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International Congress  
40th Anniversary of The Mendel Institute

## *President's Opening Address*

### **Twin Study Today**

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I wish to thank Professor Paolo Durand, Director of the International Centre of Paediatric Genetics at the Mendel Institute, for his kind words and I particularly thank him for having proposed this celebration to mark the 40th anniversary of the foundation of the Institute.

Somewhat audaciously, I borrow a metaphor when I say that the real foundation stone of the Mendel Institute is the book, "The Study of Twins" here on the bookrest [Fig. 1]. This rather large volume carries works I had collected and developed in Rome over the previous years. In the main, it relates to clinical research work which for me began in an orphanage, not too far away from here on via Nomentana, where I encountered a pair of identical twin brothers, Romolo and Remo [Fig. 2]. The boys were so alike physically that I constantly confused the two and it was this experience that drew my attention to the twinning phenomenon. The book also contains a bibliographic list of over 7,900 studies carried out on the subject of twins. One of the first, of course, is that of Darwin's cousin, Francis Galton and another example from a later period is that of Chiarugi, the Florentine anatomist.

Published in 1951, "The Study of Twins" provoked such overwhelming interest in the medical world that it led me to vigorously promote two initiatives which began to take shape the following year. In 1952 the first issue of the journal "Acta Geneticae Medicae et Gemellologiae" was published and the construction of the Gregor Mendel Institute of Medical Genetics and Gemellology got under way to be finally inaugurated on 6 September 1953. One of the earliest and certainly most important figures in establishing the Institute is here with us today, Dr. Ildo Avetta, the Roman architect who designed the building. Let me take this opportunity to thank him once again for his brilliant work which has drawn the attention and admiration of many over the years.

Here, before you, is the complete 40-volume series of Acta Geneticae Medicae et Gemellologiae from its birth to date. [Fig. 1].

A word which stands out in both the name of the journal and the Institute is

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Fig. 1

“Gemellology”. This is a completely new word which I coined to go beyond the descriptive definition of twinning and, indeed, beyond the case study approach restricted to any single aspect within a twin pair considered worthy of note, thereby more appropriately emphasizing the truly scientific value of this extraordinary versatile and multi-purpose instrument available to genetics, the science first explored by Gregor Mendel in 1865. In 1956 we published the handwritten text of Mendel’s work, with a facing translation in Italian.

I might add, the word itself ‘Gemellology’ has bilingual roots; it comes from the Latin “gemellus” and Greek “logos”, just as the word “Television” is formed from the Greek “tele” and Latin “visio”.

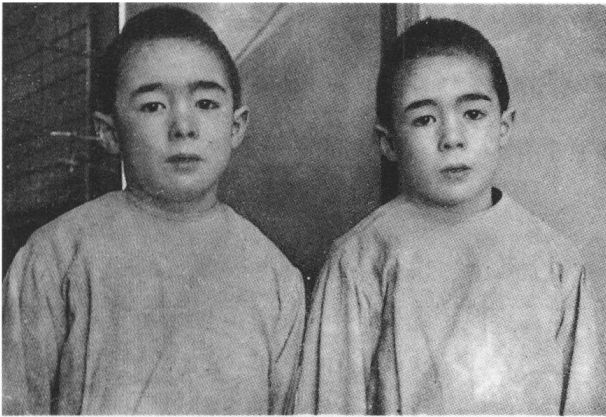


Fig. 2

Twin study, or gemellology, may be defined as a ‘high-powered’ branch of genetics because when two or more identical siblings are affected by the same disease and external factors have been excluded as the cause, then the disease is most definitely a hereditary one and, as such, its origin can be traced back in the genealogical tree of that family on either the paternal or maternal side or on both sides. In addition, the same disease may also be found in other descendents of the family.

In Fig. 3, for example, is a pair of twins who came to visit us recently from Cambridge, England. In their genealogical tree, twins were found in both the paternal and maternal lines [Fig. 4]. While it should not be forgotten that twinning is, in itself, a hereditary factor its exact mechanism remains unknown. One could surmise that some multifactorial mechanism is involved whereby the interaction of a number of genes has the power to provoke the duplication of the zygote, ie. that first cell born from the union of the male gamete or spermatozoon with the female ovum. Another reflection could be that this multifactorial mechanism provokes the duplication of a single primitively-formed embryo during its morule or blastocyst stage. Twins produced in this manner are termed monozygous and, as you can see here, they embed in the uterus with one or two placentae and one or two amniotic sacs [Fig. 5]. One of the major difficulties in interpreting the twinning mechanism, however, stems from the fact that within the one family tree both monozygotic and dizygotic twins can be found. Dizygotic twins possess



