°C temperature) as indicated in Table X.

Calculated in days, the average interval between the moment of fertilization and the insect's birth is nine days (216 hours). In order to check the variation of this interval with respect to the parents' age, we made crosses in which the age of one parent was held constant, that is, six days (age of greatest fertility for both male and female subjects), whereas the age of the other parent varied at two, four, six, eight and ten days. The ten-day limit was chosen because in practice it corresponds to the limit of female fertility. The results we obtained are shown in Table XI. We can state that the length of the development period depends on the age of the parents and therefore on gametic age. Furthermore, these results demonstrate a greater influence of the mother's age in comparison with the father's.

The difference of the influence of parental versus maternal age on the vitality of the conceptus requires the solution of the

TABLE X

DEVELOPMENTAL STAGE IN DROSOPHILA*

Age in Hours	*Stage*
0	Fertilization
22	Eclusion from egg
47	First molt
70	Second molt
118	Puparium formation
214	Pupa ready to emerge

* From M. Demerec: *Biology of Drosophila,* 1965. Courtesy of Hafner Publishing Co., New York and London.

TABLE XI

DURATION OF DEVELOPMENT IN DROSOPHILA (FROM FECUNDATION TO EMERGENCE IN DAYS) ACCORDING TO PARENTAL AGE

Sex of the Parent With Variable Age	*Age of One Parent in Days**				
	2	*4*	*6*	*8*	*10*
♂	8.5	8.7	9.1	9.3	9.9
♀	9.2	9.5	9.3	10.3	10.6

* The age of the first parent is variable, that of the second one is constant and always corresponds to 6 days.

problem represented by the apparently diverse stability of male and female gametes.

The existence of differential behavior in individual aging as concerns gametic efficacy, according to whether one considers aging in the father or the mother, has been proved in man by Penrose[13] through analyses of the initial correlations made by the method of partial correlation coefficients. The values of coefficient r obtained by Penrose in the study of the correlation between mongolism and age of the parents were the following: age of the mother and mongolism, 0.36; age of the mother and age of the father, 0.83; and mongolism and age of the father, 0.29. Utilizing the correlation between age of the parents in order to study the correlation between mongolism and age of the father while hypothesizing a constant age of the mother, Penrose obtained a value of the correlation index equal to 0.01 ± 0.04, a value so close to 0 as to be able to consider the correlation as nil.

The difference in behavior of gametes with respect to aging does not depend on preferential action of the factors of aging on one gametic line rather than another, but on the different modalities of the gametes' being made ready in the two sexes.

In female gametogenesis in the human species, the number of gametes is determined from the sixth month of intrauterine life. From that moment gametic readiness remains blocked at the diakinesis stage of meiotic division for all the egg cells. As a direct consequence of this, in cycle after cycle maturing from

13. Penrose, L. S.: In *Ann Eugen, 14*:125, 1948.

menarche onward, the eggs remain in a critical stage of instability (the stage of meiotic division) for a longer time the more advanced in age the moment of maturation. The only selection possible is the one determined by the fact that, of the four cells produced by meiotic division, only one assumes the value of gamete.

With reference to the male line, on the other hand, the state of readiness is continuous, and the stage of meiotic division is attained in a relatively brief time interval. Furthermore, in the human species, about 10 million spermatozoa are prepared for each fertilization. Aging acts upon this multitude like a selective factor, permitting fertilization only to the most efficient gametes. In our opinion, this may explain the fact that the negative influence of maternal age, that is, the decay of the female gamete, is greater than that of the male gamete.

These researches and considerations have led us to the opinion that our model allows for the interpretation, in a special way, of the stability of the ergon and the duration of the chronon in the gametes of both sexes, and, consequently, in the zygote that is generated at different parental ages. In this connection, we think that, among the progenetic factors understood in a very broad way by Turpin,[14] the age of gametes should be emphasized, not as representing an additional factor, but rather as an authentic genetic factor which reflects the gene's fourth dimension and constitutes a specific and important competence of chronogenetics.

In the light of the E/C system, the effect of chance is explained on the order of birth with regard to a given disease and on the death of a given conception's product. This chance is, in our opinion, a corollary to the decay of gametic information occurring in conjunction with the advancing age of the parents.

The existence of a decline in the time of informatic efficiency of gametes is derived from what the progenetic studies on hereditary material, transmitted from one generation to another, indicate regarding the exhaustion of the gamete's information

14. Turpin, R.: *La Progénèse*. Paris, Masson et Cie., 1955.

TABLE XII

CORRELATION BETWEEN MATERNAL AGE AND INCREASE OF ANOMALIES IN THE CONCEPTUS

Conceptus	*Maternal Age in Years* 26-30	31-35	36-40	Over 40
Stillborn*	230	270	350	550
Malformed*	17	19	22	33
Mongoloid†	110	130	170	315

* In 10,000 births over three years. (Data from the Italian Institute of Statistics.)
† In 10,000 births over one year. (Data from J. Oester, *Mongolism,* 1953. Danish SC. Press, Publisher, Copenhagen.)

and its correlation with parental age. In particular, the negative correlation between the mother's age and gametic information is known. The statistics drawn from the increase of anomalies in conceptions with increasing maternal age represent, in our opinion, the best proof of the exhaustion of genic actions in time. For an immediate evaluation of this phenomenon, Table XII shows, classified by age of the mother, data of the Central Institute of Statistics referring to stillbirths and malformations among all births in Italy in the course of three years, and data concerning the number of mongoloid births reported by Oester[15] in one year among 10,000 births. The same data have been reproshown by J. Stene et al.[16]

With respect to Down's syndrome, besides the influence of maternal age, a relative influence of paternal age has been recently shown by J. Steene et al.[16]

The study of individual genealogical trees enhanced with chronological data can also provide interesting indications. A family with Fabry's disease (cornea verticillata and angiokeratoma corporis diffusum) is represented in the genealogical tree

15. Oester, J.: *Mongolism.* Copenhagen, Danish SC. Press, 1953.

16. Stene, J., Fischer, G., Stene, E., Mikklesen, M., and Pertersen, E.: Paternal age effect in Down's syndrome. *Excerpta Medica, International Congress Series, No. 409:*397, 1976.

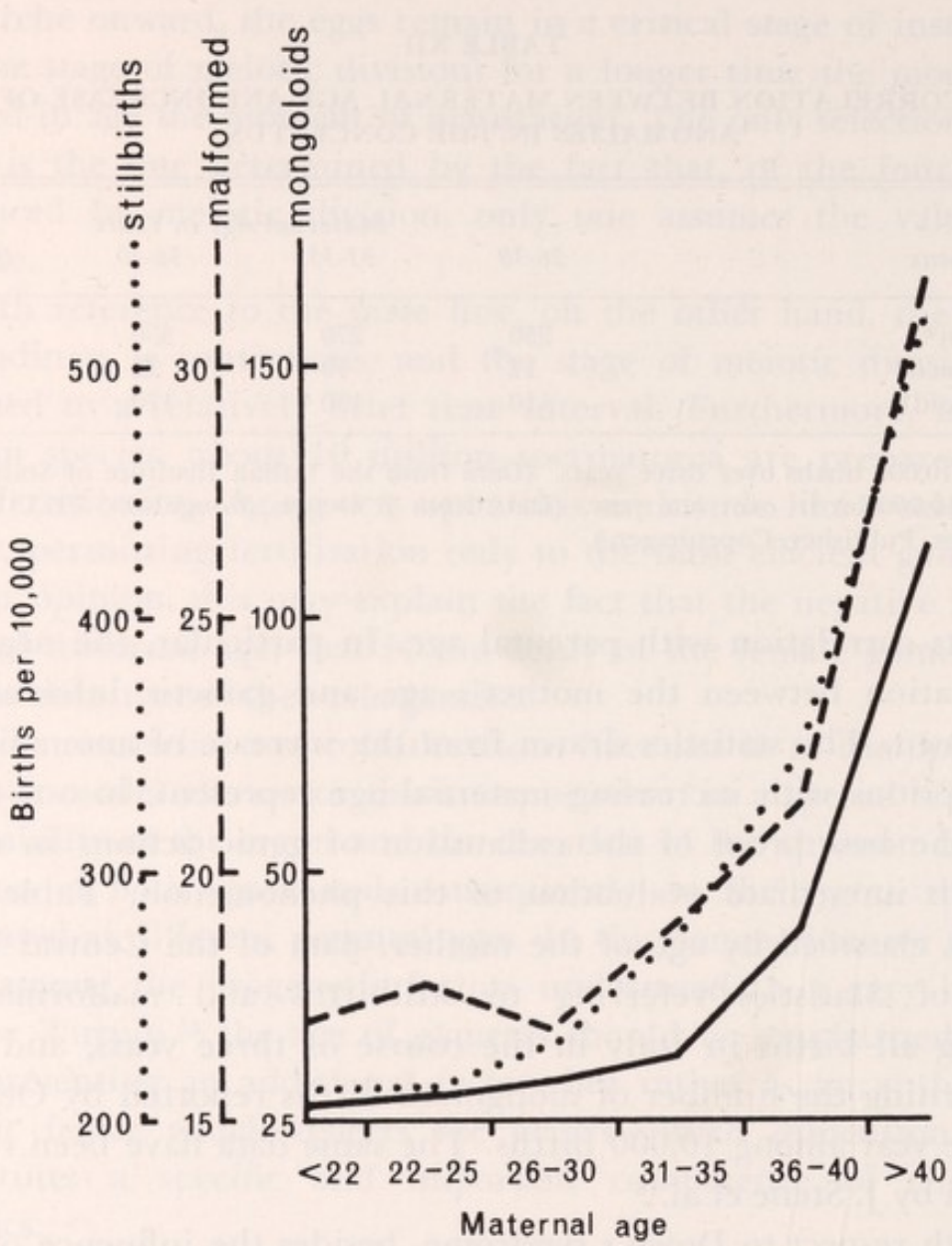


Figure 25. Stillbirths, congenital malformations and mongolism in relation to maternal age. A negative correlation exists between maternal age and the efficiency of the information contained in the gametes. (Data from the Central Institute of Statistics; and J. Oester, *Mongolism,* 1953. Danish SC Press, Publisher, Copenhagen.)

assembled by Franceschetti[17] (Fig. 26). In the fifth generation, a sibship is noted in which the total picture of the disease is present in five of fourteen living brothers and/or sisters, transmitted to them by their mother. In order of birth, they occupy the

17. Franceschetti, A. T.: La cornea verticillata (Gruber) et ses relations avec la maladie de Fabry (angiokeratoma corporis diffusum) . *Ophthalmologica, 156*:232-238, 1968.

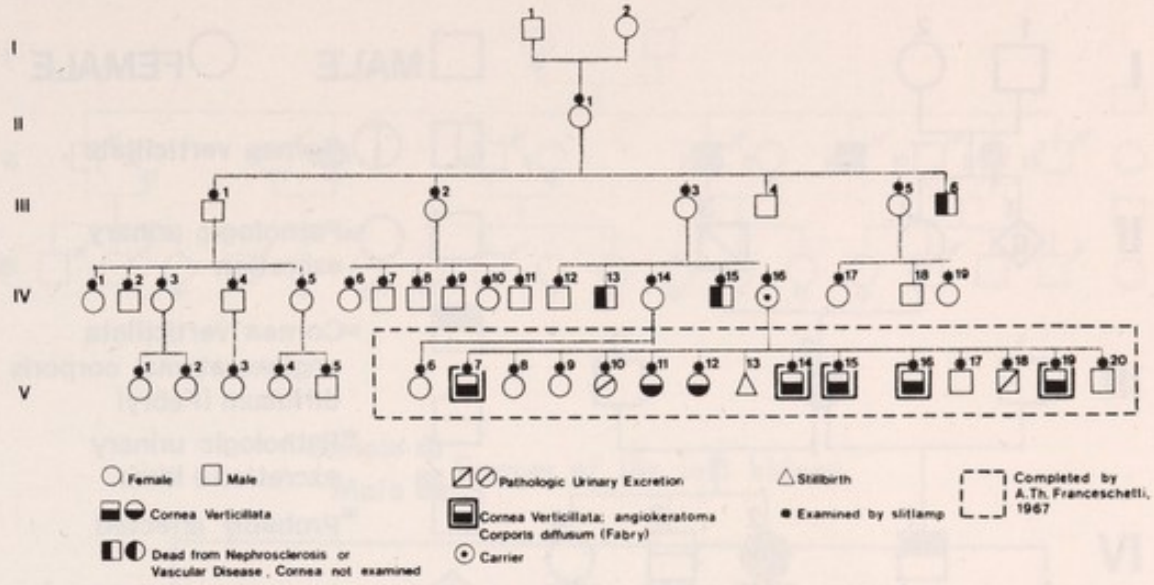


Figure 26. Progressively anticipating age of onset in Fabry's disease. (From A. T. Franceschetti: Cornea Verticillata (Gruber) et ses Relations avec la Maladie de Fabry (Angiokeratoma Corporis Diffusum), *Ophthalmologica, 156:*232, 1968. Courtesy of publisher.)

places we will now indicate along with (in parentheses) the age of onset of the disease: first born (twenty years), eighth born (twelve years), ninth born (eleven years), tenth born (nine years), thirteenth born (five years). In the first born, the defective genotype demonstrates its informatic activity until the twentieth year; in the thirteenth born, on the other hand, the information is exhausted at the age of five. Between these extremes the diseased siblings have progressively decreasing ages of onset. Thus there is confirmation of the progressive decline of the specific genotype's stability at the level of the gametes of the carrier mother.

Another tree assembled by Denden and Franceschetti[18] in connection with Fabry' s disease is reproduced in Figure 27. In the third generation we note the presence of a woman carrier who had a son with the complete syndrome by her first husband and another son with the complete syndrome by her second husband. The onset of the disease in the two half-brothers coincides. It occurs in both at age sixteen, showing that the values of the ergon of the specific allele in the maternal gametes more or less coincide, in spite of the diversity of paternal gametes.

18. Denden, A., and Franceschetti, A. T.: Cornea verticillata: Ein symptom des Morbus Fabry-Anderson. *Ber Dtsch Ophthalmol Ges, 69:*145-148, 1969.

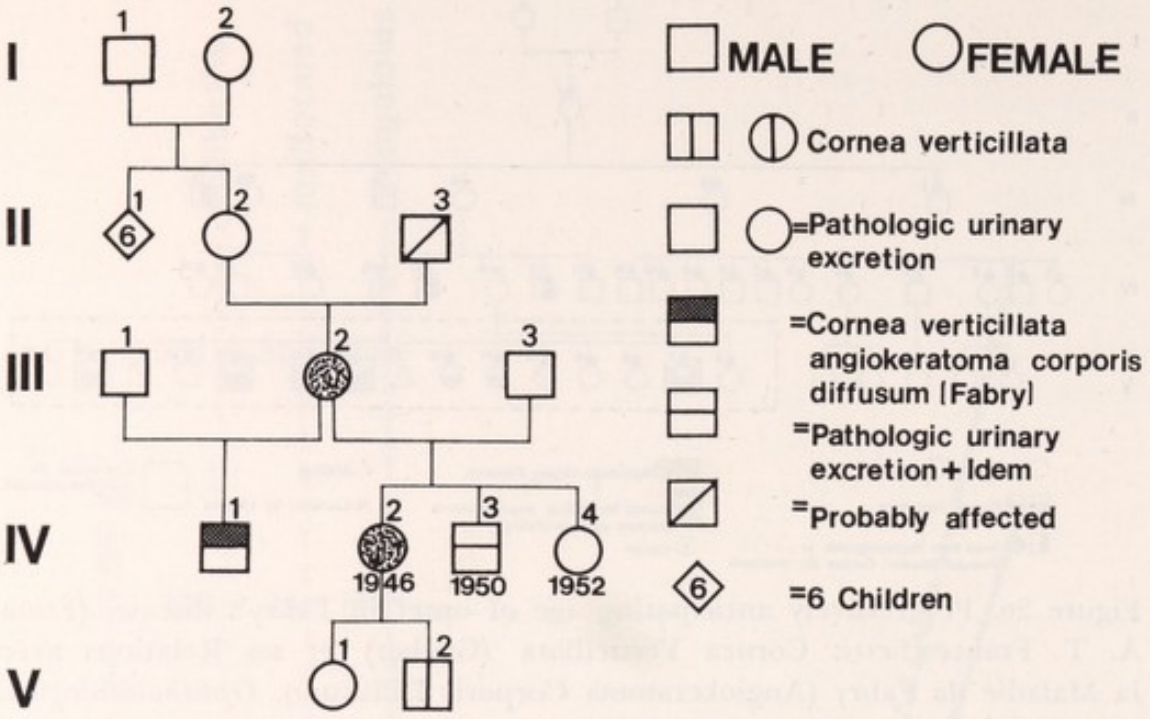


Figure 27. Concordant age of onset in Fabry's disease. (From A. T. Franceschetti, and A. Denden, Cornea Verticillata: Ein Symptom des Morbus Fabry-Anderson, *Bericht; Deutsche Ophthalmolgische Gesellschaft (Munchen), 69:*145, 1969. Courtesy of publisher.)

A different disease, consisting of cancer of the left kidney occurring four times in the same sibship (cf. Fig. 28) has been studied by two different teams of Parisian doctors, Bernades et al.[19] and Valleteau de Moulliac et al.[20] These works lead to conclusions analogous to the previous ones. It is probable, as the clinicians believe, that the familial nature of the cancer is due to a hereditary damage of the HLA system. In any case, the chronogenetic evidence—that the age of onset of the disease is inversely proportional to the patient's birth order—is significant. The linear regression of age of onset according to birth order enables us to trace a curve representing the decay of the defective allele in the gonad of the parent who transmits the damage.

19. Bernades, P., Molas, G., Beaugrand, P., Camey, M., Denis, M., and Dupuy, R.: Cancer du rein gauche chez trois membres d'une même fratrie. *Sem Hôp Paris, no. 43, 48:*2813-2816, 1972.

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

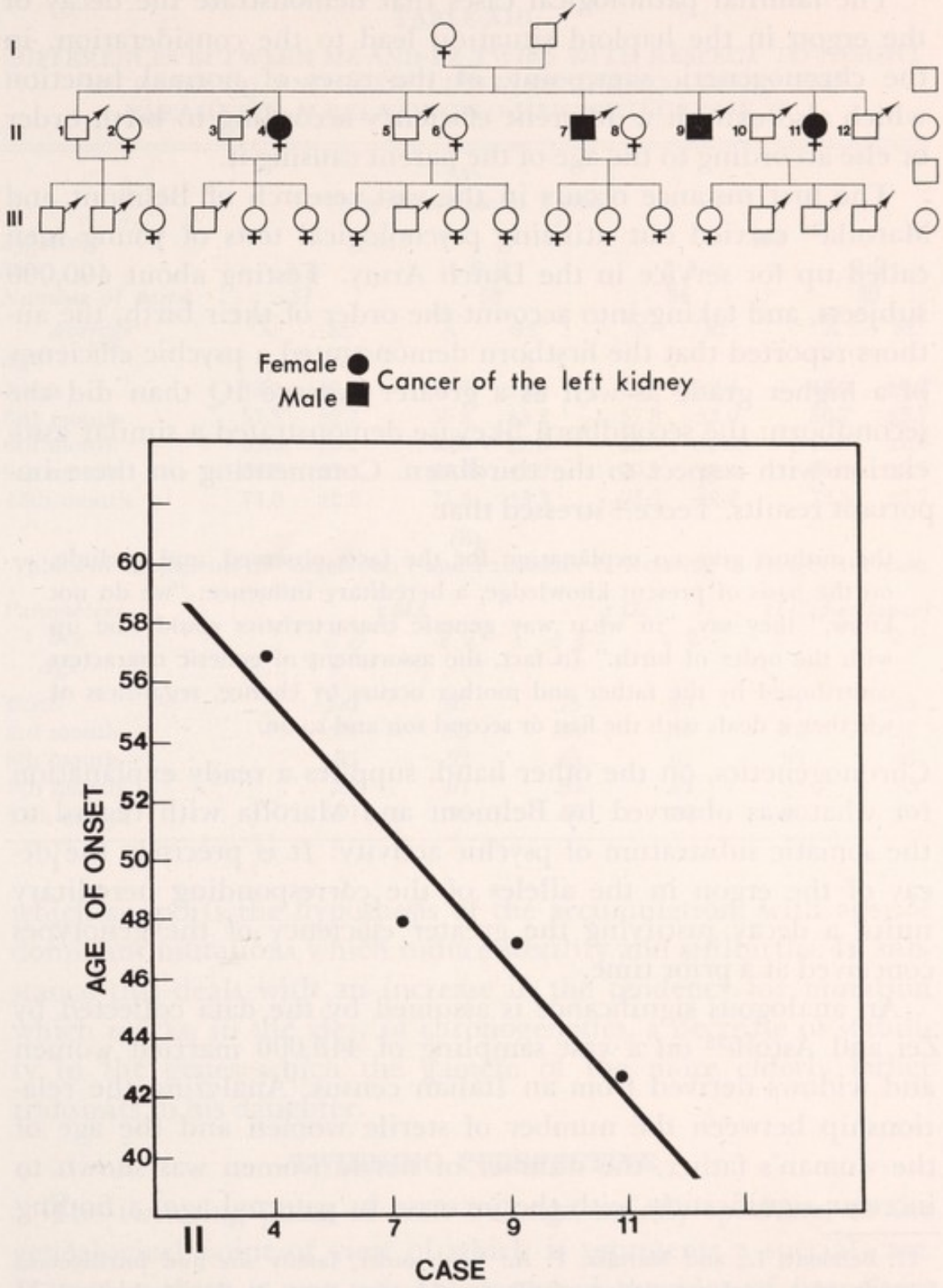


Figure 28. Cancer of the left kidney. Family tree showing repeated cases of cancer in one sibship with progressively earlier age of onset.

The familial pathological cases that demonstrate the decay of the ergon in the haploid situation lead to the consideration, in the chronogenetic viewpoint, of the cases of normal function which also exhibit a different efficiency according to birth order or else according to the age of the parent causing it.

The first instance occurs in the vast research of Belmont and Marolla[21] carried out utilizing psychological tests of young men called up for service in the Dutch Army. Testing about 400,000 subjects, and taking into account the order of their birth, the authors reported that the firstborn demonstrated a psychic efficiency of a higher grade as well as a greater average IQ than did the secondborn; the secondborn likewise demonstrated a similar association with respect to the thirdborn. Commenting on these important results. Tecce[22] stressed that

> the authors give no explanation for the facts observed, and exclude, on the basis of present knowledge, a hereditary influence: "we do not know," they say, "in what way genetic characteristics could line up with the order of birth." In fact, the assortment of genetic characters contributed by the father and mother occurs by chance, regardless of whether it deals with the first or second son and so on.

Chronogenetics, on the other hand, supplies a ready explanation for what was observed by Belmont and Marolla with regard to the somatic substratum of psychic activity: It is precisely the decay of the ergon in the alleles of the corresponding hereditary units, a decay justifying the greater efficiency of the genotypes conceived at a prior time.

An analogous significance is assumed by the data collected by Zei and Astolfi[23] on a vast sampling of 440,000 married women and widows derived from an Italian census. Analyzing the relationship between the number of sterile women and the age of the woman's father, the number of sterile women was shown to increase significantly with the increase in paternal age, a finding

21. Belmont, L., and Marolla, F. A.: Birth order, family size and intelligence: A study of a total population of 19-year-old men born in the Netherlands is presented. *Science, 182:*1096, 1973.

22. Tecce, G.: In *Paese Sera, no. 62, 26:*3, 1974.

23. Zei, G., and Astolfi, P.: *Associazione Genetica Italiana, Riunione di Parma, 17-18 octobre, 1974* (Italian Genetics Association, Parma Conference, October 17-18, 1974).

TABLE XIII

DIFFERENCES BETWEEN MZ AND DZ TWINS WITH RESPECT TO HEIGHT INCREASE (A) AND COEFFICIENTS OF CORRELATION *r* AND PARAMETER *H* RELATING TO HEIGHT INCREASE (B)

(A)
Height Increase in Twins

Zygotism	*MZ*				*DZ*			
Sex	♂♂		♀♀		♂♂		♀♀	
Number of pairs	37		38		34		30	
Average	$\overline{X}$	S±	$\overline{X}$	S±	$\overline{X}$	S±	$\overline{X}$	S±
Age								
Birth	48.2	±2.3	47.9	±3.6	48.3	±2.4	48.0	±4.2
3rd month	57.5	±2.7	55.8	±3.2	57.8	±3.0	56.7	±3.7
6th month	65.6	±3.2	63.9	±2.9	66.0	±2.7	64.9	±2.5
9th month	69.5	±2.8	68.6	±2.9	70.9	±2.4	68.9	±2.9
12th month	74.0	±2.9	71.6	±3.3	73.3	±2.8	73.5	±3.7

(B)
Values of Coefficients of Correlation *r* and Parameter *H* Relating to Height Increase

Parameters	*r MZ*		*r DZ*		*H (Inheritance)*	
Sex	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀
Age						
Birth	.90	.97	.73	.89	.77	.89
3rd month	.93	.95	.88	.86	.62	.82
6th month	.95	.92	.55	.62	.95	.88
9th month	.94	.91	.55	.64	.93	.85
12th month	.91	.92	.66	.82	.90	.71

which supports the hypothesis of the accumulation, with age, of dominant mutations which induce sterility and stillbirths. In substance this deals with an increase in the tendency for mutation which marks, in the view of chronogenetics, a decrease of stability in the genes which the gamete of the more elderly father transmits to his daughter.

TWINNING PERSPECTIVE

The twinning point of view belongs, strictly speaking, to the genealogical point of view of which it represents a special case. However, since it was twins that started the idea of hereditary time, and since twinning has available to it a doctrine as well as an *ad hoc* methodology that we have already applied in the field of chronogenetics, we shall deal with it separately.

The twin method makes it possible to cope with the problem

TABLE XIV

DIFFERENCES BETWEEN MZ AND DZ TWINS WITH RESPECT TO WEIGHT INCREASES (A) AND COEFFICIENTS OF CORRELATION *r* AND PARAMETER *H* RELATING TO WEIGHT INCREASE (B)

(A)
Weight Increase in Twins

Zygotism	*MZ*				*DZ*			
Sex	♂♂		♀♀		♂♂		♀♀	
Number of pairs	25		25		25		25	
Average Age	$\overline{X}$	S±	$\overline{X}$	S±	$\overline{X}$	S±	$\overline{X}$	S±
Birth	2.597	± .387	2.540	± .642	2.695	±.275	2.560	± .508
3rd month	5.104	± .803	4.911	± .736	5.271	±.647	4.970	± .690
6th month	7.021	± .987	6.736	± .670	7.637	±.740	7.053	±1.142
9th month	8.563	±1.228	8.479	± .923	9.238	±.905	8.564	±1.006
12th month	10.041	±1.207	9.422	±1.007	10.050	±.897	10.107	± .946

(B)
Values of Coefficients of Correlation *r* and Parameter *H* Relating to Weight Increase

Parameters	*r MZ*		*r DZ*		*H (Inheritance)*	
Sex	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀
Age						
Birth	.62	.84	.30	.39	.45	.74
3rd month	.79	.81	.60	.71	.48	.36
6th month	.81	.71	.48	.39	.62	.53
9th month	.76	.75	.44	.41	.57	.58
12th month	.88	.82	.12	.37	.86	.72

of the inheritance of biological time in general by means of the study of the dynamics of growth in MZ and DZ twins. Alfieri and Gatti-Foglia[24] of the Mendel Institute studied height development of both types of twins using seventy-five MZ and sixty-four DZ pairs and weight development among fifty MZ and fifty DZ pairs, all of whom were studied longitudinally during the first year of life. The results are indicated in Tables XIII and XIV. The data assembled represent trimestral parameters of development, and the relationship of the values in the two groups proves that these chronological characters are inherited at the rate of

24. Alfieri, A., and Gatti-Foglia, I.: *Weight Increase of Twins and Singletons in the First Year of Age*. First International Congress of Twin Studies. Rome, October 28-November 2, 1974.

