

## TWIN STUDIES IN GENETICS<sup>1</sup>

LUIGI GEDDA

### SUMMARY

Almost one century after Galton's first scientific formulation of the Twin Method, based on the comparison of MZ and DZ twin series, not only twin studies play a fundamental role and the Interzygotic Test is widely applied in human and especially medical genetic research, but new methods have also been worked out, such as the Azygotic Test and the Twin Clinical Method.

Moreover, the study of twins has more recently led to new insights into the study of biological times, with the development of the modern branch of Chronogenetics.

---

Since I came to Israel in 1968 for the Congress of Fertility and Sterility and thus had the opportunity of better knowing Professor Halbrecht, I have felt for him personally, his school, his research, the highest admiration. The identification of a new human-embryo normal hemoglobin and the description of the *icterus neonatorum precox* are by themselves sufficient to illustrate, even in front of genetics, the figure of this illustrious master.

Therefore, I am particularly happy to be present here, at the Hasharon Hospital, on a day that marks a great success in Professor Halbrecht's professional and scientific career. First of all, to present to him and to Mrs. Halbrecht my most cordial congratulations. Secondly, to establish a first connection between what *already* is the "Research Institute of Human Reproduction and Fetal Development of the Tel-Aviv University Medical School and the Hasharon Hospital" and what *shall be* the "Luigi Gedda Institute for Medical Genetics and Twin Studies" — simply represented by a cornerstone now, but to be built, God willing, in Jerusalem on the Mount of Olives. This must also be Professor Halbrecht's wish — and I thank him for that — since he suggested as a title for my lecture today, "The Importance of Twin Studies in Genetics."

This is a very wide subject, on which Professor Lamy, other students, and I myself, have written a large number of publications: it is in a way a big meal, out of which I can only serve you the hors d'oeuvre and thus stimulate your appetite.

---

<sup>1</sup> Lecture given to the International Seminar on Human Reproduction, held in Petah Tiqva, Israel, on 21 September 1972, on the occasion of the inauguration of the Research Institute of Human Reproduction and Fetal Development of the Tel-Aviv University Medical School and Hasharon Hospital, Petah Tiqva, Israel.

The twin method was first scientifically formulated by Francis Galton in 1882, in a terse style, with the binomial, Nature and Nurture. In fact, the comparative study of identical, or MZ, and nonidentical, or DZ, twins, makes it possible to discriminate, within the phenotype, between the characters of hereditary (i.e., genotypic) origin, and those of environmental (i.e., paratypic) one. Mathematicians got hold of this dilemma and produced a forest of formulae aiming to make it possible to compare the two series of twins, and therefore carry out, in other words, the genetic analysis of the phenotype through the Interzygotic Twin Test, i.e., through the comparison of MZ and DZ twins.

Obviously, this test must be based on the determination of zygosity. Therefore, its use must be preceded by the individuation of the best method to determine the zygosity of each twin pair. The problem consists in establishing, first of all, the best hereditary traits not affected by the environment, and their minimum number for the comparison to be significant. This classic research, that makes it possible to establish the hereditary conditioning of a structure or function of the organism, is always useful, even precious, and is in fact carried out in our Institute every day.

However, the study of twins has progressed to a second stage, that we call of the Azygotic Twin Test. In fact, after suggesting the term, *Gemellology*, for the scientific study of twins, and founding, for its development, the Mendel Institute in Rome, we endeavored to establish new methodologies, aiming to avoid, as far as possible, the heavy condition of zygosity determination, that always requires an individual study of every twin pair. In other words, we endeavored to study twins according to the methods and goals of Population Genetics.

We started from the consideration that the frequency of a phene, i.e., of a hereditary character, is higher in the twin sample of a population than in a nonselected sample of the same population, as a result of the total concordance of MZ and the higher probably of concordance of DZ pairs.

Moreover, the population frequency of opposite-sex (and therefore DZ) twin pairs, makes it possible to derive the frequency of MZ and DZ pairs in the twin sample under consideration.

