Sixth International Congress on Twin Studies

Closing Address by Luigi Gedda

My dear Colleagues:

At this closing session of our Congress, I have to say that the study of twins, gemellology, no longer has a closed existence nor is it a private garden of medical genetics, but must be considered an essential part of modern medicine. This is so, because it helps medical research, and its applications involve all mankind, not twins alone. I state this on the basis of the research you have done throughout the whole world, and particularly that which we of the Mendel Institute have conducted.

My encounter with the application of gemellology to medicine was by chance. I came from the Turin Medical Clinic, where I had studied hematic glutathione in its two forms, oxydated and reduced glutathione, in patients with different diseases.

On moving to Rome and becoming the doctor at an orphanage, I was struck by the extraordinary resemblance between a pair of MZ twins, named of all things Romulus and Remus, who frequently were mistaken one for the other. It was then that I thought of studying in these twins hematic glutathione. The result was concordant in the two specimens. But the greatest surprise was when, in repeating the dosage on the following days, the figures of the oxydated and reduced glutathione were different but still concordant in the two subjects. Evidently, I was helped by the fact that Romulus and Remus lived in the same environment and were similarly exposed to the times of the day, meals, physical exercise, schooling, etc.

I read with great pleasure a recent article in the Annals of Human Genetics in which Board, Webb and Coggan from the Australian National University attribute the localization of the human glutathione-S-transferase three genes to bands of chromosomes 11 and 12. The authors state that: "Multiple glutathione-S-transferase isoenzymes have been described in man and their expression appears to be regulated by genetic, developmental and environmental factors". Apart from the specific localization possible only today, the same conclusion was reached many years ago in a simple way: the method of twins.

Subsequently, I came across the time parameter with the case of 20-year-old MZ twins about whom I reported at the International Congress of Human Genetics which I promoted in Rome in 1961. These twins were in military service, one in Trieste, the other in Taranto, 700 km apart, when they both came down with measles at the same time – an unusual age for this childhood disease. The simultaneousness of the event was so significant as to make one think that the identical immunizing defenses were missing in both of them at the same time.

Based on these and similar observations, I stated at that Congress that one of the gene's characteristics is its time dimension, that is, its lifespan.

For a better explanation of my thought, I used a metaphor. As in birthday cakes, man's life can be represented by many lit candles, which, in my comparison, do not stand for the years of the birthday person but for the genes present at the instant of the individual's conception. Each candle has its own length and represents the variability of this hereditary length. The candles burn down and go out little by little at different times according to their length because of the independence of the hereditary characters established by Mendel. In collaboration with Professor Brenci, I developed the concept of the gene's temporal dimension, demonstrating that, like a candle, a gene has a time of onset, a time of duration and a time of extinction.

Monozygotic twins are the natural demonstration of this. Why is there so great a resemblance between these twins that they are mistaken one for the other, if not because they have inherited the same times of the genes of development? Why do these twins come down with hereditary illnesses at the same time, if not because the information that corresponds to a protein necessary to the organism has itself an equally abbreviated lifetime?

The normal and pathological identicalness of monozygotic twins is so well-known and proverbial that one does not usually think of its enormous scientific value in that it demonstrates the existence of a timer. This timer works in the depth of the hereditary patrimony of every living thing, twin or single born, animal or vegetable: its genome.

We illustrated this aspect of genetics in a book entitled "Chronogenetics", that is, the heredity of time, published in 1974, in which we called the degree of stability of the gene that contains its information "Ergon", and the duration time of the information itself, "Chronon".

The Ergon is based on *accidental* stability factors such as the number of copies of a gene ("redundance") or the number of "codons" utilized for the coding of an information ("synonymy"), and on *random* stability factors such as the different "repair" systems.

Knowing molecular genetics, we can add that these information timers which represent the gene's fourth dimension are located in the DNA helix, hence in the nucleus of every cell.

Each of you probably wears a wristwatch that tells you the time indicated by the sun and its connected phenomena, such as the time of sleep, lunch and supper, but perhaps you have never thought of possessing in your bodies a vast number of clocks in the billions of cells that make up your organism. The time on your wristwatch is anonymous, that is, it is the same for everybody, while hereditary time is personalized, that is, it marks the stages of life of the individual and interacts with the normal and mutational characteristics of the environment in which the individual finds himself.

