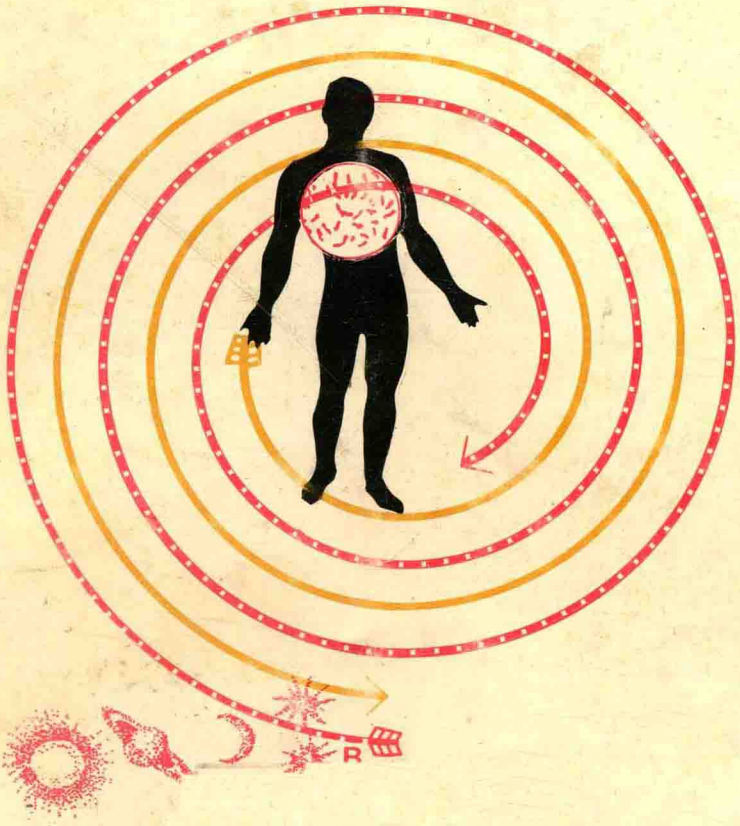
CHRONOGENETICS

The Inheritance of Biological Time



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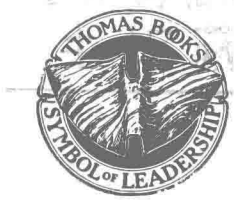

CHARLES C THOMAS · PUBLISHER
Springfield · Illinois · U.S.A.

Published and Distributed Throughout the World by

CHARLES C THOMAS • PUBLISHER
Bannerstone House
301-327 East Lawrence Avenue, Springfield, Illinois, U.S.A.

ISBN 0-398-03641-1

Library of Congress Catalog Card Number: 76-56201

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Library of Congress Cataloging in Publication Data

Gedda, Luigi.
Chronogenetics.

Translation of Cronogenetica.
Bibliography: p.
Includes index.
1. Biological rhythms. 2. Genetics. I. Brenci, Gianni, joint author. II. Title. [DNLM: 1. Genetics, Human. 2. Time. 3. Hereditary diseases. QH431 G295c]
QH527.G4313 574.3'1 76-56201
ISBN 0-398-03641-1

Printed in the United States of America
C-1

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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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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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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-

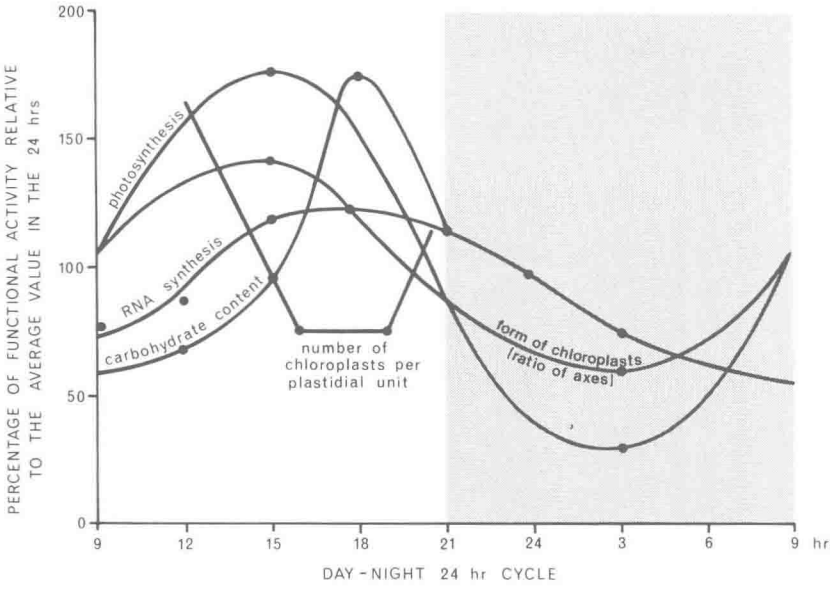

Figure 1. Temporal distribution of five functional activities of the chloroplasts of *Acetabularia mediterranea* cultivated in controlled conditions, in the light from 9:00 AM to 9:00 PM and in the dark from 9:00 PM to 9:00 AM the following morning. The curve relating to the number of chloroplasts per 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