

## THE WILLIAM ALLAN MEMORIAL AWARD LECTURE

### Human and Medical Genetics: A Scientific Discipline and an Expanding Horizon

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I am deeply honored in receiving the Allan Award. I feel gratified to join the company of scientists such as Newton Morton, Oliver Smithies, James Neel, Vernon Ingram, Harry Harris, and Jérôme Lejeune whom this Society thought worthy of this Award. In considering my predecessors, I feel dwarfed by their achievements which have been so important in recent advances of human genetics. Nevertheless, I am grateful and delighted that you have seen fit to recognize my efforts.

I owe much to my teachers as summarized on the scientific pedigree (fig. 1) and particularly to my colleagues in Seattle. Stanley Gartler exemplifies how a basic Ph.D. geneticist uses clinical data for fundamental insights into genetic phenomena in man. Eloise Giblett's critical mind, no-nonsense attitude, and willingness to hear out and discuss ideas have been of great help. Over the years research fellows such as Philip Fialkow, George Fraser, and George Stamatoyannopoulos remained in or returned to Seattle and became independent and well-recognized scientists. A few years ago I was able to convince Akira Yoshida—an outstanding protein and enzyme chemist—that an appropriate field of action for men of his training might be *human* biochemical genetics. He joined our team, and his achievements in the delineation of the molecular lesions of the G6PD molecule are now well known. These people, our research associates Jean Bryant, Onchie Carino, and Amelia Schultz, and many others in the Departments of Medicine, Genetics, Pediatrics, Pathology, Preventive Medicine, and Anthropology, as well as the many research fellows from this country and abroad,\* have made life in Seattle intellectually exciting. Any measure of success I owe to these associates.

The task facing the Allan Award winner in delivering a speech to this Society is difficult. No definite tradition regarding the nature of the address has yet been established. Current soul-searching and identity crises in academic circles make a survey of

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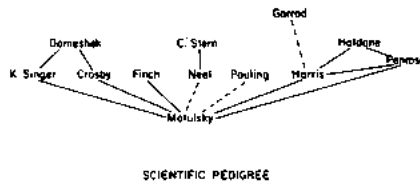


FIG. 1.—The pedigree includes scientists with major impact on intellectual development. Dashed lines refer to men who have had such influence through ideas rather than by direct work in their laboratories. Dameshek, Stern, and Haldane are “scientific grandfathers,” respectively. (Dr. Sturtevant first suggested and used such scientific pedigrees.)

the current scene in human and medical genetics more appropriate than a purely scientific paper.

#### CURRENT STATUS OF MEDICAL GENETICS

The field of human and medical genetics lacks clear-cut demarcation. Unlike other fields, such as biochemistry, which are recognized as specific disciplines in medical schools or universities, medical or human genetics lacks independent status. In fact a similar situation exists in our parent field of genetics, which often is not represented independently but is found in various biology departments. Genetic concepts permeate many areas of basic biologic sciences and of clinical medicine. In addition, genetic ideas are being applied to sociology and other behavioral sciences. Since the field is relatively new, there is no uniformity in background and training among its practitioners. Some human geneticists are fundamental scientists who largely work in the laboratory; others are clinical investigators who work at the bench and with patients. Some are clinician-scholars interested in the classification, description, and natural history of genetic diseases, and others are interested primarily in genetic counseling. Some human geneticists are explorers and spend their efforts in studying various exotic populations; others are mathematically inclined and devote their time to theoretical models. Still others with a similar background are more interested in experimental data and have become experts in computer application. Since genetics has become popular in medical schools, it is not uncommon to find physicians or other scientists with some cytogenetic training being considered as geneticists by their colleagues. In other medical schools, those who work on the biochemistry of the inborn errors of metabolism, which happen to be genetic in origin, have been designated the local geneticists. Our colleagues in basic genetics like to point out that the study of genetic diseases alone does not qualify a person as a geneticist. The lack of a broad genetic background among such scientists makes for a lopsided image of the field in some medical schools.

The number of medical schools who have divisions, departments, or units of medical or human genetics is not large. Geneticists are working in many places, ranging from Ph.D.'s in departments of anatomy, to serologists in blood banks, to physicians interested in genetic disease. Ph.D. geneticists in college departments of biology continue to be a significant proportion of human geneticists, although this group has become proportionately smaller as the field has enlarged. This group works largely with classical, formal techniques.

University presidents and deans who look at this heterogeneous group of individuals ranging widely in skill and talents find it difficult to see any clear patterns for the establishment of administrative units. In a few medical schools, departments of medical genetics have been established. In other schools, divisions of medical genetics have been created within departments of medicine and pediatrics and have a scope somewhat similar to that of independent departments. Departments, rather than divisions within departments, have the advantage of more solid local administrative support—an important feature in these days of diminishing outside grants.

