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Medical and Clinical Genetics: Their Roots and Challenge

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The origins and development of human, medical and clinical genetics are interwoven and yet each of these disciplines follows its own path.

The beginnings of a systematic human genetics can be traced to the middle of the 19th century, but it took human genetics almost 100 years to mature fully and influence medicine. Its origins can be traced to the work of three scientists: Galton, Pearson and Bateson.

In 1865, 6 years after Darwin had published *Origin of Species* in London, and the year when Mendel's paper, "Experiments on Plant Hybrids", was published in Brunn, Galton, also in London, set out his first ideas on human heredity. His thinking then developed in two directions. The first laid the foundations for the scientific study of human heredity through biometrics and quantitative genetics. This part of Galton's thinking is summarized in his epitaph: "the dominant idea of his life's work was to measure the influence of heredity on the mental and physical attributes of mankind".

Galton's other line dealt with the application of heredity through eugenics, a word that Galton coined to signify "well bred". He wanted, I quote his words: "to produce a highly gifted race of Man by judicious marriage through several generations". Families of merit should be identified and positively encouraged to breed; conversely, the "weak could find a welcome ... in celebrate monasteries".

Galton's intellectual successor was his friend and collaborator, Karl Pearson, the first Galton Professor of Eugenics at University College in London. The programme of the Galton National Eugenics Laboratory, run by Pearson, was addressed to human inheritance using statistics and biometry; but Pearson steered clear of the politics of eugenics.

Meanwhile, in 1900, Mendel's work was rediscovered and his ideas on heredity were immediately taken up vigorously by the biologist William Bateson, who launched mendelism and published in 1902 and 1909, *Mendel's Principles of Heredity*, which became obligatory reading for anyone working in genetics. In 1911, Bateson observed a striking departure from Mendel's law of indipendent assortment and, with Punnett, made the key discovery of coupling and repulsion. However, the interpretation that they had

discovered the manifestation of the closeness of genes on the chromosomes, i.e. linkage, came from Morgan's *Drosophila* school at Columbia University.

With the writing on mendelism and the experimental work on mendelizing traits, the stage was set for a clash between two opposite views. Bateson, on the one had, was the protagonist of mendelism and so of quantal inheritance. Pearson, conversely, rejected mendelism and was dedicated to the study of quantitative characters through biometry. The fusion of these opposing principles into one coherent whole was finally accomplished by Ronald Fisher in 1918 and was based on his concept that the continuous variation of biometricians was a cloak that covered the discontinuous variation caused by independent genes.

Departing from the direction of quantitative biometrical genetics, human genetics was following mendelism through the work of Archibald Garrod, at the same time laying the foundations of medical genetics. Garrod was a children's physician and, later, a regius Professor in Oxford, and made observations on what he later called "the inborn errors of metabolism". His first paper, in 1902, was on alcaptonuria. The familial occurrence of the condition and the fact that 60% of the parents were first cousins were in keeping with Mendel's laws. "We note", wrote Garrod, quoting Bateson "that the mating of first cousins gives us exactly the conditions ... to enable a rare ... recessive character to show itself", as the character derives from the gametes of *both* parents. Clearly, just what Mendel had said.

By 1923, Garrod had collected other inborn errors and was stressing chemical individuality which, he said, resided in proteins. For him, pathology was a matter of molecules, foreshadowing the concept of molecular disease. But, in spite of the importance of what he was saying, his work lay forgotten, by doctors and scientists alike, for many years.

In America also, mendelism was being espoused by biologists and was taken up with zeal by Morgan's group at Columbia, who integrated it into the chromosomal theory of heritance, which is, linked to the names of Boveri and Sutton. But a second group in the States was attracted to mendelism, people who were interested in human inheritance and were personified in Charles Davenport. Davenport was deeply interested in galtonian eugenics and believed that even complex human traits such as mental illness, feeblemindedness or alcoholism could be reduced to the principles of simple mendelian inheritance whenever they showed family clustering, and he was prepared to see these ideas put into practice. In America, eugenics moved quickly to early practical applications, concentrating more on negative than on positive interventions. Many people had suggested that eugenic goals should be achieved by curbing the reproduction of those affected by heritable disorders and, as mental retardation and mental illness were assumed to be in this category, it was suggested that sterilization of the affected would be needed to minimize the heritable burden on society. Compulsory sterilization laws were introduced in a number of states of the Union.

Meanwhile, the eugenic movement in Britain had been steering the rather different course of positive eugenics along such lines as educating the public, largely though the efforts of the Eugenic Education Society.

