Am J Hum Genet 30:123–131, 1978

Medical and Human Genetics 1977: Trends and Directions

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A presidential address to the American Society of Human Genetics is a difficult assignment. No clear tradition exists as to the nature of the topic. Muller's very first address in 1950, "Our Load of Mutations," [1] became a controversial classic in human population genetics. Dunn's 1961 discussion on "Cross Currents in the History of Human Genetics" [2] is an outstanding contribution to the history of our field. In the 1960s and early 1970s no presidential addresses were delivered. In recent years, McKusick reviewed the evolution of clinical genetics [3], Hamerton discussed the controversy surrounding the XYY problem [4], and Childs dealt with the lack of genetic knowledge among the public and in the medical profession [5].

Our field has matured and become institutionalized in recent years. From the viewpoint of medicine, genetics was considered somewhat esoteric and abstruse until recently and was considered irrelevant either as a basic science or as an applied field. With this image, physicians and other scientists in the medical sciences did not enter the field and those who did had to have imagination and daring. Basic geneticists deplored the lack of scientific rigor in human genetics, and most of this group turned to more tractable fields for their work. The perception of eugenics as the political arm of human genetics further added to the questionable reputation of the field in responsible scientific circles. All this has changed, and our field is fully recognized as a respectable basic and clinical specialty.

Concepts and Techniques in Human and Medical Genetics

The important concepts of genetics had been laid down many years prior to their introduction into human genetics. Their application to man, however, had to wait for appropriate methods. Our intellectual indebtedness to the early geneticists from Mendel to the drosophilists and plant cytogeneticists must never be forgotten in our excitement over new findings in our species. It is noteworthy that the methodology which allowed the flowering of human genetics was usually introduced from other fields. Biochemical methods such as electrophoresis and enzyme assays made possible our understanding of polymorphisms and inborn errors of metabolism. Cytologic methods allowed the clear visualization of the human chromosome set, and later banding techniques made the full identification of each and every human chromosome possible. Cell hybridization techniques enable construction of detailed genetic maps

Presidential address presented at the annual meeting of the American Society of Human Genetics, San Diego, California, October 20, 1977. This work was supported by grant GM15253 from the National Institutes of Health.

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which may rival those of drosophila and mice. Immunologic techniques led to the discovery of the HLA locus in man. Progress in science requires both concepts and methods. The successful application of a variety of usually nongenetical methods to genetic concepts has made human and medical genetics such a flourishing discipline.

The boundaries of human genetics are indistinct and blurred. It is sometimes said that future progress in the sciences, particularly in those areas of importance for human health and welfare, will increasingly come from interdisciplinary fields by applying concepts and techniques from one field to another area. The success story of human and medical genetics can be cited as an example of such interdisciplinary research. We must therefore continue to be on the lookout for methods from other fields of the physical and natural sciences to be applied to our area.

Human vs. Medical Genetics

Our field has become "medicalized." The vast majority of the work and subject matter under study is of medical interest. Genetics has given medicine a rich intellectual foundation and has made possible many practical medical applications. Thus, professional positions and funding are most readily available under medical auspices. These developments have also helped to professionalize our field. However, the total contribution of human genetics to knowledge and to human welfare does not stop with its medical application.

Most of medical genetics in recent years has been solidly based on Mendelian and chromosomal models, and the action of single genes and detectable chromosomal aberrations and their effects have been studied with much success. Thus, almost two-thirds of the abstracts of this and of our last meeting deal with biochemical genetics, cytogenetics, or somatic cell genetics. Most progress in human genetics has been made by the imaginative study of monogenic and chromosomal traits in the laboratory. Most data in these areas are noncontroversial and accepted by all observers. We are on more shaky ground in behavioral genetics in which investigations have been by necessity based on phenotypes extensively influenced by culture and environment and far removed from primary gene action. Based on familial resemblances, heritabilities are calculated and inferences are made regarding the degree of genetic determination of the characters studied. Unlike studies using the Mendelian approach, the role of specific genes or chromosomally-determined characters cannot be directly approached since they are unknown. The pathway from genotype to phenotype is not considered, and a given phenotype alone is used for study. Since behavioral phenotypes strongly depend upon environmental influences, twin and adoption data are often utilized to make inferences about the contribution of the environment. Twin data in behavioral genetics are particularly treacherous in making such inferences since heredity and environment become hopelessly entangled. A statistical superstructure takes off from simplified assumptions which are often forgotten in arriving at conclusions. In fact, the entire logical foundation for this work using the analysis of variance, has been called into question by one population geneticist [6]. Estimates ranging from 0%–80% heritability for a trait such as IQ have been calculated by various workers using the same data. The suggestion that ethnic differences in IQ may have a genetic basis have further inflamed this field.