Medical genetics in Europe has not reached institutional maturity either. Excellent centers exist, scattered in England, France, Germany, Holland, Switzerland, Italy, and the Scandinavian countries. Their organization differs considerably from country to country; recent development aiming at the establishment of human genetics institutes in most German medical faculties is of particular interest. One contrast between North America and Europe is the relative isolation of the various European university institutes. The easy cross-fertilization between basic scientists and clinicians and the mutual stimulation of scientists with different interests are often lacking. Ideally, a unit of human genetics should exist within a university where scientists interested in the fundamental aspects of biology and genetics can interact with those whose main concern is with human and medical application. Progress in the genetic aspects of the behavior and social sciences also appears favored by location of the biologic, medical, and social sciences on the same campus.

While the lack of a clear-cut delineation of medical genetics makes for slower institutional growth, this flexibility probably has some advantages. If a field becomes administratively rigid with well-defined boundaries, the advent of new scientific developments and directions may cause rapid obsolescence of its structures. We are all aware of this in certain areas in biology. Universities may thus become top-heavy with departments no longer relevant to the current state of science. Conversely, the newer fields will find it difficult to find funds and space. The Rockefeller University in New York solves this problem by building research units and laboratories around an outstanding investigator rather than having all scientific fields represented. This organization is one which universities cannot easily emulate because of their teaching and service obligations. The lack of a specific institutional base for medical genetics makes it more difficult for the less adventurous to seek a career in the field. Fewer workers consequently will devote their total energies to the area, since much genetic work will be on a part-time basis. Growth will be slower as compared with the potential that follows with full institutional recognition. Scientific advances in human genetics in the recent past argue that the lack of institutional units probably has not hampered progress. Yet, I believe that progress in the future requires a more solid foundation rather than the flexible and opportunistic organization seen heretofore.

#### MEDICAL GENETICS AND SPECIALTIES IN MEDICINE

Early interest in medical genetics in the United States often came from people with training in internal medicine rather than pediatrics. This is remarkable, since illnesses with genetic etiology are more frequently seen in children than in adults. However, the academic tradition in pediatrics was such that fewer pediatricians obtained their

expertise in the area of genetic and developmental disorders. It is relatively recent that many academic pediatricians have become intensely concerned with genetic factors. The need for medical geneticists in departments of pediatrics is great and will continue for some time. My pediatrician friends tell me that pediatricians as a group are pragmatic in inclination, possibly explaining the earlier lack of interest in genetics when the field was largely theoretic. The division of patients by age groups in departments of internal medicine and pediatrics continues as a deterrent toward the best application of genetic research, teaching, and training in medical schools. Pediatricians usually do not examine adults; therefore, full family studies which include adults may not be prosecuted with the necessary vigor and care. Similarly, internists are neither trained in nor accustomed to examining children. Medical genetics cuts across all age groups and is involved in the biology and pathology of the gamete, embryo, fetus, newborn, child, adult, and aging individual. Medical geneticists are the generalists of academic medicine. Familiarity with the human organism in both childhood and adulthood is required, and training in both pediatrics and medicine is desirable for clinical geneticists. Furthermore, many genetic diseases are found in specialty areas such as ophthalmology, otolaryngology, dermatology, neurology, and psychiatry. Unlike the usual specialist, the medical geneticist needs to be acquainted with a large variety of conditions in different fields. This wide range of theoretical and clinical knowledge gives the field strength in that medical geneticists are more likely to see the "forest from the individual trees."

#### STATUS OF PUBLICATIONS IN GENETICS

For a relatively small field which has not reached institutional recognition, the number of journals dealing with human genetics is remarkable. In September 1970 there are at least eight journals dealing with human and medical genetics alone. Two more journals deal with the social and eugenic implications of human genetics. Two more are concerned with human cytogenetics. In addition to the specific journals of human genetics, a considerable amount of material of interest to human geneticists appears in general journals such as *Science* and *Nature*, as well as in various pediatric, internal medicine, and medical specialty journals. Human geneticists, therefore, more so than many other specialists, have to keep up with a tremendous amount of literature. Although human geneticists as a group compare well with any other group of medical scientists, a considerable amount of trivial data finds its way into the different publications. Every editor is well aware that most rejected papers are ultimately published in other journals. The *American Journal of Human Genetics* rejects about 50% of submitted papers; many of these are published elsewhere later. It would be of interest for information specialists in association with experienced biomedical scientists to investigate the signal/noise ratio of publications in different fields of biology and medicine. How would our field compare with others?