With regard to hereditary time, I recall that last month in Turin a baby girl was born to a mother who, eighteen months before, had born another baby girl by means of in vitro fertilization. Five embryos were implanted in the woman

to obtain the first pregnancy, and four were kept in liquid nitrogen. Upon being thawed out for the second pregnancy, two were found to have deteriorated and two were transferred to the woman. From one of these, the second girl was born. Hence, there were two persons born and seven sacrified. This outcome is sad from the ethical point of wiew and also from the scientific one, because it shows that criopreservation can damage the embryo.

The newspapers presented this event as the birth of a twin from a frozen embryo. As a researcher of twins, I say the two infants cannot be considered twins because they did not have simultaneous development in the uterus, nor simultaneous birth, and will not be able to have the same hereditary time. Sisters, yes, but not twins.

To justify the suppression or the criopreservation of the zygotes obtained by in vitro fertilisation, the term of pre-embryo was recently proposed. I want to state that this concept is unwarranted because each human zygote is already fully representative of human identity. In this, the second centenary of the rights of man, I ask myself about the rights of children: are they lower or higher than the rights of parents? Surely, at the time they are embryos, their rights should be higher because embryos are undefended and vulnerable. And, looking towards the future, the rights of a child should be considered to be higher than those of the parents, their entire life and social commitment being at stake.

The existence of hereditary time is a phenomenon which interests modern medicine, and the study of twins will deepen and improve its utilization. In fact, each branch of medicine can make use of hereditary time for the prevention of the diseases with which it deals.

Hereditary pathology marks the time it first manifests itself and recurs in predisposed family members. For example, we have studied the syndrome of progressive muscular dystrophy of the pelvic girdle in four families: in the first family, with two cases starting at age 2 and age 1, respectively; in the second family, with four cases at 8, 7 and 7½, respectively; in the third family, with three cases at 10, 9 and 9½, respectively; in the fourth family, with two cases at 12 and 12½, respectively.

Similar observations were made in other families stricken with very different hereditary illnesses, from intestinal polyposis to adenocarcinoma of the colon and uterus, from psoriasis to cardiac infarct, from cataract to Fabry's syndrome. In the pedigrees of these families we have found the imprint of hereditary time as to the age of onset, and now and then, as in enuresis, in the different ages in which recovery takes place, which varies from family to family.

Onset ages of the illnesses I have cited, similar within families and different among families, are not those of twins but of relatives, and indicate the presence of a hereditary time in which the deficit of the genetic information manifests itself at similar ages.

Careful study of the age of manifestation of hereditary diseases in families enables us to locate the probable age of onset and to prevent the disease with adequate therapy. Hereditary time is therefore an underlying dimension of preventive medicine for every disease of a hereditary nature, and family and eugenic consultants cannot dismiss it.

Particularly two branches of modern medicine have a specific interest in hereditary time: auxology and geriatrics. The successive manifestations of development from birth to puberty, as well as, in senescence, the variability of the times heralding the decline and disappearance of useful or indispensable information, may be forecast through careful study of these ages in the family profile.

The future advantage will be very much broader if the study of twins is intensified and deepened, particularly with the study of twins separated following marriage. This affords data on such different environmental factors as geography, eating habits, professional and stress elements which can have a positive or negative influence on hereditary time in ages of adulthood and senility.

We believe and propose that the ambitious project of the Human Genome Organisation (HUGO), which is to decipher the entire human genetic code, could avail itself of the permanent comparison of the DNA of MZ twins in order to identify pieces of variability produced by the environment, such as methylation.

When Gregor Mendel discovered that the characteristics of the *pisum sativum* twins were hereditary, he continued his research and formulated the laws regulating the inheritance of characters. Thus, gemellologists and geneticists should formulate the laws regulating the heredity of genic time and its relationship with astronomic time.

In conclusion, I strongly suggest that not only we, but all doctors, researchers and psychologists working in hospitals, clinics and laboratories, as well as in private practice, should ask patients if they are twins. If they are, then in the interest of the patient and science itself, we should ask to see their cotwin, thus keeping ourselves up to date with this body of knowledge which reaches across every branch of modern medicine.