By the thirties, biochemical genetics was underway. The potent trigger that fired the imagination of human biochemical geneticists was the work on the fungus *Neurospora*

begun in 1940 by Beadle and Tatum, who demonstrated the range of metabolic defects that mutation could produce. Garrod was being rediscovered, as Beadle acknowledged in his 1958 Nobel lecture. The studies in 1949 on sickle cell disease, and on carriers for the trait, by James Neel, and the work into the physical properties of sickle cell haemoglobin by Pauling and Itano, made "molecular disease" as it came to be known a household word. Blood group genetics was also moving. In 1901 and 1902, Landsteiner and his pupils in Vienna discovered the ABO blood group system, and its precise inheritance was worked out by Bernstein in 1924. The other major blood group system, Rh, discovered in 1939 by Levine and Stetson, was related to pregnancy isoimmunization and erythroblastosis fetalis, which became preventable some 15 years later by work in Britain and the United States, a major triumph of preventive medicine.

Between 1930 and 1940, human genetics was being freed from the fettle and chains that had tied it to the main line eugenic movement. This severance was probably an important determinant of progress and acceptance by the scientific community. Indeed, Batteson had already cautioned in 1919 against the confusion between eugenics and genetics. By 1938, Lionel Penrose had completed his famous Colchester survey on mental deficiency, a milestone for human genetics. Along with Penrose, other scientists, e.g. Huxley, Haldane and Hogben, were critical of eugenics, and the war speeded up its demise, coupled as it was to racism and awful persecution.

In 1945, Penrose was appointed to the Galton Eugenics Chair at University College. In keeping with his views, he changed the name of the *Annals of Eugenics* to the *Annals of Human Genetics* and the Galton Professorship of Eugenics to that of Human Genetics. In the United States, Davenport had retired from his position and a scientific committee of the Carnegie Institute declared that human genetics research should not be done "under a eugenic rubric". In 1948, the American Society of Human Genetics was formed and H.J. Muller, who had been awarded the Nobel Prize for his experimental work, was elected its first president. Also in 1948, Haldane, writing on the formal genetics of humans, was establishing the study of human gene's linkage as a research priority, the basis for an "enumeration and location" of all human genes. However, because experimental breeding is not possible in humans, we are almost the worst possible organism for this research.

In the fifties, a revolution took place in genetics. In 1953, more precisely on April 23rd, Watson and Crick suggested a novel molecular structure for DNA, adding that it had not escaped their notice that the manner of pairing proposed by them provided precisely the copying mechanism demanded for DNA, which had been indicated as the carrier of the genetic specificity "of the chromosomes and thus of the gene itself" by the observations of Avery and his coworkers in 1944 and by the experiments of Hershey and Chase in 1952. And so molecular genetics was born, ready to open new trails and look at new horizons.

But human genetics was at a relative standstill, and was largely irrelevant to medicine, while clinical genetics was practically non-existent except for the work of, literally, a handful of pioneers in genetic counselling. But at the end of the fifties, a change of pace occurred, triggered by discoveries on human chromosomes and their anomalies.

In 1956, Tjio and Levan showed that the human somatic chromosome number was 46, not 48 as hitherto believed. In 1959, the XO sex chromosome anomaly was confirmed in Turner syndrome by Ford and his associates and the XXY sex complement was

described by Jacobs, Strong and their colleagues. Now came the realization that one should look for autosome anomalies too. While in Britain, Mittwoch's observation was the lead that directed attention to Down syndrome, Jerome Lejeune, in France, had been impelled by other considerations to do chromosome studies in this condition, and early in 1959, with Marthe Gautier and Raymond Turpin, discovered trisomy 21. The months and years that followed saw in quick succession observations of a number of other sex chromosome and autosome developmental anomalies. Shortly there after, the unexpectedly high proportion of chromosomally abnormal human conceptuses was being highlighted. By 1970, just as the impetus of descriptive cytogenetics was diminishing, chromosome banding was introduced, making possible precise chromosome identification and the detection of discrete changes in chromosome structure.

It is difficult to synthesize the influence that the chromosome work has had on human genetics, and I can discern five lines of descent, each with scientific or practical applications.