Another development in this area has been the popularization of the new field of sociobiology, a specialty which explains social behavior in animals using biological and evolutionary concepts. The seminal synthesis of this field by Wilson is a brilliant achievement [7]. However, using facile generalizations from lower species, this topic has become overpopularized in its possible human applications. *Time* magazine recently devoted a large portion of an issue to sociobiologic claims that most behavior of man is programmed genetically. The public does not realize that the vast majority of professional human geneticists have little to do with such work. The claims of the less inhibited sociobiologists make our field again somewhat suspicious in the eyes of the public who derive their information from the media. Let us not forget that human genetics was horribly misused by the Nazi government of Germany in the 1930s. Somewhat later, from the opposite end of the political spectrum, the Lysenkoists destroyed human genetics in the Soviet Union. As responsible human geneticists, we must speak out and differentiate those findings which are generally accepted biological realities from others which are interpretations and flights of fancy. There is no question that the central nervous system follows the same basic biological laws as all other organ systems. Genetically controlled variation in structure and function of traits under control of the human central nervous system is therefore expected. It is consequently highly probable that mental abilities and personality traits within the normal range have genetic determinants. The extent and nature of such genetic determinants remain largely unknown. However, a zero heritability for IQ for example as claimed by some environmentalists is altogether unlikely.

Until we are able to deal with this genetic variability using neurophysiologic, biochemical, or completely novel techniques rather than biometric methodology, the polemics regarding the extent of heritability and of possible population differences will continue. It is interesting to note that these discussions are carried out largely by individuals not primarily identified as human geneticists.

Regarding sociobiology, it seems likely that some aspects of human behavior may be programmed genetically by natural selection through many generations of evolution. It is improbable that the human species is entirely autonomous in its behavior and that genetic determinants of its central nervous system can be entirely overridden. Nevertheless, the human species differs from all others in its possession of culture so that human behavior is expected to be less biologically controlled than that of other species. To learn more about these matters, experimental designs that attempt to dissect human behavioral patterns into subcomponents with attention to their biologic substrate are needed. We should, therefore, be cautious without condemning the claims of sociobiology as applied to man. We must realize with the critics of sociobiology that claims of genetic determinants of IQ and of innate behavior patterns could be misused to justify discrimination and social injustice. However, the possible danger of misuse should not be a reason to condemn and stop research into the genetic sources of behavior. More such research is needed. It is unlikely, however, that current approaches and methodologies will give us the necessary data. Particular care must be taken to sort out political biases from the interpretation of data. Admittedly such objectivity is difficult because of the impossibility of completely dissociating ourselves from our social and cultural environments.

The Mendelian paradigm as utilized by most geneticists emphasizes chromosomal and action of single genes. The Galtonian paradigm uses biometric techniques without attention to individual gene action. The gulf between these two approaches is widening. It would be unfortunate if the two schools of thought were to stop communicating with each other. Clearly there is great need for a mechanistic-biologic approach to behavioral genetics. Unfortunately, there are several reasons why such genetic-biologic studies are not likely to be carried out soon: (1) the Mammalian nervous system is very complex; (2) good models for single gene action in the nervous system are as yet nonexistent; (3) neuroscientists usually have no genetic background, and few geneticists are acquainted with the neurosciences; and (4) medical geneticists largely work with disease and are less interested in normal human variation. As long as the image of human genetics among biologically oriented neuroscientists and behavioral scientists is that of biometry, such investigators will show little interest. Their biological approaches and insights are needed for progress. There are many opportunities for the adventurous human geneticists for most exciting discoveries! This new behavioral genetics needs fostering and more attention.