#### TRAINING OF HUMAN AND MEDICAL GENETICISTS

What type of people are being attracted into human and medical genetics at the present time? Some students are taking a basic science degree in genetics with a major

in human genetics. The number of departments where such individuals can get strong Ph.D. training in human genetics is small. Increase in manpower in this nonmedically trained group is an additional reason for the further establishment of human genetics units in the various universities. The best type of training requires that such departments are working in collaboration with the medical school. Ph.D. candidates in human genetics need to develop experience in working with human material and need to become accustomed to collaborative relationships with physicians early in their training.

Most Ph.D. students in genetics are not primarily interested in human genetics. Some of the brightest students are fascinated by molecular biology and are attracted to graduate schools where that work is done. With the progress of molecular genetics in the last 10 years and the availability of research and training grants, probably more students have been trained in these areas than can be absorbed by college faculties and research institutes. Consequently individuals already trained or still in training will have difficulty finding jobs consistent with their background. The potential surplus of such highly trained basic scientists may lead to a group of disgruntled men who will not use their full training. Medical schools and hospitals still suffer from a shortage of geneticists. The impact on human and medical genetics may be marked if a significant number of fundamentally trained individuals would shift emphasis from basic genetics to human genetics. Research in human genetics by such individuals is likely to yield high dividends. One of the obstacles to full implementation of such career shifts is a lack of background in *human* biology. It might be worthwhile to consider retraining schemes. Special training institutes and summer courses to acquaint Ph.D. basic geneticists with human biology could be easy ways of solving this problem. The simplest way of acquiring training in human biology and pathology, however, is by attending a medical school.

Quite a few young physicians these days aspire to a career in medical genetics. Demand for trained individuals is still quite high. With the development of increased elective time, summer research projects, and Ph.D.-M.D. type programs, many medical trainees have had significant exposure to research, often in medical genetics. In fact, because medical genetics attracts research-minded individuals, the number of trainees who have had previous research exposure is increasing.

Training in medical genetics ideally has three facets: (1) research work; (2) clinical work with genetic diseases, including genetic counseling; and (3) course work. Since most medical geneticists will be expected to teach, a strong background in the various aspects of general and human genetics is required. Ideally, training should prepare for the research problems of the future and requires an excellent background in genetics and molecular biology. A good knowledge of statistics is also desirable. Since most of these medical geneticists will ultimately be working in clinical departments, broad expertise in the many aspects of genetic disease is required. Such specialized knowledge can best be obtained by frequent exposure to a variety of genetic problems as they present in the clinic or hospital. Emphasis on laboratory research is considered important since the most significant advances in medical genetics are likely to come through the laboratory, and a large proportion of medical geneticists must contribute to that knowledge by research.

Some recent developments are disquieting. Young physicians in medical genetics—and this applies to other branches of medical research—become compartmentalized in their approach to patients on the one hand as compared with laboratory research on the other. Such individuals select research problems similar to those investigated by geneticists or biochemists with a Ph.D. degree. A choice of problems identical with those pursued by basic scientists reflects a lack of imagination. Hopefully, M.D. investigators in clinical departments will acquire an excellent background in basic science and then concentrate on those experiments of nature we call “disease.” The fundamental scientist is less likely to be aware of the myriad of problems posed by patients, and nontrivial problems of this nature do still exist. *Not* working on disease-related problems is a waste of years of medical training in most cases. If the clinical investigator will not work on clinically related problems, who will?

Working with human patients, families, and populations is logistically more difficult than setting up a bench experiment which can be started and often finished at a planned time. The ability to pursue patients and study subjects away from the hospital seems to go with certain temperaments. Some individuals never develop the inclination to do this type of work. The person who is committing himself to a career in medical genetics should realize that a large portion of his time will often be spent in such “busy” work. While trained family workers can be helpful, much must be done by the investigator himself. Most physicians with the usual training expect the patient to come to the office or laboratory. It is common experience that important specimens will be missed in this manner and that the medical geneticist must actively pursue his patients and study subjects in the home.