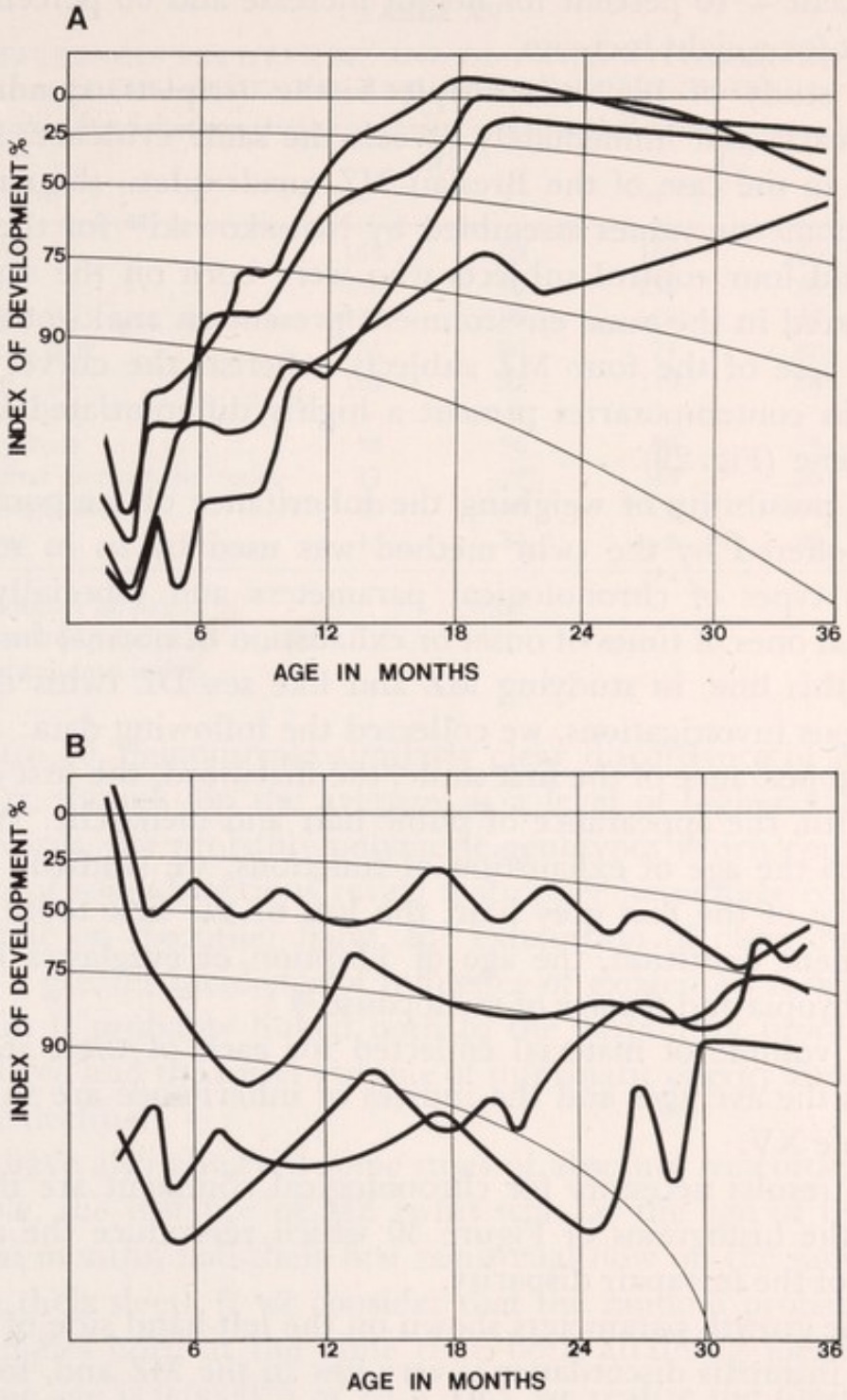


Figure 29. Developmental curves in the MZ quadruplets of Breslau *(A)* as compared to four nonrelated singletons *(B)*. (From T. K. Nowakowski, as reviewed by Gedda, in *La Recherche, no. 55,* April, 1975. Courtesy of publisher.)

83 percent ± 10 percent for height increase and 60 percent ± 15 percent for weight increase.

The study of higher multiple births (triplets, quadruplets, etc.) clearly and immediately reveals the same evidence. For example, in the case of the Breslau MZ quadruplets, the curves of anthropometric values assembled by Nowakowski[25] for these subjects and four control subjects who were born on the same day and reared in the same environment present an analogous course in the case of the four MZ subjects, whereas the curves of the nontwin contemporaries present a highly differentiated individual course (Fig. 29).

The possibility of weighing the inheritance of temporal characters offered by the twin method was used by us in studying various types of chronological parameters and especially those punctual ones of times of onset or exhaustion of normal functions. Along this line, in studying MZ and like sex DZ twins through numerous investigations, we collected the following data: the age of the appearance of the first smile, the first word, the first deciduous tooth, the appearance of pubic hair and menarche. With regards to the age of exhaustion of functions, we studied: the appearance of the first grey hair, the loss of the first tooth of the permanent dentition, the age of adoption of eyeglasses because of presbyopia and the age of menopause.[26]

The volume of material collected for each of these items, as well as the averages and the indices of inheritance are indicated in Table XV.

The results necessary for chronological comment are illustrated in the histograms of Figure 30 which reproduce the average values of the intrapair disparity.

In the growth parameters shown on the left-hand side of Figure 30, the intrapair discordance is very low in the MZ and, for every temporal parameter, decidedly lower than that of the DZ. On the other hand, the parameters of aging, shown on the right-hand side

25. Nowakowski, T. K.: Uniovular quadruplets of Breslau. *Acta Genet Med Gemellol (Roma), Suppl. to vol. 22:*154, 1974.

26. Gedda, L., and Brenci, G.: Chronology of the gene. *Acta Genet Med Gemellol (Roma), 20:*323-349, 1971.

TABLE XV

DIFFERENCES BETWEEN MZ AND DZ TWINS WITH REGARD TO DEVELOPMENTAL AND SENESCENT PROCESSES

	MZ		DZ		
Development	*n**	*r*	*n*	*r*	*H*
First smile	153	.99	108	.50	.95
First word	155	.99	230	.86	.91
First steps	187	.96	128	.66	.90
First pubic hair	63	.99	71	.88	.94
Menarche	167	.92	119	.66	.75
Senescence					
First grey hair	38	.96	35	.73	.85
Loss of first permanent tooth	17	.72	16	.56	.36
Use of eyeglasses	35	.86	24	.64	.86
Menopause	14	.85	6	.23	.79

**n* is number of pairs.
r is correlation index.
H is inheritance index.

of Figure 30, demonstrate similarly clear discordance of MZ and DZ pairs, though, on the average, at a level of higher values. In other words, the probably polymeric genotypes which control the starting of some functions reveal a stronger hereditary conditioning, while on the other hand, the exhaustion of other functions reveals a greater incidence of influence of exogenous factors. The situation is probably linked both to the variability produced by life as lived and the lower volume of informatic energy and its progressive decline.

We have also observed some cases of absolute concordance, for example, the instance of MZ twins who, at the age of ten years and ten months, had their first menstrual flow on the same night and in their sleep. If we consider that the random probability of two females born at the same time both attaining menarche at the same age is 0.000025 or 25×10^{-6}, we realize the limit of certainty offered by the twin method in order to demonstrate the hereditary nature of the phenomenon. The contemporaneous onset of menarche for other pairs can and have been modified by paratypical events, but still be within the limits indicated by the averages which are significantly lower than the disparities present

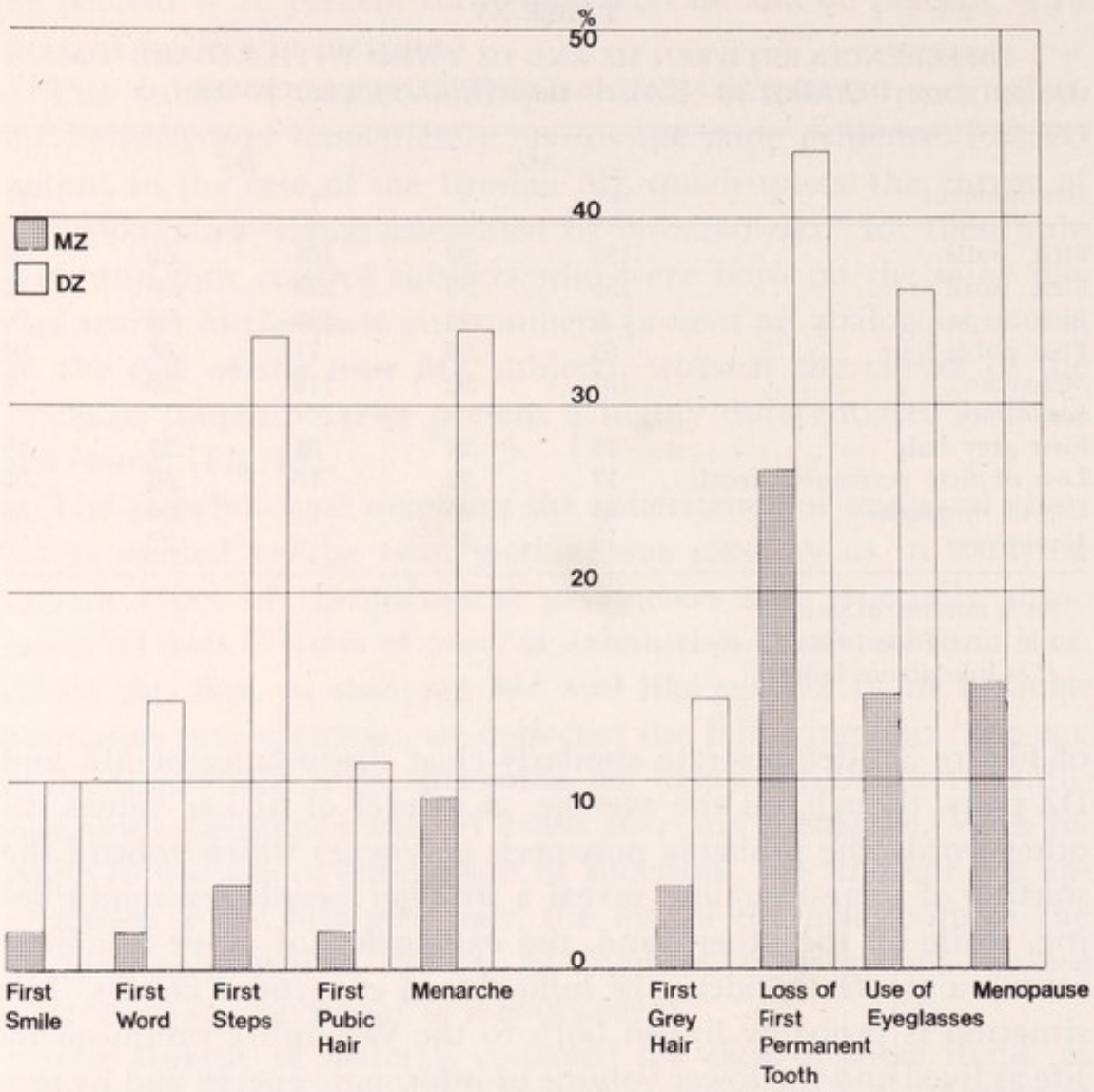


Figure 30. Intrapair discordance in MZ and DZ twins in the chronon of ontogenetic functions and in phenomena of recession.

in DZ twins. The verification offered by the twin method proves controlling the onset of such functions.[27]

The twinning material used to study pheno-time, or the punctual chronon of onset and ending of different pieces of information, has also served to study an informatic period, the linear chronon of duration of menstrual flow in the year of menarche of MZ and DZ twins. The average duration of flow in days of the twins (first born and second born) is represented in

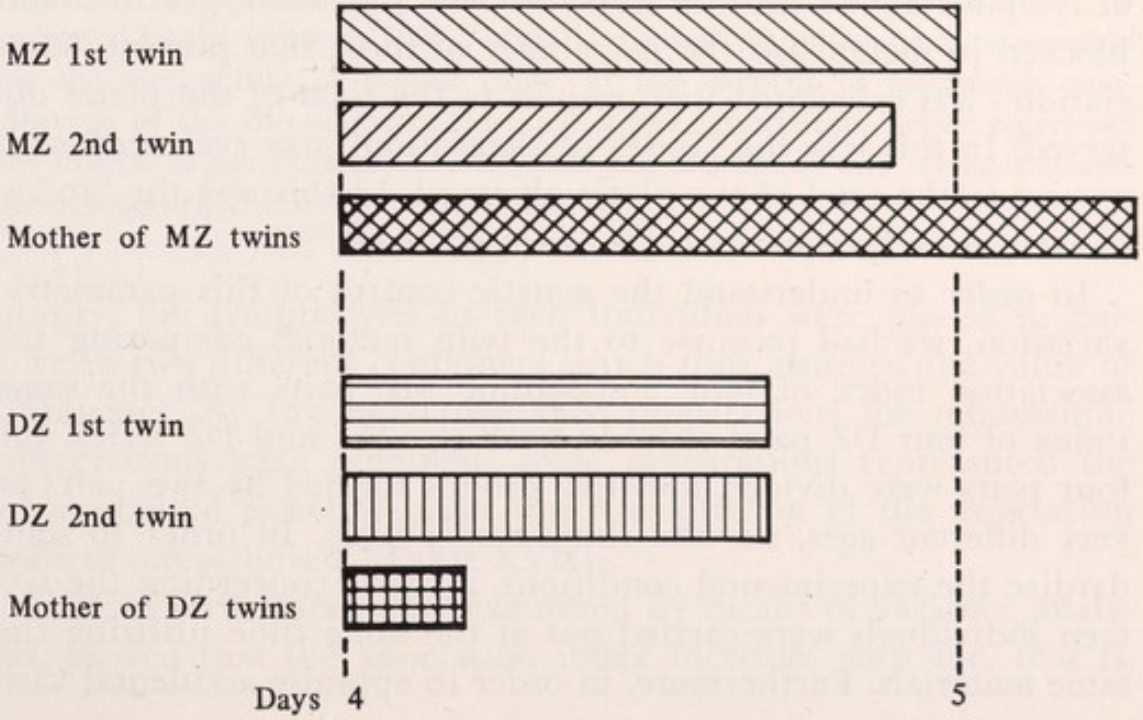
27. Gedda, L., and Brenci, G.: *Twins as a Natural Test of Chronogenetics.* First International Congress of Twin Studies. Rome, October 28-November 2, 1974.

Table XVI where the values of flow of the mothers of both types of twins is also reported. From these data, it is found that the average number of days of flow is significantly higher in MZ twins and their mothers and lower in DZ twins and their mothers. This result also means that the linear chronon, or the chronon of duration, is hereditary in character like the punctual chronon of onset and ending. Secondly, the evidence points to a special phenomenon: The duration of flow differs according to the type of twins, and the phenomenon not only concerns the twins per se but the family space as well, being common to their respective mothers. The menstrual "hyperflux" that we observed can be related to a "hypermaturation" of the fertilized egg upon separation in secondary zygotes of the first totipotent blastomeres.

TABLE XVI

DURATION OF FLOW (DAYS)

	1st twin	2nd twin	Mother
MZ (76 pairs)	5.03	4.91	5.34
DZ (81 pairs)	4.70	4.69	4.23



The twinning viewpoint has additionally served us in the experimental study of mitosis from its chronogenetic aspect. Many researchers have concerned themselves with the identification of the genes that control the equational distribution of the patrimony of information duplicated in the mother cell to the daughter cells. However, while the modalities of redistribution, that is, the phases of mitosis (the individualization of chromosomes upon their migration towards the cell poles and the formation of the two daughter nuclei) are known, the genes presiding over these transformations or phases are hardly known at all. Some have been identified as genes that control the disjunction of the pairs of homologous chromosomes in metaphase, with their mutants responsible for nondisjunction; but the known genes represent only a small part of those involved in the mitotic process. Since the temporal validity of efficiency of the genes responsible for the mitotic mechanism cannot be directly evaluated, we structured the experiment in such a way as to be able to evaluate the phenomenon by means of a parameter which represents its inverse. We studied the association which comes about when, in metaphase, acrocentric chromosomes are not distributed as they should be, because they remain "associated," or opposed or conjoined in a rather large measure as shown in Figure 31. On plates of lymphocytes in culture, stimulated by phytohemaglutinin and blocked in metaphase, the percentage of those that present "association" was calculated with respect to the total of the plates observed. In this way the "index of association" was evaluated with respect to the total of the plates observed. In this way the "index of association" was evaluated for each proband.

In order to understand the genetic control of this parametric variation, we had recourse to the twin method, comparing the association index of four bimasculine MZ pairs with the same index of four DZ pairs only. In both the MZ and DZ series, the four pairs were divided into two groups formed by two pairs at very different ages, six and sixty, respectively. In order to standardize the experimental conditions, all tests concerning the sixteen individuals were carried out at the same time utilizing the same materials. Furthermore, in order to appraise accidental vari-

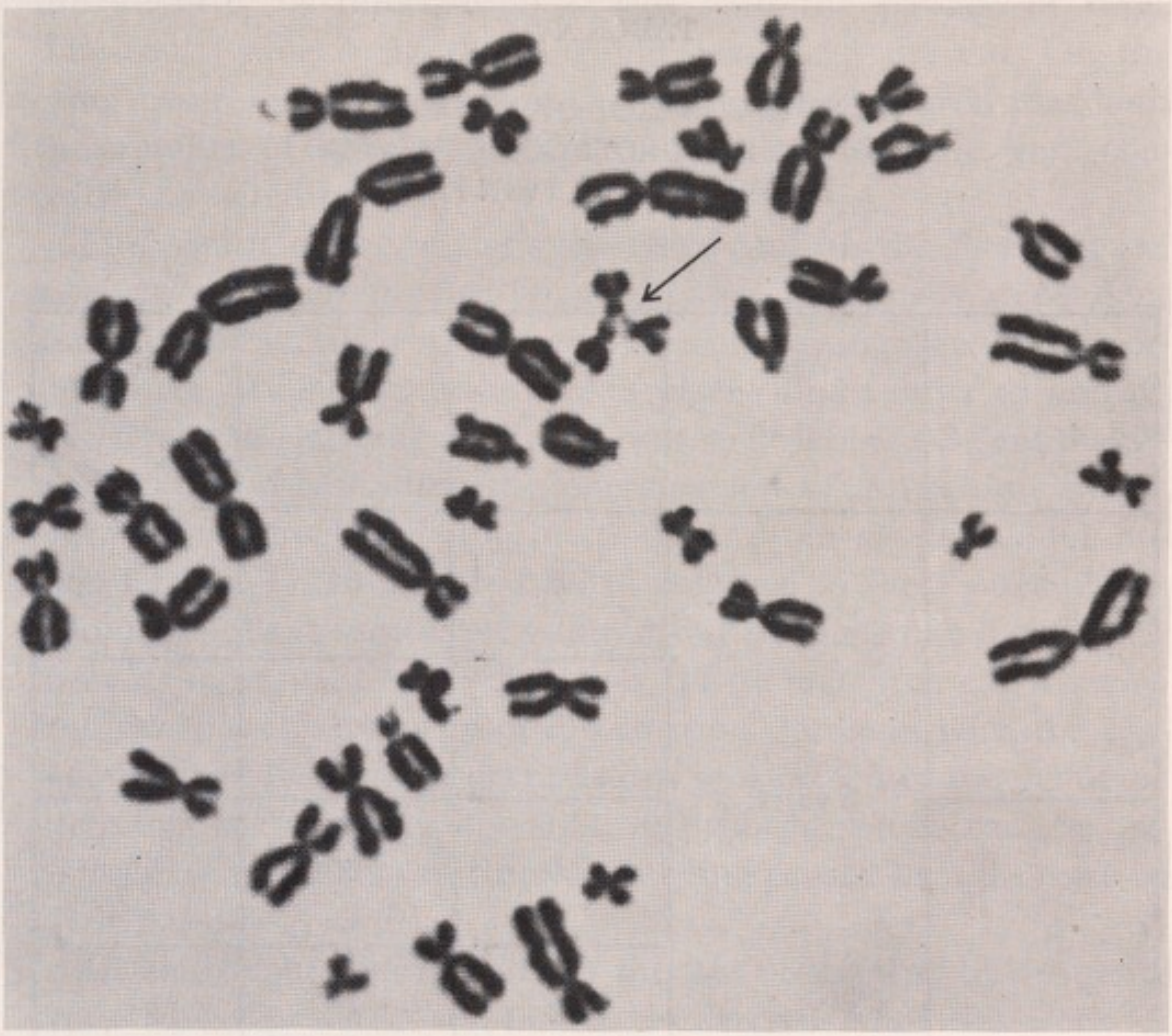


Figure 31. Metaphasic plate with association of acrocentric chromosomes, as indicated by the arrow (×5000). Mutations provided by the genes responsible for the mechanisms of mitosis cause, at the moment of metaphase, non-cleavage of the chromosomes. The parameter, association, hence represents the inverse of the efficiency of the genes just mentioned and serves to evaluate it, together with its temporal variability.

ability, the lymphocytes of each individual were placed in culture in two different containers which thus assumed the value of duplicates. By the usual methods, preparations for microscopic observations were obtained; these preparations represented the experimental material upon which evaluation of the association indices was achieved (Table XVII).

The experimental data, examined by means of variance analysis, proved that the association index increases with age, that is,

TABLE XVII

GENETIC CONTROL OF ASSOCIATION INDICES IN MONOZYGOTIC (MZ) AND DIZYGOTIC (DZ) TWIN PAIRS

Pairs	Age	Twin	MZ	DZ
I	6 years	A	64	68
		B	61	56
II		A	60	60
		B	62	55
I	60 years	A	74	75
		B	70	79
II		A	82	72
		B	76	81

the quantity of information lessens with the passage of time. The test's value is significant at the level of 1 percent. On the other hand, the application of the twin method proved that both the number of associations and its variation in time were controlled by heredity.

The results of the analysis therefore confirm the fact that the mechanisms occurring before mitosis are genetically dependent and that their efficiency lessens with increasing age of the organism in which the mitosis takes place. The results of our research are in agreement with those of Prokofieva-Belgouskaya[28] who analogously studied the phenomenon of association by examining the nuclei of fibroblasts taken from six-month-old human fetuses. The association index obtained in these early phases of ontogenesis is significantly lower and parallels our data which show its increase at succeeding ages. These matching experiments confirm that the quantity of information decreases with the passage of time, that such a decrease can be ascribed to the genotype directing that activity and that the phenomenon can be explained, according to our model, as being caused by a decrease in genic stability.

An additional confirmation of the loss of stability of the genotypes which preside over mitosis is derived from the work of Fitzgerald et al.,[29] who studied the distribution of the metaphasic plates of individuals of varying ages by the number of chromosomes and were able to demonstrate that the frequency of the plates with aneuploid mutations was correlated with an increase in age. The increase in aneuploid metaphases is primarily due to an increase of plates with 45 chromosomes which results from a dischronic disjunction of the centromere. The increase in aneuploid frequencies differs in intensity between the sexes. In males it goes from 0.8 percent of aneuploid metaphase in the twenty- to forty-year-old group to 0.9 percent in the forty- to sixty-year-old group, and 1 percent in those over sixty years of age; in females, on the other hand, the increase is much more

28. Prokofieva-Belgouskaya, A. A.: In *Exp Cell Res, 49*:612, 1968.

29. Fitzgerald, P. H., Pichering, A. F., Mercer, J. M., and Miethke, P. M.: In *Ann Hum Genet, 38*:417, 1975.

marked and goes from 1.3 percent in the twenty- to forty-year-old group to 2.3 percent in the forty- to sixty-year-old group and reaches 4.5 percent in the group over sixty years of age.

The age decay of genetic material also applies to pathology: In ataxia telangiectasia, e.g., Al Saadi and Palutke[30] have recently found that the incidence of lymphocytary clones with chromosome 14 arrangements increases with age.

It can therefore be stated that even on the cytological level, the existence of a hereditary regulation of the characteristic times of life is proven, and that this regulation is correlated with the age of the living being in accordance with the hypothesis of the E/C model.

PROBABILISTIC PERSPECTIVE

In a practical sense the possibility of having the definition of ergon understood as an initial stability (zygotic) and that of chronon understood as an average life expectancy of a hereditary piece of information depends upon the possibility of defining the type of correlation which exists between the boundaries of these two characteristics of hereditary information. In other words, it is necessary to define the function of stability decay in time. However, before attempting this, it is preferable to state that decay is a variable process and the consequence of at least three groups of factors.

A first group is one that determines the mutagenic capacity of the environment in which hereditary information is placed to operate.

A second group of factors is determined by the increase in length of the operative periods of information, in that there has been proof of the increase of instability for every single informatic sequence during transcription because of despiralization, especially during replication where the probability of errors of replication is added to the chemicophysical instability of monocatenary strands.

Finally, a third group is determined by the modification of the

30. Al Saadi, Al, and Palutke, M.: Evolution of chromosomal aberrations in ataxia telangiectasia. *Excerpta Medica, International Congress Series, No. 278*:397, 1976.

intensity of the mutagenic factors present in the environment with time; in particular, we recall the accumulation of cellular catabolites and the increase in free radicals.

Starting off from the description of decay due to environmental factors, it is possible to create a mathematical model that describes the intercurrent relationships between ergon and chronon. For the first type of decay, this seems possible and in agreement with the majority of "mutagenists" after having defined, with a fair approximation, the action of the mutagenic factors of the environment as normal.

The model is analogous to that of the decay of radioactive nuclei with different possibilities of decay so as to describe the phenomenon of an information that can "mutate" in many ways. It is possible to show that a nuclide's different manners of decaying are characterized by constants of partial decay, and that total decay for that nuclide is represented by the constant of total decay equal to the sum of the partial ones.

Besides the interpretation of the partial constants of decay, the model related to radioactive substances makes possible a mathematicoprobabilistic description of the average life of the radioactive atom. The effective life of an atom may vary, if the decay is accidental, between 0 and 00, but the average life referable to a great number of radioactive atoms of the same species is a definite quantity—very important for us in that it is conceptually comparable to the chronon of a piece of information.