1. There was a direct input of new knowledge into human genetics, a major scientific advance in its own right.
2. There was a change in ideas about the formal genetics of sex determination in humans, adumbrated in 1956 but not developed until 1959. The sex chromosome anomalies had shown the Y chromosome to be sex determining and to direct testis formation, and that it was obviously incorrect to apply the *Drosophila* model to human beings.
3. The relationship between proliferative somatic chromosome anomalies and cancers, an idea which had originated with Boveri in 1914, could now be explored.
4. Human genetics could now turn from an observational to an experimental science through the application of chromosome techniques to somatic cell hybridization. I shall return to this below.
5. A new clinical discipline was established: clinical genetics.

For a variety of reasons, the chromosomal work alerted clinicians to human genetics. An important factor was undoubtedly the ability to actually see what could go wrong with the human genome: it did not require interpretation of mathematical or chemical formulae. The net result was the realization that genetics was obviously on the way to becoming an integral part of the scientific basis of medicine, and had clinical implications. Clinical genetics required medical genetic knowledge and skills in genetic counselling coupled with clinical expertise. In addition, after 1960, genetic counselling was changing, becoming less probabilistic and more real, and needed the support of biological and laboratory disciplines and the organization of network of population services.

Two further developments of fundamental importance need mention. In 1961, Mary Lyon proposed the hypothesis of X chromosome inactivation in the female mammal, stimulated by observations on coat colour and texture variegation in mice heterozygous for X-linked genes, and based in part on Ohno' demonstration that Barr's sex chromatin mass was formed by only one of the two X chromosomes of normal women, and in part on the fact that XO females could survive and be fertile, at least in mice, suggesting that females basically needed only one X chromosome.

The other major advance was somatic cell hybridization and genetics. Fusion of different cells in culture had been observed in the early 1960s and its potential usefulness to human genetics was seen by Pontecorvo who wrote: "if we want a breakthrough in human genetics we have to concentrate on methods that bypass sexual reproduction". "The methods of genetic analysis developed for diploid fungi could be applied to the ... diploid somatic cells ... of man"; and so indeed they were. Cell fusion also made it possible to produce interspecific hybridis, which were essential for human gene analysis, and the way lay open to experimental gene assignment han human gene mapping.

By 1974, cell hybridization had already made it possible to map 33 genes to 18 of the 24 human chromosomes, remarkable achievement if we remember that the first ever chromosome assignment of a human gene was in 1968. By 1988, McKusick was reporting that out of almost 800 genes assigned to individual chromosomes, over a half had been mapped by cell hybridization.

The early 1970s saw the rise in a "new genetics". Its origin lay in a brilliant fusion of the ideas and techniques of molecular biology, and rested on the application of the methods of recombinant DNA technology to produce hybrid DNA molecules. By 1972, it had become possible to isolate DNA and cut it into segments of manageable size using specific restriction enzymes. A selected segment of this DNA could then be inserted into the DNA of a viral vector, and through the vector incorporated into prokaryotic or eukaryotic cells. By 1973, a group of senior scientists was expressing deep concern about some experiments planned with recombinat DNA, leading in 1974 to an internationally agreed research moratorium, to provide time to assess risks and guard against them. Recommendations and guidelines to ensure safety, followed; these were quickly put into operation, and supervisory bodies were set up.

Recombinant DNA methods can be applied to the recognition, even prenatally, of single-gene diseases and carrier states, either directly or through linkage to polymorphic segments of functionless DNA close to functioning genes. However, recombinat DNA technology has other implications for medicine. However, recombinat DNA technology has other implications for medicine. Take cancer as an example. It is apparent that, irrespective of cause(s), the origin and subsequent behaviour of cancer cells depends on a number of mutations in the genetic controls which constrain cells from unruly growth or prevent the organism from disposing of them as unwanted parasites. Thus cancer, ultimately, involves a perversion of the genetic machinery of the cell. Much that we know comes from the intensive molecular study of those rare cancers that are clearly heritable in a simple mendelian manner; and it is believed that there is practically one hereditary cancer for each of the commoner and non-inheritable forms of malignancy. Detailed work on cancer, especially on cellular proto-oncogenes and suppressors, is attempting to probe the molecular basis of malignant transformation. A number of such proto-oncogenes, some dominant, others recessive, are already known in humans. For some, linkage group assignment and even the chromosome map position has been worked out. The ways in which their normal activity may be perverted are being actively explored, for example, when proto-oncogenes are mutated, or amplified, or disturbed by chromosomal rearrangements which set them out of context and may remove them from the control of suppressor genes. Interest is also addressed to imprinting, in relation to changes that occur in cancers.