### *Teaching of Human Genetics*

Many, including nongeneticists, would agree that knowledge of the basic principles of genetics is desirable for the general public. Such an understanding is particularly worthwhile with the realization that social and behavioral differences between individuals may have a genetic basis. In addition, the possibility of biologic engineering even in its most benign aspects requires an informed citizenry before such procedures are instituted. Education in human genetics should start at the elementary school level. Such an approach requires that primary school teachers have a good foundation in human genetics which they could impart in simple ways to their students. High schools should see the offering of various courses in human biology with a strong emphasis on human genetics. Such courses also should be required in the nonacademic streams of high schools. Again, trained teachers are required. The initial emphasis, therefore, will need to be on college courses in human genetics. At the present time, genetics is widely taught in colleges. However, many courses are given with the technical emphasis required by aspiring biologists or geneticists. Often the courses are not up-to-date. There is definite justification for college courses in *modern* human genetics to deal with the field in a less technical manner. Human genetics can be taught without reference to detailed DNA biochemistry or recombination mechanisms and other such phenomena. Courses dealing with the cultural and social aspects of human genetics are needed. The approach exemplified by Lerner's book, *Heredity, Evolution and Society*, shows that such courses are feasible. Student demand for relevance can

be met by such courses. Many of us need to take more of an interest in this area of instruction.

Physicians have the greatest need to be informed, both in their technical role, because of the considerable frequency of genetic disease, and as citizens because they are likely to become initially involved in application of the more far-ranging schemes affecting reproduction and genetics. While medical schools generally recognize the need for instruction in human genetics, the reasons cited earlier make for an extremely variable pattern of courses.

#### CONCEPTS AND METHODS IN HUMAN GENETICS

Human and medical genetics has considerable appeal to those who are interested in the theoretical and intellectual basis of biology and medicine. The background and approach of human geneticists encourage a synthetic view of human biology and disease with potential insight into relationships which are not as apparent to other observers. Just as genetics provides the theoretical framework for biology, so does medical genetics provide much of this framework for medicine. The intellectual appeal of human genetics lies in its proven record in the generation of new concepts and hypotheses which have been heuristic and have led to new insights. Examples are the one-gene/one-protein hypothesis, the hypothesis of X-chromosome inactivation, the theory of XX/XY sex determination, the concepts of pharmacogenetics and genetic heterogeneity, and the theory of gene duplication. While most scientists do not consciously try to discover new concepts, they will usually search for hypotheses to explain poorly understood scattered phenomena. This observation appears particularly true in human genetics. The high frequency of broad generalized concepts in our field should continue to attract some of the most able young investigators. However, ideas alone are not sufficient. Ingenious mathematical and statistical techniques have been developed to extract a maximum of information from a minimum of often biased and skewed data. Furthermore, the field has a strong laboratory basis, and various laboratory methods have contributed significantly to its progress. Thus, the sex chromatin test led to a flurry of new discoveries. More followed when it became possible to examine human chromosomes directly. The recently introduced "flashing Y technique" allows better studies dealing with the biology and pathology of the Y chromosome. The "fingerprinting" and other methods of peptide analysis have given us new insights into the molecular mechanism of mutation. Electrophoresis, and particularly starch gel electrophoresis, has been an invaluable method in demonstrating the ubiquity of biochemical polymorphisms with many implications for population genetics. Simple screening tests make it possible to study enzyme deficiencies and enzyme aberrations in many subjects, providing material for our ultimate understanding of population structure. Somatic cell hybridization promises to make linkage studies simpler and offers insight into genetic control mechanisms. All of these techniques were not available 25 years ago. It is conceivable that methods analogous to those we use today may be hidden in departments of chemistry and physics only waiting to be transposed to our laboratories.

Lack of contact between different areas of science may lead to considerable retardation in knowledge. Cytogenetics was advanced among plant cytologists, yet a

simple technique for the visualization of human chromosomes was not developed until the mid-1950s. The method could have been discovered some 35–40 years earlier. The reason for the gap was partially related to the lack of genetically trained investigators in medical schools and medical research institutes. Genetics as a science was developed largely in universities and agricultural institutions away from medical schools. While physicians were aware of the importance of hereditary factors, the lack of laboratory methods to demonstrate cytologic or biochemical effects of gene action and the lack of contact with geneticists discouraged human genetics research in the medical schools. Investigations in medical schools were carried out by those who dealt with disease phenotypes and simple traits in family groupings, such as by Dr. William Allan whose memory is honored by this Award.

The usual approach in the investigation of disease is to reduce a complex process into its components. Such a procedure applies the various methods of basic science (physics, chemistry, structural biology, etc.) toward an analysis of the pathophysiology, biochemistry, and genetics of the disease process. In this approach, basic science concepts and methods which were developed in their own right are applied to elucidate abnormal function. The reverse process, that is, the discovery of basic scientific principles by the investigation of clinical phenomena, has occurred repeatedly in medical genetics recently. The XY and XX sex determination and the discovery of a single amino acid substitution as the cause of sickle-cell anemia have already been mentioned and are good examples. The existence of a single clone of protein-producing cells in multiple myeloma in man and mouse has provided a rich source of material for the study of the molecular biology of antibodies. Demonstration of G6PD deficiency as the cause of drug-induced hemolytic anemia was followed by many different types of studies in clinical medicine, formal and developmental genetics, molecular pathology, embryology, population genetics, and anthropology. In fact, using hemoglobin and G6PD variants alone, an entire course of human genetics with all its principles could be taught.