If average life is indicated by τ, this simply results in the case considered; in the inverse of the constant of decay, that is $\tau = 1/\lambda$. This average life corresponds, in terms of hereditary information, to the concepts of chronon, and γ, the coefficient of decay, to the degree of the information's instability, and that is to the opposite concept to that of stability, or ergon.

The specific model of the E/C system was produced in collaboration with Rossi and Sangermano of the Institute of Calculation of Probabilities of the University of Rome.[31] As a first

31. Rossi, C., and Sangermano, R.: *Variability of Information's Quantity as Starting Ergon Parameter.* First International Congress of Twin Studies. Rome, October 28-November 2, 1974.

logical step, the three parameters of stability were operatively defined: molecular stability (α), redundance (β), and repair (γ), relating stability to a process of decay described by means of a function analogous to that of radioactive nuclei. The parameters were defined by considering α as an aleatory variable representing the number of nucleotides G in third place in a triplet of a DNA molecule (and hence the number of G $\equiv$ C couples). In this system, alpha's distribution is calculable with good approximation if one admits that, for the third position of each triplet, both A (and hence the A = T couple) and G (hence the G $\equiv$ C couple) have a probability equal to 50 percent. In this hypothesis a Bernoullian distribution is obtained which approximates a normal distribution. The parameter β was defined as the number of redundant molecules, valid in general to time $t = 0$ (formation of the zygote). Theoretically, $0 \leq \beta \leq n$; in practice, when β reaches a certain limit below 1, the gene can be considered inactive.

Calling p the probability that a molecule be valid and assuming that there be a stochastic independence between molecule and molecule, the distribution of β is Bernoullian between 0 and $n \doteq 20$, of which one disregards the part between 0 and 1. In fact 20 is the evaluation of the average redundance obtained from the relationship between the number of gene functions (about 60,000) and the number of DNA molecules (about 1,200,000) in a nucleus of the human species. Finally, the parameter γ was defined as a constant that represents the repair probability of a given DNA molecule in the unit of time.

Thus defining the stability parameters, it is possible to describe mathematically the process of decay of hereditary information. In fact, as time passes, irreversible transformations can be generated in the DNA molecule that are not present at the initial time $t = 0$. The decay of hereditary genic information consists exactly in the accumulation of such accidental transformations that can be generated both in a valid molecule, making it invalid or mutant, and in a nonvalid one, letting it remain the way it is.

Selecting a suitable time unit so that in such time no more than one irreversible transformation called μ can be generated, the probability that there may be an error in the time unit (rate

of mutation), as well as the speed of the decrease in the number of valid molecules results in a proportionate forecast, in accordance with $\mu(t)$, to the forecast of the total number of still exact molecules to the time t. The latter is represented by an aleatory function $M(t)$, whose solution $p[M(t)]$ allows the forecast of the number of still exact molecules at a given time t. Having defined $p[M(t)]$, we can define its inverse and consider the forecast T of the time needed for $M(t)$ to reach the lower limit which renders the gene inactive, that is to say T, the average life of its information.

The correlation between efficiency decrease of a hereditary character in time, that is, of the quantity of the corresponding information with respect to the diminution of the corresponding stability-duration of a gene, can be illustrated in the following way (Fig. 32): In a continuous space, two parallel planes represent the genotype and the phenotype; in both of them, the ordinates indicate the energies, and the abscissas the times. On the genotypic plane the energy corresponds to the stability of the information (ergon), while the time corresponds to the average life of the gene (chronon). On the phenotypic plane, the values corresponding to the manifestation of the character are reported. The theoretical gene represented in the drawing has the following characteristics: an initial ergon (E_i) with its own curve of decay and a time of dying out of the ergon (E_t), to which the information's limit of duration corresponds (C_t). Parallel with the continuation of the information on the genotypic plane, one or more manifestation periods may exist. For the sake of simplicity only one period of manifestation (M) has been shown which goes from an initial time of manifestation (tm_i) to final time (tm_t). In this interval, the quantity of information decreases by a quantity correlated to the corresponding decrease of the ergon's stability on the genotypic plane.

The cause of this correlation between stability (ergon) and quantity of information has to be studied because the decrease of one stability parameter, that is, redundance, is immediately reflected in the quantity of information available. It is, in fact, evident that if one piece of information is composed of 10 re-

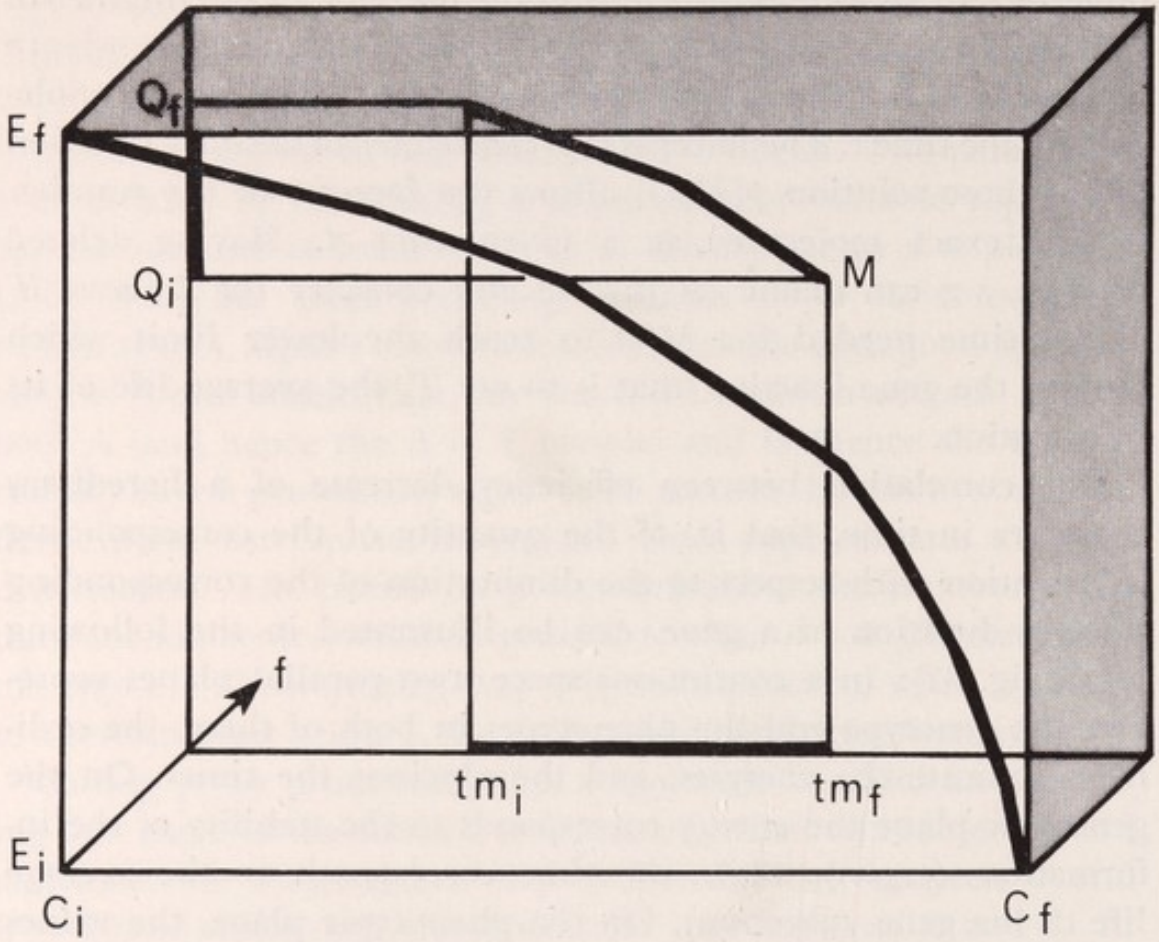


Figure 32. Ergon/chronon model. The two parallel planes represent the genotype (front) and the phenotype (rear). The letters indicate respectively: C_i and C_f, initial and final chronon; E_i and E_f, initial and final ergons; Q_i and Q_f, initial and final quantity of information; M, manifestation; tm_i and tm_f, initial and final time of manifestation.

peats and each of these has an average life probability, there will be—if the modifications of the single repetitions are independent among themselves—a series of successive temporal stages in which the information will have 10, 9, 8 . . . 0 efficient repetitions. The number of these repeats will be reflected in the informatic flow, in that, on a par with synthesis velocity, the quantity of information available will be different.

The probabilistic estimate presently represents a possibility that is still as far away from a simple practical application as one could think will occur in future. Looking to tomorrow and to the needs of preventive, prognostic and eugenic medicine, it

is to be hoped that the practical application of probabilistic extrapolation may concern the evaluation of the individual genotypes that are involved, benefiting from the techniques developed by cytogenetics and molecular genetics through the quantity of residual information (that is, the flow of the primary result of the gene because of the unit of time) in order to dole out the ergon and hypothesize the chronon, and by which lymphocytes are utilized as a sample population of the chronogenetic situation of the entire organism. In fact, this is present in every cell on the level of the stage of decay achieved, and the genome of the circulating lymphocyte is the repeat most easily attainable on the basis of the techniques available to genetics. Estimating twice over and at a suitable distance of time the selfsame genotype involved, one will be able to single out the function of decay that may enable the available ergon to be estimated and the probable chronon to be hypothesized.

The development of probabilistic perspective is not solely a speculation of present-day chronogenetics, but a work program for the individual ascertainment and practical application of the E/C system for prognostic purposes, as well as corrective and therapeutic recycling of genes or balanced symptomatic correction of the clinical chronogenetic situation.

GENERAL SIGNIFICANCE OF THE E/C SYSTEM

The many chronogenetic phenomena, collected and enumerated in this chapter according to various types of method, prove their ability to be unified and interpreted on the basis of the E/C model.

In an effort to encompass this varied and complex panorama within a comprehensive viewpoint, it seems that, quite before anything else, we should point out the dynamic significance that chronogenetics provides for hereditary information. Such dynamism relates to information not only in the ontogenetic realm of individual living beings but to its distribution in the genealogical phylum.

The individual sequence is marked by an integration of the chronogenetic values of the ergon of the paternal allele with

that of the maternal allele. The details of this energy operation are as yet not known, but it is presumable that they will serve to explain Mendel's laws from a dynamic point of view. Up to now it could be postulated that even they will be dynamized to the point that the relationships of dominance and recessiveness and those of formal post-Mendelian genetics will become clear, not only in the static function of almost photographic structure, but also in the active function of almost cinematic development. Amphimictic integration makes available to the average life of the information of the organismic genotype a certain amount of energetic potentiality (ergon) which decreases in time and a corresponding amount of informatic time (chronon) that the ontogenetic arc renders actual in the framework of environmental requirements.

At this point, and in the perspective of the developments that chronogenetics may have in the future, we would like to observe that, in addition to the three fundamental parameters of molecular genetics to which have been entrusted the recording and control of hereditary time (synonymy, informatic redundance and repair), one will have to take account of a redundance on the cytological level due to the spatial *quantum* of organs, that is, the number of cells that the ontogenetic program achieves in successive times. This morphological parameter reflects the function of the molecular parameters, but also represents an additional, considerable source of quantitative and chronological variability as well. The influence of the environment can cause a decay, either general or special, the former being linked with the entropy of matter, the latter, instead, with the use made of the individual pieces of information and hence as a cause of a specific decay. In the ontogenetic curve the ergon becomes engaged in relationship to organismic and environmental necessities of information destined to be repeated according to the values of the corresponding chronons; upon these necessities, selection prepares and favors individual patterns of maximum relative efficiency.

As regards the genealogical phylum, the E/C system of descendants is the combined result of the chronogenetic values present in the parents' gametes and also related to their age. Even

so, we feel it logical to hypothesize the existence of a special mechanism of reintegration of informatic energy that certainly has a specific imprint and that we believe is a particular function of the meiotic mechanism in the human species. The elimination of polar globules is a sign and probably the major cause of the recycling of the alleles of the haploid equipment of the gametes, so that in normal conditions the course of the ontogenetic cycle may take place on the reintegrated chronogenetic values that rove about the average life in the species, apart from the genotypes that are incapable of being recoupled because of being individually and seriously mutated.

Chapter VII

Chronogenetics and Ontogenesis

THE TIMING OF ONTOGENESIS

CHRONOGENETICS APPROACHES the study of inheritance following an essentially dynamic method. Its goal is the study of the relation connecting the different stages of the hereditary phenomenon that genetics has established to date at a molecular and a statistical as well as a mathematical level. Its perspective is a complementary one and refers to the *continuum* of the hereditary phenomenon studied along the parameter of time.

As a matter of fact, time is the instrument genetics may use today in order to reconstruct the development of the ontogenetic program that comes about through cell division and differentiation and the utilization of information. This dynamic passage from genotype to phenotype, referred to by Mendelian genetics in the term "phenogenesis," may be viewed in the perspective of the E/C system that serves as an interpretative model.

Each dynamic aspect of heredity is interesting as an object for the study of chronogenetics, beginning with ontogenesis (ontogeny), along which heredity is manifested through integrated stages and times. The embryologic and prenatal organogenetic period is certainly the most complex stage of this process, during which timing is specific, concentrated and with little possibility of variation. Experimental embryology has demonstrated the totipotency of the cellular genome through H. Spemann's experimental work on the origin of multiple gestation.* This also

* Spemann's experiment consists of obtaining two monozygotic *Triton taeniatus* twins through median ligation of a fertilized egg. The twins resulting therefrom have, however, a volume corresponding to approximately half of the normal. (Spemann, H.: *Embryonic Development and Induction*. New Haven, Yale U Pr, 1938.)

means that the zygote possesses the programming for the timing along which normal ontogenesis will progress topographically and sequentially. In our opinion, there is no opposition between the concepts of "derepressor" and "inductor," but rather integration, even if these names come from molecular genetics and embryology respectively. Spontaneous induction is nothing more than the physiological phenomenon of which derepression is the causal moment on the genotypic level. Directly or indirectly, both of them are tributary phenomena of hereditary timing.

Ontogenesis becomes more accessible to the study of chronogenetics in the postnatal period of life; this is followed by a balanced period of homeostasis, and then by a progressive and proportional decay in the information, that is, by the period of senescence. Thus, the vital cycle of life is followed and causally reconstructed by chronogenetics as a phenomenon sustained by hereditary biological time that, in its turn, is an epiphenomenon of the degree of stability of the genes that the organism receives and transmits. Therefore, by ontogenesis we mean the construction time of a living organism, that is, the period of its development up to the period of its maintenance, although this boundary is not clear-cut in view of the dense interlacing of functions belonging to each period which is present in the transition phase.

Ontogenesis, in the perspective of chronogenetics, consists of a multitude of successive or contextual times which have their origin in the zygote and can be analyzed by the emerging activity of the genes that produce the information the organism needs in the stage of development under consideration. During ontogenesis, phenomena of recession also take place. In the human species, these concern the loss of deciduous teeth, or the shrinking of the thymus, for example. In reality, these events signify maturation of the organism, that is, ontogenetic progression and not senescence of which they appear to form a part. The function which summarizes and orders other functions, giving them a progressive significance of development *ad quem* is reproduction, towards which the other functions are directed; therefore, during ontogenesis, the function's primer aims at the achievement of the best possible conditions for procreation and their

maintenance for a certain time of reproductive activity corresponding to the period of homeostasis in the life cycle.

The operative primer of the gene, that is, its passage from the silent state to the state of informatic activity, is the basis of ontogenetic timing. This is a temporal chain device prompted by the environment through the "screw threader" of the regulatory and structural genes on which these depend. The regulatory genes act *in unison* with environmental forces on the timing of the species, while the structural genes furnish the proteins necessary to the development of the organism, both for the construction of the structures and for reaching the threshold on the level of which they can act directly or indirectly as derepressors of the operators destined to follow in the order of timing.

Ontogenetic timing is therefore a program of regulatory replacement genes, selected and rendered active by environment, which are on a "waiting list" of the appropriate derepressor. The structural genes of the respective operons proceed from these. Both types are then dependent on the timing of the gene, that is, on the operative potential that each gene has received through heredity which is designed to change into duration of the information placed at the disposal of the development calendar by the gene. This availability is precisely the chronon, the fundamental biological time from which ontogenesis draws the quantity of the information necessary for its program. Every single bit of information is available in the genes that are already prepared and definitive like those of the nervous system cells, or else in the copies produced by the duplication of the DNA molecules during the processes which supply new cells in accordance with the place, quality, quantity and time which are necessary to the organism.

In derepression, the threshold concept has a specific importance, both at the height which represents the critical intensity of derepressor stimulus, and at the depth which represents the critical intensity of operative stimulus. For greater precision, it is noted that the threshold value *(S)* signifies the quantity of information correlated to the duration of informatic flow, that is, to the chronon *(C)*. This flow is in turn closely correlated to the

stability of the gene, that is, to the value of the ergon *(E)*. Therefore, $S = E \times C$. On the other hand, threshold is a concept concerning the phenotype which signifies the minimum volume necessary to produce an effect and, as such, does not contradict the fact that the flow passes beyond the threshold according to the exigencies and the variability of the primer. This variability is stabilized within a population as a result of selection, but may recur within the fundamental biological time of the gene, that is, of the E/C system.

Ontogenesis therefore represents a closed mechanism, that is, a mechanism which looks after itself, programmed in its details commencing from the stage of the zygote, and requiring specific amphymixis to come about in a suitable environment. All of this occurs on the parameter of time in the sense that the course of the genic operationalism translates the potential chronon of every gene into an actual chronon (pheno-time), thus bringing it into play. Time, the ordinative parameter of the ontogenesis of the species, is likewise the program axis for the construction of the single individual in the species. The process that produces individualization takes place through a double temporal variability: the one of the E/C system of each gene which is of hereditary nature, and the one of the regulatory genes which is also of a hereditary nature but with an indirect effect from the environment. Paigan[1] recently noted that the transcription of structural genes coding for the enzymes of ontogenesis takes place at a variable rate according to the redundance of "Temporal genes."

During ontogenesis, some irregularities in development may take place which do not assume the significance of true pathology because they do not render the subject invalid and thus regulate themselves in a spontaneous fashion. Since the branch of medicine concerned with ontogenesis has been given the name "auxology," these subpathological forms are called "disauxias."

The study of disauxia is very important in order to check the E/C system during ontogenesis. Disauxias present significant cases of familial aggregations as observed in the two genealogical

1. Paigan, K.: Developmental genetics. *Excerpta Medica, International Congress Series, No. 32*:397, 1976.

trees of Figures 33a and b which concern speech retardation (five cases in the family) and delay in hair growth (six cases in the family). Language, as well as hair growth, depends on polymeric and polyallelic genotypes, so that while it is not possible to single out a responsible gene, it is not only possible but interesting to hypothesize the mechanism of the action which probably is due to an insufficiency of a regulating gene which fails in its function. It is less likely that these occurrences are related to a structural gene, because the retardation does not involve one component but all the phenes of function.

These insufficiencies are not permanent, that is, they do not deal with a privative mutation of the gene ergon because function subsequent to retardation becomes normal. They deal rather with a transitory insufficiency that, in the context of the E/C system, presents the possibility of explaining the two cases of ontogenetic retardation. Beginning with observation of a quantitative, temporary damage, the hypothesis of an ergon deficit may be accepted. In continuing development, the function's normalization could occur, for example, because of the slow ac-

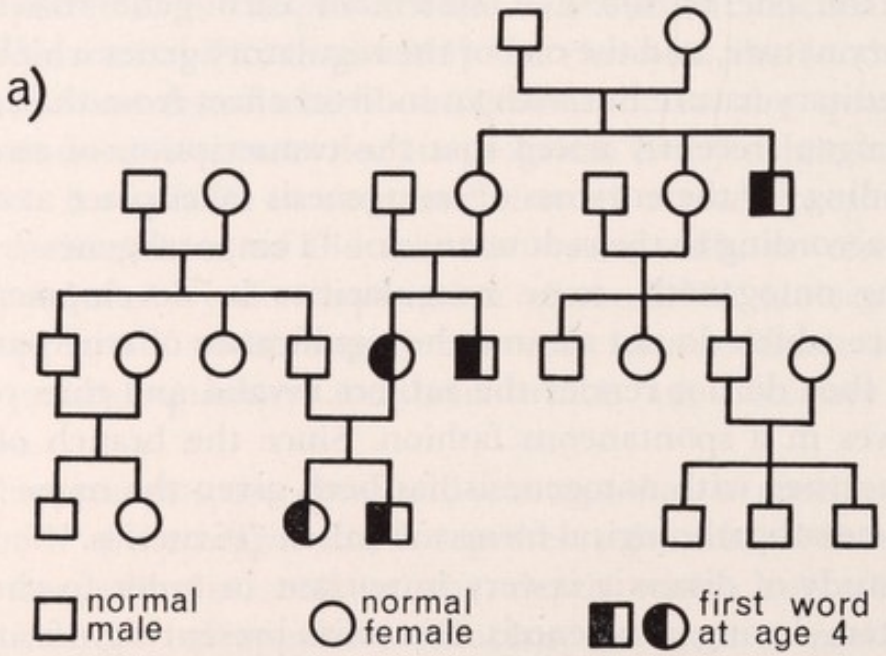


Figure 33a. Familial aggregation of disauxia showing speech delay: In a single family five cases are noted.

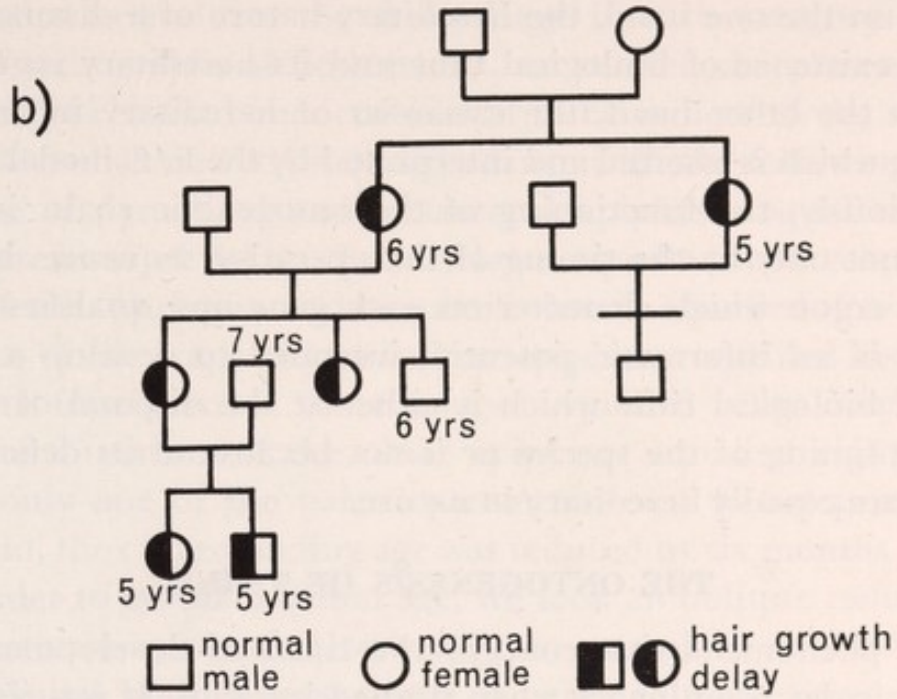


Figure 33b. Familial aggregation of disauxia showing delay in hair growth: In one family six cases are noted. The years indicate the age at which hair appeared.

cumulation of the product of information, previously insufficient until arrival at the primer threshold of the operative genes.

In every case, in light of the E/C system, these retardation phenomena presume a differential stability as well as differential times of the gene for the regulation and utilization of the information.

We believe it useful to report also the study by Bigozzi and coworkers[1a] of the delayed onset of puberty in fourteen index cases since this concerns probands of both sexes. The frequency of retardation in the family periods of the probands, compared with its frequency in the control family periods and analyzed with Haldane's sibship method, proves that delayed onset of puberty is surely brought about by a hereditary factor of dominant transmission and incomplete penetration. These researches

1a. Bigozzi, U., Toccafondi, R., and Morabito, F.: In *Proceedings Second International Congress Human Genetics, September 1961*. Rome, Mendel Institute, 1963, vol. I, p. 386.

prove, on the one hand, the hereditary nature of a disauxia, that is, the existence of biological time and its hereditary regulation, and on the other hand, the dynamics of hereditary information in time which is asserted and interpreted by the E/C model.

Obviously, the functioning of the ontogenetic chain is dominated not only by the timing of the operative sequence, but also by the ergon which characterizes each gene and qualifies it as a holder of an informatic potential intended to develop a fundamental biological time which is either at the disposal of the operative timing of the species or is not because of its deficiencies, which are equally hereditary in nature.

THE ONTOGENESIS OF TWINS

The phenomena that concern the times of development take on particular prominence when studied in twins. It was the study of twins, in the sphere of the broad, systematic investigations which they are given at the Mendel Institute of Rome, that suggested we devote ourselves to the hereditary nature of time, and we have often returned to twins to delve into problems relative to the stability and duration of information from various points of view. In fact, the high degree of concordance of monozygotic twins which is customarily utilized for the study of qualitative and quantitative characters also must be attributed to chronological characters, that is, to the various presentations of phenotime, in order to go to the study of the actual chronon, the potential chronon and the ergon.

We have studied many parameters of ontogenesis in monozygotic (MZ) and dizygotic (DZ) twin pairs of both sexes and in various ages of development. For the comprehensive view, we find it useful to fix our attention on the following parameters: (1) skeletal age; (2) dental age; and (3) menarche.

Skeletal and dental age were studied in twenty MZ twin pairs (ten male, ten female) and twenty DZ twin pairs (ten bimasculine and ten bifeminine pairs). Two pairs of the four categories indicated were of the following ages: five years, five and one-half years, six years, six and one-half years, and seven years.

In order to evaluate the skeletal age in each category on the basis of radiographs of both hands, we studied the presence and the form of certain bones considered to be indices of the skeletal age by Greulich and Pyle[2] in accordance with the following code: Presence of pyramidal and metacarpal epiphyses equalled three years; presence of the semilunary bone equalled four years; presence of the trapezius and scaphoid bones equalled five years; presence of the trapezoid and ulnar epiphyses equalled six years; complete formation of the trapezoid equalled seven years; and complete formation of the ulnar epiphyses equalled eight years. When only one of the paired parameters was found present in one hand, the corresponding age was reduced by six months.

In order to evaluate dental age, we took an oblique radiograph of the cranium intended to verify the complete mineralization of the dental buds of some teeth of permanent dentition. These were interpreted as follows: Complete mineralization of the 6th maxillary and mandibular equalled three years; complete mineralization for the 1st and 2nd maxillary and for the 1st and 2nd mandibular equalled four years; for the 4th maxillary and mandibular equalled five years; for the 3rd maxillary and mandibular equalled six years; for the 5th maxillary and mandibular equalled seven years; for the 7th maxillary and mandibular equalled eight years. At the level of four years, the intermediate values were given a reduction of three months for each unmineralized gemma; in every other age class there was a reduction of six months.

