The Institute of Medical Genetics of the University of Rome
at the Gregory Mendel Institute

Clinical Genetics*

The Contribution of Genetics to Diagnosis, Prognosis and Treatment
The Gene "Period" and the genetic conception of life

Luigi Gedda

The Committee of the Xth International Congress of Genetics had the excellent idea of acquainting the public of Montreal, Canada, with the practical utility of Genetics by organising a Public Exhibition under the slogan of: "Genetics in the Service of Man".

If we were to choose a slogan that would best summarise our work at this Conference, I think we could suggest the following: "Genetics in the Service of Medicine".

For one third of this Conference's papers, panel discussions, symposia and reports, has dealt with normal man, whereas two thirds considered diseased man. Just as, in Medicine, knowledge of normal man is the natural prerequisite for the understanding of human pathology; so in Genetics, knowledge of the heredity of normal traits, both of the individual and of the population, is the necessary prerequisite for the knowledge of Genetics of human disease.

Genetics dealing with disease now bears a name everywhere introduced and generally accepted: "Medical Genetics".

The subject of my paper, however, carries a different name: "Clinical Genetics", and I would now like to justify its choice.

Between Medical Genetics and Clinical Genetics, there exists the same difference as that which the Italian Medical School,—as well as those of other countries—admits between Pathological Medicine and Clinical Medicine: Pathological Medicine studies the theoretical pattern of disease and brings the patient in as a demonstration of its theoretical conclusions; Clinical Medicine, on the other hand, takes off from the study of the patient and then attempts to interpret the latter's morbid condition according to patterns and classifications formulated by Pathology. In the same way, Medical Genetics is concerned with establishing the theoretical patterns of hereditary disease, whilst Clinical Genetics concerns itself with the individual patient and seeks to establish the manner and degree in which his disease is related to hereditary causes. Medical Genetics and Clinical Genetics are therefore neither equal nor competitive disciplines, but different and complementary ones.

Medical Genetics considers the transport of morbid hereditary units from one generation to another along the main branches of the genealogical tree, the various combinations that the meeting of these units may originate, the effects that occur when these units pass from parents to children through the gametes, as also other problems for which heredity of disease is as an interhuman phenomenon. In Copenhagen, I called it the "continuum interhumanum mor-

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bi". In actual fact, Medical Genetics cannot be fully understood without a realisation that hereditary disease has a dimension of its own that extends beyond man himself to include his ancestors, descendants and collaterals. The case of an intervening mutation, on the other hand, concerns only his descendants. That is why Medical Genetics is, essentially, transhuman and interhuman, and rightly belongs in the broader branch of science called simply "Genetics" (24).

With Clinical Genetics, it is another matter. The origin of the term "clinical" gives the discipline's exact nature,—the Greek word "*κλίνη*" signifying *bed,* that is man confined to his bed, a person who is ill. The general problems of the departure and arrival of morbid genes, as well as that of any other inherited aberration or pathogenic anomaly are, therefore, left by Clinical to Medical Genetics. Clinical Genetics centers its attention on the patient, and its concern is to supply those facts and findings that can be useful in diagnosis, prognosis and treatment of the individual patient.

Consequently, Clinical Genetics' scope, kept at the level of the diseased individual, must of necessity be of a more restricted nature, but it also gains in depth, in immediacy, in reality.

Clinical Genetics is, therefore: Genetics at the patient's bedside, where the family doctor will inevitably be met. He may or may not be a Geneticist which, to-day generally at least he is not. Besides, the family doctor, or physician, cannot limit himself exclusively to the hereditary aspects of disease. He must consider and deal with the totality of the morbid phenomena altering the individual's homeostasis and threatening his life (2). A disease is a complex phenomenon in which four causal factors, at least, can be distinguished: hereditary causality, environmental causality, psychosomatic causality, and reciprocal causality. By the latter, I mean the phenomena of secondary reaction that can arise from the interaction of the original phenomena constituted by the first three factors described. In other words, disease is the result of summation of the action of different pathogenic phases. The attending physician must cope with the total condition, even if of mixed origin.