#### CURRENT STATUS OF AREAS IN HUMAN GENETICS

Figure 2 attempts to indicate the current state of development of a variety of selected fields in the areas covered by medical genetics. The scale is arbitrary and one could argue about the estimates. There probably is little question that measured against the yardstick of ultimate and complete knowledge, the field of biochemical genetics is most advanced. However, even here large gaps remain. The redundancy of DNA in mammalian chromosomes is completely unexplained. The regulation of gene action in mammalian cells remains poorly understood. A tiny fraction of the total number of polymorphisms that must exist in man has been discovered. Many of these problems no longer are unique to human and medical genetics. It is likely that many answers to the questions posed will come from geneticists not necessarily identified with human genetics.

Human cytogenetics has made considerable progress since the first demonstration of the 46 chromosomes in 1956. Much progress has been a mop-up operation and has involved phenotype descriptions. However, we still have no good ways of identifying the individual human chromosomes. We still do not know the chromosomal location



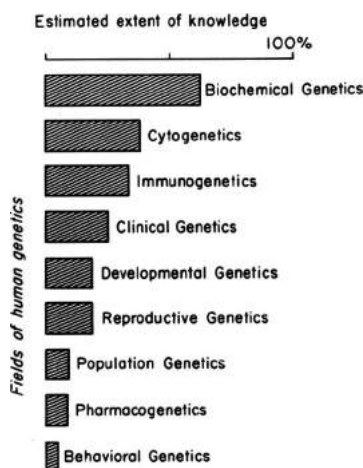


FIG. 2.—Estimated knowledge in 1970 compared with the ultimate and complete understanding of each field.

of most human genes. Normal mechanisms, such as pairing of homologous chromosomes and crossover, remain poorly understood. The etiology of the common chromosomal aberrations (such as the common trisomies) remains unknown, and the high frequency of chromosomal aberrations in our species is a riddle. The phenogenetics of the chromosomal errors is obscure. How does the addition of a single chromosome lead to complex malformations?

In immunogenetics, considerable progress has been made in understanding of the immunoglobulins, but the genetic basis of antibody variability still escapes us. Recent years have also seen the elucidation of gene action in the ABO blood group system. However, in most other blood groups we remain at the phenomenologic level with serologic descriptions, and little is known about the details underlying the genetic determinants. International collaboration has led to brilliant developments in histocompatibility testing, but the reason for the remarkable heterogeneity at the histocompatibility loci remains obscure.

In developmental genetics, the main problem remains that of gene control, that is, what makes genes turn on and off. What programs the development of the embryo? What is the significance of developmental genes such as fetal hemoglobin? How common are they? What is the genetic basis of birth defects? In clinical genetics, we understand the mechanisms of many autosomal recessive and X-linked recessive diseases and traits. However, gene action in the autosomal dominant diseases again is largely unknown. How does a mutation cause neurofibromatosis or polycystic kidneys? Many diseases such as diabetes, atherosclerosis, hypertension, and duodenal ulcer appear under polygenic determination. While the formal demonstration of such polygenic action is important as an initial approach, the ultimate understanding of the genetics of these disorders requires an analysis of the specific genes which comprise the different polygenic systems. We are almost completely in the dark regarding such genes. It is conceivable that many human polymorphisms may be com-

ponents of polygenic systems making for resistance and susceptibility to some of the common diseases. At the present time we are largely in the descriptive phase of delineating the extent of polymorphisms in different populations. It is reasonably certain that chance alone cannot explain their existence. The possible selective factors causing this remarkable heterogeneity which is not confined to human populations remains unknown. More investigators are becoming concerned with human population structure, yet our understanding of the human gene pool remains rudimentary.

A poorly developed area of research in medical genetics might be termed "clinical population genetics." The term refers to the detailed study of patients and their families for a specified disease or symptom complex, such as has been done to some extent for deafness, blindness, mental retardation, etc. We lack data of the exact extent of the genetic determination in many disorders such as various endocrine disorders (e.g., hyperthyroidism or hyperparathyroidism) and many other diseases. A study of unselected consecutive patients using genetic, biochemical, and clinical methods is likely to yield considerable knowledge of potential benefit to patients and their families. Studies such as the natural history of polycystic kidneys done by Scandinavian investigators in the past are examples of this sort. However, since most clinicians are not oriented toward a population approach and since population geneticists usually are not clinicians, this field (with a few exceptions) has been rather undeveloped. While such work lacks the immediate excitement of some other areas in human genetics and takes a great deal of effort, it will provide the necessary background for much other work.