Common Diseases

The polarity between Mendelian and biometric approaches to human genetics can also be illustrated by current work on the genetics of common diseases. Apart from the common birth defects, there are the common diseases of adulthood, such as coronary heart disease, diabetes, and hypertension, and the common psychoses, such as schizophrenia and the affective disorders. Their impact on public health in the Western world and other developed countries is considerable. Most genetic work uses the medical diagnosis of the disease as the phenotype for genetic study. Familial aggregation in twins and family members are then investigated. Absence of the disease in marriage partners and adoptive studies are used to rule out common environmental factors which might mimic genetic patterns. Not unexpectedly, such studies have shown that genetic factors are involved in the etiology of most diseases. Heritabilities are often computed but have been of little theoretical and practical use.

A new field "genetic epidemiology" is being developed around such studies. As in behavioral genetics, more laboratory approaches based on the pathophysiology of the disease are needed. The probability that meaningful knowledge will be produced here is greater than in studies of the genetics of normal behavioral variation since the underlying biology is better understood.

While the total genetic contribution to these diseases involves many genes, I consider it likely that in many instances a few genes play a major role in etiology; the remainder of the genes provides the "genetic background." A search for such major gene action using laboratory approaches followed by appropriate statistical analysis has therefore a high priority and is likely to make for better understanding and successful management of these disorders. The genetic dissection of the hyperlipidemias as a predisposing factor to atherosclerosis [8] and of the various subtypes of diabetes [9] are examples of this approach [10].

Neel, in his address to this Society on its 25th anniversary in 1975 [11], suggested that medical geneticists work on only 1%–2% of the total content of human genetics as

judged by the abstracts submitted to this Society. He queried how future historians of science will view this phenomenon. One reason for such narrow concentration is the "medicalization" of our field. A further important explanation is that scientists appropriately will select problems which can be readily solved. The essence of the best scientific investigation is the choice of nontrivial problems which can be solved by existing concepts and methods. Medawar referred to science as the "art of the soluble" [12]. Much work in human genetics in the early part of this century dealt with the socially important issues of criminality, alcoholism, mental retardation, and mental disease but brought discredit to human genetics by its naive "geneticism" which paid little attention to important environmental factors. Fundamental research of that time concerned with Mendelian characters in plants and animals and the elaboration of the chromosome concept in lower species turned out to be of much greater relevance to human and medical genetics in the long run than the more "relevant" work on the social issues of the time.

Similarly, many of the crucial problems in human genetics cannot yet be readily solved. Many observers might point out that in view of the complexity of genetic and environmental factors involved, a Mendelian approach which attempts to isolate individual gene action in the multifactorial common diseases and normal behavioral traits is simplistic. Current biometrical approaches after all are possible and while not providing full answers have sharpened the issues and posed some problems more clearly. My contention is that the time is ripe to attack some of these problems using current concepts and biologic laboratory methods. Common diseases particularly might profitably occupy more of the attention of medical geneticists and their colleagues in relevant fields.

What are some other trends making for a narrow view of medical genetics? Many fields in medicine have made their greatest progress when fundamental biochemical and pathophysiologic mechanisms were applied to explain various disease entities. Hematology and endocrinology are excellent examples of such developments. These fields owe their progress to the use of basic biologic principles in preventing and treating disease. For example, the understanding of disorders caused by clotting defects has benefitted enormously from physiologic, biochemical, and genetic input. Thyroid disorders have become equally clarified by attention to basic science fields. Any attempts at classification of diseases in these areas which used descriptive and clinical criteria alone would have been only partially successful. By analogy, some current attempts at the classification of birth defects and syndromes will remain imperfect until the fundamental science base of these conditions is better understood. However, when combined with fundamental approaches, the results in etiologic understanding can be spectacular. The various enzyme defects in the mucopolysaccharidoses became clear when the clinical-genetic efforts of McKusick and others [13] were combined with the biochemical approaches pioneered by Neufeld [14].

Many medical geneticists now devote their principal efforts to syndrome and heterogeneity identification, and the previous neglect of this area is rapidly being taken care of. Efforts to understand the mechanisms of these complex birth defects have not had a similar renaissance. I am concerned about this imbalance since ultimate

understanding, prevention, and treatment require multiple approaches. Only a few clinical geneticists study developmental biology or developmental biochemistry, and the model of the clinical investigator equally at home in the clinic and in the laboratory becomes less common.