Fig. 3

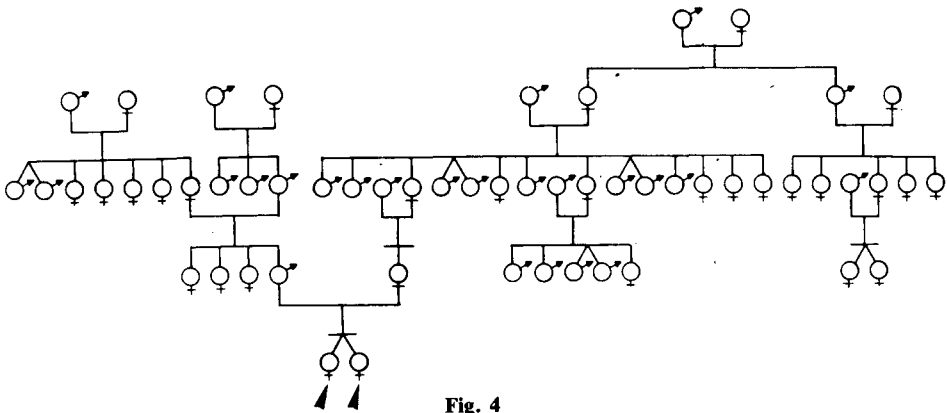


Fig. 4

different hereditary characteristics and, for example, the more common expression of this difference is the opposite-sexed pair. This genealogical chart clearly shows such a situation; the parent couple produced two sets of dizygotic twins and the mother's sister a pair of monozygotic twins [Fig. 6].

The frequency of twinning is well known. In Rome, the ratio is approximately 1 for every 80 singleton births. We will, of course, have figures on other ethnic regions from the Congress presentations this afternoon and tomorrow.

I now turn to another aspect of gemellology which I believe merits attention. In 1989, Gedda, Brenci and Carrega of the Mendel Institute conducted a study of Italian data