The determination of skeletal and dental age in each of the eighty twins examined on this basis led to a correlation coefficient r as follows:

	MZ	DZ
Skeletal age	0.94	0.81
Dental age	0.95	0.84

The significance of the coefficient is proved by Holzinger's in-

2. Greulich, W. W., and Pyle, S.: *Radiographic Atlas of Skeletal Development of the Hand and Wrist.* Stanford, Stanford U Pr, 1959.

heritance index (h^2)* for a value of 0.67 (probable error = 0.13) in the case of skeletal age, and 0.68 (p.e. = 0.14) in the case of dental age. In both instances, weight of heredity in the determination of the development times of the bones and teeth corresponds to two thirds of the causal factors.

The third research which concerned menarche was conducted on 167 MZ pairs and on 119 DZ bifeminine pairs living in Rome. The twin analyses gave the following correlation coefficients:

	MZ	DZ
Age of menarche	0.92	0.66

Holzinger's index is 0.75 (p.e. = 0.02) and thus we see that the influence of heredity in determining first menstruation is the highest among the research parameters, that is, it is equivalent to three fourths of the phenomenon. Chern[2a] et al have recently obtained a similar result studying the same parameters on a non-twin material consisting of 400 families and calculating the mother-daughter and sister-sister correlation values.

While these researches concern punctual times, such as mineralization of the bones and teeth or menarche, they more broadly involve stages of ontogenesis in the sense that the attainment of each stage presumes the end of the previous ontogenetic period and hence concerns its duration.

The first result of these investigations on ontogenesis of twins is therefore a full confirmation of our basic statement that ontogenetic timing is a function of heredity. Yet the significance of

* Holzinger's h^2 index (inheritance or heredity index) represents an estimate of the weight that heredity has on the manifestation of a given character. Such estimate is accomplished by comparing the interpair variances (σ^2) for a given character in monozygotic (MZ) and dizygotic (DZ) twin series. The usual formula is

$$h^2 = \frac{\sigma^2 DZ - \sigma^2 MZ}{\sigma^2 DZ}$$

and is based on the hypothesis that the variability between cotwins is, in the case of MZ twins, attributable only to the environment, whereas in the case of DZ twins, it is due both to environment and heredity.

2a. Chern, M. M., Bearman, J. E., Anderson, V. E., and Gatewood, L. C.: Inheritance of menstrual traits. *Excerpta Medica, International Congress Series, No. 465*:397, 1976.

twin research takes us a step beyond this. It especially calls attention to the meaning of the disparity of r between MZ cotwins, which is nothing like one would think, since MZ twins have an identical genome, but is in fact on the order of 6 percent for skeletal age, 5 percent for dental age and 8 percent for the onset of menstruation.

The weight of environment, evaluated on the discordance of

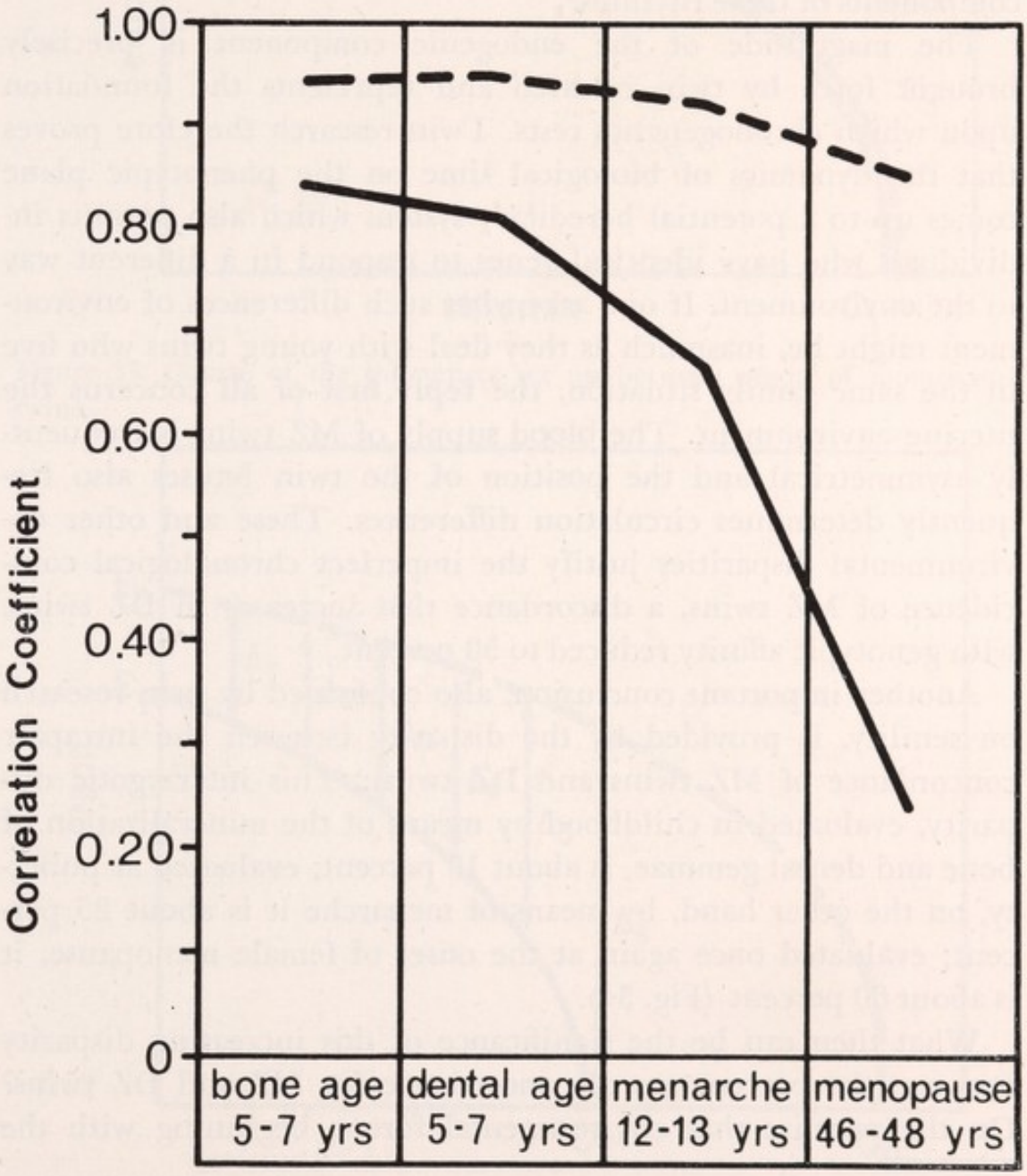


Figure 34. Course of the intrapair correlation coefficient in series of monozygotic twins *(dashed line)* and dizygotic *(solid line)*.

MZ twins for the three parameters considered, is reduced to 5 to 8 percent. This environmental variability is not only significant as proof of what we have stated many times, that is, that phenotypic times are of a mixed nature, but it is also significant as proof of the rather narrow margin upon which the influence of the rhythms induced by the environment work. How justified is Reinberg's[3] anxiety to penetrate the mystery of the hereditary components of these rhythms?

The magnitude of the endogenic component is precisely brought forth by twin research and represents the foundation upon which chronogenetics rests. Twin research therefore proves that the dynamics of biological time on the phenotypic plane comes up to a potential hereditary system which also permits individuals who have identical genes to respond in a different way to the environment. If one asks what such differences of environment might be, inasmuch as they deal with young twins who live in the same family situation, the reply first of all concerns the uterine environment. The blood supply of MZ twins is frequently asymmetrical and the position of the twin fetuses also frequently determines circulation differences. These and other environmental disparities justify the imperfect chronological coincidence of MZ twins, a discordance that increases in DZ twins, with genotypic affinity reduced to 50 percent.

Another important conclusion, also confirmed by twin research on senility, is provided by the disparity between the intrapair concordance of MZ twins and DZ twins: This interzygotic disparity, evaluated in childhood by means of the mineralization of bone and dental gemmae, is about 10 percent; evaluated at puberty, on the other hand, by means of menarche it is about 25 percent; evaluated once again at the onset of female menopause, it is about 60 percent (Fig. 34).

What then can be the significance of this increasing disparity between the percentages of concordance for MZ and DZ twins? On the premise that environmental forces, beginning with the

3. Reinberg, A.: In *La Recherche, no. 10, 2*:241, 1971. Biological rhythms. In Macorini, E. (Ed.): *Encyclopedia of Science and Technique,* 5th ed. Milan, Mondadori, 1953.

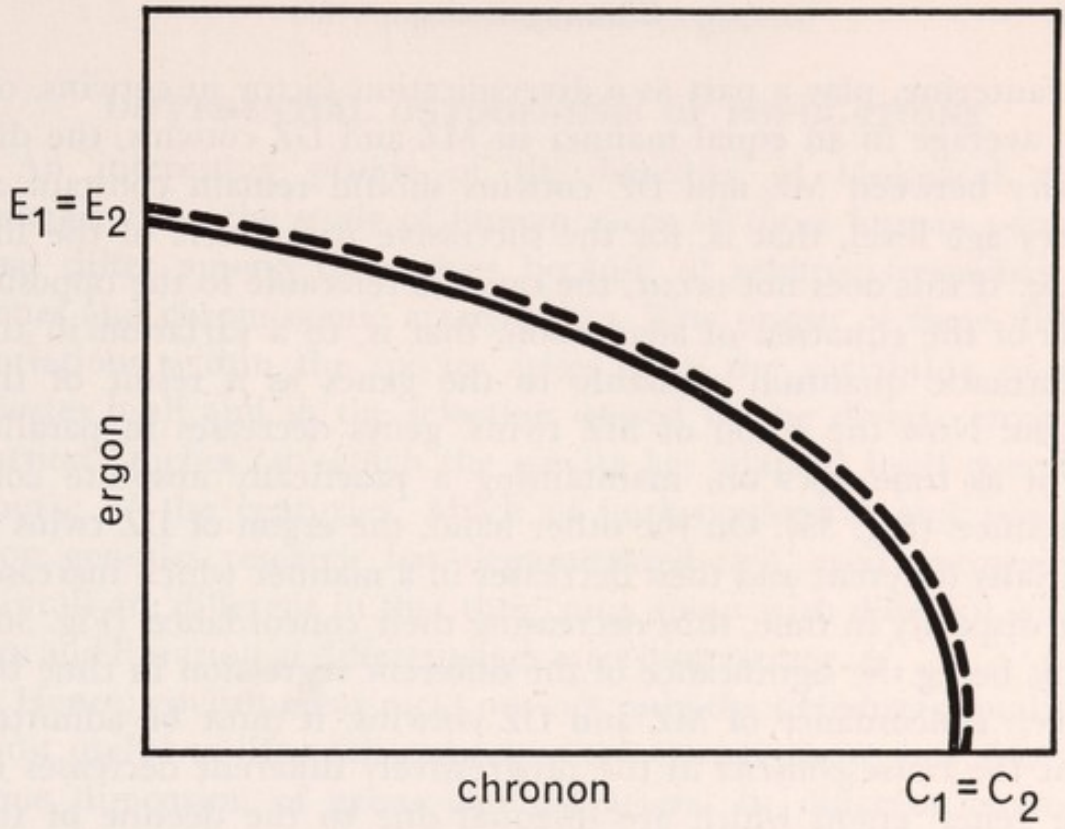


Figure 35. Course of the differences set up between ergon of monozygotic twins.

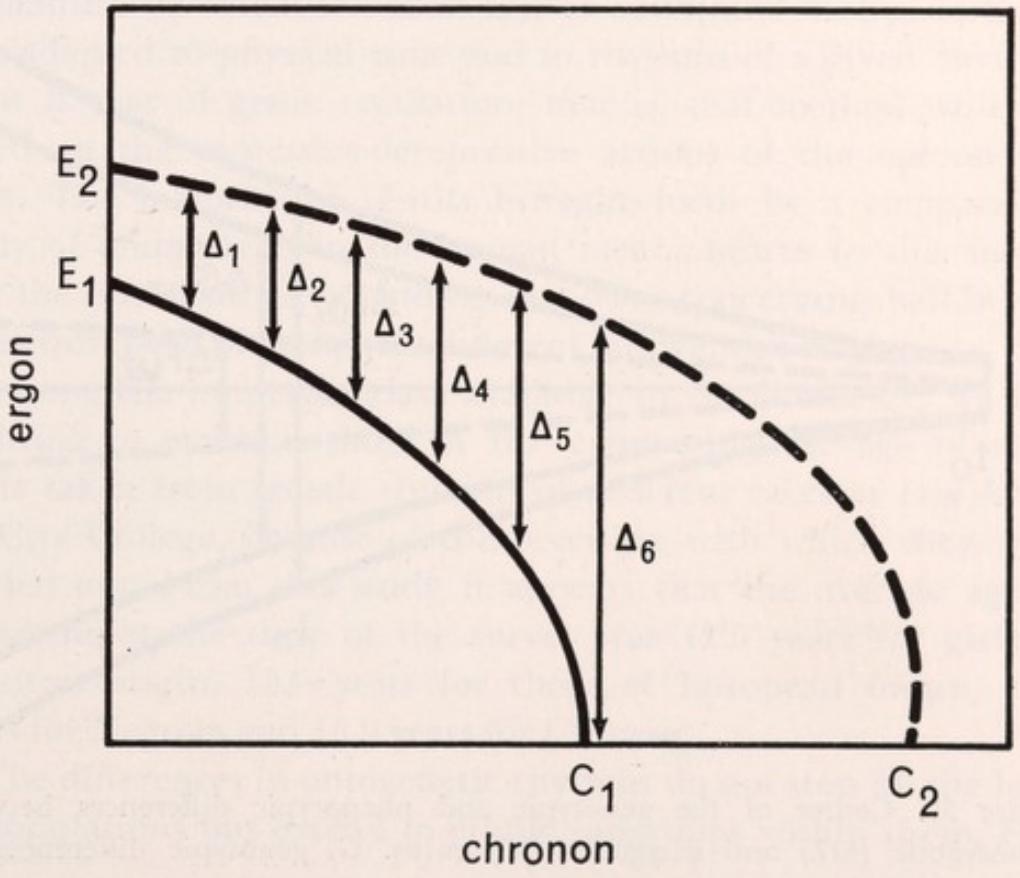


Figure 36. Course of the differences set up between ergon of dizygotic twins.

intrauterine, play a part as a diversification factor in cotwins, on the average in an equal manner in MZ and DZ cotwins, the disparity between MZ and DZ cotwins should remain constant at every age level, that is, for the successive parameters of the life cycle. If this does not occur, the cause is referable to the opposite side of the equation of adaptation, that is, to a variation in the informatic quantum available to the genes as a result of the ergon. Now the ergon of MZ twins' genes decreases in parallel form as time goes on, maintaining a practically absolute concordance (Fig. 35). On the other hand, the ergon of DZ twins is initially different and then decreases in a manner which increases the disparity in time, thus decreasing their concordance (Fig. 36). This being the significance of the different regression in time between concordance of MZ and DZ cotwins, it must be admitted that the cause consists in the progressively different decreases in the genes' ergon which are unequal due to the decline of the hereditary material as postulated by the E/C model (Fig. 37).

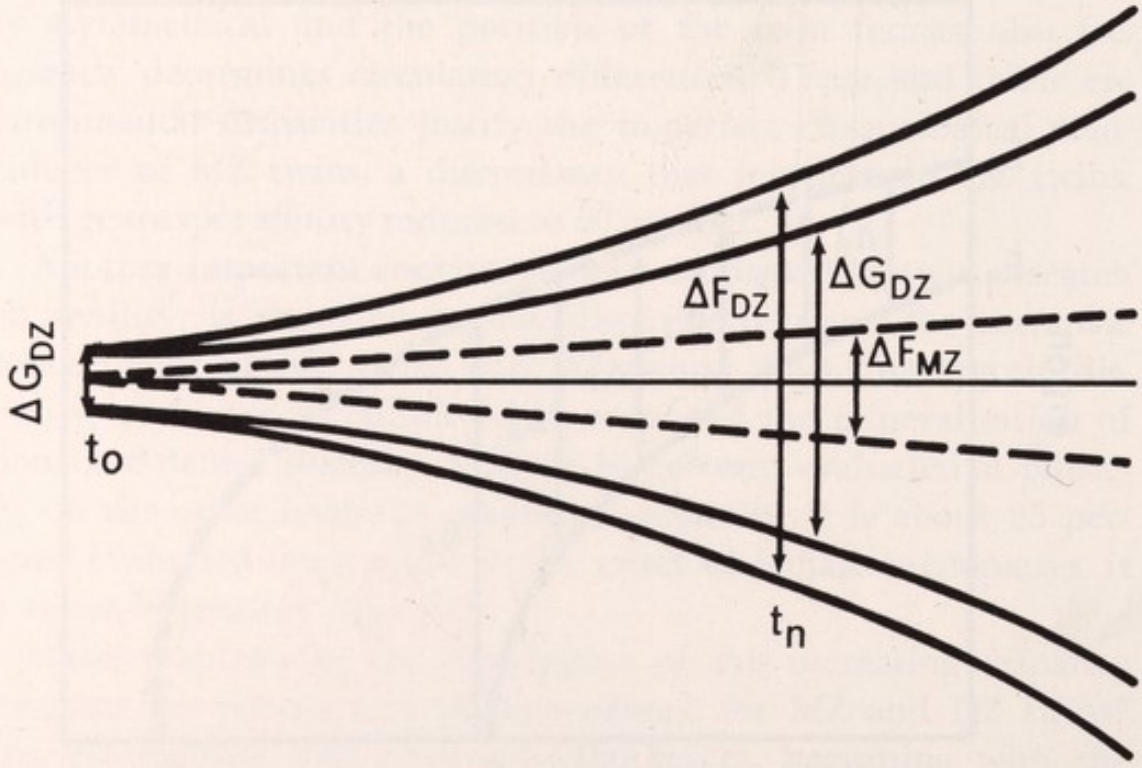


Figure 37. Course of the genotypic and phenotypic differences between monozygotic (MZ) and dizygotic (DZ) twins. *G*, genotypic differences; *F*, phenotypic differences; and *t*, time.

DIFFERENTIAL ONTOGENESIS OF POPULATIONS

An interesting profile of the heredity of biological time emerges from the study of human races, of those human peoples that differ among themselves because of relative frequency of genes and chromosomic arrangement. The origin of these differentiations within the species arises from the variability of the species itself and in the selection caused by the diverse environmental "niches" to which the species has adapted itself over the course of the centuries. Much of anthropological and population genetics research has demonstrated that even ontogenetic stimuli are different in that they come about with different intensity and duration at different ages according to race.

Hence, environment picks out not only the hereditary qualities most useful to life with respect to the environment, but also the time dimension of genes and characters. In different environments, the genotypes segregated according to an identical quality may give rise to different biological times. The most probable mechanism by which selection acts to determine biological times best adapted to physical time and to rhythms of a given environment is that of genic regulation, that is, that method which is based on the repressive-derepressive actions of the operon systems. The majority of results brought forth by a comparative study of ontogenesis in the human race conform to this model and the observations, including our own, concerning half-breeds (mestizos) born of races with different ontogenetic timing.

Among the numerous data available in the literature, we feel it fitting to mention those of Ito[4] concerning the age of menarche taken from female students of different races at Los Angeles City College, because of the precision with which they were carried out. From this study it appears that the average age of menarche at the time of the survey was 12.5 years for girls of Mexican origin, 12.9 years for those of European origin, 13.1 years for Negroes and 13.9 years for Chinese.

The differences in ontogenetic rhythms do not stop on the level of populations but extend to ethnic subgroups within them. Hal-

4. Ito, P. K.: In *Hum Biol, 14*:279, 1942.

TABLE XVIII

VARIABILITY IN SPEED OF GROWTH
IN DIFFERENT HUMAN POPULATIONS*

Populations	*Age Classes*			
	0.75 Years	*7.5-12 Years*	*12-15.5 Years*	*15.5 Years*
French	–†	+	+	–
Chinese	+	–	+	–
Japanese	–	– –	+ +	+
Indians	+ +	–	– –	–
Negroes	+ +	–	– –	–
Primitive American populations	+	+ +	– +	–
Filipinos			– –	+

* From P. Lester, and J. Millot, *Les Races Humaines,* 1936. Courtesy of Armand Colin, Publisher, Paris.

† + + is very accelerated growth.
+ is accelerated.
+ – is medium-normal.
– is retarded.
– – is very retarded.

brecht and collaborators[5] have proven that women belonging to Ashkenazi and non-Ashkenazi groups of Jews differ significantly both for distribution of age of menarche and for length of the menstrual cycle.

The table of Lester and Millot[6] illustrates the difference in the rate of growth of the different racial groups (Table XVIII). We obtained an additional demonstration of the influence of heredity upon the ontogenetic timing of the different races by studying timing in half-breeds of two parental races with diverse ontogenetic times.

Study of the data surveyed by Gedda, Serio and Mercuri[7] on the children resulting from the cross between Negro soldiers of the American armies and Italian women during the war years 1943 to 1945, from an anthropometric and population point of view, proves that the majority of the characters studied in the

5. Halbrecht, I., Sklorowski, E., and Tsafir, J.: In *Acta Genet Med Gemellol (Roma), 20:*384, 1971.

6. Lester, P., and Millot, J.: *Les Races Humaines.* Paris, Armand Colin, 1936.

7. Gedda, L., Serio, A., and Mercuri, A.: *Half-breeding in War and Other Cases.* Rome, Edizioni G. Mendel, 1960.

TABLE XIX

HEIGHT (cm) OF MULATTO CHILDREN AND OF AMERICAN WHITE AND NEGRO CHILDREN AT SIMILAR AGES*

Age	*Whites*		*Mulattoes*		*Negroes*	
(Years)	♂	♀	♂	♀	♂	♀
9	127	—	130	—	129	—
10	131	—	131.2	—	133.6	—
11	137	139	145	144.6	138.7	141
12	142	145	146	150	142.2	146.8

* From L. Gedda, A. Serio, and A. Mercuri, *Half-breeding in War and Other Cases,* 1960. Courtesy of Edizioni G. Mendel, Publisher, Rome.

samples composed of mulattoes present values intermediate between those of parental races.

This is true not only for the majority of the absolute values, but also for dynamic parameters of ontogenesis such as the skeletal age and dental age. It was possible to observe that the experimental values for both of these parameters anticipate the value predicted on the basis of available data on ossification and dentition in white individuals by about three months for whatever statistical age, whereas the same data appear late with respect to the ossification and dentition times of the Negro race. On the other hand, some anthropometric parameters of intermediate values present the phenomenon known by the name of "heterosis" or "hybrid vigor." For example, Gedda, Serio and Mercuri[8] studied the height of thirty-five mulattoes, according to age, and compared these values with the average height of Negroes and whites. The data are shown in Table XIX.

Using the average values shown concerning mulattoes and the corresponding values of whites reported by De Toni[9] and of Negroes reported by Royster and Hulvey,[10] we have constructed a graph (Fig. 38) that proves both the different development of the parental races and the statural heterosis of mulattoes on an age-related basis.

8. *Ibid.*

9. De Toni, F.: *Human Growth.* Brescia, Editrice La Scuola, 1954.

10. Royster, L. T., and Hulvey, C. N.: The relations of weight, height and age in negro children. *Am J Dis Child, 38:*1222, 1929.

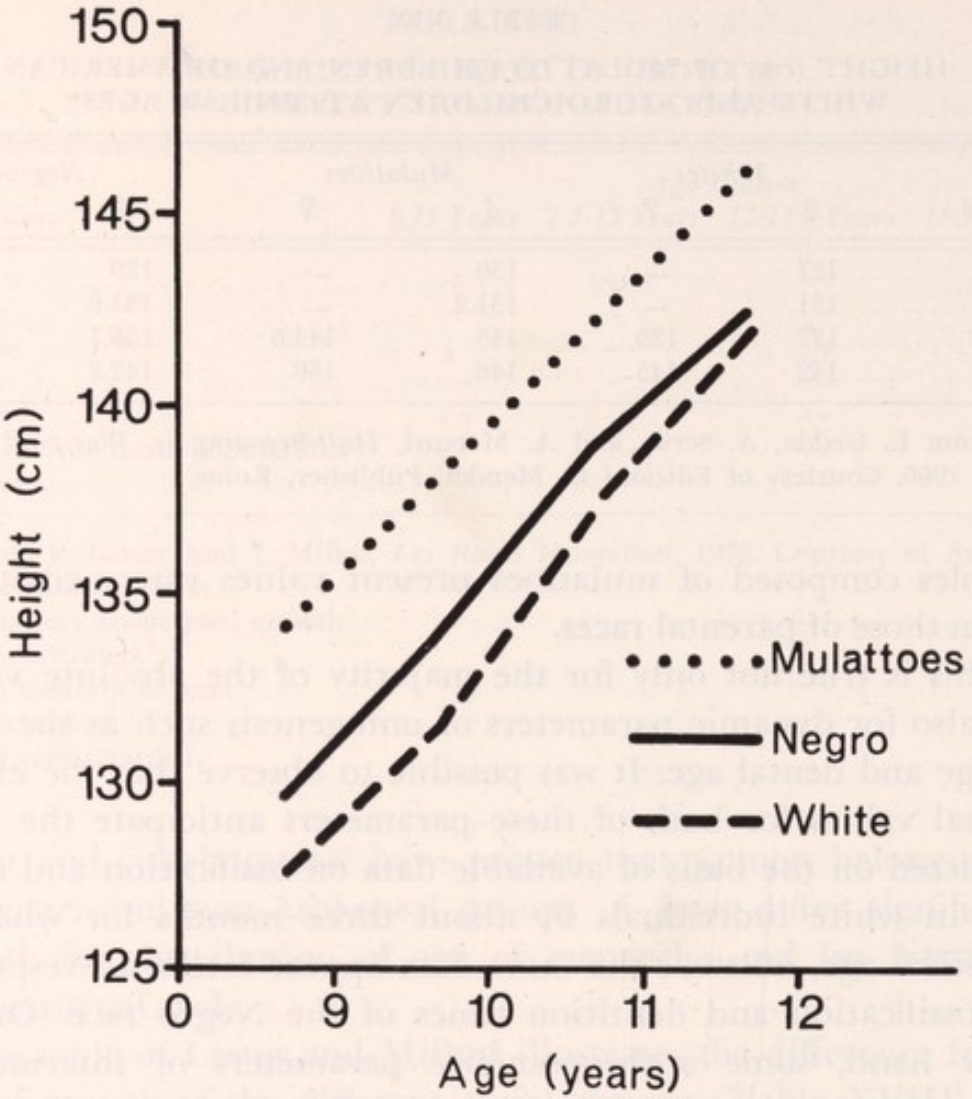


Figure 38. Difference in height development among parental races (White and Negro) and the respective mulattoes. (Data from F. De Toni, *Human Growth,* 1954, Editrice La Scuola, Publisher, Brescia; and L. T. Royster, and C. N. Hulvey, The Relations of Weight, Height and Age in Negro Children, *American Journal of Diseases of Children, 38:*1222, 1929.)