Substantial effort in recombinant DNA research is being devoted to the study of complex disorders with a genetic component that afflict a not insignificant proportion of

people, such as schizophrenia, maniac-depressive psychosis, vascular disease, essential hypertension and the two types of diabetes mellitus.

Recombinant DNA methods are also being applied in developmental biology. Most of the work is experimental, but in humans, the study of genes involved in the control of cell growth and that could be active during development is proceeding quickly. General features of the control of gene action during development, for example through chromosome inactivation and imprinting, are also being actively pursued.

The organization of recombinant DNA research on human genes changed in the mid-eighties. Until then, it had been conducted relatively unsystematically. But in 1985 in America, the idea arose in three different quarters for a concerted and comprehensive approach to a complete mapping and sequencing of the whole human genome.

The first step was taken by Robert Sinsheimer, Chancellor of the University of California in May 1985, and in March 1986, Renato Dulbecco was writing: "We have two options: either to try to discover the genes involved in malignancy by a piecemeal approach, or to sequence the whole genome? A little later that year, Charles De Lisi, a director in the US Department of Energy, was struck by the same idea".

In 1986, a special committee examined the matter, and in 1988, the Human Genome Project was launched and an office set up at the National Institutes of Health, with James Watson appointed as associate director. The idea is massive both in terms of human and financial commitment. It aims at identifying the position of each segment of DNA and each gene. It must therefore deal with the some 3,000 million base pairs of haploid DNA spread across the 24 chromosomes and standard mitochondria of the human genome, which has from 50 to 100 thousand genes, each "gene segment" perhaps about 30 thousand base pairs long, of which the core may be only about 10%, namely 3,000 base pairs. It has been said that the cost of the project could be about one to two dollars per base pair, spread over a period of some 15 years. It hinges on four interrelated parts. The first aim is to build up a linkage map of disease genes. The second is to construct a physical map, ordering all the DNA sequences. The third and most exciting and labour-intensive phase is that of sequencing the individual components of this map. The fourth component is the setting up of a computer facility sufficiently powerful to deal not only with the size but also with the almost unimaginable complexity of the operation. Mindful of the ethical and social implications of this endeavour, right from the beginning, effort and funds were invested informing and educating the public. Other countries with a tradition of genetic research joined the venture shortly after its establishment to make it an international effort, and them Human Genome Organization was established to harmonize and coordinate activities. From April 1993, Francis Collins has directed the Center at the NIH, which has six major sections, ranging from Medical Genetics to Diagnosis and Gene Therapy.

What has been achieved so far? By 1992, the total number of mapped functional genes, other transcribed DNA sequences and pseudogenes was over 2,300. The annual increment of such structures was about 500; among these mapped sequences in 1992 there were some 80 disease genes including, for example, those for Marfan syndrome, retinitis pigmentosa, defective limb development and early onset familial cancers of the breast and possibly ovary. In addition, 2,000 important DNA marker sequences, used as map reference points, had also been mapped. In fact, the complete data base was over 8,000 reports on different types of DNA sequences. By 1993, a first-generation physical

map of the human genome had been produced, which should help in constructing detailed maps of all the human chromosomes.

On the more applied side, the genes well over 80 sets of major genetic diseases have been cloned and for many, precise DNA-based diagnosis is possible, including prenatal recognition for over two dowen.

Let me now look to the future. Probably the clinically most important challenge from genetic knowledge is when it addresses treatment. In general, genetic diseases have proved no less amenable to treatment than non-genetic diseases. The treatment of genetic conditions by avoidance, correcting, diet, vitamin supplementation, replacement, enhancing gene activity, transplanation of cells or organs are all well established. Hower, all in all, treatments so far have not always, perhaps even not often, been completely satisfactory and many serious diseases have proven untreatable. It is thus obviuos that the methods of the new genetics promise a direct approach through the replacement of faulty genes. It is now possible to insert genes into mammalian cells and demonstrate their activity. It is experimentally feasible to remove gene-defective cells, correct them by insertion of a normal allele, and reinsert them into the abnormal donor using a viral carrier, a method known as ex vivo correction. In vivo correction is also experimentally possible, generally by using a viral carrier to deliver the correcting allele to the required body cells. Thus, practical problems apart, numerous and difficult to solve though they may be, the correction of gene defects by direct gene therapy appears to be possible in humans.

An important distinction must be made between genetic modification at the somatic level and that of the germ line, the aim of which is hereditary transmission. At the moment, the consensus is that deliberate germ-line engineering should not be contemplated.