In behavioral genetics, few will deny that genes are active in the central nervous system as in all other tissues, but the nature of that action remains entirely unknown. Some of our best-known colleagues in molecular biology have turned their attention to the investigation of behavioral phenomena in lower species. The genetic problems posed by *human* behavior are enormous and demand new approaches and insights. We need more sociologists, anthropologists, psychologists, neurochemists, and neurophysiologists to obtain a rigorous background in human genetics as well as for human geneticists to get a better background in some of these areas. As Jim Neel has remarked, this area of research may be the most crucial one for survival of the human species. If we could learn more about the biologic basis of aggression, we might find means to control nuclear war with its potential destruction of Western civilization. Reproductive genetics is another new area of recent interest to human geneticists which concerns genetic determinants of gamete formation, fertilization, and early development, and has some overlap with cytogenetics and developmental genetics. I did not use a separate category for formal genetics, but our modest knowledge of human linkage groups remains an important gap which needs filling.

Two types of technologic development promise many applications in human genetics—computer and automated laboratory techniques. Computers are making it possible now to digest large amounts of population data and deal with them in a variety of ways never before possible. For instance, we have collected laboratory and other demographic data on over 25,000 individuals in Greece in a study of malarial selection of various blood traits. Analysis of this material would be impossible without computers and remains a big "headache" even with computers. As office terminals linked

to computers with large capacities become available, this work should simplify in the future. Last year, a 17-year-old high school student in one week worked out and debugged a fairly complex program dealing with the establishment of a data bank of G6PD variants using a time-sharing computer. As young people are learning to work with computers as a natural extension of our modern environment, we can expect rapid progress in data utilization.

Computerized data records promise to be helpful in the orderly keeping of various genetic records. Using automated laboratory techniques, a variety of genetic and nongenetic traits will be screened at birth, in school, and before marriage. Hopefully, pattern-recognizing devices will do rapid chromosomal analyses; this material can be stored in computers as a permanent genetic and medical record of an individual. Information from doctors' offices and hospitals could tie in with such records so that every time an individual appears in a medical facility, a printout of previous data could be obtained. Along with these developments, we must learn to preserve the confidentiality of such records.

Recently a molecular biologist, Dr. Gunther Stent, suggested that our society is coming close to the ultimate in possible knowledge in biology and other sciences, and that the intellectual excitement of the sort associated with the flowering of molecular biology no longer can be expected in the future. In looking at our abysmal ignorance concerning most of the phenomena of mammalian and human genetics as well as our lack of knowledge of the etiology of most genetic diseases, I cannot share Stent's pessimism (or some might call it optimism). While my vantage point is considerably less lofty than that of Stent, I can foresee many exciting and unexpected discoveries of considerable intellectual excitement and potential significance in human and medical genetics for a long time to come. Having lived through most-exciting times in biology, some of us have become pretty jaded. We get dispirited when progress in the laboratory slows and when the latest journal issue contains no really startling discoveries. (The contrast between the basic journals and those dealing with human genetics is often quite painful in this respect.) But exponential growth is unlikely to last in any field. We may be nearing an area where the "hot" discoveries may slow down in our field. "Homo scientificus" has existed for a very short time in human evolution. Hopefully, many generations of our descendants will follow, and the scientists of the future will want to and still need to make discoveries.

#### STATUS OF GENETIC COUNSELING

Genetic counseling is an important part of the activities in human genetics. As patients and their doctors are becoming increasingly aware of genetic factors in disease causation, more and more individuals will come to their medical advisers as well as to medical geneticists to ask about recurrence risks of diseases in their families. In most instances such advice can be given fairly securely, based on the principles of Mendelian inheritance or on empiric recurrence risks. As genetic education improves, most physicians will be able to perform genetic counseling for many diseases. Our nongeneticist medical colleagues soon will learn that there is no mystique about genetic counseling and will not need to refer these cases. In complex situations or obscure diseases, referrals to medical geneticists will continue, and we can be of real

help. Since genetic advice requires accurate diagnosis, medically trained geneticists would appear to be the ideal genetic counselors.