The new generation of young physicians aspiring to careers in medical genetics realizes that most positions in the field are under pediatric auspices. Pediatrics requires genetically trained people for diagnosis and treatment of the many genetic diseases and birth defects which have been described. The wide diagnostic spectrum and heterogeneity of these diseases make extensive exposure to clinical cases and a wide knowledge of the literature essential. To become a knowledgeable pediatric geneticist is a time-consuming job. Skills of laboratory research are therefore much harder to acquire because of time constraints during the training period. Moreover, there are many deterrents to a faculty career these days such as problems with obtaining grants and more restrictions on clinical investigation. The current social climate in medicine which puts a high premium on primary care rather than on research is a further important contributing factor to discourage young physicians from research careers.

Medical geneticists with the M.D. degree will increasingly be clinical experts in the developmental, genetic, and cytogenetic disorders of childhood. This area requires the largest manpower for management and counseling. As genetic counseling becomes more popular, the role of counseling services is increasingly taken up by advice to families with these diseases. The formal genetics of these disorders is often obscure. Even if chromosomal aberrations are found, they are de novo defects. Genetic transmission does not follow simple rules, and genetic advice must be based on empirical evidence. As genetic counseling increases in volume, the recurrence risks become lower since Mendelian genetic diseases with discrete high recurrence risks constitute a smaller fraction of the total counseling population. The budding medical geneticist's time and effort, therefore, is largely taken up with nosology, descriptive cytogenetics, and counseling. Large areas of medical and human genetics are never encountered in his work, and the need for a thorough background in genetics may not be readily apparent. I am worried that the current preoccupation of a large fraction of medical geneticists with clinical descriptive work may lead to a dilution of effort in the investigations needed to elucidate the mechanisms responsible for many of these disorders. Better education of clinical investigators in the fundamental sciences during their training together with direct involvement in the laboratory will provide a corps of researchers most likely to make the relevant discoveries. It may be unwise to attempt to create faculty types who are equally adept at clinical work, laboratory research, and teaching. Training programs might be differentiated into (1) clinical programs with some academic work in genetics and related fields for M.D.'s who would largely fill the expanding needs in genetic services; (2) combined clinical and research training, ideally for future faculty members in clinical departments, which would allow significant time for research; and (3) pure research training largely for Ph.D.'s not involved in clinical practice; combined training programs between medical genetics units and basic science departments such as cellular biology, biochemistry, or basic genetics might be created for these individuals.

Basic Scientists in Medical Genetics Research

Basic scientists with few exceptions do not know the details of problems in clinical genetics. We need to attract the very best basic scientists to work in these areas. As shown by the mucopolysaccharidoses, the pay-off can be great. The problems of multifactorial diseases and their solution are by no means trivial and require the highest scientific imagination. There has been extensive expansion of Ph.D. training programs, and the number of biomedical Ph.D. scientists has grown substantially over the last 10 years. In fact, manpower committees now advise reduction in Ph.D. training programs to avoid unemployment of Ph.D. scientists in the biomedical sciences [15]. Most basic scientists have had orthodox training in their field with little involvement in the problems which concern us most as human geneticists. Our problems are often "messy" and cannot be readily solved by simple experimentation. It is therefore understandable that most basic scientists will shy away from clinically relevant problems. Yet the decisive steps to solution of these dilemmas are likely to come from basic scientists attuned to these problems. With a reduced supply of medically trained investigators who use basic science skills in clinical investigations, we should make special efforts to attract basic scientists to the many clinical problems which have defied solution and are now dealt with on a descriptive level.

The creation of more departments of human and medical genetics in medical schools (in distinction to units in departments such as pediatrics or medicine) would allow more research in medical genetics if innovative arrangements would be created for joint appointments. Departments of medical genetics particularly would give outlet to scientists whose entire orientation is to medical genetics and who cannot fulfill service obligations of the parent department such as pediatrics. Basic scientists with a full-time commitment to medical genetics could work in such departments. It would be undesirable however if activities in departments of medical genetics were largely basic and of little relevance to disease. The area of greatest need requiring emphasis is that of investigation of man and disease using the most sophisticated concepts and methods of basic science. Basic research in fundamental genetics has considerable administrative support in universities and many highly talented scientists are working in the field.