The treatment of the phenotype, ill as a result of so many intervenient causes, must be undertaken by the doctor in his capacity of physician, in a total, comprehensive manner. And Genetics, realising that doctors must face many and different clinical situations essentially concerned with the phenotype, undertakes to submit its own findings and criteria that they may be the better equipped for their battle against disease.

It is in this contribution made by Genetics to Clinical Medicine for the diagnosis, prognosis and treatment of the individual patient that, in my opinion, Clinical Genetics consists.

Having thus examined the matter of the definition of Clinical Genetics, it now behoves us to consider its qualifications,—or competence—to enter the field of human pathology, and the extension or limits within which it should assert itself.

It would seem to me that Clinical Genetics is well qualified to cover the whole of the pathological field. Not always for the same reasons, perhaps; nor in the same measure. But in every case, it would, undoubtedly, be justified, and this, always, on a strictly objective basis.

No one would think of denying the competence of Clinical Genetics for dealing with diseases of hereditary origin, but very few are the Medical Schools that have at till undertaken to consider human pathology from the starting point of biological heredity. Any willing to do so, would soon realise how great is the number of diseases that can be traced back to a hereditary, and therefore genotypical, aetiology.

Pathological conditions observed in intrauterine phenomena,—such as abortions or malformations induced by the action of lethal or sublethal factors—have been, so far, only superficially studied, or simply held to be of environmental nature and, therefore, of obstetrical incumbency. The prevailing hereditary nature of this antenatal pathological field is recognised at present (10, 12, 13, 23, 30, 37).

At the other extreme, we know of a large number of diseases affecting normal biochemical functions that can be grouped under the general heading of molecular heredity (1). These constitute whole chapters now taught in Medical schools under the headings of metabolic diseases, blood diseases and the like (32). Between these extremes of structural and functional damage due to a morbid heredity, there exists a great range of hereditary diseases in which damage is interdependant and variously associated. It is because of this, that after working four years on a Treatise entitled " De Genetica Medica ", (the first volume of which has just been published), I have chosen the colours of the rainbow to distinguish the seven fundamental parts of the Treatise, and as a means of coping, by the judicious use of intermediary shades, with the rapid extension of our knowledge in the field of pathology. This is an editorial device, but it also symbolises the annexations made by Medical Genetics in Human Pathology.

Although I cannot now go into the detail of all diseases, I do think I should point out the progress of Genetics in such specialised fields as ophthalmology, dermatology and oto-rhinolaryngology where, specially since the introduction of modern therapeutic methods, it is known that hereditary causality accounts for the greater part of morbid casuistry (3, 36).

The problem of the competence of Genetics varies in the case of diseases fundamentally determined by environmental factors. These diseases, such as infectious diseases, would appear at first hand to be foreign to Genetics, or simply connected,—as they are in fact—to the Genetics of the morbid agent (protozoon, protophyte, virus), or of its intermediary hosts. Allergic and professional diseases are so intimately connected with their environment that some of them did not even exist before man's invention of new products, such for instance, as nylon-allergy. However, even in these cases the frequency of the disease is not only linked to an external cause, but also to a " diathesis ", a term by which empirical medicine used to signify the presence of an endogenous causality. Considering, therefore, the matter with a Geneticist's eye, it is possible to admit: 1) that a heredity of disposition does exist; 2) that a heredity of disposition is not, of itself, sufficient—the presence of an external causal factor being necessary; 3) that within many and vast ranges, hereditary causality, though not of itself sufficient, is, not withstanding, necessary (25).

We know of infectious processes in twins that suggest the existence of a hereditary pattern (6, 7, 8). For instance, the case of a pair of MZ twins, aged 20, both in military service, one at Trieste and the other at Taranto (over 2.000 km distant), both contracting measles at the same time. Another pair of MZ 5-year-olds, simultaneously succumbing to polio with identical and superposable paralytic effects. Still another pair, described by Messeri with identical mirror-imaging sequelae (27). In this respect, I consider it useful to stress the fact that the clinical « superimposition » in monozygotic twins is more than the simple « concordance » because it means the non-casual concurrence of many statistical units (17).

I think that in cases such as these, it would be useful to speak of *concausal heredity,* and in the clinical approach to such diseases, the competence of Genetics is obvious. This criterion applies to TB, asthma and many other diseases.