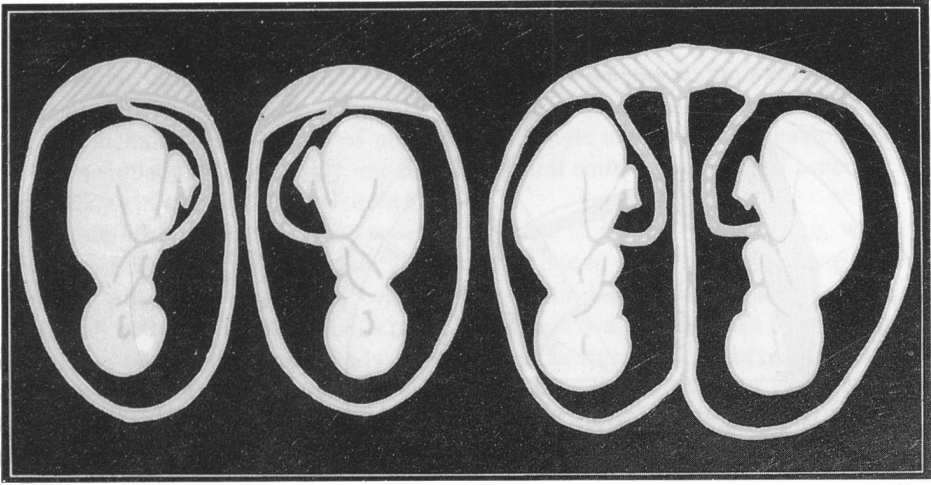


Fig. 5

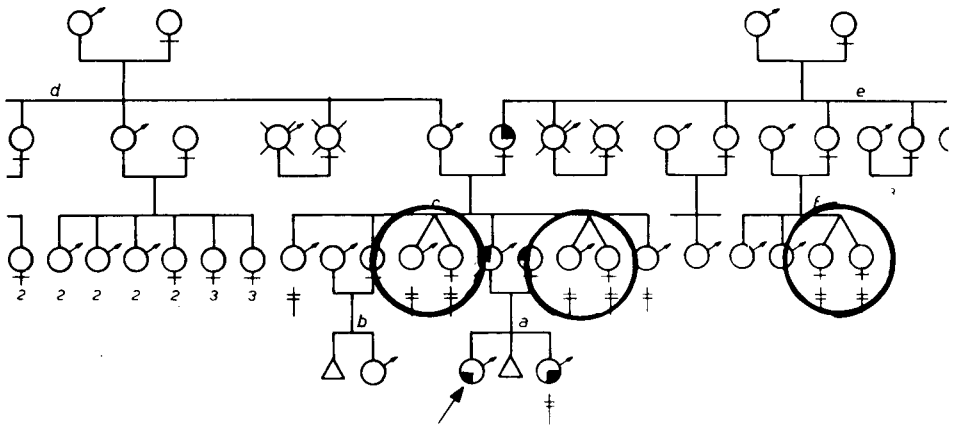


Fig. 6

for the period 1980 to 1985 to investigate how twin birthrates related to the months of the year, compared to singleton birth rates. It emerged that twin births reach a maximum of 1,4 times more than the average singleton rate in the months of November and December [Fig. 7]. Recently, our editing office received an interesting manuscript from Drs. C. Dionne, M. Soderstrom and S. Schwartz of the Department of Epidemiology, Washington University. These researchers address the same problem from another angle — the time of conception rather than birth of twins vs. singletons related to the calendar year. They conclude that twins are conceived 1,6 times more frequently than singletons in the period March through August. Such studies on the conception and birth rates of twins are important because besides clarifying the more obvious hereditary component involved they also indicate the possible influence of exogenous factors, such as seasonality, on this phenomenon.

TWIN / SINGLE BIRTHS x 1000  
( Italy - 1980 - 1985 )

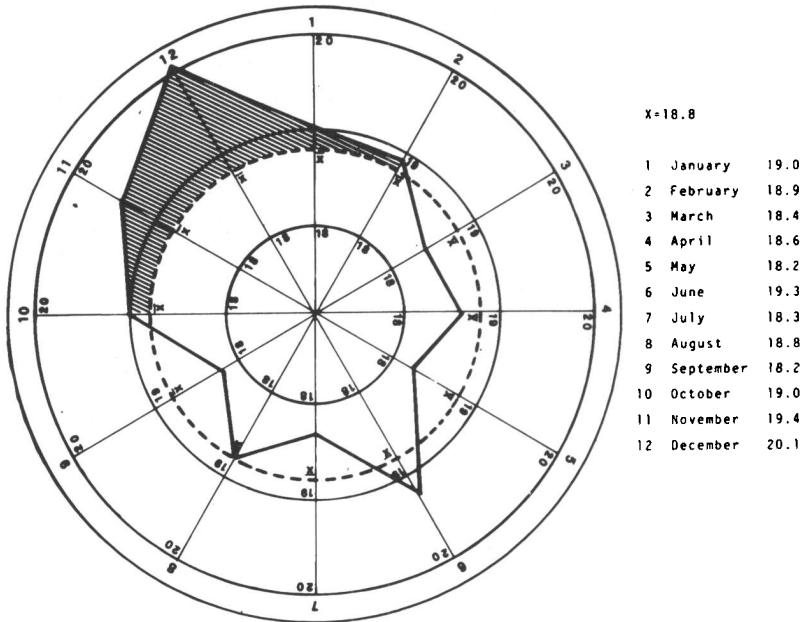


Fig. 7

Another surprising aspect of the genetic mechanism of monozygotic twinning is laterality, where one twin presents a particular characteristic on the right side of the body and the cotwin presents the same characteristic on the left. For example, one twin may be right-handed while the other is left-handed; one may kick football with the right foot while the other kicks with the left; one may have a hair whorl at the nape of the neck curling to the right while the other has a hair whorl in the exact same position curling to the left or, finally, an extreme example where one twin presents “situs inversus viscerum”.

Having ascertained the identicalness of MZ twins, the next important theme to be considered is the simultaneity of their development, in other words, their ontogeny, as this too occurs synchronously. That is to say, if an MZ twin pair are reared in the same environment and in the same manner then the stages of their development are simultaneous. The appearance of the first tooth, the initiation of phonation, of ambulation, of tendon reflexes and attentiveness etc., all occur contemporaneously in the pair. This means that the chain of operative genes and mounting of the corresponding phenes are naturally bestowed with identical timing. This chronological identicalness is much more complex than it appears at first sight because, as I will explain later, it also implicates the metabolic functions.

At a certain age, the development of the organism usually reaches its final stage of completion. The initiation of this is announced by the onset of puberty which, in MZ twins is also a contemporary occurrence. In fact, on more than one occasion, we have

come across female MZ twins whose first menstruation appeared the same night. This event marks the adult, or what is called homeostatic, phase of the phenotype and it is then that environmental influences begin to impose on the monozygous isochronal phenomenon. This refers not only to the external environment but also to the internal one and includes the adoption of alimentary, lifestyle and cultural behaviours which may, individually or collectively, modify the natural course and physical aspect of any given MZ twin pair, males or females alike.