The genetic mechanisms operating in the various different cases are different because, as far as skeletal and dental age is concerned, segregation follows the Mendelian model of intermediate heredity, while as regards height, heterosis takes place. The hybrid vigor is a phenomenon that genetics has standardized in corn *(Zea mays)* and speaks of as being due to "epigenesis" or the effect produced by genotypic environment which influences the specific genotype. Evidently this deals only with a hypothesis,

whereas it is certain that the phenomenon of heterosis, like every other one which relates to development, concerns the inheritance of time. In our opinion, this name covers the modalities of the interaction of the alleles that have different states of stability, being the result of very different environmental selections.

CHRONOGENETICS, HOMEOSTASIS AND REGENERATION

One of the fundamental properties of life is adaptation, understood as the capacity of an organism to react to environmental stimuli. In the final analysis the adaptive reactions take place, in the majority of cases, by permitting the organism to survive and reproduce. This continuous relationship of action-reaction between environment and organism unfolds from the beginning of life (formation of the zygote) until the death of the organism.

The adaptive reactions that allow the unchanging continuation of the vital processes, notwithstanding variations and environmental shock, are called homeostatic physiological reactions. Obviously, homeostasis involves the entire life span, but the term is also used in a limitative and temporal sense in order to indicate the period of life interposed between ontogenesis and senescence and broadly interpreted as a period of state. The fundamental difference between adaptive reactions during ontogenesis and reactions which come about upon completed development lies in the fact that the former are part of an operative sequence already innate and causally determined in the ontogenetic "timing" of the species, while the latter occur sporadically, that is, punctually every time conditions capable of determining their activity manifest themselves in the environment.

This is a very general draft in that independent homeostatic regulations exist even during ontogenesis, just like successions of interconnected regulations likewise exist in the period of state and the subsequent period of senescence. All these mechanisms have as a common denominator that of producing a certain informatic activity necessary to the organism *hic et nunc*.

The continuous adaptation process of the organism to the en-

vironment occurs by means of operative mechanisms which act on different levels. The model of the operon clarifies the molecular support of homeostasis, which takes place by activation and repression of the regulatory and structural genes. Biological time is involved in these homeostatic reactions in that the continuous or extemporary responses of the organism to the promptings of the environment may occur. Ergon and chronon thus permit the involved gene to comply with the request, and the more the genic variability of the E/C system is selected in accordance with the environment, the more likely it is that this will happen, as was seen in connection with the races.

According to the aphorism of Beadle and Tatum, "one gene, one enzyme,"[11] the genic impact upon homeostatic regulation takes place on an enzymatic level: (1) through the induction of enzyme synthesis by means of the derepression of the operator genes; (2) through blockage of synthesis on the level of transcription (repression); and (3) through availability of energy, ribosomes, amino acids and other substances, on the level of translation.

For (1) and (2) the qualities of the genic ergon (redundance, synonymy, repair) and hence, the possible duration of the chronon, are directly involved. The dynamics of homeostatic balance occurs in optimal conditions as long as the E/C system permits it; when, however, the stability of the gene and the duration of the information are exhausted, the system's decay requires a replacement of the supply on the part of other genic complexes, and senescence begins.

On the plane of the homeostatic mechanisms immediately dependent upon heredity, that is, beyond enzymatic regulation, homeostasis occurs in many ways, for example, through feedback based upon the quantity of the substratum, of the coenzyme, or of the energy mediators, or else through mechanisms of a different nature, such as the variations in membrane permeability. In all these homeostatic articulations, heredity acts in a significant manner, but hereditary biological time is less easily disentangled from phenotypic and environmental interactions.

11. Beadle, G. W., and Tatum, E. L.: In *Proc Natl Acad Sci USA, 27*:499, 1941.

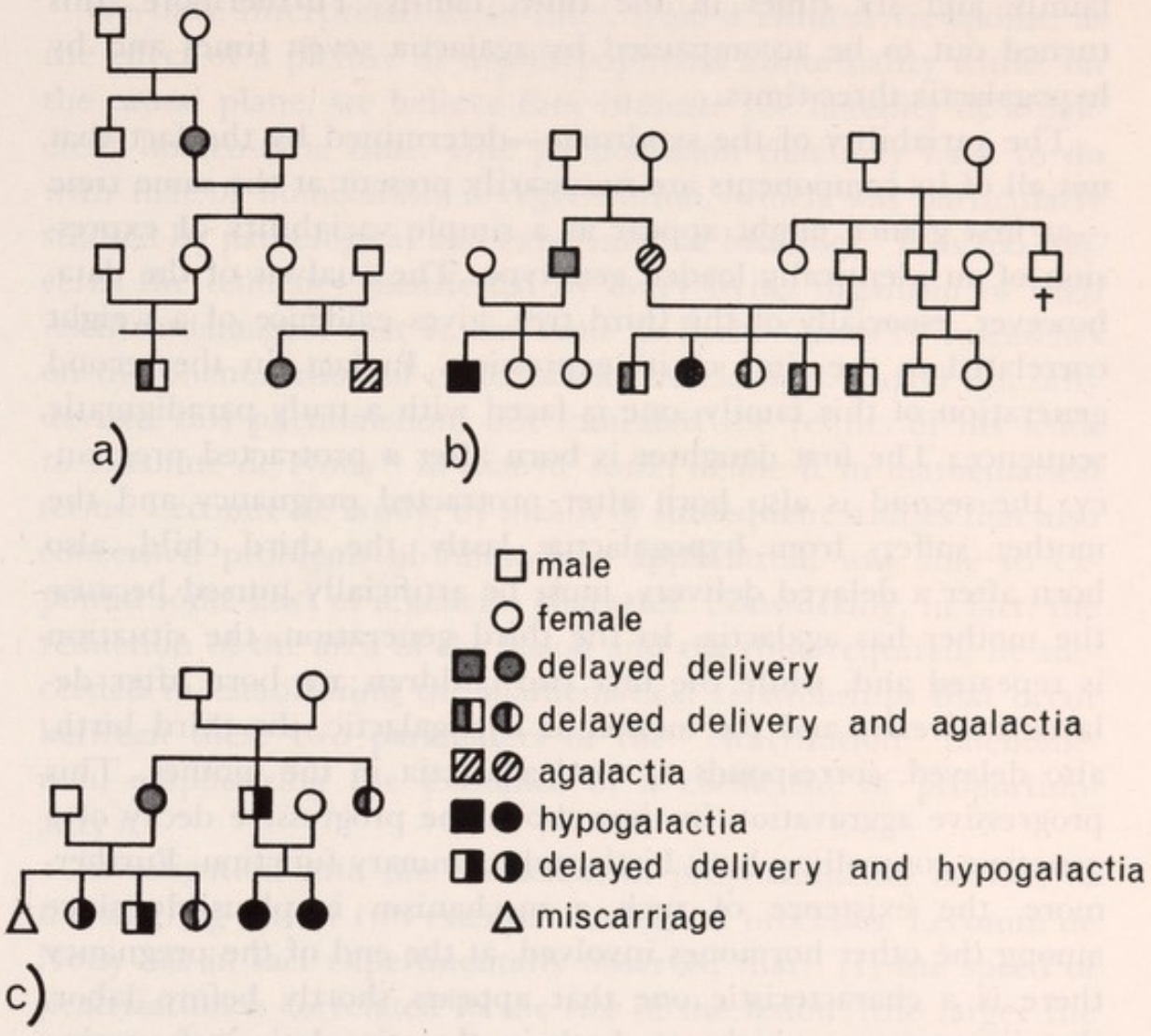


Figure 39. Familial aggregation of protracted pregnancy, agalactia and hypogalactia in three different family groups (*a, b* and *c*).

One level where hereditary biological time emerges and strongly imprints characteristic and important functions upon itself is the hormonal one. The control of endocrine production clearly begins with heredity, from the chronological point of view as well.

All of this can be exemplified on the basis of three families studied with Bolognesi.[12] A significant aggregation of protracted pregnancy was noted in these three families, that is, with a duration greater than 290 to 296 days (Fig. 39). Delayed delivery was verified three times in the first family, five times in the second

12. Gedda, L., Bolognesi, M., and Brenci, G.: In *Acta Med Auxol, 1*:115, 1969.

family and six times in the third family. Furthermore, this turned out to be accompanied by agalactia seven times and by hypogalactia three times.

The variability of the syndrome—determined by the fact that not all of its components are necessarily present at the same time—at first glance might appear as a simple variability of expression of an identically loaded genotype. The analysis of the data, however, especially of the third tree, gives evidence of a weight correlated to the time of its expression. In fact, in the second generation of this family, one is faced with a truly paradigmatic sequence: The first daughter is born after a protracted pregnancy; the second is also born after protracted pregnancy and the mother suffers from hypogalactia; lastly, the third child, also born after a delayed delivery, must be artificially nursed because the mother has agalactia. In the third generation, the situation is repeated and, while the first two children are born after delayed deliveries and the mother is hypogalactic, the third birth, also delayed, corresponds to total agalactia in the mother. This progressive aggravation in time shows the progressive decay of a genotype controlling both birth and mammary function. Furthermore, the existence of such a mechanism is plausible since among the other hormones involved, at the end of the pregnancy there is a characteristic one that appears shortly before labor, that is, oxytocin, which acts both in the stimulation of uterine contractions by increasing the permeability of potassium from the myometrial membrane, lowering the threshold of excitability, and on the level of the myoepithelial cells of the mammary gland causing, together with prolactin, the secretion of milk.

A gene with a reduced ergon in the control of the operon on which the information of oxytocin depends is, in our opinion, the most probable explanation of the situation described. In fact, the flow of information, lessened by the reduction of the ergon, does not permit the attainment of the operative threshold after a period longer than normal because of the accumulation of a quantity of information equivalent to that imprinted by individuals with analogous genes that are more efficient in average-normal time.

We have interpreted these cases, from a clinical viewpoint, as the effect of a picture of hypohypophysial abnormality while, on the causal plane, we believe they indicate the heredity of a deficient homeostatic time. One phenomenon that may have to do with that of homeostasis is regeneration, which was particularly studied by pathological and experimental histology. This too concerns the tendency manifested by every living organism to keep itself undamaged, that is, the same as itself. Carrel's[13] researches on the phenomenon of cicatrization are classical. Carrel not only devised this phenomenon, but indicated the results of his work to Lecomte de Noüy[14] so that he could define it in mathematical terms. Lecomte de Noüy, by means of subsequent studies that also concerned problems of immediate application, was able to expound some laws of a general character. Considering, in fact, the reduction of the area of the lesion and the time required, he succeeded in establishing the mathematical relationships that occur between these two parameters of the "cicatrization" phenomenon, emphasizing the existence of a coefficient of proportionality k.

Investigation into the coefficient of proportionality has led to the singling out of two essential biological processes. Lecomte de Noüy has in fact experimentally observed that: (1) the speed of cicatrization is correlated to the size of the lesion (the larger the lesion, the greater the speed); and (2) given an equal area of lesion, the speed of cicatrization is faster in younger than older people.

The experimental study of the course of the coefficient of proportionality, in connection with age and which Lecomte de Noüy declares to be a means of measuring aging, led the author to also define this factor in mathematical terms:

$$S = S_0 e^{-kt}$$

where S_0 is the initial surface of the lesion; e is the base of natural logarithms; t is the interval of time elapsing between the beginning of the lesion and the time when the surface S is measured;

13. Carrel, A.: *L'Homme Cet Inconnu,* Paris, Plon, 1935, p. 284.
14. Lecomte de Noüy, P.: *Entre Savoir et Croire,* Paris, Hermann, 1964.

and finally, k is the coefficient of proportionality, the measurement of aging.

Evidently the conclusions of Carrel and Lecomte de Noüy are easily placed in the widest framework of the E/C system when one thinks, in terms of molecular genetics, that injured tissue frees a derepressor of mitotic activity and that mitosis obeys specific genotypes which feel the effects of age through a decay of the ergon proportional to the duration of the chronon. Besides, Lecomte de Noüy's exponential equation practically overlaps the one we obtained hypothesizing the decay of a gene as a decay due to independent events.

Chapter VIII

Chronogenetics and Disease

CHRONOGENETICS AND SENESCENCE

When Terenzio[1] defined old age as a disease *(senectus ipsast morbus),* he unwittingly grasped the chronogenetic link uniting senility with disease, because senile involution and hereditary pathology are in fact connected in that they represent a diminution of the ergon below the genetic threshold, that is, below the required flow of genetic information corresponding to the organism's need. This analogy is pertinent but relative since, on the plane of a deficient ergon, old age is distinguished from disease in that in old age a total deficit is involved, while in disease, this deficit concerns a limited number of genotypes and, at times, a single genotype. At any rate, the common denominator of a deficient ergon is the reason we deal with senility and disease together. This subject is immense and cannot be discussed here in its entirety, therefore those aspects treated in this chapter have an indicative significance, that is, they serve as examples of the applications that chronogenetics can be considered to possess in the study of third age and disease.

Senescence corresponds to the period of life in which the majority of genes present a diminution in their ergon as a cause of a progressive diminution of informatic availability. This definition of senescence represents a corollary of the E/C system, that is, it derives directly from our interpretation of biological time. After the conclusion of ontogenetic timing and the period of homeostasis, the organism enters into a phase in which information begins to age, that is, in which there is a reduction in the volume and speed of the informatic flow. This phase concludes with the exhaustion of the duration of the chronon or the total absence of information.

Numerous objective data, both clinical and analytical, support this interpretation, commencing with the longitudinal study of

1. Terenzio, A. P.: *Commedie.* Bologna, Zanichelli, 1973.

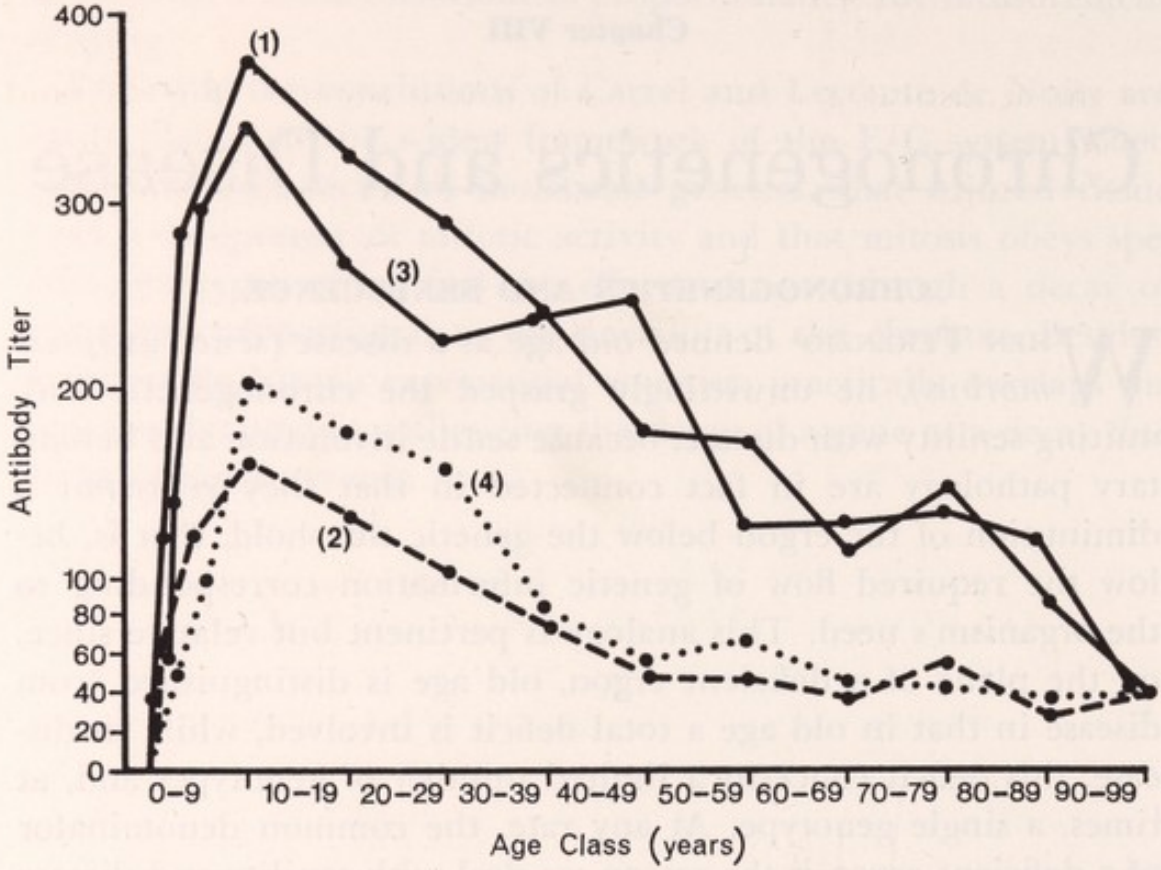


Figure 40. Antibody variation (isoagglutinin α and β of blood groups A, B, and O) according to age: (1) isoagglutinin α of group O; (2) isoagglutinin β of group O; (3) isoagglutinin α of group B; and (4) isoagglutinin β of group A. (From O. Thomasen and K. Keetel, in *Zeitschrift fur Immunitaetsforschung (Stuttgart), 63*:67-93, 1929. Courtesy of publisher.)

single pieces of information which correspond to a primary product of the gene. For example, with regard to natural antibodies of the blood groups, Thomsen and Kettel[2] were able to demonstrate (Fig. 40) that the levels of individual antibodies of the blood groups, in normal conditions of the host, increase during infancy to a maximum at ten years and then decrease in accordance with curves that follow similar courses and reach minimum values in the most advanced years.*

Analogous conclusions may be drawn from clinical data reflect-

2. Thomsen, O., and Kettel, K.: In *Z Immunitaetsforsch, 63*:67-93, 1929.

* In this connection, we wish to emphasize how much the most recent views concerning the structure and function of antibodies are in conformity with the genetic situations foreseen by the E/C system. Today, the antibody molecule, strictly specific with respect to the antigen, is thought to be composed of four amino acid chains united by disulphide bonds. Of these, two are produced directly by the re-

ing more complex phenomena where the informatic activities of numerous genotypes converge, as would appear from the curves of the acoustical perception of sound frequencies† (Fig. 41) and from the table on the adjustment of vision function‡ (Table XX). These conclusions show the quantitative diminution of the

sponsible cell: Of the two primary chains, one is longer or "heavier" (H), and the other shorter or "lighter" (L); each one is composed of a constant trait (c) and a variable trait (v). Each primary chain corresponds to two genes, one controlling the constant trait and the other the variable trait. The model described presupposes that, in the same cellular environment, the genes which codify the constant and the variable traits respectively have different somatic mutation rates, these being the variability produced by mutation. In order to admit—as required by the theory and numerous observations upon which this is based—this diversity between "constant genes" and "variable genes," it is necessary to assume a differential stability, given their identical environment, and hence the necessity of conceiving the genes that codify the constant traits and the variable traits of the antibodies as genes with different ergons. The greater or lesser stability of these genes placed before immunological defense explains the normal and pathological hereditary variability of the immune system.

† In presbyacusia, that is, a decrease in acuteness of hearing, three elements are conspicuous: the hereditary element, the ecological element and the occupational element. Auditory senescence is the result of three factors: physiological presbyacusia due solely to age, socioacusia resulting from the environment, and occupational deafness. The etiology of pure presbyacusia has not yet been completely clarified, since two principal causes are identified today, both of a degenerative nature but involving two distinct anatomic divisions, that is, the membranous labyrinth and the acoustical ganglion.

‡ New fibers of the crystalline lens continue to be produced until the most advanced age, so that as the crystalline lens ages it increases in dimension and weight. The nuclei and cell membranes of old fibers disappear by losing water, contracting, compressing the nucleus of the crystalline lens and becoming hornlike and stiff. The remnants of the cellular nuclei in the adult nucleus of the crystalline lens can be seen with a slit lamp. The cortical stratum begins to become pigmented and lose its permeability. Colloidal bodies may appear. Chemically, the process can be defined as an increase in insoluble proteins, in lipids and in calcium, and similarly a reduction of glutathione, vitamin C and oxidative processes. These changes are alterations in metabolism. Their effect consists of a decrease of the malleable cortical stratum of the crystalline lens with respect to the hardened nucleus as to produce a reduction in the power of adjustment from birth until the most advanced age. This modification proceeds continually and slowly; it is not a cause of inconvenience until the time when adjustment is no longer possible. Atrophy of the ciliary muscle may carry out a part of the process, but it has been proved that such muscle is capable of contracting much more than necessary under normal conditions in order to produce maximal adjustment, and hence its role is of secondary importance. It has also been suggested that the development of presbyopia occurs parallel with the body's aging and can be considered as an index of the average life span foreseeable for an individual.

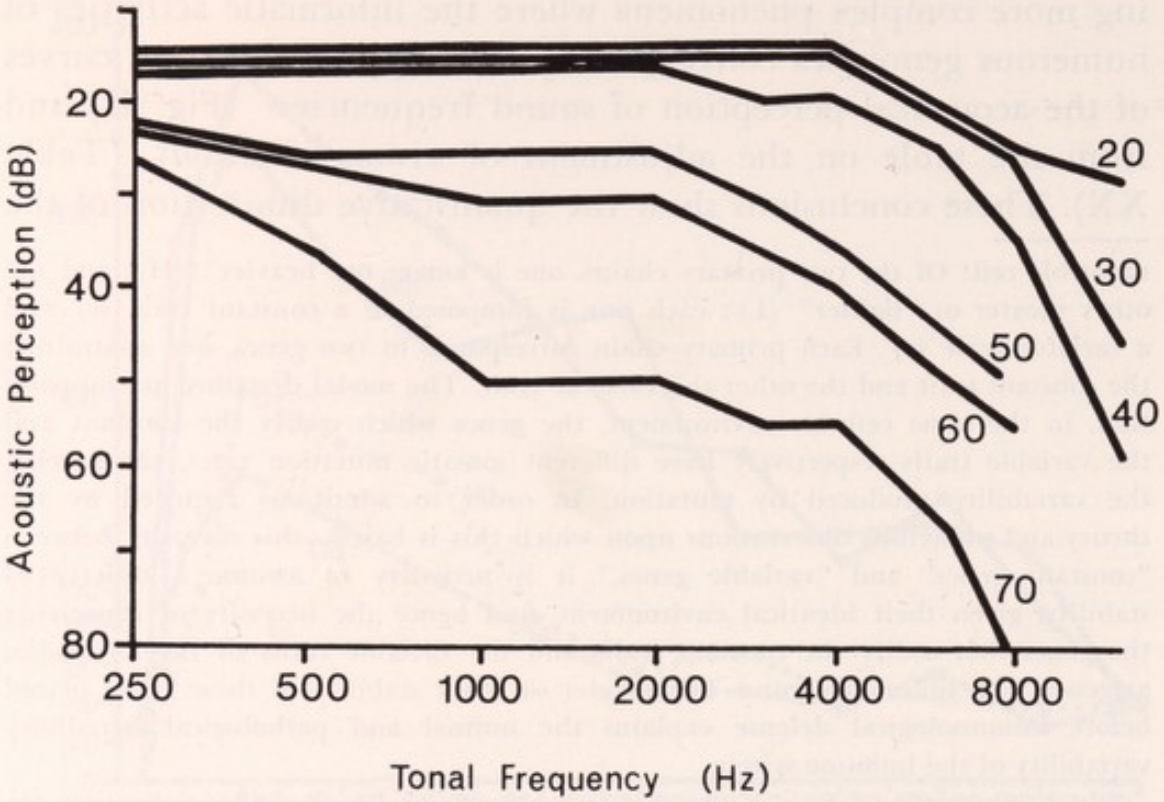


Figure 41. Variation of acoustic perception relative to sound frequencies according to age, expressed in years on the various curves. (From M. Portmann, and C. Portmann, *Précis d'Audiométrie Clinique,* 1954. Courtesy of Masson et Cie., Publisher, Paris.)

corresponding information through a progressive reduction. Analogous data can easily be gathered in connection with other functions: We limit ourselves to reproducing a synthetic graph published by Strehler and Midvan[3] which expresses the decline of a group of functional indices (Fig. 42) with age.

In order to demonstrate that the phenomena of phenotypic decline characteristic of senescence are epiphenomena of changes which take place on the genotypic plane, it is necessary but insufficient to show, as has been seen in connection with isoagglutinins, that there exists an aging of information analogous to that of organic functions. In order to go from hypothesis to proof, it is necessary to prove the hereditary nature of the phenomena regarding senescence, and we have provided this by studying three parameters of aging with the twin test: (1) the

3. Strehler, B. L., and Midvan, A. S.: In *Science, 132*:14, 1960.

TABLE XX

ADJUSTMENT OF VISUAL FUNCTION ACCORDING TO AGE*

Age (Years)	*Extent of Adjustment*	*Proximate Point (cm)*	*Age (Years)*	*Extent of Adjustment (diopters)*	*Proximate Point (cm)*
10	14.0	7.0	45	3.5	28.0
15	12.0	8.5	50	2.5	40.0
20	10.0	10.0	55	1.75	55.0
25	8.5	12.0	60	1.0	100
30	7.0	14.0	65	0.75	133
35	5.5	18.0	70	0.25	400
40	4.5	22.0	75	0.00	

* From C. E. May, *Malattie Dell'occhio,* E. Trobetta, ed., 1925. Courtesy of U.T.E.T., Torino, Publisher.

appearance of the first grey hair; (2) the use of eyeglasses for correction of presbyopia; and (3) the onset of menopause (Table XXI).

The result of the twin test for these parameters shows the hereditary nature of the individual senile phenomena which therefore should be referred to as a decline of hereditary information that, in its turn, finds a logical explanation in the decay of genetic stability. Another piece of evidence showing aging to be the phenotypic expression of a process taking place at the genotypic level is provided by the hereditary character of premature senility syndromes, such as progeria or the new entity described by Salinas et al.[3a] at the recent Fifth International Congress of Human Genetics. On this basis, the interpretation of senescence becomes obvious for each component of its total picture, and senescence may be related to a diminution of the ergon in the corresponding genotypes. In this way, it is important to note that clinical variability of aging also becomes clear on the basis of the Mendelian principle of the independence of characters. Since the individual genome is derived from the fusion of the haploid supply of paternal and maternal gametes, it is possible to explain

3a. Salinas, C. F., Jorgenson, K. J., Schuman, S. D., and Goust, J. M.: A possible new premature aging syndrome. *Excerpta Medica, International Congress Series, No. 246:*297, 1976.