The first authorized attempt at human gene transfer was in the United States in 1990, in patients with malignant melanoma. The first therapeutic attempt was for adenosine deaminase (ADA) deficiency through an ex vivo bone marrow approach. At present, to quote from the editorial in the first issue of *Gene Therapy* in January 1994: Over 200 patients world wide have now received exogenous, functional genetica material with therapeutic intent. The results of these pioneering experiments cannot be expected to be startling ... and there are many problems. But the pace of research is rapid. Gene therapy is under study for a number of single-gene diseases, for example, Duchenne-Becker muscular dystrophy, cystic fibrosis, ADA deficiency, the Lesch-Nyhan syndrome and a number of others. In cystic fibrosis and Duchenne-type muscular dystrophy, as in many other diseases, animal models, such as transgenic mice, are an invaluable asset to test therapies.

If we consider the problems that confront gene therapy, the first concern is saftey in both the short and long term, and viral vectors are a case in point. Not enough is known about them, and they may, no matter how remote the chances, become infectious or otherwise aggressive.

Then there are the problems of inserting DNA such that it does not upset neighbouring genes, including the unwanted activation of oncogenes. An alternative to gene insertion is targeted gene correction, which has many highly desirable aspects, but raises extremely difficult technical problems.

Other concerns are the selectivity, efficiency and durability of the correcting effect, but in many cases correction may not have to be 100% to be clinically acceptable. On

the other hand, and in relation to activity, an important issue is the possibility of immunological reactions by the recipient who, not having met the correct gene product ever before, may recognize it as alien and react against it.

The treatment of cancer is an important area of gene, or gene-related therapy. At present, more than ten different tumour types are in therapeutic trials. Most of the treatment systems are ex vivo. Different approaches are employed, ranging from the preparation of vaccines engineered from genes from the patient's own tumour, through the correction of oncogenes or suppressor genes, to using vectors to insert specifically into tumour cells, cytokines or genes that can activate inactive drug precursors.

A few words on the ethics of gene therapy. The first point to stress is that gene therapy has to be critically compared with existing and well-tried treatments which, though perhaps not entirely satisfactory, have stood the important test of time. However, in principle, gene therapy is not fundamentally different from, for example, organ transplantation or, more simply, blood transfusion. Two basic conditions must be met. First, we must ensure strict adherence to the hippocratic injunction to do good, but above all to do no harm. Secondly, informed consent is essential, and children demand special consideration. If these two conditions are fulfilled, there appear to be no special ethical problems relating to gene therapy or to the human phase of research that must precede its introduction into medical practice. At any rate, it is to be applauded that many countries have set up supervisory bodies concerned with gene therapy and its etichs, and we must also hope that ethical and practical issues of gene therapy and of other activities of the new genetics will be subjected to public debate in the light of the fundamental changes that are occurring in society and affecting all facets of human life and striving. Many of these changes are reflected in the practice, organization and support of medicine, and in the direction, organization and funding of biomedical research and its technological application.

Faced with these changes, on the one hand, and with the expansion of biological knowledge and its implications for the individual and for society, on the other, what does the future hold? I shall quote from the last paragraphs of John Kevles' perceptive book on the uses of human heredity. "The willingness of the individual to use rapidly developing genetics and reproductive knowledge, ... screening, ... amniocentesis, ... abortion, ... genetic therapy will probably long remain matters of private, voluntary choice. ... How the public ... will respond to the steady pressure of problems raised by the advance of genetics depends on what reconciliation society chooses to make between the ancient antinomies social obligations against individual rights. The criteria of choice are currently clouded. People may perhaps be tempted to seek rules of decision in some renewed version of Francis Galton's secular faith ... eugenics"; but we must forever and ever remember "that eugenics has proved itself historically to have been often a cruel and always a problematic faith".

As a medical man, I wish to conclude with a few words which relate to the exercise of our profession, which is facing major challenges and critical changes. While it is obvious that medicine has a social dimension, clinical practice is based on the ancient medical covenant between two individuals. The achievements of modern biology are the results of intensive reserach, and we rely on research to advance medical science for the benefit of our patients. However, in the exercise of their duties, physicians can never be the servant of science. First and foremost, the physician is "the individual servant of his [and her] individual patients".

In reality, medicine has two faces: that of a science and that of an art. Indeed, medicine is a science, albeit an applied one; its art with its morality is in the application of that science, that knowledge, to the individual. Morality and knowledge, "virtude e conoscenza", in the words of Florence's most eminent son – an apparent duality which must be unified in the practice of medicine.

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