But outside the field of causal and con-causal heredity, we also know of morbidity in which no causal factor, referable to a phenotype, exists. Here, at the FAO, it is natural to recall a sister organisation, the WHO, suggesting as this year's motto for the World Health Day, that of accidents, since they are an ever increasing source of casualties and deaths. Causality from accidents is often 100% exogenous, whether caused by street or factory accidents, poisonings, drownings, and so forth. The same argument applies to the pathology caused by weapons of all kinds, temperature, weather conditions, pressure conditions, oxygenation conditions and, generally, by the environment in which man lives. It is a very important pathology from the social

point of view in which, however, hereditary causality can be generelly ruled ont. Yet even here, where Medical Genetics does not enter for aetiologic reasons, Clinical Genetics can have something to say in the matter, since a hereditary pattern can easily be discerned in the concurring phenomena (symptoms, evolution, prognosis).

The series of hereditary patterns of exogenous disease is endless. In surgery, I would recall that cicatrisation is governed by hereditary factors. The study of the process of scarification in Jennerian vaccination, undertaken by myself on twins, proves it (11), even though, as I think, the heredity of such processes presents special traits, possibily connected with cytoplasmic heredity. The matter of grafts and of the easy rooting of homotransplantations in monozygotic twins shows that receptiveness to transplantations depends upon heredity.

Therefore, for any one of these three reasons (causality, concausality or hereditary pattern), Clinical Genetics may be considered competent to cover the entire field of human pathology. There are here whole spheres where Genetics may be profitably introduced as a new criterion for the selection and classification of morbid data and where Medicine is at present limited to a purely morphological approach (as in the case of tumours), or a purely clinical one (as in the case of allergies). Medicine itself appears to suggest this extension, since Genetics is in a position to create new perspectives in respect of aetiology, pathogenesis, equivalences and morbid associations.

Turning now from the consideration of competence to that of clinical practice, I feel I can say that the cooperation of Clinical Genetics with Medicine should be carried out on the classical lines followed by Medicine in the treatment of diseased man: diagnosis, prognosis and therapy. I consider it right that this order, both in method and in practice, should be adhered to, since one of our Conference's results should be to convince doctors: 1) that Genetics is not only a theoretical science, but also an applied one; 2) that Genetics puts its findings and conclusions at the service of Medicine; 3) that it would be desirable to include Medical Genetics in the curriculum of Faculties of Medicine.

In contributing its services to Clinical Medicine, Genetics offers approaches to research, arising from its studies and findings, all of great utility to the clinical study of the patient.

The first of these approaches would certainly be the genealogical one. In taking this approach, the geneticist not only accepts, but also intends to complete the so-called family history criterion. This history consists of a rather summary gathering of data. The genealogical criterion, on the other hand, means the setting up of such data on the lines of a family tree, completing it with the family's medical history, or at least with that of the causes of death in the family, and with the examination, where possible and useful, of available relatives; and, finally, the genetical reading of the collected data (15).

Clinical Genetics' insistence on the generalogical tree stems from Genetics' conception of man, such as it would submit to Medicine and to which I would now, briefiy, like to draw your attention. If the Geneticist were to symbolize his conception of man, he could do it by outlining an hourglass, made as we know, with two cones joined by an isthmus. Man would be this isthmus, the superior cone would represent the afferent heredity derived from father, mother and the two respective ancestries that, stemming from distant points, converge on the individual in the shape of a reversed cone, fanlike; the inferior cone could be considered to represent the efferent heredity transmitted to offspring and grandchildren, and assumes rather the aspect of an upright cone. This symbol therefore clearly shows that nothing reaches the isthmus that has not previously been contained in the afferent cone and that the subject's heredity, by the separation of its alleles, is distributed in the efferent cone.