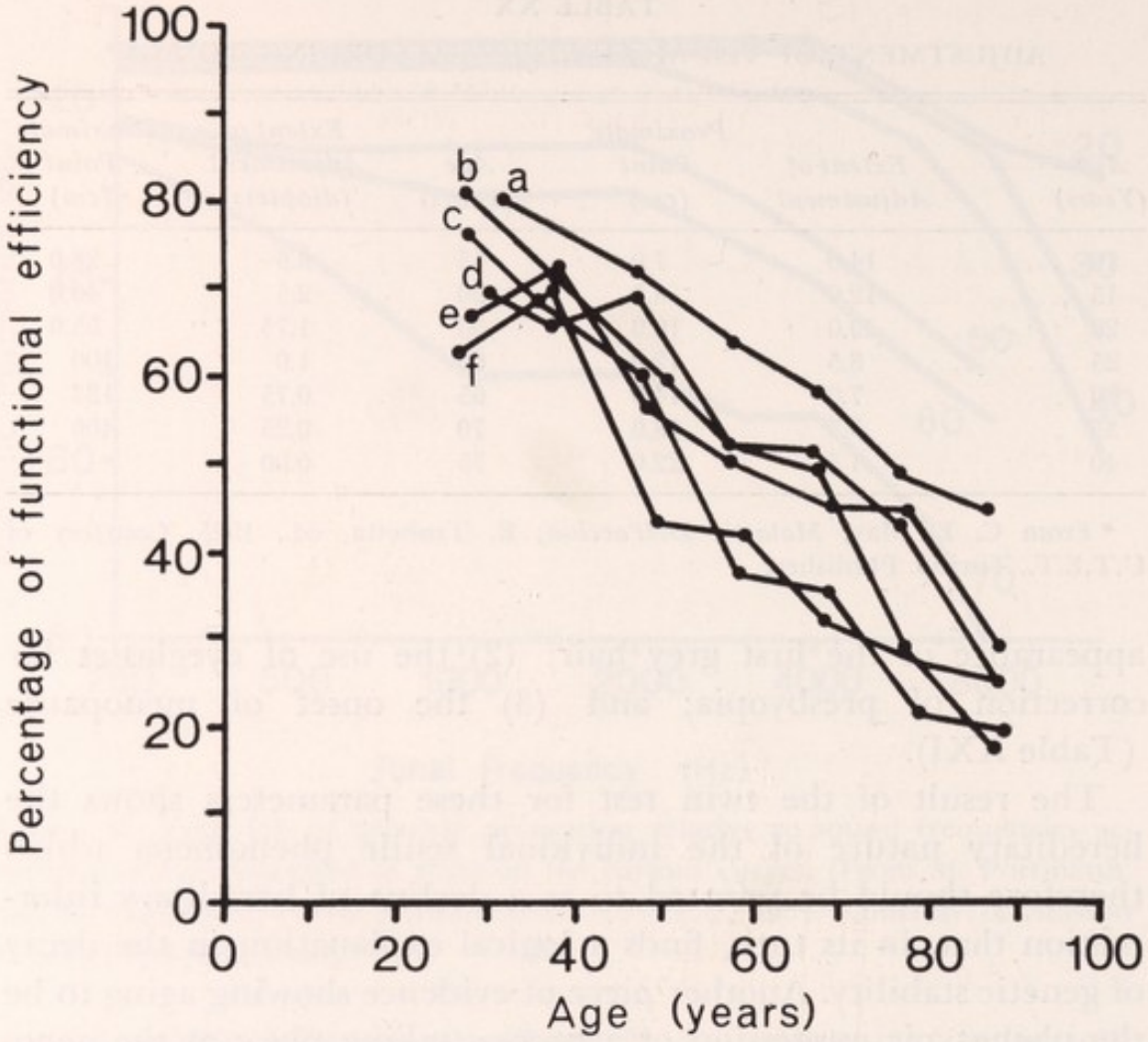


Figure 42. Age-related decline of some functional indices in man: *a*, maximum respiratory ability; *b*, standard renal range; *c*, standard cellular water content; *d*, standard glomerular filtration rate; *e*, speed of neural conductivity; and *f*, cardiac index. (From L. Strehler, and A. S. Midvan, in *Science, 132*:14, 1960. Courtesy of publisher.)

how hereditary units of different stability, that is, genes with different ergons, join in the individual heredity, giving rise to diverse combinations in the genotype of the individual, not only because of the information's quality, but also because of the different stability (ergon) and hence because of duration (chronon). From this derives an increasing degree of affinity for each piece of information as regards informatic stability in the population, in the family and in sibship respectively, an affinity which

TABLE XXI

INDICES OF SENESCENCE IN MONOZYGOTIC (MZ) AND DIZYGOTIC (DZ) TWINS

Parameters of Senescence	*Twins*	*Number of Pairs Examined*	*Coefficient of Correlation*	*Average and Disparity*	*Holzinger's Index (H^2)*	*Probable Error of H^2*
First grey hair	MZ	38	0.96	36.9 ± 9.5	85%	± 3%
	DZ	35	0.73			
Adoption of eyeglasses	MZ	35	0.86	48.8 ± 5.9	86%	± 3%
	DZ	24	0.04			
Onset of menopause	MZ	14	0.85	46.2 ± 4.2	79%	± 7%
	DZ	6	0.23			

theoretically attains identicalness in the case of monozygotic twin pairs. On the other hand, genotypic variability causes not only an interindividual variability but also a variability in the stability between genotypes of a selfsame genome in the sense that each specific genotype has its own curve of decline, and this causes it to age in a characteristic way.

The explanation of senescence according to the E/C model is also capable of pointing out the validity of the theories of aging suggested up to this point, theories which are now able to converge on the common denominator of the model based on the inheritance of biological time. Be it understood we allude to interpretations which in some way concern the genotype, because the theories restricted to the phenotypic plane offer partial explanations which cannot be considered satisfactory.

Szilard,[4] who attributes the progressive inactivation of chromosomes or groups of genes to mutagenic "hits," as well as Strehler and Midvan,[5] who ascribe the damages in heredity which come about with the passing of time to the energy fluctuations of the physicochemical cellular environment, are certainly right in pos-

4. Szilard, L.: In *Proc Natl Acad Sci USA, 45*:30, 1959.

5. *Op. cit.*

tulating the intervention of mutagenic factors, but they limit the interpretative capacity of their model when they maintain that mutagenic action comes about by chance with respect to the genes making up individual heredity. Sinex[6] indicates the transiency of DNA molecules as the reason they are easily damaged and thereby result in aging; Medvedev[7] stresses the likelihood that the damage responsible for senescence is the one that strikes the regulatory genes; Burch[8] maintains that the mutagenic action of the environment shows a predisposition on the part of a fraction of the population as a cause for aging. These authors are correct in calling attention to hereditary matter and the damage charged to it as a cause of aging; however, they express opinions which do not come to the heart of the problem. In reality, the problem consists of the heredity variability of genic stability determining the different survival rates of individual genotypes exposed to the same mutagenic actions of the environment. Furthermore, we object to the more general theory of Medvedev who maintains that senescence is a disordered ontogenesis. This is an opinion and not an interpretation. On the other hand, it is true that even in the undeniable disorder there exists an order, that is to say, an explanation which consists of the different degrees of stability of the individual genotypes, received and transmitted in accordance with Mendelian models of heredity, extending its authority to the energy parameter, to the duration and efficiency of information and hence to fundamental biological time.

The gene's chronology, based on its degree of stability, explains aging—as has been seen—in that stability is subject to a progressive and total decay, even though different according to individuals and specific genes and due to environmental mutagenic action. This decay not only maintains a firm hold onto structures and functions at the histological level, but in particular acts at

6. Sinex, M. F.: In *Science, 134:*1402, 1961.

7. Medvedev, Z. H. A.: *Protein Biosynthesis and Problems of Heredity, Development and Ageing.* Edinburgh, Oliver & Boyd, 1966.

8. Burch, P. R. J.: *An Inquiry Concerning Growth, Disease and Ageing.* Edinburgh, Oliver & Boyd, 1968.

the cytological level, for example, on a basic function like mitosis. The cycle of mitosis is strictly controlled by heredity as far as its times and limits. It has already been seen, as regards regeneration, how senile exhaustion of the ergon corresponds to a decreasing efficiency of mitosis, which is then translated into a greater slowdown of the regenerative process.

The progressive, universal degradation of heredity, indicated by the consumption of biological time, represents a type of inevitable illness that is common to all living organisms but that does not directly close the vital cycle. In other words, it does not represent *sensu strictiore* the cause of death, but for the fact that within this general exhaustion, an information necessary to life becomes absent at a relatively earlier time. This specific deficit represents the cause of death.

DISEASE AND ERGON/CHRONON SYSTEM

In the continuous context of physiological "timing," disease signals its presence in a characteristic and revealing manner. This is especially true in hereditary diseases which are directly caused by the exhaustion of the ergon and hence by the end of the chronon of one or more pieces of information. This deficit can occur at the beginning of life, or precociously in the period of autonomous life or even later, but in every case sooner than the usual and contemporaneous aging of all the genome's information. In addition, exogenous pathology often contributes to the deficit that follows upon the reduction of the chronon of a gene, though indirectly, through damage caused to genotypes predisposed to natural defenses.

In this manner, the pathogenesis of a hereditary disease theoretically and sporadically corresponds to the situation which takes place during senescence for the genotypes. They exhaust their informatic load, the difference being that, in the case of the informatic deficit of a hereditary disease, such a situation concerns a limited group of genes which, in suspending their activity, at times acutely disturb the homeostasis of an organism in biological equilibrium, whereas in senescence the deficit situation is more vast and its course is usually chronic.

Certain diseases exhibit this phenomenon in a paradigmatic manner, as evidenced by "sailor's skin," the result of intense and protracted exposure to the ultraviolet rays of the solar spectrum which produces—even in young people—the condition of wrinkled, rigid skin more frequently seen in senility.

As regards the damage that the deficient genotype responsible for disease may occasion, it is necessary to establish a classification of the genes that enter into stability crises. The division of genes into categories of "lethal," "sublethal" and "relatively fit," as employed by general genetics, is useless in that this division is limited to a statistical concept regarding the number of bearers of the gene that survive conception and the reproductive moment in a given population. For the purpose of clinical medicine as well as medicine in general, what is needed is a classification that considers the possibility of life at the various age levels of a life cycle which has already begun, leaving out of consideration the characteristics of the reproductive phenomenon that concern the particular species. From the chronogenetic point of view, genes may differ, as shown by the following.

1. *Geni quoad vitam,* when the presence of information, corresponding in quantity to the threshold of genic expression, is a condition making the organism's life possible. The genes containing essential information such as for the synthesis of polimerase and other enzymes necessary to nuclear metabolism are *quoad vitam* genes.

2. *Geni quoad valetudinem,* when the presence of information is necessary for good health but not indispensible for life that can continue even in its absence. For example, the genes whose action may be substituted, at least in part, by various homeostatic mechanisms are *quoad valetudinem* genes.

3. *Geni ad abundantiam,* when the corresponding information is not essential either for the life or the health of a subject. For example, the genes responsible for hair color and persistence are *ad abundantiam.*

The destinies of the organism and its corresponding clinical conditions differ greatly according to whether the reduction of

an ergon and the corresponding chronon strikes a gene that belongs to one or the other of these categories.

Whatever the hierarchy of the gene may be in relation to the organism's life, every gene, as far as its temporal parameter is concerned, can be classified, according to the duration of its information, as being provided with:

1. null and void chronon, when the information is absent in the zygote;
2. reduced chronon, when the information comes to an end before the average-normal age of dying out;
3. normal chronon, when the information is present in a quantity greater than the threshold value necessary for the average-normal duration of the information itself.

Hereditary disease or death intervenes when the quality of the null and void or reduced chronon concerns a *quoad valetudinem* or *quoad vitam* gene.

In Figure 43, the correlation of the E/C system with health and disease is shown. In the circle that represents the gene of the individual, I is the information contained in the gene and E is the ergon or degree of the gene's stability. In the rhombus that represents the phene, P is the quantity of protein synthesized on the basis of the information, transmitted via the phases of transcription (t') and translation (t''), and C is the chronon or duration of information in direct proportion to the ergon's values and the quantity of protein (primary product of the gene) placed at the disposal of the organism.

On the upper level, the value of the normal ergon permits a normal duration of the chronon and therefore furnishes normal information and the production of a normal phene.

At the middle level, the value of the ergon is less than the normal, and therefore the chronon is reduced; at the time of the chronon's exhaustion, the specific protein begins to fail in the phene, and the corresponding hereditary disease will become evident.

On the lower level, the ergon is absent and therefore the information is lacking in the embryo. According to the type of gene

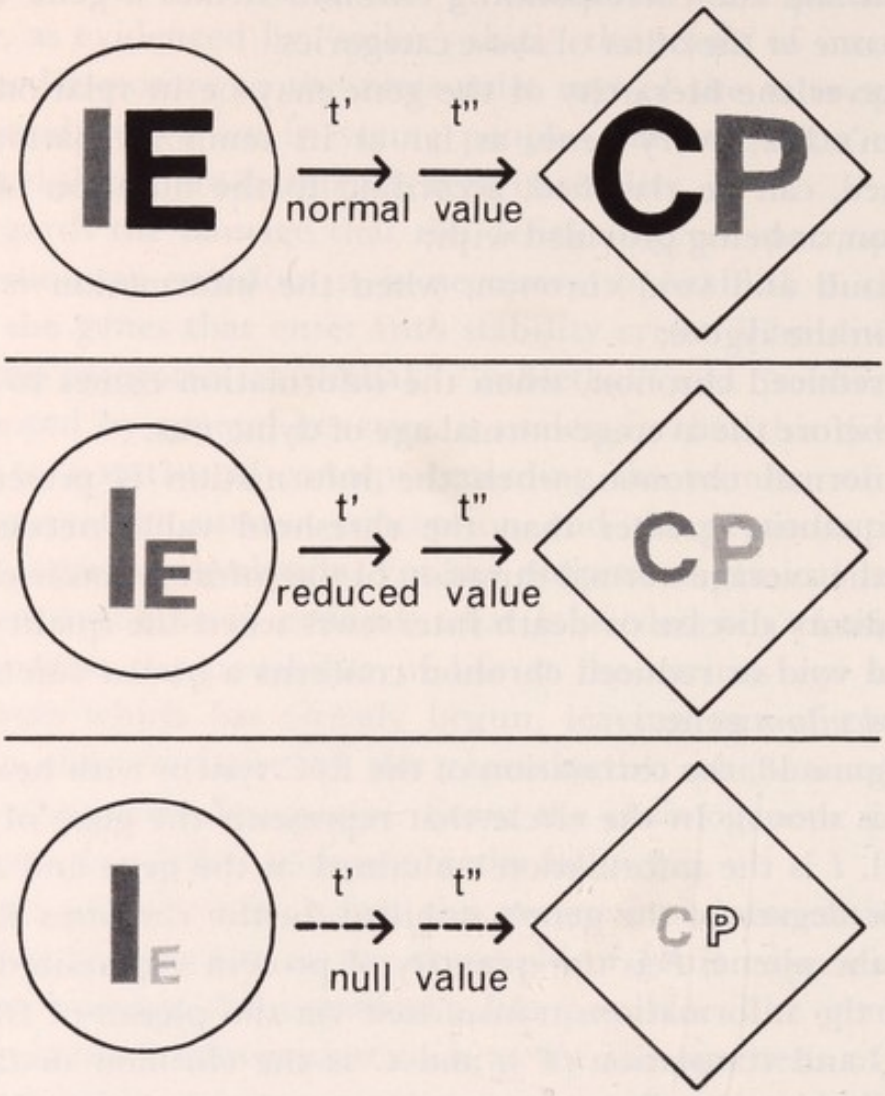


Figure 43. Correlation of the ergon/chronon system with the state of health/disease of an individual. Every circle represents the gene with a piece of information *I* and an ergon *E*, that is, a stability that varies in the three cases considered: normal situation; situation with reduced ergon; and situation with ergon practically null and void. Every rhombus represents the phene, and P is the protein of the organism synthesized via transcription *(t')* and translation *(t")* of the information *I* of the gene. *C* is the chronon, that is, the duration of such information; it too is variable. In the situation with reduced ergon *(at the center of the figure)*, the chronon also is smaller. For this reason, at a certain time, since the information is lacking, the protein can no longer be synthesized, and this deficiency will cause a hereditary disease to appear. When the ergon is practically nil *(at the bottom of the figure)*, the information already begins to fail in the embryo and causes embryopathy, malformations or the death of the conceptus. (From L. Gedda, and G. Brenci, in *Scienza e Tecnica, 72*:175, 1972. Courtesy of Mondadori, Publisher.)

involved, this may cause an embryopathy, a malformation or the death of the conceptus.

In the majority of cases, the consequences of a null and void ergon on the ontogenetic level escapes control in that the arrest of the embryogenetic processes because of the lack of a link formed by the protein that must be produced by the gene with a null and void ergon is resolved by the death and elimination of the conceptus. The complexity resulting from the existence of the gene with a null and void ergon may be realized when one thinks that the enormous number of malformations gathered up to now by teratology represents only a minute part of the changes rendered possible by operative arrests of embryogenesis. The inheritance of these changes is beyond any doubt, since it is possible to show that the frequency of malformations in the population is constant for a given environment-population combination, while the likelihood of malformations increases four times in the subpopulation made up of families in which a malformation has already occurred. One apparent exception to genetic determinism is provided by induced malformations, for example, the thalidomide-induced phocomelias. This exception is apparent in that the etiopathogenetic mechanism in this case is partially hereditary. In actual fact, it deals with the blockage of an operon brought about by the action of an external repressor, thalidomide. However, the threshold value of the repressive action is a function of the involved operon's stability, as has been shown by the birth of both healthy babies and malformed babies among mothers who had taken the drug in equal dosages at the same period of gestation.

The impact of biological time in disease, which we shall discuss in a more detailed fashion later, as far as the genealogical and clinical perspective is concerned, also stands out when the phenomenon of disease is considered from the standpoint of population genetics. In reality, by subjecting the data contained in the reports of the World Health Organization[9] to chronogenetic analysis, it is possible to make interesting observations concerning, for example, malignant tumors of the respiratory sys-

9. World Health Organization. *World Health Statistics Report, 25*:4, 1972.

TABLE XXII

RATE OF DISEASE PER 100,000 INHABITANTS CONCERNING VARIOUS NEOPLASTIC DISEASES IN SELECTED COUNTRIES IN 1969*

Age Class	*Tumors of Trachea, Bronchi and Lungs*				*Tumors of the Liver and Biliary Paths*				*Acute Leukemia*			
	U.S.A.	*England*	*Poland*	*Israel*	*U.S.A.*	*England*	*Poland*	*Israel*	*U.S.A.*	*England*	*Poland*	*Israel*
1-4	—	0.1	0.1	—	—	—	—	—	2.8	4.4	3.2	4.3
5-14	—	—	0	—	—	—	0	—	3.1	2.1	2.1	2.8
15-24	—	0.1	0.1	0.2	—	0.1	0.2	0.4	3.3	1.8	1.6	3.9
25-34	1.7	1.6	0.5	0.3	0.6	0.7	0.7	1.2	1.7	1.5	1.3	2.2
35-44	9.7	11.7	3.3	3.6	3.5	3.6	2.1	2.3	2.7	2.2	1.9	4.6
45-54	41.0	55.2	11.7	20.6	16.5	10.3	5.7	9.0	7.7	5.1	4.2	7.9
55-64	116.3	164.3	30.4	60.4	44.4	29.8	13.9	28.3	15.9	8.7	7.2	18.4
65-74	182.6	239.0	40.3	122.9	89.1	60.9	23.0	56.1	33.6	17.1	11.6	37.1
74 e >	159.8	163.2	17.6	154.8	144.9	89.6	22.7	77.4	67.3	26.5	8.3	53.6

* Data of the World Health Organization (1972).

tem, the liver and the biliary tract, as well as acute leukemia. Lining up the frequency of these diseases in the order of the age at which they arise in countries which are sufficiently differentiated from the population and environmental viewpoint, i.e. the United States, England, Poland and Israel, it is possible to prepare tables (for example, Table XXII) in which the disease rate takes a characteristic course when correlated with age. We are dealing with a constant model of exponential type which indicates a progressive deficiency of genotypes of defense against the causes of disease, a deficiency that increases with age. Only in the tumors of the respiratory system do we note a regression in the last age group, due probably to ascertainment. Furthermore, if the rate of morbidity for the median age class (fifty-five to sixty-four) is examined, a substantial diversity because of differing environmental conditions may be observed in the indices even in countries that are very similar. The rate of disease is:

1. for tumors of the respiratory apparatus, greatest in England, medium in the United States, least in Israel and Poland;
2. for tumors of the liver and the biliary tract, greatest in the United States, medium in England and Israel, least in Poland;
3. for acute leukemia, greatest in Israel, medium in the United States, least in England and Poland.

If one bears in mind that the coefficients of industrialization and diet factors are analogous in England and the United States, the data assume a demonstrative value in the sense of imputing to heredity a different course in time, in accordance with ethnic considerations.

In other words, the trends of the four population groups express a receptiveness quantitatively different according to ethnic factors and age. While Poland always presents the lowest values, Israel, the United States and England alternate in presenting the highest values for leukemia, liver and biliary tumors and tumors of the respiratory system, respectively; in other words, a characteristic receptive variability exists in time on the part of different races. From the chronogenetic point of view these differences

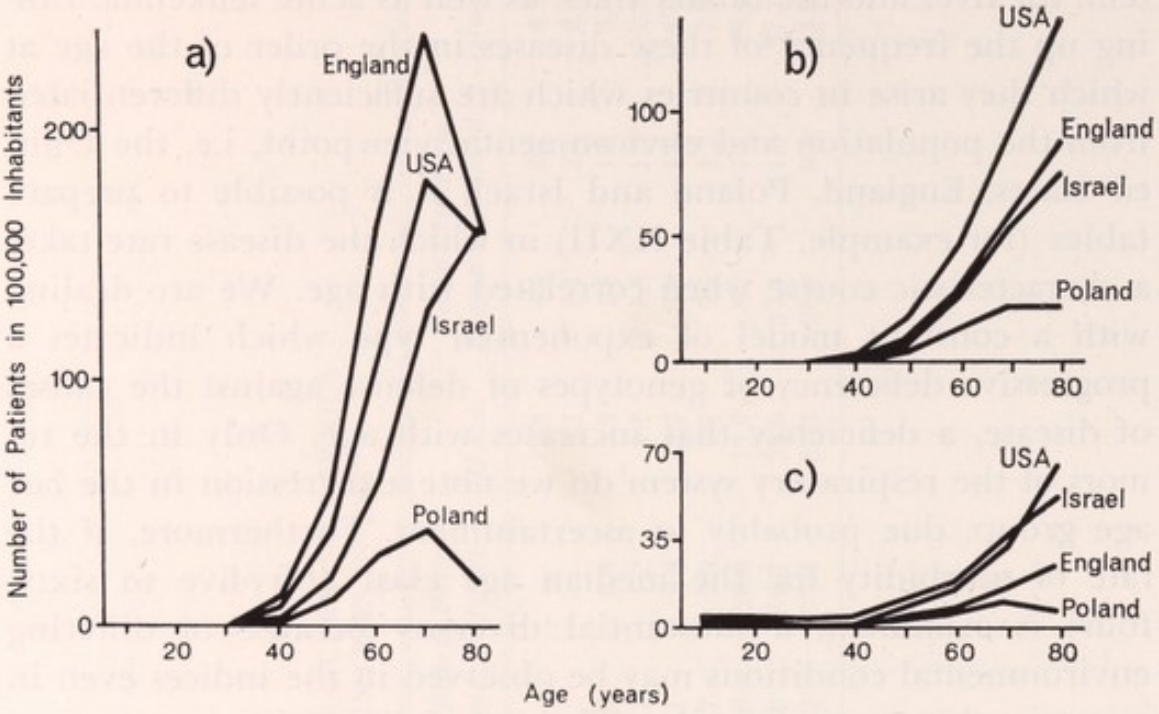


Figure 44. Ethnic variability in the frequency of disease in accordance with age: *a)* tumors of the respiratory system; *b)* tumors of the liver and biliary tract; and *c)* leukemia.

and their ethnic variability are more clearly evident in the graphs that follow the frequency trends of these diseases in time in these different populations (Fig. 44).

The hereditary variation in the age that the individual types of tumors become evident, singled out on the basis of analysis of the different populations, can be explained in terms of the E/C system. Stocks[10] has already discussed it in the following terms:

> The appearance of a susceptibility to cancer in a particular organ may be the result of the gradual exhaustion of the ergon/chronon system regarding the genes responsible for resistance to cancer (Gedda and Brenci). Such degradation of the E/C system of the genes in time, in the way these authors have defined it, can bear upon the characteristics observed of the incidence of cancer not only of the intestine/stomach but also of the lung.

The conditions necessary for the development of an altered cellular clone capable of giving rise to a tumor depend upon:

10. Stocks, P. In *Br J Cancer, 24*:215, 1970.

1. the occurrence of an anomalous cell different from the similar normal cells;
2. the vitality of the anomalous cell;
3. the reproductive capacity of the anomalous cell;
4. the impossibility of recognition of this new and different cell by the defense system of the organism.

The first condition can evidently occur for very different reasons in that an anomalous cell is usually the result of a somatic mutation, and the causes are therefore as numerous as are the mutagenic factors that can act upon that cell. The second and third conditions are directly dependent upon the type of mutation which has taken place. The fourth may depend on both the specific characters of the mutant cell that render it unrecognizable on the part of the defense system and upon a loss that strikes this system rendering it incapable of recognition. Accepting the concept of a differential genic stability, the first three conditions are obviously a function dependent upon the ergon and therefore on the chronon of the genes. It is, however, the fourth condition in particular, especially if one were to accept as a mechanism that of a loss of the capacity of recognition, that stresses the importance of the E/C model. Suffice it to recall that, notwithstanding the relatively low probability of occurrence of the first three conditions ($1 : 10^9$), the high number of cells present in a human organism makes the possibility of the first three conditions almost continuous in time. From this premise, it follows that the establishment of a tumoral clone depends in large part not on the appearance of a cell capable of giving rise to a tumoral clone, but on the capacity of recognition and destruction of this cell on the part of the organism. In the final analysis, the problem is therefore reduced to the temporal stability of the pieces of information that preside over the mechanisms of recognition and of information of the antibodies, that is, over the E/C system of the genes of these mechanisms.

In this connection, we note that Bartalos[11] has pointed out that normal and tumoral cytogenetic phenomena may represent the

11. Bartalos, M.: In *Acta Genet Med Gemellol (Roma), 20*:350, 1971.

effect of an interaction between genetic and environmental factors, understood as an interconnection between "oscillatory" phenomena along the coordinate of time.

THE "TIMING" OF DISEASE

The relationship that time establishes with disease is so fundamental that it can be symbolized by the Aesculapian caduceus representing a snake entwined about a staff: The snake is disease, time is the staff. A careful study of the timing of disease transfers this symbolic relation to clinical reality. Rainer[12] has pointed out the following temporal aspects of disease, subject to probable genetic control: age of onset, sequence of signs and symptoms of the illness, duration of the disease, periodicity of the disease, temporal relationships between clinical episodes and biological events. Time's imprint upon disease commences at the very moment of the latter's beginning. The age of onset is bound up with biological time in the sense that not only does every inherited disease have a general regulation as to the age of the persons stricken but, within the limits of the average time of onset, each family presents its own temporal variability.