One definite fact is that the singleton birthrate is gradually decreasing, while the birthrate of twins is on the increase. This is mainly due to what is called 'assisted procreation', or 'in vitro fecundation' whereby, ovulation is pharmaco-induced, and more often than not multiple ovulation is provoked. These ova are fertilized by spermatozoa in vitro, ie. outside the female body and then four or five of the embryos produced are manually placed in the uterus of the woman. Frequently, a number of embryos embed in the uterine wall. When two do so, then two fetuses, or twins, are produced. This practice has become so widespread that twin study cannot ignore its existence. Assisted fecundation, however, also means that excess embryos are preserved in fridges for eventual use at a later stage. To all effects, these embryos are authentic twins. In other words, human beings that degrade with the passing of time and which at a certain point are used for experimental research or otherwise eliminated. Something which may happen, as, in fact, recently happened in France, is that a woman going through divorce proceedings asks to have the refrigerated embryos, obtained with her husband, destroyed. This can only be defined as a multiple slaughter, or in today's terms a 'Sarajevo-type twinning', which the socio-sanitary world seems to ignore, but which, thankfully, the Church justly condemns.

Another, even more serious type of twinning massacre was published some days ago in the British Journal of Obstetrics and Gynaecology. It reported on a research study carried out by Anthony Abbas, Research Fellow and Kypros Nicolaides, Professor, at the Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, London together with Mark Johnson, Research Fellow at Chelsea and Westminster Hospital, London and Niklaus Bersinger, Biochemist at the Department of Obstetrics and Gynaecology, University of Berne, Switzerland. The research was aimed at measuring the levels of alpha-fetoprotein in the maternal serum of 12 multifetal pregnancies before and after iatrogenic reduction of these down to two twins only in each case. These multiple gestations were 2 cases of 3 fetuses, 5 cases of 4 fetuses; 2 cases of 5 fetuses; 2 cases of 6 fetuses and 1 case of 8 fetuses. Reduction in all cases was obtained by transabdominal injection of potassium chloride directly into the hearts of the 'excess' fetuses. This, therefore, is a carnage of 32 fetuses carried out between the 8th and 9th week of gestation [1] and, I should think, is enough to give us an insight into the fate that can befall the product of multiple pregnancies, which, for the most part, are the result of induced ovulation and assisted fecundation.

*Multifetal pregnancies resulting from assisted fecundation did not exist 40 years ago.* However, even then, as I said earlier, twin study was acclaimed as a highroad in approaching the problems of human genetics. At that time, Prof. Frugoni, who had earlier written the preface to the "The Study of Twins" and Prof. Puntoni, President of the Faculty of Medicine at the University of Rome "La Sapienza", began to appreciate the importance of genetics to the scientific curriculum of medical students. Until then,

genetics was taught by biologists who, for obvious reasons, were not in a position to offer the more in-depth knowledge required to understand the hereditary diseases of man. As a result, these two Professors requested and obtained permission from the Faculty to establish a Chair in Medical Genetics. The assignment was 'entrusted' to me and I recall how, from the very first lesson, this hall was overcrowded with enthusiastic medical students. Within a short time the Ministry of Education publicly announced the first State Examination in Medical Genetics and the other two successful candidates who joined me were Ruggero Ceppellini and Luigi Cavalli-Sforza. I still clearly remember how nervous I was when I delivered my inaugural lecture in the Great Hall of the Studium Urbis on 21 January 1961. In the years that followed, we established a post-graduate specialization school in medical genetics and, on attaining particularly high-standard results, we proceeded to assign university lecturing posts and to propose our candidates for the Chair of Medical Genetics in universities throughout Italy.

I am proud to say a number of our candidates were successful, namely, Prof. Del Porto who was assigned the Chair in Aquila, Chieti was given to Prof. Casa and the Chair in Human Genetics at Ancona went to Prof. Milani-Comparetti. There are, of course, others to whom I owe a special thought, like, Prof. Di Raimondo who came to the Mendel from the University of Bari to afterwards become Director of the Institute of Human Genetics at the Spallanzani Hospital in Rome; Profs. Alfieri, Allori and Cavalieri who, having obtained their lecturing diplomas at the Mendel later became, respectively, Director of the Institute of Human Genetics at the San Filippo Neri Hospital in Rome, Director of the Hospital in Palestrina and Scientific Director of the "Istituto Dermatologico dell'Immacolata" in Rome.