On these bases, the difference of frequency of the trait between the twin sample and the nonselected sample is established. This difference is obviously a function of the mode of inheritance of the trait. Therefore, once the model individuated, that better fits the experimental difference between the two frequencies, the mode of inheritance of the trait or disease may be, with suitable calculations, deduced: dominant, recessive, sex-linked, etc.

In a similar way, other parameters, such as frequency of manifestation, penetrance, and couple-effect, may also be deduced. The couple-effect refers to nongenetic factors that influence the concordance of twins, such as placentation and generally those factors stemming from a common prenatal and postnatal environment.

The interzygotic and the azygotic tests are now the railroad on which the train of twin research runs. How interesting this research is, is demonstrated by the papers on twins, from all over the world, continuously published on our specialized quarterly,

---

*Acta Geneticae Medicae et Gemellologiae*, as well as by the large success of the First International Symposium on Twin Studies, held in Rome in 1969, and the success we may already foresee for the Second Symposium, scheduled for 1974.

I would now like to get you more closely interested to the study of twins and inform you on two particular scientific utilizations of this method. The first one concerns the Twin Clinical Method; the second one, the study of *Chronogenetics*.

By the term, Twin Clinical Method, we meant to stress the fact that not only series of MZ and DZ twins are useful, but also one signal pair of MZ twins may provide a precious genetic test. The method has been given this name because it is centered on the two cotwins of one single MZ pair, one or both of which affected by a disease.

According to whether only one or both twins are affected, and to whether in the same or a different environment, there may be the following four cases.

(1) *Both Twins Affected in the Same Environment*. Here, each twin has the value of a statistical universe that may be compared with his cotwin's one, just as in the interzygotic test, with the advantage that, while in the latter the comparison is made on stable and standardized characters, in the twin clinical method the comparison is made on rapidly evolving characters where not only organic symptoms, but also times, may be compared.

(2) *Only One Twin Affected in the Same Environment*. This is the classic case of an endogenous disease that may affect only one twin; for instance, poisoning. *Coeteris paribus*, this is a unique occasion to study the morbid picture in absolutely paradigmatic conditions. It is just as if the comparison could take place between the same individual at the same time healthy and ill — a comparison, in other words, between an individual and himself. The study of the disease, i.e., of its semeiotics and pathogenesis, may thus be carried out under optimum conditions.

(3) *Both Twins Affected in Different Environment*. This is the classic case of hereditary diseases, and it is a precious opportunity, offered to medical genetics, to recognize the genetic nature of an obviously hereditary and inheritable disease.

(4) *Only One Twin Affected in Different Environment*. This case, if the hereditary nature of the disease can otherwise be shown, is very useful to study the influence of the environment on the penetrance and expression of the disease.

The twin method may also prove of basic importance for the study of biological times, i.e., for the development of that branch of genetics we call *Chronogenetics*.

The twin material has in fact a peculiar characteristic, that is, genotypic and phenotypic *synchrony*. This chronological concordance goes normally unobserved, being covered by the qualitative concordance that catches one's eye and makes a twin the

double of his cotwin. Chronogenetics was born from the study of twins, when we noticed that, *coeteris paribus*, MZ cotwins may show the phenomenon of dynamic isoglutathionemia, i.e., an identical rate of blood glutathione with synchronous shiftings from the oxidized to the reduced phase, and viceversa.

At the Human Genetic Congress, held in Paris last year, I have presented, in co-operation with Gianni Brenci, a series of researches aimed to establish the existence of the *Ergon/Chronon System*, i.e., of a direct and constant relation between the gene's stability (that we call Ergon) and the basic biological time consisting in the duration of the information (that we call Chronon). In our opinion, the sixty-thousand genes that make up the individual genotype may have different life durations, i.e., each gene has its own particular Chronon that may not coincide with the life of the individual.

The best way to advance these studies is provided by twins, on account of their synchrony. In fact, the basic biological time has a decreasing period that varies in the different ages of an individual, and undergoes a continuous interaction with the environmental cosmic times that hide it and make its study difficult. The variability of the selection coefficient (due to the progress of public health and nutritional conditions) and the variability of the mutation coefficient (due to the increasing ecologic pollution) hamper a family chronobiological research, because the times of gene extinction undergo an environmentally induced variability, such that it is practically impossible to use samples of relatives of different age, i.e., generated in different times.