The development of intrauterine diagnosis is giving an exciting new dimension to genetic counseling and allows definite rather than statistical diagnosis with selective abortion of affected fetuses. However, apart from the chromosomal aberrations, relatively few conditions can be diagnosed in this manner. The vast majority of diseases associated with structural protein abnormalities and/or dominant inheritance remain undiagnosable by this method. Similarly, all the common birth defects of complex etiology, such as cleft palate and CNS malformation, cannot be detected. In our excitement about a new method we should not lose a sense of proportion, particularly since the total impact of intrauterine diagnosis on public health is not very large today. However, techniques of fetal visualization and fetal biopsy may make it possible in the future to diagnose a variety of other conditions heretofore inaccessible to diagnosis.

The popularization of genetic counseling is bringing a new development. Responsible and well-informed healthy couples now sometimes appear before genetic counselors before marriage. These young people would like to know whether certain diseases could affect their children or simply want to be informed about the chances that their children will be healthy. They expect a genetic "checkup" to give them this information. With better availability of screening for heterozygotes, we are entering a new area and may at least provide the rudiments of the desired genetic checkup. While at the present time we do not have sufficient knowledge or techniques to test for many heterozygote traits, some of us should get involved with the planning of premarital clinics for this type of counseling. If such units were established (and I do not advocate such centers for the immediate future), there would not be enough personnel in medical genetics available. Already, some colleges have foreseen the need for genetic counselors of paraprofessional training both for conventional needs and for the genetic counseling of the future. This development comes at a time when paramedical personnel are used much more extensively in all areas of medicine. Sarah Lawrence College in New York is pioneering in the establishment of curricula dealing with the biologic, social, and psychologic aspects of genetic counseling; graduates of the program could function effectively under the supervision of fully trained medical geneticists. This type of occupation should provide an important outlet for many young men and women who are attracted to service-oriented aspects of human genetics. At the present time there are few job outlets for these individuals.

#### HUMAN GENETICS AND THE PUBLIC

Since the large majority of the public is poorly educated in science, most people do not realize what scientists do. On the other hand, a field such as human genetics is of considerable interest to people since most parents see themselves in their children and are therefore interested in how heredity works. The advent of molecular biology, with resulting newspaper publicity on genetic engineering and the possibility of tailored genetic design, is bringing our field into the public domain. The public image of the "mad scientist" manipulating human genes may be gaining strength along with occasional memories of a eugenic past which was tied up with an elitist and racist world

view. The horrible excesses of Hitlerian Germany committed in the name of human genetics still are remembered by many. In general the swing from the purely social concerns of the early eugenicists to the entirely medically oriented preoccupation of recent decades has helped to make the field respectable in the eyes of the public. However, history repeats itself, and concern with the social and public issues of human genetics is again appearing.

It would be interesting for a social survey organization to canvass the attitudes of various groups in the population toward human genetics. Even with the negative feelings mentioned, I believe that the public expects more than we can deliver in the foreseeable future. The possibilities for genetic engineering are far from realized and will require considerably more work before we dare apply such techniques to human beings. It is important to emphasize this fact very forcefully.

In these days of diminishing research support, it is fashionable to point out that many scientific advances have taken place in the last two decades, and that a diminution of research support will prevent the solution of many important public health problems. While there is general merit in this argument, it is dangerous to promise breakthroughs if, in fact, such breakthroughs cannot be justified based on extrapolation of present knowledge. Most birth defects, as well as most common diseases such as atherosclerosis, hypertension, cancer, schizophrenia, and diabetes, do have genetic determinants. However, the nature of these genes is entirely unknown, and disease control for these disorders, based on genetic principles, is difficult to visualize within the present framework of our knowledge. I do not foresee genetic or environmental control of most of these diseases in the next 25 years. Promise of disease control by spokesmen for medical research has not yet led to differences in the frequency of birth defects or common diseases of middle age. Morbidity and mortality have not significantly decreased. It is, therefore, dangerous to tell the public that research in genetics is the panacea which will bring forward prevention and cures of many of our ills.

On the other hand we can point to many advances of practical significance: (1) we can detect chromosomal and biochemical disorders in utero allowing selective abortion of affected fetuses; (2) our understanding of the mechanisms of Rh hemolytic disease has led to preventive treatment by which this condition can be almost completely eliminated; (3) the development of histocompatibility testing now allows organ grafts with much less fear of rejection; (4) the development of simple screening tests to detect individuals susceptible to drug reactions allows prevention of such reactions; (5) the understanding of the genetics and pathophysiology in a variety of diseases allows preventive treatment of previously unsuspected affected patients—Wilson's disease and polyposis of the colon are examples; and (6) genetic counseling of the old-fashioned conventional type has many practical applications in preventing diseases within families. While the total public health impact of the examples cited may not be very large considering all diseases, other such discoveries are very likely to come from research in our field and other fields in the years to come. What we need, therefore, is continued orderly support of research in a variety of areas in genetics and elsewhere, since it is impossible to predict from which direction the practical advances will come.