In reality, medicine has not waited for chronogenetics to point out the age of the disease's onset. Table XXIII shows some examples of those which are medically treated currently. In the sphere of the average age of onset of hereditary disease, the compilation of data on family groups of lesser temporal variability is important because it proves that the temporality of disease is a character that obeys the laws of heredity in resembling quantitative characters. Familial evidence of a characteristic, constant age of onset is particularly evident in the field of hereditary myopathia. Del Porto and collaborators[13] of the Mendel Institute of Rome have gathered a number of genealogies relative to hereditary myopathic syndromes, classified on the basis of the clinical picture and the time of onset of disease, as well as its course and its outcome. Some examples are taken from this material; we con-

12. Rainer, J. D.: In *Acta Genet Med Gemellol (Roma), 20:*359, 1971.

13. Del Porto, G., Del Porto-Mercuri, A., and Brenci, G.: In *Acta Med Auxol, no. 1, 4:*33, 1972.

TABLE XXIII

AGE OF ONSET OF SOME HEREDITARY DISEASES*

Disease	*Clinical Form*	*Age of Onset*
Spinal muscular atrophy (Werdnig-Hoffmann atrophy)	Early infantile	3 months
	Late infantile	3 years
	Juvenile	5-8 years
Progressive muscular dystrophy	Duchenne's syndrome	3-5 years
	Scapulo humeral	10-40 years
	Pelvic girdle	20-30 years
Porphyria	Congenital Erythropoietic Protoporphyria	Present at birth
	Intermittent Hepatic	20-30 years
	Cutanea tarda	50 years and over
Mucopolysaccharidosis	Hurler's syndrome	Present at birth
Congenital myotony	Oppenheim's syndrome	Present at birth

* From L. S. Penrose, in *Annals of Eugenics, 14*:125, 1948. Courtesy of publisher.

sider them paradigmatic of the repetition, in the same sibship, of an identical clinical picture with the age of onset differing in a characteristic manner in different genealogies.

For Duchenne's syndrome (average age of onset in the literature is four years), cases a) and b) of Figure 45 show the repetition of an onset age different from the average in the two sib-

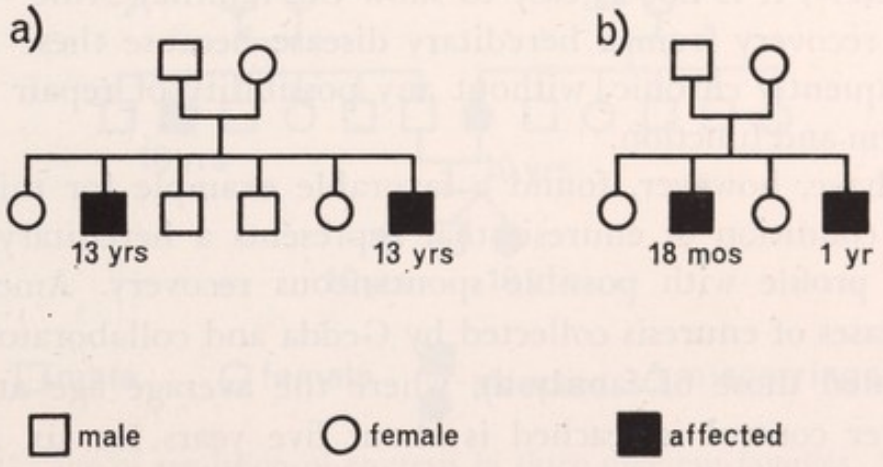


Figure 45. Duchenne's syndrome in two pedigrees. Age of onset is similar within each sibship but differs greatly between the two pedigrees.

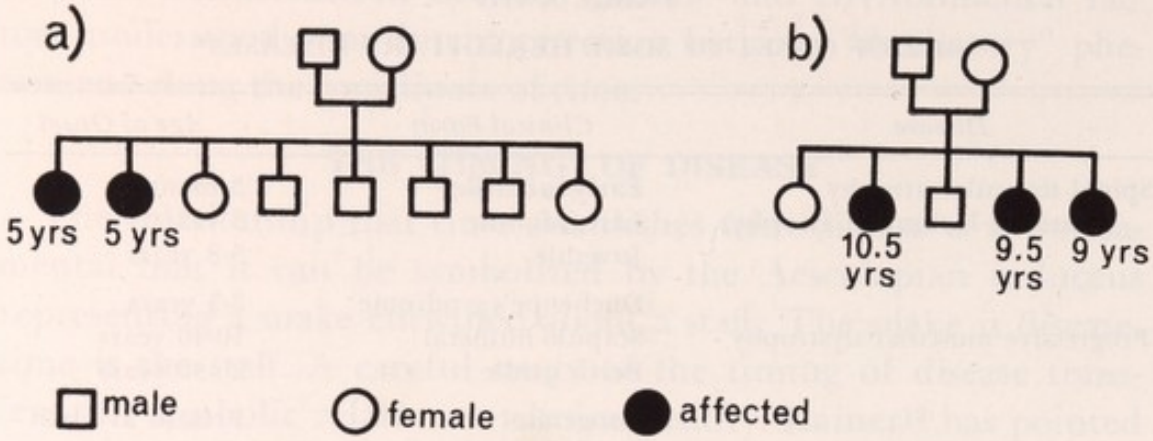


Figure 46. Pelvic girdle syndrome in two family pedigrees. In this case, as in Figure 45, a marked familial aggregation with regards to age of onset is observed.

ships: thirteen years in the first instance and twelve to eighteen months in the second. For the pelvic girdle syndrome (average age of onset in the literature is twenty to thirty years), the family a) reported in Figure 46 shows the existence of a uniform early age of onset of five years and in family b), a short range of nine to ten and one-half years.

While a family tree may indicate the hereditary nature of a disease, intrafamily chronological variation, thus reduced so as to appear almost nonexistent, confirms that the temporal character of onset age is an integral part of the diseased heredity. Unfortunately, it is not as easy to show the familial "rule" for the age of recovery from a hereditary disease because these diseases are frequently chronic, without any possibility of repair of normal form and function.

We have, however, found a favorable example for this proof in the condition of enuresis that represents a hereditary pathological profile with possible spontaneous recovery. Among the many cases of enuresis collected by Gedda and collaborators,[14] we mentioned those of family a), where the average age at which sphincter control is reached is about five years for six affected individuals; family b), where enuresis disappears at fourteen to

14. Gedda, L., Alfieri, A., and Tatarelli, R.: In *Acta Med Auxol, no. 1, 4*:13, 1972.

fifteen years in five affected persons; and finally of family c) where, for four probands, the typical age for restoration of normality is ten years (Fig. 47).

In order to demonstrate the chronogenetic profile concerning the outcome of diseases characterized by the death of the strick-

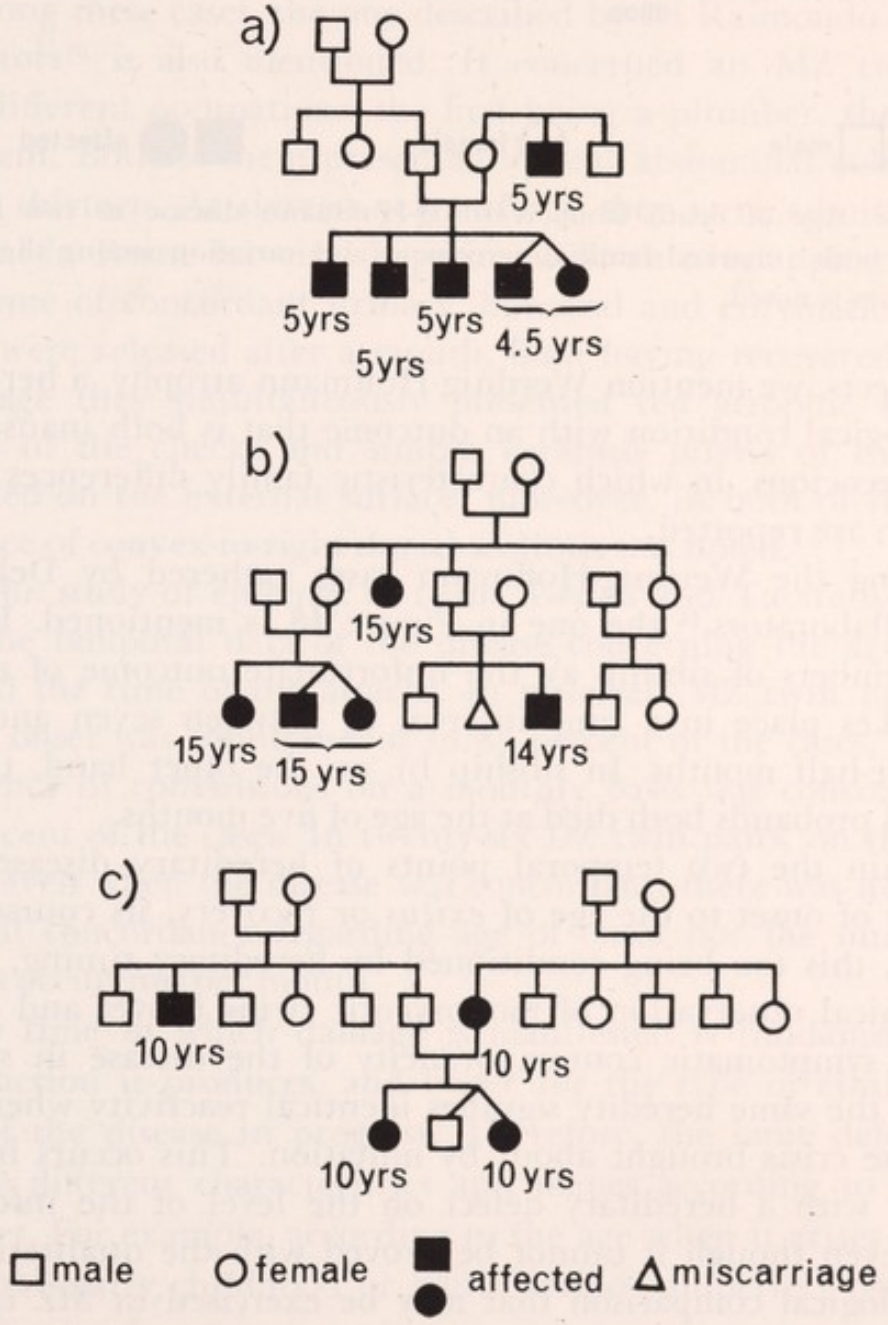


Figure 47. Age of remission of enuresis in three different families. A marked similarity is noted for the age of recovery; there is always a notable variation among the various genealogies.

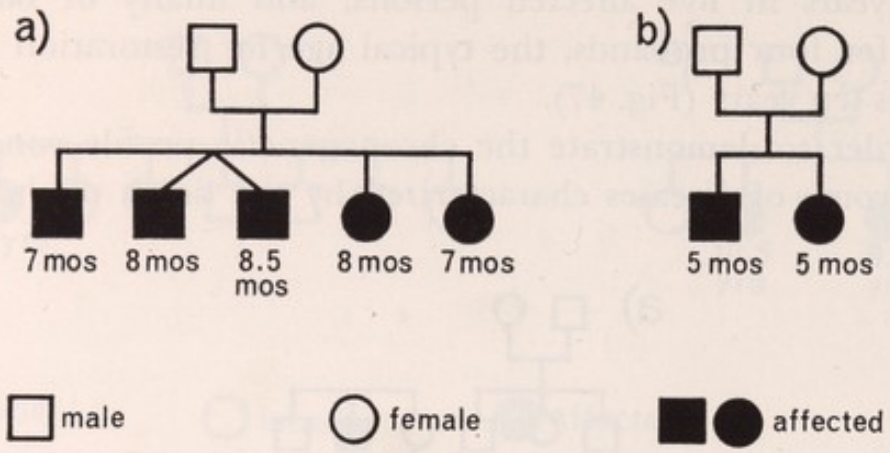


Figure 48. Age of death from Werdnig-Hoffmann disease in two families; here too both a marked familial agreement and variation among the various genealogies is noted.

en subjects, we mention Werdnig-Hoffmann atrophy, a hereditary pathological condition with an outcome that is both inauspicious and precocious, in which characteristic family differences of age of death are reported.

Among the Werdnig-Hoffmann cases gathered by Del Porto and collaborators,[15] the one in Figure 48 is mentioned. For the five members of sibship a), the unfortunate outcome of the disease takes place in a time interval of between seven and eight and one-half months. In sibship b), on the other hand, the two affected probands both died at the age of five months.

Within the two temporal points of hereditary disease, from the age of onset to the age of *exitus* or recovery, its course is extended, this too being conditioned by hereditary timing, just as the clinical observation of monozygotic twins proves and details.

The symptomatic contemporaneity of the disease in subjects having the same heredity signifies identical reactivity when faced with the crisis brought about by mutation. This occurs in every subject with a hereditary defect on the level of the informatic crisis, even though it cannot be proved with the qualitative and chronological comparison that may be exercised in MZ cotwins. Among the cases observed at the Mendel Institute of Rome, we cite two MZ twins who, having both a mother and a sister affilict-

15. *Op. cit.*

ed, also presented allergic asthma at the age of one year. When tested for cutaneous sensitivity they showed equal positive reactions to house dust (++) and mildew (+); given desensitization treatments, they recovered. At the age of six they both presented phimosis, umbilical hernia, bilateral inguinal hernia and hypertrophy of the tonsils.

Among these cases, the one described by Di Raimondo and collaborators[16] is also mentioned. It concerned an MZ twin pair with different occupations, the first being a plumber, the second a student. Both of them presented violent abdominal colic at the age of thirteen. At sixteen years of age they were admitted to a hospital in Rome for viral hepatitis with an overlapping clinical syndrome of concordant urinary, humoral and enzymatic nature. They were released after a month, both having recovered; at the same age they simultaneously presented red atrophic keratosis pilaris of the cheeks and simple keratosis pilaris of the limbs localized on the external surface; moreover, in both of them the presence of convex-to-right dorsal scoliosis was noted.

In the study of epilepsy in twins, Gedda and Tatarelli[17] evaluated the temporal data of the disease concerning the age of onset and the time of the attacks. In nineteen MZ twin pairs, the age of onset was simultaneous in 83 percent of the cases, and the frequency of convulsions on a monthly basis was concordant in 60 percent of the cases. In twenty-six DZ twin pairs, on the other hand, even when the disease was concordant, there was no chronological concordance regarding age of onset nor the number of attacks occurring per month.

The time in which damage is manifested is fundamental for the reaction it produces, and hence for the type of clinical picture of the disease in progress. Therefore, the same defect may assume different characteristics and names according to the age of onset. For example, according to the age when it arises—in the perinatal, early childhood or adult period—imperfect osteogene-

16. Di Raimondo, F., Rosci, M. A., and Leoni, G. C.: In *Acta Genet Med Gemellol (Roma), 19*:331, 1970.

17. Gedda, L., and Tatarelli, R.: In *Acta Genet Med Gemellol (Roma), 20*:380, 1971.

TABLE XXIV

COMPARISON BETWEEN AGE OF ONSET OF SOME HEREDITARY DISEASES IN PARENTS AND CHILDREN*

Disease	*Number of Parent-Child Couples*	*Age of Onset (Average Value in Years)*		
		Father	*Child*	*Difference*
Peroneal atrophy	86	24.30	19.36	4.94
Muscular dystrophy	90	27.44	21.00	6.44
Hereditary glaucoma	113	42.08	30.66	11.42
Huntington's chorea	153	40.80	31.98	8.82
Diabetes mellitus	216	60.29	43.06	17.22
Mental diseases	1,728	50.50	34.20	16.30
Dystrophia myotonica	51	38.48	15.24	23.24

* From L. S. Penrose, in *Annals of Eugenics, 14*:125, 1948. Courtesy of publisher.

sis is called Vrölik's syndrome, Löbstin's syndrome and osseous fragility respectively; this phenomenon signifies a different reactive variability of the organism with respect to a damage brought about by the same information. It appears in different periods of biological time, and therefore encounters a different equilibrium of ontogenetic, homeostatic and recession times. Furthermore, the different ages of onset of the same hereditary disease cannot be explained without recourse to the hereditary variability of the time of the gene, hence to the genetic variability of an identical piece of information, that is, in terms of the E/C system.

The course of disease, studied in chronogenetic terms, brings a dynamic of biological time, which is often rather complex, to the forefront, such as that which is hidden under the name of so-called "early" or "premature" appearance. This phenomenon became apparent when genetics began to concern itself with the age of onset of hereditary diseases. In 1948 Penrose[18] published a statistical survey of the average age of onset of some hereditary diseases comparing parents and children (Table XXIV). It was noted that the average age of onset for the children was younger than the average age for the parents. This phenomenon was explained by Penrose himself as well as by Steinberg[19] as the effect

18. Penrose, L. S.: In *Ann Eugen, 14*:125, 1948.
19. Steinberg, A. G.: In *Ann NY Acad Sci, 82*:2, 1959.

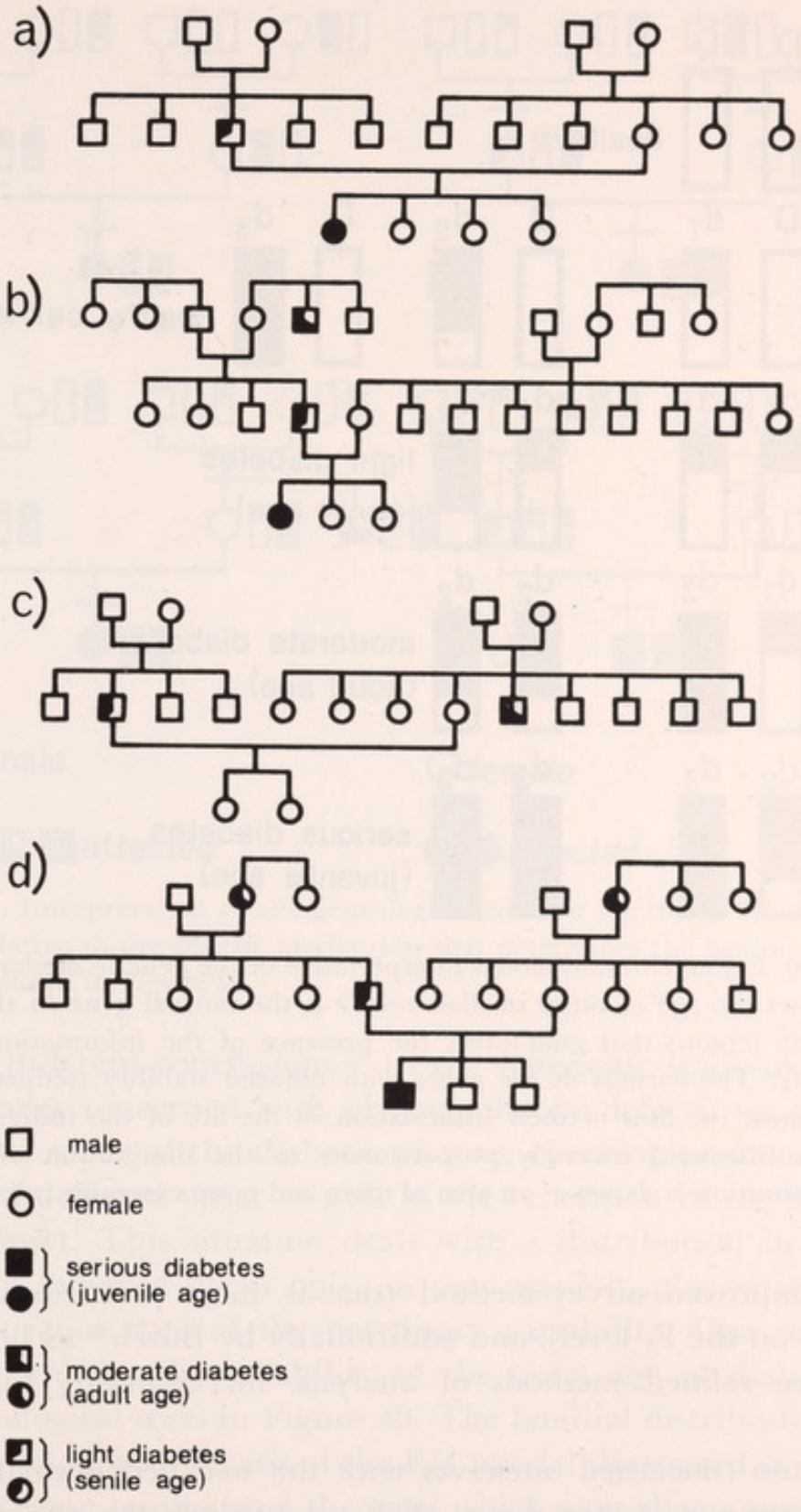


Figure 49. Variability in the age of onset of diabetes. The cases occurring in four different family genealogies are shown.

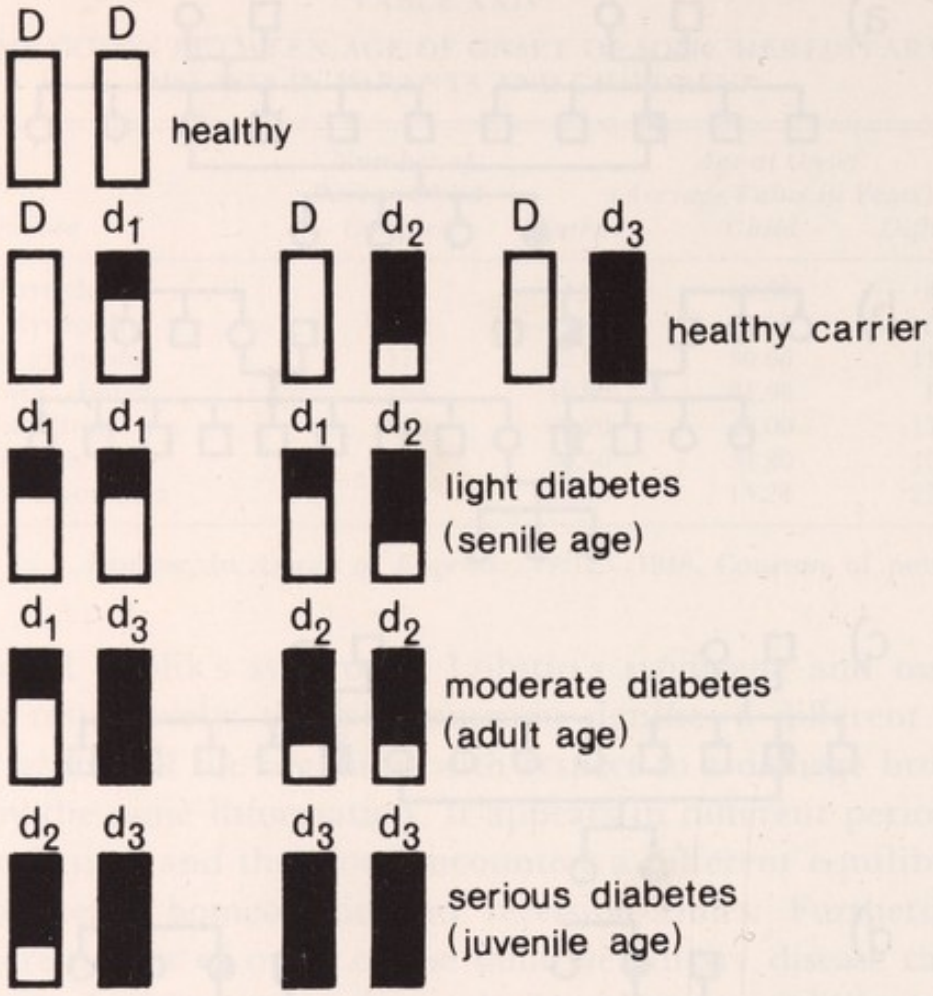


Figure 50. Ergon/chronon model interpretative of the genetic mechanism that determines the age of onset of diabetes. *D* is the normal gene in that it has a stability (ergon) that guarantees the presence of the information for the entire life. The various *d*s are genes with reduced stability (reduced ergon) that exhaust the flow of their information in the arc of the individual life, in times (chronon) inversely proportionate to the diminution of stability (this diminution is shown as an area of more and more extensive color).

of an improved survey method (that is, more precocious and attentive on the F_1 level), and additionally by Burch[20] as being due to more refined methods of analysis, for example, functional proof.

We too concerned ourselves with the so-called premature age of appearance of hereditary diabetes because the phenomenon has evident chronogenetic implications. However, we have

20. *Op. cit.*

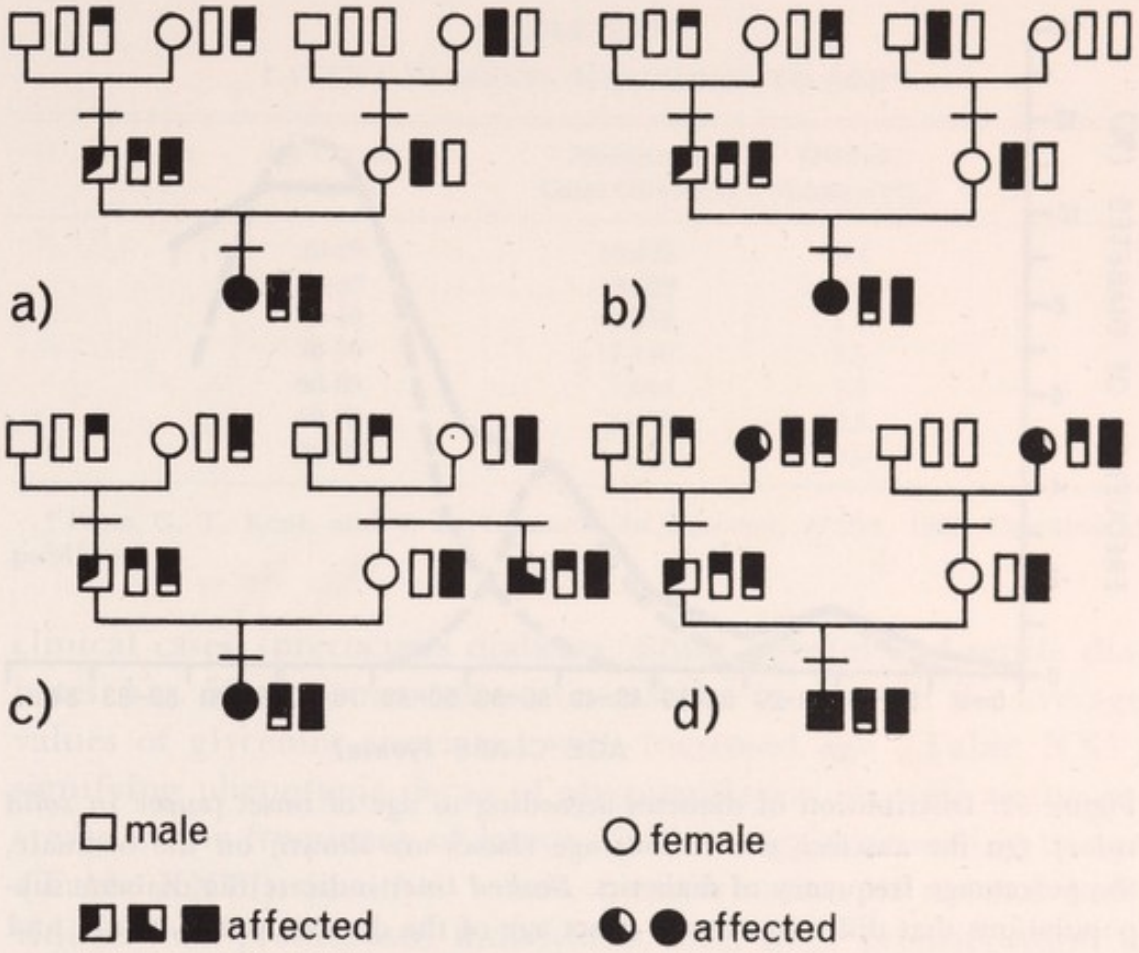


Figure 51. Interpretation of the genealogical trees in Figure 49 based on the model, relative to the genetic mechanism that determines the age of onset of diabetes, shown in Figure 50.

reached different conclusions.[21] In the systematic study of genealogical trees concerned with glycoregulatory defects, we studied the age of onset of the diabetic picture, checking phenomena of early and deferred onset as well as the repetition of the average age of onset. This situation deals with a distribution in which early and deferred mean only, in our opinion, plus-variance or minus-variance data of the hereditary variability. One sees, for example, the family variability of the onset age of diabetes in the genealogical trees in Figure 49. The familial distribution may be interpreted on the basis of the E/C model illustrated in Figure 50, as likewise results from the trees which were diagrammed and reproduced in Figure 51.