Although genetics has contributed enormously to the major developments achieved in medicine over the last decades, there still remains a distinct split in medical thought on the subject. On the one hand, there are the phenotypists who occupy themselves exclusively with the phenotype or, more simply, that which can be seen in the human body (coming from phaino = see), while on the other, there are the genotypists who, through the study of the cell nucleus, concentrate all their efforts in the identification of the genes responsible for individual diseases. This latter line of thinking stems from the fact that the human body is made up of billions of cells that contain the double helix DNA which carries those particular genes capable of generating the necessary substances for the production of human tissue, i.e. the phenotype. It is hoped that these differences in medical approach, between phenotypists and genotypists, will be bridged culturally by twin study, given its singularly neutral dictate in placing equal importance on the double identity of both the phenotype and the genotype of the human being.

With these words, I have strayed away a little from the theme of twins but I take the subject up again to say that the opening of the Mendel Institute procured for us a growing number of twins, almost all in early infancy, whose parents sought medical assistance. To meet this need we opened an out-patients clinic for twins. In the early stages, general medical visits were conducted free of charge but as time passed and the more specialized clinics were set-up it became necessary to introduce a nominal remunerative system to cover expenses. Today, we have 15 specialists who visit our 20.000 twin pairs registered at the Institute.

Naturally, the study of hereditary diseases in singletons also developed and kept pace over the years with the 'twin' activity of the Institute. In this regard, I should like to



thank Prof. Durand for his work as Director of the Paediatric Centre and Prof. Mandelli for his consultancy on leukaemia and other hereditary diseases of the blood; Prof. Mariani for his work on the heredity of haemophilia and coagulopathies; Prof. Pachi for his obstetric consultation to mothers in multiple gestation and Prof. Mastroiacovo for his consultancy on the study of congenital malformations. Another precious instrument is the clinical and bibliographic archives on twins affected with autoimmune diabetes which Prof. Leslie of London kindly consigned and up-dates at our Institute.

Along the road, the health welfare institutions began to show an increasingly active interest in twins. Many Clinics began to collect data on twins and to form registers of particular cases treated but these do not allow for investigation of the more ramiform aspects of twinning. It was necessary to direct a greater multidisciplinary study of the phenomenon. As a result, in 1974 a Society to suit this aim was founded and we named it "The International Society for Twin Study" (ISTS). The Society held its first Congress in Rome in 1974. This began the agenda of three yearly congresses held in Washington in 1977, Jerusalem 1980, London 1983, Amsterdam 1986, returning to Rome in 1989 and in Tokyo in 1992. The proceedings of these seven Congresses are gathered in our journal AGMG, with the exception of those from the Jerusalem meeting which, through the competent collaboration of Prof. Parisi, were published in six volumes by an American publisher. One of these volumes carries the title "Intelligence, Personality and Development". The title in itself denotes how psychologists too began to take an interest in gemellology and confirmation of this is the Paris 1986 publication by Prof. René Zazzo, called "Les jumeaux, le couple et la personne". On our own front, a growing interest in the psychology of twins was confirmed by the requests we received from professors of psychology at "La Sapienza" for our assistance in the revision of degree theses on themes such as the sleeping patterns and dreams in twins.

While the study of the concordance in the behaviour of MZ twins separated from birth informs us of their concordant psychological characteristics which are hereditary, the study of the relationship which exists between an MZ twin pair highlights the extraordinarily singular characteristics of their relationship which are not to be found in any other interpersonal rapport.

A well-known peculiarity which, for example, distinguishes this intrageminal relationship in MZ twin pairs is that, prior to school-going age, they often create their own 'secret language'. In other words, they create a method of communication using 'sounds' rather than words to identify people and events. They get great enjoyment in using their secret language which the other members of the family do not understand but this is also to their detriment because they learn to speak properly much later than other children of their age. We, in fact, advise parents to discourage the twins, as far as possible, from communicating in this manner. This intervention might mean interfering with their natural friendliness which, however, often lends itself to the family depiction of these healthy youngsters as ruffians, particularly MZ male pairs.

The social popularity of twins has led to the publication in the United Kingdom, Australia and the United States of magazines exclusively dedicated to these children. We receive copies of these at the Institute and I have become quite fond of browsing through their contents which always have a happy and comforting warmth about them. In these countries, also, the mothers of twins have formed Clubs so they can exchange informa-

tion on all sorts of problems relating to the upbringing and education of their twin children.