If we furthermore consider this image in accordance with the spirit of Mendel's laws and specially in accordance with the principles of independence of traits, we may say that the

characteristic traits of each single human organism preexist in the afferent and prolong their existence in the efferent cone, so that, both in the ascending and in the descending ones (as well as in that of the collateral consanguinity), they may be investigated, compared and evaluated to advantage. In other words, the genealogical criterion makes possible a kind of genetistic dissection of the phenotype, whether healty or diseased, that may serve different purposes, some of which could be the following:

a) The identification of the hereditary nature of the subject's illness by means of its incidence in the consanguinity field, and through differential diagnosis by means of possible phenocopies that do not correspond to hereditary models. Human Biology has, in fact, a rather limited reactive imagination and may produce a phenotypically identical reply to causes of a hereditary or non-hereditary nature, or of mixed nature. Only the genealogical criterion makes possible the differential diagnosis between genocopies and phenocopies.

b) The identification of the phenes, that is of the hereditary morbid units that, because of the characteristic traits of independence, appear disconnected and disseminated in the afferent and efferent cones. This result of what I call " genetistic dissection " of the morbid phenotype makes it possible to distinguish the morbid associations that are occasionally present in the patient (but disappear in the ramifications of the family tree), from the significative morbid associations repeatedly found in various positions of the genealogical tree, either because of a common source, or because of some other reciprocal relation that is not only casual.

This taking to bits of the patient's semeiotic background does away with phenotypical superstructures and establishes the true dimensions of the disease, whether from hereditary cause or concause. And in the case of a strictly hereditary nature, a more exact evaluation of the symptoms is secured.

c) The identification of the morbid genotype circulating within the consanguinity makes possible the discovery in the propositus of microforms of diseases not yet clearly evident, or of symptoms not identificable by means of clinical examinations, but whose appearance in the family tree may lead one to suspect their presence. We may even consider the possibility of succeeding in detecting the occurrence of potential heterozygous conditions or " metaforms ", due to carried alleles, on the basis of the indications of the family tree.

A second principle established by Genetics, of possible use to Diagnostics, is the " Progenetic Criterion ". We feel it necessary to keep separate the Progenetic Criterion from the Paragenetic Criterion—we shall come back to this point—in the sense that both the one and the other refer to non-genotypical agents, capable of influencing the genotype proper. In respect of progenesis, these factors act during the pre-conception or pre-zygotic period, and therefore, on the gametes; whereas in the case of paragenesis, they affect the product of conception in the prenatal period.

The Progenetic Criterion is known through the studies of Turpin (35), and is of particular value inasmuch as it deals with the influence parents' age bears on their offspring, to the extent that the bulk of observations made in respect of the births themselves can be referred back to the parents' ages. Whereas in non-pathological biology the most evident progenetic case is that of dizygotic twin conception (prevailing mostly in women between 35 and 40 years of age),—in pathology we have interesting data such as that of the greater frequency of mongoloid births of mothers in that same age group. This statistical coincidence of the main phenomena should suggest some interesting working hypotheses. Furthermore, this variability of morbid Progenetics should be a warning to physicians of the possibility of a variation in human pathology that should be added to the other criteria of variability, suggested by Population Genetics in respect of the breaking of isolates, of marriages effected at a more advanced age, and other similar causes.

The Paragenetic Criterion refers to certain

characteristics of the endouterine *habitat* and provides information on the hereditary background of the product of conception. At the Mendel Institute we have adopted the term of "paragenesis", firstly to indicate the general conditions of pregnancy such as duration and prenatal care, the mother's diet and living conditions,—all quite apart from any pathological alternatives. We have, besides, extended the concept of paragenesis to the given characteristic traits of the endouterine *habitat* such as foeto-placental circulatory conditions. We were led to this by studies on twins in respect of congenital heart diseases of hereditary nature (20). In the study of these malformations, the most striking factor is the prevalent discordance registered between monozygotic cotwins. In other words, the highest frequencies of congenital concordant heart diseases not only do not constitute a characteristic of monozygotic twins, but would appear to be an even greater one in dizygotic twins. In a report presented at last year's European Congress of Cardiology (19) we interpreted this fact by linking it to another subject of our research, namely, twin placentation. The latter may be single or double, both in monozygotic as in dizygotic twins. We have been able to show (22) that in this phenotypical variability observed at birth, the type of placentation is of the utmost importance since it results in a greater variability amongst monoplacental twins. For the single placenta results in more frequent disparities between the two foetuses, nourished as they are by blood from one and the same placenta. It is on this basic observation that we have formulated the hypothesis that a discordance of congenital heart disease in monozygotic twins can be related to the more frequent occurrence, in their case, of the single placenta. The twin subjected to the greater foeto-placental circulatory deficiencies thereby becomes an easier subject for the penetration of the hereditary factors of malformation. This example suggests a paragenetic factor and leads one to think that a faulty formation of the placenta, or other conditions of the same kind, can add to the patient's history of morbid heredity.