The most correct method to evaluate the average Chronon of a chronological hereditary character is to make a horizontal comparison between a twin sample and a nonselected sample from the same population.

Along this direction our research is continuing, and I will only add that its practical aspects are of particular value in the field of geriatric syndromes. The latter, in fact, are nothing but hereditary diseases at the limit; i.e., they represent, like any hereditary disease, the extinction of the gene's Ergon that is responsible for an information that exhausts its Chronon in a time conditioned by heredity and that can therefore be foreseen. This particulate extinction of the liferime of single genes (i.e., of the Ergon/Chronon System) accounts for the higher similarity of close relatives in the old age with respect to previous life periods, insofar as many nonessential and differentiating genes have already become exhausted, while those existential genotypes that relatives may share become stressed.

Medvedev made the subtle observation that the geriatric age represents the period of a confuse and inexact ontogenesis. We note, on the other hand, that in this disorder there must be an order, for inexactitude and disorder repeat themselves in cotwins in overlapping pictures, such that the individual mode inheritance of the gene extinction may be individuated.

The study of twins has now spread out in every field of human and medical genetics, also because of the simple and fundamental reason that, while general genetics may apply the experimental method — namely, experimental crossing — human

genetics can in no way do that, because of moral principles: and none better than us, who are guided by the commandments given to Moses by God, is aware of this impossibility. In this perspective, the study of twins appears as an experiment devised by Nature herself.

Concluding my brief notes, I wish to point out that the study of twins requires as far as possible large and up-to-date Twin Registers. Our own one in Rome now includes fifteen-thousand twin pairs, whom we study longitudinally through periodic medical visits during the whole lifetime. It should thus be possible to make very interesting comparisons with the data from the twin register we plan to start in Jerusalem in the near future. Of course, the latter shall be open to any research worker willing to take advantage from it and carry out genetic studies on structures, functions, and diseases.

Allow me, therefore, to conclude with a most cordial "Good-bye in Israel." *Lehit-raot.*

#### RIASSUNTO

A quasi un secolo dalla prima formulazione scientifica, ad opera di Galton, del metodo gemellare, basato sul raffronto tra serie di gemelli MZ e DZ, non soltanto gli studi gemellari hanno un'importanza fondamentale ed il Test Interzigotico è ampiamente applicato nelle ricerche di genetica umana e soprattutto medica, ma nuovi metodi sono anche stati elaborati, quali il Test Azigotico ed il Metodo Clinico-Gemellare.

Inoltre, lo studio dei gemelli ha più recentemente condotto a nuove osservazioni nell'ambito degli studi sui tempi biologici, con lo sviluppo di una nuova branca moderna, la Cronogenetica.

#### RÉSUMÉ

Après environ un siècle de la première formulation scientifique par Galton de la méthode gémellaire, basée sur la comparaison de séries de jumeaux MZ et DZ, non seulement les études gémellaires jouent un rôle fondamental et le Test Interzygotique est largement appliqué dans les recherches de génétique humaine et surtout médicale, mais de nouvelles méthodes ont aussi été élaborées, telles que le Test Azygotique et la Méthode Clinique Gémellaire.

Plus récemment, l'étude des jumeaux a aussi bien conduit à de nouvelles observations dans le secteur des temps biologiques, avec le développement d'une nouvelle branche moderne, la Chronogénétiq.

#### ZUSAMMENFASSUNG

Fast ein Jahrhundert nach Galtons erster Formulierung der Zwillingsmethode, die auf einem Vergleich zwischen EZ- u. ZZ-Serien beruht, greift die Human- u. vor allem die Medizingenetik nicht nur immer wieder auf die Zwillingsforschung und den Interzygotischen Test zurück, sondern es wurden auch neue Methoden wie der Azygotische Test und die klinische Zwillingsmethode ausgearbeitet.

In neuerer Zeit führte sodann die Zwillingsforschung auch zu neuen Beobachtungen auf dem Gebiet der biologischen Zeiten und zur Entwicklung einer neuen modernen Branche, der Chronogenetik.

Prof. L. Gedda, Piazza Galeno 5, 00161 Rome, Italy.

---