From more detailed study of the relationship between MZ cotwins it has emerged that, quite often, up to the age of puberty a kind of hierarchy exists between the two. In these cases, one is the leader because he/she thinks and acts on behalf of his/her cotwin as well. This behavioural component is usually well-hidden but it needs to be uncovered because, in many circumstances, it is the cause of the pair behaving as a single entity in facing certain environmental realities and, unwittingly, it calls for others to treat them as a single individual.

Unfortunately, in some MZ pairs, who I think are in some way definable as psychopaths, their extraordinary simultaneity can lead to tragedy. The cases which come to mind are those of the 20 year-old MZ pair from Foligno who committed suicide contemporaneously in 1991, the 19 year-old MZ pair from Udine who repeated the same desperate act a year later, and the most recent 30 year-old MZ pair from Montecatini who took their lives in 1993. There is no doubt that gemmology can serve tremendously in avoiding the occurrence of such tragic events.

Allow me to carry your thoughts to the more serene horizons of gemmology that provide us with knowledge relating, not only to the psychology of twins, but to the more vast conception of the human psyche as a whole. I cite the cases of school-going MZ twin youngsters who were all invited to draw a common picture. The theme was "My family at the dinner table". One of each pair was seated in two separate rooms, thereby communication between cotwins was impossible and all were supplied with the same boxes of colouring pencils. There were extreme differences in the pictures drawn by the respective cotwins of each MZ pair. This exercise was repeated with pairs of Arab monozygous twins by Dr. Manuela Martins at our Institute of Medical Genetics and Gemmology in Jerusalem which I established years ago despite the many difficulties that the Intifada created and continue to do so up to today.

Here are samples of the Italian MZ twin pairs [Fig. 8a-b] and the Arab MZ pairs [Fig. 9a-b].

Accordingly, it can be said that certain psychological functions existing within the psyches of MZ twins are concordant and are, therefore, hereditary, while at the same time there are other different psychological functions in each twin. We cannot but define these differences as exogenous, or for name's sake, individual. The most evident expression of this in adult MZ twins is their different choices of marital partners. To date, we have rarely come across an MZ pair in conflict for reasons of competition or jealousy, and even less often on the choice of partner which normally goes beyond the person for him/herself to include what he/she represents e.g. social standing, profession and everyday lifestyle preferences. This diversity, which is in contrast to the identicalness or hereditary similarity of MZ twins, confirms that all human beings possess an individual freedom of conscience and sense of responsibility irrespective of their kindred status.

Recently, many articles appearing in the most prestigious international medical press demonstrate that twin study is, at this stage, a solid framework upon which the medical world can verify its theories, its diagnoses and establish appropriate therapeutic treatments for twins.

Molecular genetics was also born 40 years ago when Watson discovered the helical structure of the DNA. Since then it has taken gigantic steps in discovering the geno-