The paragenetic parameter is very wide, since in its range it can include maternal influence on the foetus' passive immunizing reactions that produce a foeto-maternal incompatibility. And it may possibly even condition the active immunizing reactions the individual will have in the course of his own life. Progenetics and Paragenetics are therefore two wide conditioning spheres that envelop the hereditary sphere proper, and upon which they converge.

Clinical Genetics, furthermore, contributes to Diagnostics with the "Cytogenetic Criterion". One of the characteristic features of our Conference is that it is taking place at a time of ever increasing interest in Cytogenetics. One of our most attended Symposia was precisely the one dealing with Chromosomal aberrations. I therefore feel exempted from the duty of illustrating the substantial contributions made by Cytological Genetics in recent times to the diagnostics of disease, conditioned by a non-Mendelian hereditary mechanism. In the field of Cytogenetics, I would like to recall the contribution of Torrioli and others of the Mendel Institute (33, 34), who have furthered the understanding of the problem of nuclear sex by showing on staminal cells of bone marrow and on white cells of circulating blood (both normal and leukemic), that the difference between cells of male and female subjects does not consist only in the number and relation of the "drumsticks", but that the fundamental phenomenon is related to the mean volume of the nucleus which is larger in female cells than in male cells.

From another point of view, but always in connection with the cytogenetic morphological reference, it would appear possible to say that the secret of many diseases is still enclosed in the mysterious protoplasmic heredity to which I have referred, since 1949, to explain the behaviour of the glutathionemic system in twins, of those two zygosities that do not find a full explanation in the mechanisms of nuclear heredity. Beside the formula summarising the mendelian pattern of some traits (genotype), it

would seem necessary to find an individual formula for the characteristic traits that do not follow the mendelian pattern (4, 5).

In the second place, Clinical Genetics can put its principles and findings at the service of Prognosis. The study of consanguinity gives the full dimensions of a hereditary disease. Since hereditary diseases derive from a single punctate mutation which can be analogous but is not always identical, they present an unmistakable family gene (*genius familiaris morbi*), whether in respect of severity (*quoad vitam*), of symptomatology, of evolution, or of effect (*quoad modum*) (9). If a hereditary disease is found to repeat itself in the same genealogical tree, this should be known not only because of its presence that confirms its hereditary nature, and therefore confirms the diagnosis; but also in respect of duration characteristics, complications, morbid associations, etc., all of which greatly contributes to the disease's prognosis in the propositus.

At the Montreal Congress I reported on investigations carried out at the Phthisiatric Hospital of Rome, where with Volta and Bresadola, I made comparative studies of the evolution of TB in single-born brothers hospitalized for treatment in that institution, and repeated the procedure with non consanguineous controls (16) The results give readings on the symptomatology, the evolution and the treatment of the disease.

On the strength of these and similar considerations, we have deemed it advisable to suggest the adoption of the principle of "clinical risk" in medical reports for life insurance purposes. This is complementary to the well-known eugenic principle of "morbid risk". In other words, the study of the genealogical tree makes possible the prognosis of the characteristics and the dangers of the disease under consideration. This is what is meant by "clinical risk" (14).

The cycle of applied Medicine closes with Therapeutics, to which Clinical Genetics can also offer a useful collaboration.

When preparing our Conference's program, requests were received suggesting that a Symposium should also be held to consider and discuss Pharmacogenetics. It was, unfortunately, too late for this, but the request was fully justified. It is due, precisely, to a pharmacogenetical observation that "enzymopenia" was isolated; this being the characteristic trait of families, upon which the action of primaquine produces a typical hemolitic reaction. Primaquine is an antimalarial: and the observation of this drug subsequently permitted the isolation of a hereditary enzyme deficiency as the cause of favism. There are many observation available, though not all yet adequately classified, pointing to the two principal hereditary aspects of the organism's reaction to drugs: tolerance and sensitivity (28, 29). Therapeutic prescribing should take into account family reactivity to medication, since to-day's socialised medicine tempts both patient and doctor to recur to it in greater measure than in the past. This hypertherapy induces an increase in allergic diseases. Family intolerances to salicylates and derivatives, as other idiosyncrasies to medicaments, are old and well-known observations of pharmacogenetics.