21. Gedda, L., Casa, D., and Brenci, G.: In *Acta Genet Med Gemellol (Roma), 16*:217, 1967.

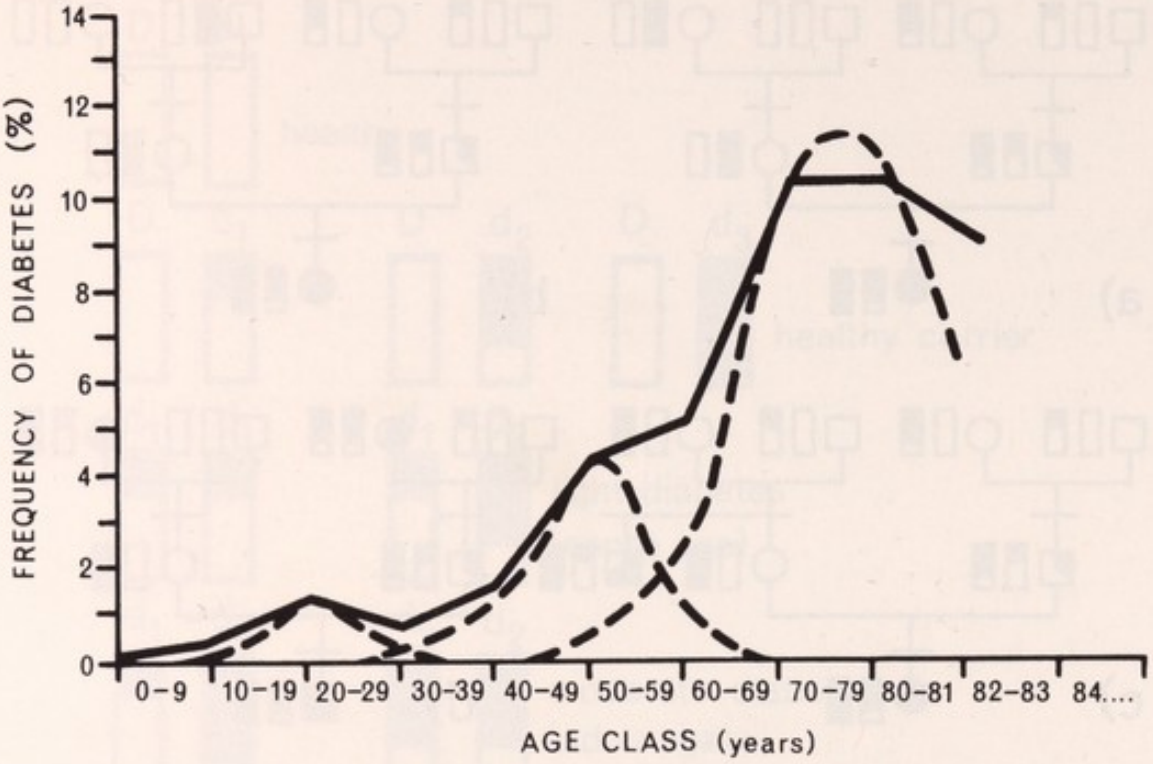


Figure 52. Distribution of diabetes according to age of onset *(curve in solid color)*. On the abscissa, the various age classes are shown; on the ordinate, the percentage frequency of diabetics. *Dashed lines* indicate the diabetic subpopulations that differ in average onset age of the disease: young, adult, and senile diabetes, respectively.

Numerous population reports drawn up both by us and other researchers confirm the hypothesis of a strong genetic conditioning of the temporal parameters of diabetes. On the phenotypic level, in addition to the well-known trimodal distribution of

TABLE XXV

AVERAGE VALUES OF GLYCEMIA (mg% OF BLOOD GLUCOSE) AFTER PRETREATMENT IN CLINICALLY HEALTHY SUBJECTS*

Age Classes (Years)	*Subjects* ♂	♀	*Total*
18-24	94.6	104.1	99.7
25-34	101.5	109.5	105.7
35-44	115.2	117.6	116.7
45-54	118.2	133.1	125.8
55-64	130.1	145.2	137.8
65-74	139.8	159.7	150.7
75-79	154.4	178.7	166.3

* From U. S. National Center for Vital Statistics, 1964.

TABLE XXVI

LATENT DIABETES ACCORDING TO AGE*

Age Classes (Years)	*Number of Cases Observed*	*Diabetic Subjects (%)*
20-29	16,423	0.1
30-39	18,629	0.5
40-49	23,632	1.4
50-59	17,140	3.5
60-69	7,654	7.5
70-79	2,498	12.5
80-89	360	20.0

* From G. T. Kent, and J. R. Leonards, in *Diabetes, 17*:274, 1968. Courtesy of publisher.

clinical cases (precocious diabetes, adult diabetes and senile diabetes, Fig. 52), it is necessary to recall the increase in the average values of glycemia associated with increased age (Table XXV) signifying phenotypic decay of glycoregulation, as well as the increase in the frequency of latent diabetes, again according to age (Table XXVI), in other words, transformation of normal individuals into predisposed individuals, and, since predisposition is a genetic status, the possibility of transformation of a "normal" genotype into a predisposed genotype.

TABLE XXVII

FREQUENCY OF FAMILIAL INCIDENCE OF DIABETES ACCORDING TO AGE OF THE SUBJECT*

Age Class	*Diabetic Subjects*		*Nondiabetic Subjects*	
	Number	*Family Incidence of the Disease (%)*	*Number*	*Family Incidence of the Disease (%)*
20-29	25	64	18,882	28
30-39	123	56	21,873	32
40-49	409	50	26,679	30
50-59	709	40	18,964	26
60-69	673	39	8,316	25
70-79	373	29	2,586	21
80-89	77	18	359	15
90-99	11	18	18	13

* From G. T. Kent, and J. R. Leonards, in *Diabetes, 17*:274, 1968. Courtesy of publisher.

On the genotypic level, we observe the declining familial incidence of diabetes with the increase in age of the subject (*cf.* Table XXVII).

In our opinion, this last datum, reported by Kent and Leonards,[22] is explainable only in terms of E/C. Familial incidence may diminish with age only to the extent that senile and adult diabetes may be caused by genotypes with slightly reduced ergon that have received their relatively stable information from parents with relative or even normal stability and hence with a relative probability of deferred clinical expression. At the level of juvenile diabetes, serious genetic damage, that is, a greatly reduced ergon, involves parents and blood relatives who are carriers of the same type of damage and therefore have a greater likelihood of clinical expression.

PROGNOSIS AS PERSPECTIVE TIMING OF DISEASE

One aspect of disease to which biological time contributes in a broad sense is the possibility offered to medicine of forecasting the disease, if it has not already manifested itself, or else of forecasting its development and outcome if it is already present. In particular, since both social and individual medicine today strive especially to be preventive, forecasting and prognosis gain special importance when studied in the framework of hereditary biological time, which is the clue of the medical projections into the future.

Prognosis, as distinguished from diagnosis, is not punctual, but relates to course and outcome, that is, to a succession of occurrences inherent to disease, occurrences that can be forecast on the basis of genetic and clinical experience as well as on the basis of pure calculation. It deals with forecasting a chain of pathological phenomena, destined to follow one another in time, like the timing of a disease that is not the result of a direct observation but rather a projection, that is, a conjecture regarding the future which, though subject to a margin of error, is interesting and useful. In chronogenetics, medical prognosis therefore assumes the meaning of a "perspective timing."

22. Kent, G. T., and Leonards, J. F.: In *Diabetes, 17*:274, 1968.

The aspects of prognosis entering into the purview of chronogenetics are the following:

1. *eugenic forecast,* which concerns possible individuals who do not exist because they have not yet been conceived, but who may be born of the amphymixis of the gametes of parents genetically known;
2. *prenatal forecast,* which concerns the conceived individual, where the diagnosis of a possible disease is made in the uterus;
3. *postnatal forecast* (or preventive check-up), which concerns a phenotypically healthy individual, whose future pathology we would want to know;
4. *clinical forecast,* which concerns the individual with a disease in progress.

Each of these prognoses represents the extrapolation in future time of phenomena ascertained in present or past time. These prognoses can be constructed in that in normal or diseased conditions biological time represents a continuum in the individual and in the species that permits logical extrapolation thereof.

Eugenic forecasting departs from the meticulous study of the genealogical trees which join in the conjugal design with special reference to the study of diseases and causes of death manifested in the single individuals of the two families. On this level, the hereditary diseases which are most conspicuous are those in which there occurs a complete absence of informatic action of the known genotypes because they allow the utilization of Mendelian models for the forecasting of disease variability as a result of certain unions. For a better perspective, eugenic forecasting should be integrated in E/C terms, that is, through the study of the age of onset of the disease in question in consanguinity of sick individuals. This permits an evaluation of the genic ergons involved and hence a calculation of genotypic variability in more precise terms than occurs when one limits oneself to judging the extent to which subjects resulting from a certain mating are ill or not. In fact, temporal integration also permits pinpointing the most probable age of onset of the disease and the possible seriousness of genic damage. The genetic risk of transmitting

certain hereditary illnesses shown to exist by familial anamnesis is the result of a calculation of probability which is expressed in percentages, together with forecasting concerning the gravity of the defect that chronogenetic analysis of the crossbreeding can suggest.

Prenatal forecasting is also an anticipation of the future but focuses on a single human being and does not concern future conceptions. Prenatal forecasting is represented, for example, by an attempt at diagnosis through amniocentesis from the fourteenth week of pregnancy on. When malformations are feared, this can be integrated with photographic and radiographic evidence obtained by ultrasonics, etc. Diagnosis becomes prognosis with particular regard to the development of the gestation, followed by the birth and independent life of the subject under examination. At this level, the observation of chronogenetic data takes on fundamental importance in that preventive forecasting should be made whenever possible before informatic absence manifests itself as clinical damage. This method of proceeding has already been successful on the level of some oligophrenias caused by disordered metabolism involving some amino acids. In these cases, early detection of genotypic damage through perception of disordered metabolism in cell cultures procured by means of amniocentesis has permitted the adoption of therapeutic measures (maternal diets) before the onset of clinical damage, thus avoiding the appearance, for the entire life span, of genetic damage.

Postnatal forecasting or preventive check-up is the judgment with which chronogenetics will, in the near future, have to accompany the practice of a periodic check-up, on the basis of which preventive medicine is taking a position to attack the epidemiology of endogenous diseases. Gedda[23] has proposed a series of checkpoints for school-age children at which doctors could examine the fundamental parameters of development, integrating them with calculated observation of the phenotype for those

23. Gedda, L.: Prospettive per un check-up auxologico. *Acta Med Auxol, 4*:7, 1974.

eventualities indicated by chronogenetic analysis of familial anamnesis. Even at later times, this check-up, which various types of organizations require of their employees or which an individual may wish for his own reassurance, may reveal certain indicators which should never be ignored or neglected. Chronogenetics is able to suggest this because the treatment of hereditary damage can not only be foreseen early but realized by means of stimulation of the missing information, or substituting information, or else by the external administration of primary substances needed by the organism as it is about to come into deficit or when it has begun the critical period.

Finally, clinical forecasting is as ancient as or even more so than the word "prognosis," which goes back to Hippocratic medicine. Prognosis, which forecasts the development and outcome of disease, is therefore an empirical form of chronogenetics *ante litteram,* exercised from time immemorial on the basis of experience, that is, on the average data of disease furnished by medicine. Genetics can supply to this analysis a singular subtlety, bearing in mind preceding chronological events occurring to ancestors and, in general, to blood relatives.

In the four eventualities mentioned, prognosis is formulated as a risk of disease, departing from anamnestic and clinical data, with reference to the laws of heredity, and possibly from empirical risks deducible from health statistics. Hence, it deals with an indirect evaluation of pathological occurrences having a high probability of taking place in future time. The hypothesis can be made that, in the future, chronogenetic forecasting can also take into account the direct exploration of individual hereditary matter, that is, of a reference to the normal or deficient state of the ergon.

The techniques used today to derepress or block cellular mitosis *in vitro,* as well as the detection of metabolic disturbances through dosages of metabolites of cells cultivated *in vitro,* are roads which are open for evaluating the stability of the genotypes responsible for these functions, as well as the quality and duration of the specific information that must be controlled.

Close collaboration between chronogenetics and cytogenetics can carry forward prognosis as a tool for preventive and curative medicine.

Prenuptial eugenic forecasting, prenatal and neonatal diagnosis of diseases to be dealt with opportunely, the systematic check-up of the healthy individual and clinical prognosis in the course of independent life are concrete aspects of modern medicine that find scientific verification in chronogenetics. In fact, hereditary biological time is the common denominator of these phenomena and therefore represents the calendar and clock the physician needs to forecast the occurrence of the disease, struggle with it, and cure it.

Chapter IX

Time and Non-Time

TIME IN THE PRESENT

UP TO THIS POINT we have seen how time, marked by matter through a calendar of progressive decline, found in life a source of resynthesis, that is, a new, many-faceted time that begins again every time a living being commences its vital cycle. It deals with inherited biological time that examines a programmed resynthesis in detail, because it aims at producing innumerable forms of life, but is organized in accordance with progressive plans, replacing or contextual, that make up *Homo sapiens.*

The subject of time, till now spoken of in accordance with the observations made by other authors as well as ourselves, a subject that we formulated into a single concept, i.e. that of inherited biological time as a recapitulatory, perspective guide to hereditary phenomena, now presents the possibility of being taken in the opposite sense. This seems to be the proper moment to reconsider this road, regressing along it by means of an inverse perspective of the phenomenon of time which may appear after the experimental and bibliographic researches we have conducted. In this chapter, our travel backwards on the road of time cannot help but be abbreviated and hence synthetic, but we are thinking of taking it again in the future, when the implications of our views for the science of heredity and the art of medicine will be sufficiently mature and evident.

The farthest point in this long process of the formulation of time and, in time, the closest point from which one should depart for this backward journey is the reflected position that time assumes in man's psyche where it not only operates but clarifies itself, in that man gets both consciousness and awareness from time.

In other words, man is not only a result of time but also a be-

ing who is aware of its meaning, its mechanisms and its characteristics because he (man) is not limited, as are the higher animals of other species, to having only an instinctive consciousness of "before" and "after," but man can transform this presence of time in his subconscious in terms of rationality and expectation. For this reason, man, from the farthest reaches of his existence in time, has tried to rationalize time directly, or else by means of a chronological rationalization of space, and has created different systems for measuring time through clocks and calendars of various sorts. In spite of the thousand forms in which time appears in reality and in spite of its relativity, man, in accordance with the possibilities and requirements of his psyche, has been able to make time abstract, that is to say, he has found how to grasp its concept as an absolute which links the varied phenomena of time presented to him by reality. The concept of time as abstract therefore represents the most elaborate phenomenon produced on the level of the human psyche as concerns time itself.

FROM THE PRESENT TO THE TIME OF HOMINIZATION

By time in the present, we mean the human species and the environment in which it lives today, an environment which is composed of other plant and animal species in the immense niche of matter making up the cosmos. This reality, from the viewpoint of time, consists of at least three phases: time conceptualized, reflected and reproduced by man; hereditary biological time, which characterizes man and the other living beings; and physical or cosmic time, which is present in the entire universe.

In suggesting that we reascend the flow of time, at the very onset we must try to reach the one marked by the presence of man in the cosmos, that is, of hominization. About 2000 millennia have passed from the remote time of the Quaternary to the present day . . . an enormous time from the perspective of each individual man, but brief if considered with respect to the times that precede the appearance of man. Going back to it we are faced with the results of the effect of the human psyche upon our planet and, today, on the other heavenly bodies as well, which have been reached by man through the fruits of his labor.

What these fruits might be is not a problem that concerns chronogenetics, since we are interested in time as a pathway to go back along the chain of the causes that have produced the present reality. In this light, the amygdala, the almond-shaped utensil constructed in the Quaternary by *Homo faber* who chose the stone that could be useful to him and gave it the most suitable form, and the electric razor that other men construct today and which we use, are equally the result of man's labors, i.e. the "fruit," and thus stand as a testimony to human intelligence. It is in no way strange that the time lived by the human species has produced so prodigious a separation of civilization. It is, however, important to affirm that all this happened on the parameter of time as a progressive development of a quality that man possessed from the beginning and that begins precisely with hominization—the rational psyche.

The road covered from then to today, in the judgment of the geneticist, is certainly the fruit of a genotypic variability determined both by the casual combination of paternal and maternal genes in the genome of the individual children as well as by mutation. In addition, the phenomenon of environmental selection has operated on this variability, isolating the best genomes in the fight for life.

In other terms, the utilization of time that the human species has made is surprising for the layman but does not astonish the geneticist because it is the psychic equivalent of what takes place, on the level of biological characters, by means of an increasing variability of the forms and functions contained in the heredity of the species, selected by the environment and renewed in amphimixis, and further enriched by the human psyche which is capable of creative abstraction and elaboration.

We are in agreement with the "chance and necessity" formula of Democritus and J. Monod[1] as a key to explain the life of man going back from today to the time of hominization. In our opinion, "chance" means utilization of variability through the combinations of the Mendelian lottery and "necessity" means the set situation in which man finds himself biologically and psycho-

1. Monod, J.: *Le hasard et la nécessité*. Paris, Sevil, 1970.

logically obliged to follow the program which is inscribed in his nature and develops in time.

Having arrived in this manner to the origin of humanity, that is, the epoch that is still vague but which paleontological research will succeed in working out regarding the exact time and the place of hominization, we must point out two problems which seem to us to have matured sufficiently for a convincing solution to be reached.

The first problem refers to the single origin of hominization, that is, to the monogenesis of what Teilhard de Chardin called the human phenonemon.[2] The reproductive equivalence of the existing races which repeats the biological qualities of primitive men is a phenomenon which requires such affinity as cannot be imagined if not as the fruit of a single programming and therefore of a single origin. Whatever might have been the vicissitudes of the species in prehistoric time, time itself undoubtedly served to segregate racial and subracial variabilities, but it is not probable that it has been able to develop phyla of the human species which are biologically different and originally distinct.

The second problem concerns the meaning of hominization with respect to preexisting biological reality, that is, the nature of the phenomenon of hominization in the context of the phenomenon of "life" that had dominated for long ages, evolving forms and functions of other species not endowed with the human capacity of utilizing time through abstractions of thought.

What took place with hominization, and from then to today in a relatively brief time, demonstrates a fact that the history of living matter represents a *unicum* not only with respect to time and to the place which has been mentioned, but also with respect to its quality.

The effect of hominization represents a positive leap in quality that cannot be the result of genetic lottery among preexisting qualities, since they were absent in previous forms of life, but the beginning of a new type of specific programming which starts off in a definite time and place on our planet.

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2. Teilhard de Chardin: *Le Phénomène Humain*. Paris, Seuil, 1955.

FROM HOMINIZATION TO THE ORIGIN OF TIME

Passing over man, inverse progression in time leads to the eras in which other animal and vegetable species still living today on Earth populated the planet in man's absence, along with many others that presently are extinct. These eras represent extremely long periods which do not offer the innovations produced by human civilizations going back in time. There were changes in a number of species representing a diminution in quantity as well as quality, as time passed to the point before which animals were capable of flying and before plants were linked to terrestrial places. Thus it appears that about 3 billion years ago hereditary biological time appeared in minimal forms of life.

The originality of the living species appears linked to the changes in the environment that, in effect, are less hospitable the further back one goes in physical time, as if the appearance of new ways of hereditary biological time were correlated to the appearance of new ecological possibilities adapted to foster them.

The problem of the horizontal relationship between species and environment is an open problem in which the necessities imposed by the environment on the development of programming are sufficient to recognize and justify a proliferation of mixed times induced by the rhythms of the environment.

The intraspecific and interspecific polymorphism of life, that is, the forms through which biological time is expressed, become less apparent along the backward path we are traversing and disappear in the azoic period. In the distant past, the cosmos is all there is, scanning its times which will play so great a part in formulating the rhythms of the biological time of the plants and animals, especially under the form of the solar system cycles. What occurs because of the mixture of the two times, that is, the cyclical conditioning of biological time, can lead us to think that even for cosmic time, the possibility of a cyclical renewal such as that of life in the succeeding generations may be valid. But this is a question of an interpretation of human feeling scientifically misapplied, because—at least as concerns what we know on the basis of experimental data—the cycles of cosmic time do

not return to the level of origins as occurs with biological time through reproductive resynthesis, but they fatally follow slow and progressive degradation.

Hence, it is the energy decay of the cosmos which takes first place when, in the perspective adopted by us, one reaches and passes beyond the frontier of life. It is a panorama of matter which transforms itself, that is, its physical state, its chemical equilibrium and its spatial disposition. Space and time enter into competition in the configuration of matter without life which, for immense epochs, without the covering and aspect which will be given to it afterwards by living creatures and man, shows the naked reality of its being stripped of every superstructure produced by biological time. This reality lies in an irreversible energy decay which foreshadows the forms of living matter and seems to have prepared them from very distant times, times when radiant energy was certainly impracticable to life and it was necessary that energy be split, broadening and subdividing at first in the heavenly bodies and finally in those destined to compose the solar system and Earth, where complex forms induced in matter of biological time could have begun to exist and proliferate in a direct way, that is, genetically.

The overturned optics through which we have been looking in order to reascend the flow of time and arrive at primitive cosmic times, having behind us the experience and the recollection of the multiplicity and beauty of the universe, enables us to give a more adequate sense to this phenomenon of entropy which, considered in the cold light of a physicochemical occurrence, does not assume its exact significance—that of a cofactor of life for the moment in which life will scan its innumerable individual times in the sphere of a cosmos in a process of energy decay.

The majesty of cosmic time does not prevent science from going back to it by means of datings, since, on the contrary, its calendar is more practicable than the calendar and dating of biological times as a general rule. For this reason, cosmologists have been able to fix point 0, which marks in time itself the origin of the decay of matter, that is, of cosmic time, and, at a calculated distance, the origin of individual hereditary biological times. In

time 0, as is probable, it is not a question of matter *sensu strictiore,* but of energy, from which, by successive evolution, through the proliferation of times, everything that is real of the past and present has its origin.

NON-TIME

On the threshold of the entrance to time where we now find ourselves, we cannot put behind us the absolute scientific autonomy that we have cultivated in our research and therefore apologize if, for the final considerations, we do not draw upon those sources of knowledge that we regard to be fully valid, but that are extraneous to the presuppositions and method that we have followed up to now.

On the line which governs the hypothesis of the researcher's work and his research, we can now comprehensively consider the immensely broad stream of the phenomena that articulate time in the river bed of its course from the origin to the reality of today . . . origin that to cosmologists seems to clash with the impact of an energy quantum from which matter is derived with its cosmic time and then life, with the added proliferation of biological time that characterizes it and with the succeeding integration of human thought. The fundamental consideration that we must now make concerns the continuous, irreversible process of energy decay carrying with it, as phenomena of the opposite indication, on one hand the decay of matter, and on the other, the evolution of life, but it will inevitably mark a second crucial point for both in the future, that is, of the end of time.

Entropy therefore places us before the downward delimitation of the phenomenon of time, which implies a corresponding delimitation at the height, that is, a beginning, whether it coincides —as it seems—with the energy impact or is explained in some other way. Time, on the basis of experimental data, therefore had an origin, as it will have an end.

The discussion of the origin, because it leads us to a conclusion acceptable in terms of scientific knowledge, that is, valid even in the absence of a surveyable reality as an object of experience, can only be a negative knowledge, that is, such as to state what

the origin of time cannot be. This brings us to the affirmation constituting the arrival point of our road backwards in time: time is preceded by "Non-Time."

Even reduced to a negative formulation, the origin of time takes on some significance which can arouse the interest of the researcher, especially as regards the way non-time exists, which, not being time, does not become time. The essence of time, in fact, consists in the becoming of phenomena. The sequentiality of phenomena is extraneous to non-time, since otherwise it would be an improper non-time and therefore also a time.

How one proceeds from non-time which does not become time is a great mystery, but the existence of the two counterposed poles must be admitted even if we do not succeed in constructing a causal link: on one hand, the immutable being of non-time, on the other, the being which becomes through time. Even nothingness is a non-time but this is not non-time that can resolve our problem of time, because from nothingness, nothing can proceed. Non-time postulated by time is a non-time that preexists time and generates it with its content. On the other hand, if non-time has produced time, we must attribute to it the projecting of time, that is, of those phenomena scanned by time in the general and individual forms and structures, systematic and particular, biological and ecological, of matter without life and that which is organized on the genotypic and phenotypic level, of matter without thought and that endowed with thought that interprets, reproduces and amplifies reality.

In the realm of this hypothesis, the only one possible when one thinks, for example, staying on the subject of genetics, of the structure and function of the double spiral of deoxyribonucleic acid discovered by J. D. Watson, F. H. C. Crick and M. F. H. Wilkins, one must grant these scientists the great merit of having clarified a mechanism that operates on the molecular level and assures the transmission of the characters discovered by G. Mendel. But neither the mathematical model framing these phenomena, nor the structure and function of DNA which carries them out are the creation of the authors mentioned: They are obvious-

ly preexisting realities which these man have been able to arrive at and have had the talent to explain, and an effect of the programming that regulates the phenomena articulated in time, which is due to non-time.

Therefore, non-time as the holder or keeper of programming has a countenance that is integrated with the one of being the origin of time, that is, the principle that sustains and accomplishes the program: Non-time is therefore, mysteriously, programmer and author. On the other hand, a fundamental character of the programmer and author is that of having no time, therefore time with its implications and phenomena coexists with non-time, and non-time is, so to speak, like a mother bearing within herself the child.

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