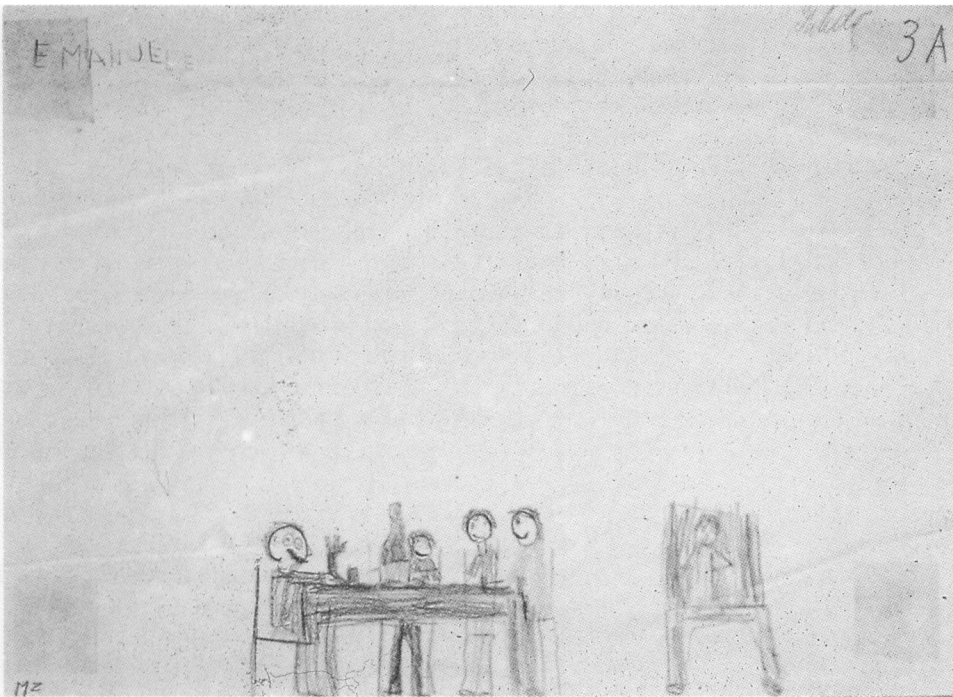
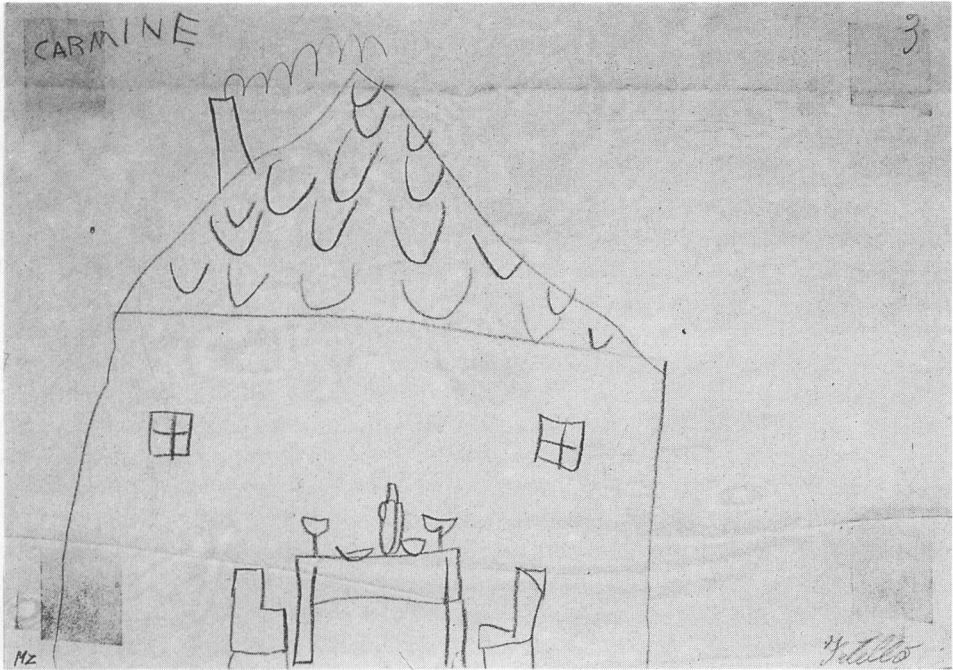