The Effects of Diversification in Medical Genetics

The trends of more nosologic work and more genetic counseling in medical genetics have several other signposts. An admirable new journal, *The American Journal of Medical Genetics*, provides an outlet for the large volume of work in the area of medically relevant genetics. Will the *American Journal of Human Genetics*, the official organ of our Society, become a journal entirely devoted to formal genetics, population genetics, and biochemical genetics? This development would be unfortunate since it would hasten further the split between the clinically involved medical geneticists and those with other interests. The growth of a field with its resultant diversification historically has usually led to new journals, specialized meetings, and the organization of new societies. The development of the Birth Defects conferences as a yearly forum for the clinically interested group of medical geneticists is in keeping with these developments. Great care needs to be taken that with the development of a clinical subfield its scientific basis does not suffer.

Genetic Services Outside Medical School?

Another issue is that of increasing service commitments in our medical schools. Medical schools in general derive an increasing amount of their financial resources from practice activities. Expanding activities in clinical genetics such as biochemical and cytogenetic laboratory diagnosis, counseling, screening, and outreach programs have largely been sponsored under medical school auspices. This development is leading to inroads of the medical geneticist's time who spends a large part of his activities in a variety of far-flung activities. This trend leads to further decreases in the amount of time available for in-depth research. There is no question that expertise in medical genetics lies in the medical school. Yet, the delivery of routine medical care including various genetic services is less efficient and more expensive in medical school settings. Would it be better to aim at the ultimate development of loosely affiliated units in health departments, group clinics, or hospitals to do the bulk of the work in genetic services? With such a system we might restrict ourselves to rather small but high quality clinical genetics units in the medical schools where only the more complex problems are seen. Imaginative use of various new administrative facilities might bring genetic services to more people at a lower cost with no loss of quality. At the same time, our research efforts would be developed in more depth and breadth with ultimately better practical results. Our noncentralized system of medical care allows experimentation with various modes of delivery of genetic services. Since the delivery of genetic services has not yet become institutionalized into definite patterns, trials of different systems with careful assessment is still possible.

New Societies and Boards in Medical Genetics

Another development relating to the growth of our field and more extensive clinical involvement has been the ongoing clamor for the establishment of specialty boards in medical genetics. This year I appointed a broadly based committee under the chairmanship of Dr. Rimoin, which represents both nonmedical, medical, and clinical geneticists to consider this issue. McKusick's presidential address of 1975 [3] suggested that boards would be inadvisable since (1) most geneticists are not in practice; (2) geneticists would lose their status as the last generalists; (3) medical genetics boards would not be able to accommodate all the different medical subspecialists; and (4) boards might run the risk that the field would be deprived of the enrichment provided by non-M.D. scientists. The Rimoin committee has placed before the Board of Directors a recommendation that a new group, "The American College of Clinical Genetics," be created to consider the many problems concerning the nonresearch and service functions of medical genetics including specialty boards. It was felt that the American Society of Human Genetics is largely a research and scholarly society and should not concern itself with problems such as standards and accreditation.

A new "society" devoted to the practical aspects of our field would be another benchmark in the growth of a specialty. As in most other specialties, it is likely that in the future most medical geneticists will be practitioners rather than researchers. Yet, the field of human and medical genetics is relatively small and is likely to remain institutionally based for a long time. I am concerned that in the process of natural

evolution and specialization, our field in all its branches might lose by diversifying at this stage. It would be paradoxical if with growth less significant and important research might be performed.

SUMMARY

Our field is in a rapid state of evolution. The broader concerns of human genetics not of immediate medical interest such as behavioral genetics are often investigated by persons not trained or identified as human geneticists. Both medical genetics and human genetics in general have prospered when various biologic techniques have been applied to genetic concepts. A search for novel biologic methods may provide new insights and may bridge the gulf between Mendelian and biometric approaches in studies of behavior and of common diseases.

Medical geneticists need to broaden their fields of interest to encompass other fields than those of pediatric interest alone. We need to attract more basic scientists. Our field is evolving from a largely research oriented science to a service-oriented specialty. This logical development is a sign of increasing maturity and makes available to the public the results of our research. The resulting stresses and strains need careful watching to prevent their slowing the momentum of our science which can contribute continued insights into the many problems of behavior, health, and disease.

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