New and significative observations come from the field of anaesthesiology, a field that affords rewarding opportunities in which to study man under the influence of substances, which in similar doses and in other circumstances could not be studied in man. I recall Lehmann's and Simmon's experiences with two brothers submitted to surgery. Suxamethonium hed been given as a sedative and in the course of the operation, apnoea was observed in each subject,—of 90' in the one, and of 45' in the other. The study of pseudocholinesterase, the specific enzyme of suxamethonium, brought to evidence the presence in the brothers of 12 and of 18 units, respectively, when the normal rate in serum of human blood is of 60 units (26).

In collaboration with the anaesthetist Rizzi, I have studied the effects of general anaesthesia on consanguineous subjects and we have been able to note significantly concordant reactions in cardiocirculatory responses, in the pattern of

vomiting on recovering consciousness, and during nocturnal rest. We have, likewise, noted concordant psychological reactions at recovery of consciousness (18).

These findings draw attention to a characteristic aspect of pharmacogenetics related to the psychic reaction and tropism in respect both of pharmaceutical and of voluptuary substances. I recall Fischer's studies on MZ twins brought up separately, and those of Friberg, Kaij, Denker and Jonsson on monozygotic pairs, that proved the hereditary component of the habit of smoking.

Thus we can state that human life, as a whole, in all the facets it presents to Medicine, can be assisted by Genetics, as applied to the individual patient.

The Florentine physician, Prof. Greppi, at the recent Medical Week of Roman Hospitals in which Senility and its problems was considered, remarked that in old age, man more than ever betrayed family traits, and requested the Geneticists' opinion on the subject.

May I be allowed to reply to Prof. Greppi from this chair and with a comparison. As in a birthday cake, so man's life at every stage can be represented by many candles, with this difference: the number of candles is very great, as many as there are genes, and all candles are present at the time of birth. And I would like to draw your attention to this aspect of the gene: its *time dimension i. e. its gene "period"*. Each gene carries a load qualitatively and quantitatively determined in time. If we accept this comparison of the candles, we then must say that every candle has its own length and that the difference in these lengths is hereditary and individual. If disease does not crop up to blow one, or all of them, out head of time, these candles consume and extinguish themselves spontaneously at different times, according to their length. Senility corresponds to the period of their going out.

As the phenotype gradually extinguishes its life light, according to the rhythm fixed by the heredity of each individual trait, it is natural that what Prof. Greppi observed should occur,—that is, that the organism should reveal in this gradual extinction, the family pattern of senescence. Therapeutics, therefore, can be extraordinarily assisted by the principles afforded by Genetics in this respect, for the prescribing of those medicaments required to substitute reactions and syntheses progressively lost; and to maintain the functional balances that tend, at this time, to become disrupted, always according to a family pattern.

Statistics show that the maximum life span, or ceiling, does not tend to register noticeable modifications in spite of the enormous advances made by modern therapeutics (31). The increase observed in the average lifespan is, above all, due to the conquering of diseases that prematurely blow the candles out. The progress of causal therapeutics consists in taking this mean duration of human life to its ceiling,—and it is consistently doing so at the present time. It is therefore incumbent upon Medicine to produce, in like measure, a rational therapy by which to substitute progressively extinguishing genes. It will be the way to make for a happier old age, and perhaps to increase the ultimate limits of human life. Genetics can, no doubt, be of value in the solution of so important a problem.

Therefore: in the face of such undeniable and unarrestable events such as population explosion, the opening up of isolates, the increase of ionising radiations and the increased volume of therapeutic possibilities, and of other similar events all threatening to modify human variability and to give human pathology a quantitatively and qualitatively new dimension, it would seem then that the time has come for Genetics to render a most excellent service to man by making its experience also available to modern Medicine.