Fig. 8a-b

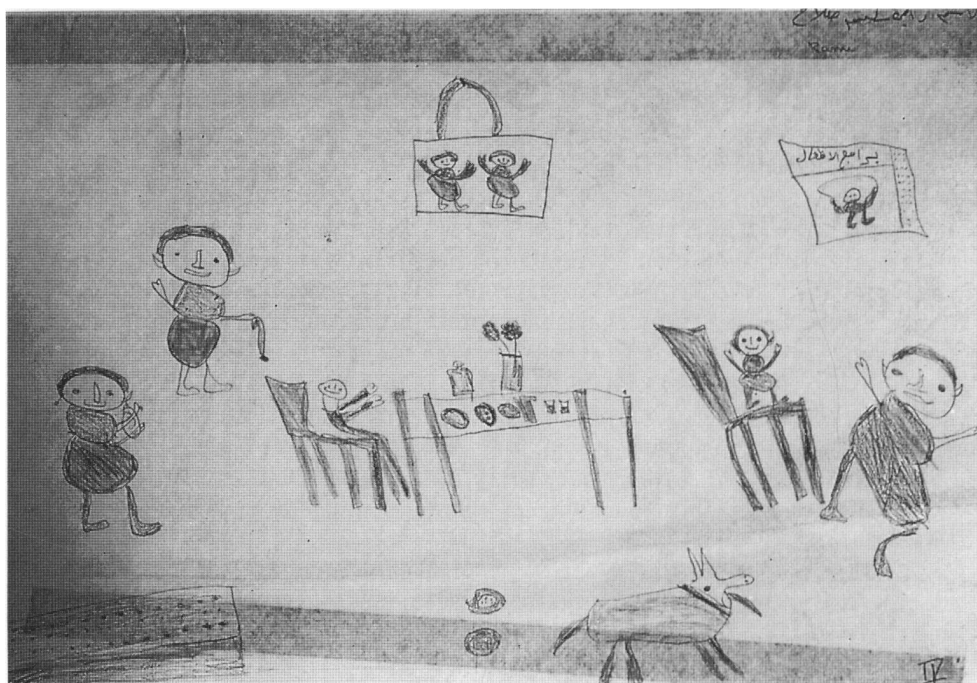
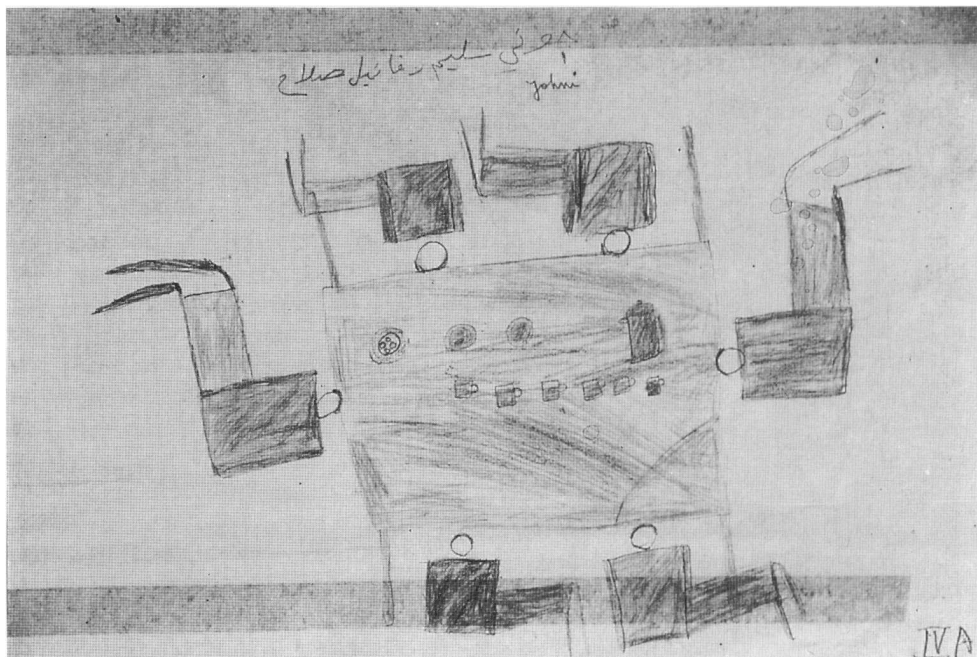


Fig. 9a-b

types responsible for the structure of, and disease in, the human body. These results are clearly expounded in the global project The Human Genome and sustained by the therapeutic experiences gained in attempting to substitute diseased genes with healthy ones in cases of hereditary disease. This fascinating branch of genetics can also find that gemellology holds a wealth of information which could prove useful to both theoretical genetics and clinical medicine alike.

In relation to this, I mention a research project which I have been working on for some years together with Gianni Brenci and which I should like to propose now to those Colleagues who have honoured me with their presence here today.

The starting point was the revelation of the identicalness of the fractions oxidized and reduced by haematic glutathione in monozygous twins; an identicalness which, over time, maintains a constancy in its fluctuations. Data relating to DZ cotwins who have relatively different values led us to note that the identicalness of the body and of the metabolism depends on the stability of the genes over time. We named this stability "Ergon" and the average lifespan of the gene and its information "Chronon".

We called this phenomenon, which implicates forms and functions of the phenotype, 'Chronogenetics' and from this our concept of the temporal dimension of the gene was born. This concept finds confirmation in the cases of hereditary diseases where this genic dimension is either shortened or absent. This is also the case in the ageing process where the genes demonstrate their progressive decrease, some earlier and some later, according to the familial model. Hereditary diseases, therefore, just like the damages of ageing, reflect the stability of the gene, that is, its duration in time which is hereditary [2]. To consider the duration in time of the gene's activity, I think, can be of assistance to clinicians both in the prognosis of hereditary disease and in the treatment and prognosis of senility.

This is a contribution which Twin Study offers to Clinical Medicine.

To conclude, illustrious Authorities, Colleagues and Friends I wish to recall the document on the status of the family which His Holiness, Pope John Paul II, issued yesterday. Indeed, the telegram, which Prof. Durand kindly read to us at the opening, is an efficacious synthesis, reviving my hope that Medical Genetics and Gemellology will continue to be a scientific support to the Divine Will as regards human procreation. I pray to God that, in this society which tends to forget transcendence, the Mendel Institute can continue to serve the splendour of the Truth which must, in the forthcoming century, bring about the fraternity of all peoples.

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