## RESPONSIBILITIES TOWARD THE PUBLIC

Most research scientists in the biomedical sciences are more interested in discovering new facts and concepts rather than in applying research findings to public health. This phenomenon is expected, since the research scientist, with a few exceptions, is more a man of thought or of action in the laboratory rather than a lobbyist in Congress, in the board rooms of government, or in the public sector. Consequently, most of us will turn to a new research problem rather than make sure that what had been found earlier is fully utilized. We expect various social agencies, including public health departments, or practicing physicians to apply our research findings. With the rapid discovery of new findings, the required middlemen and social institutions often do not exist or cannot or will not act.

A good example is the neglect of implementation of the scientific findings in sickle-cell anemia. It has been known for the past 20 years that about 10% of the American black population are carriers of the sickling gene. Simple inexpensive tests to detect such carriers have been available for a similar period of time. The genetics of sickle-cell anemia is well defined, and we know that 25% among the offspring of two sickle-cell trait carriers will have a child affected with a disease requiring considerable medical attention throughout childhood and adolescence, usually resulting in premature death. About one in 400 black children in the United States will develop this disease. Compared with all other autosomal recessive disorders in this country, sickle-cell anemia has the highest frequency. Yet no public health agency spreads this information to the public at risk. Theoretically, it would be quite easy to test schoolchildren for the sickle trait and counsel the relevant population how to prevent this disease. Even parents who have a child with sickle-cell anemia often are not given the required advice to prevent a second affected child. The black community has only recently become aware of this problem and is urging various agencies to action. The sickle-cell anemia problem, unlike the problem of cancer of the lung induced by smoking, has no economic interests to make a preventive campaign so difficult. Admittedly, there are many practical and behavioral difficulties in a genetic counseling program based on the prevention of matings between heterozygotes. It is likely that testing of heterozygotes along with perfunctory counseling is not going to have much of an impact. However, if heterozygote testing is associated with an educational campaign in the schools and with propaganda through newspapers, magazines, radio, television, film strips, and movies, much more success could be expected. Such a campaign might not be inexpensive but certainly most of its techniques have been well developed by "Madison Avenue." Hopefully, in the not-too-distant future, intrauterine diagnosis of sickle-cell anemia may become possible. This approach, followed by selective abortion, would seem easier in the long run than one based on the avoidance of matings between heterozygotes or on complicated therapies of the disease, such as bone-marrow transplantation.

An interesting example of the interaction of science and society lies in the development of intrauterine diagnosis of genetic disease. This rather striking development is appealing and can be understood easily by the public. Science writers and writers for women's magazines have become interested, and many articles have appeared which

cite the significance of this approach. At the same time, the necessary large-scale scientific facilities for testing of amniotic cells are not available, nor is the full fetal and maternal morbidity and mortality of this procedure entirely known. We face, therefore, a situation where the public and the medical profession demand a service which is only available in relatively few institutions. It can be expected that this demand will lead to the establishment of amniotic-cell testing by laboratories lacking the required scientific background. Fortunately, at the same time, competent laboratories will be forced to transform a research procedure into a service operation much more rapidly than without public demand. While the proliferation of poorly based facilities must be decried, strong public demand will help to get this procedure properly established in a much shorter period of time than if the process were left entirely to research scientists and to the medical profession.

Another aspect of applied research in human genetics needs comment. Since genes have a differential distribution in various populations, screening and population studies often need to be oriented toward a certain ethnic group or race. Testing for G6PD deficiency and sickle-cell trait has the highest yield in black populations and could hardly be justified in a Caucasian population in Seattle, for instance. Tay-Sachs disease occurs in Ashkenazic Jews with a fairly high frequency, and testing would not be warranted in other populations. The climate of the times in the black community is such that separatism is no longer considered undesirable by many black leaders. Screening for a genetic trait largely confined to blacks might be more acceptable now than it was in the past. Genetic public health measures in general will require better records of the population origin of individuals for appropriate screening. While such a procedure may be distasteful, the medical facts require such knowledge. Hopefully, physician and hospital records, as well as birth and marriage certificates, will begin such listings as ultimately will the census. To make such procedures more acceptable, public education will again be required.

Human geneticists must be in the forefront in exploring and explaining the true facts about race and the significance or lack of significance of racial differences. We are in the position to clearly point out when scientific data show unequivocal differences between races (e.g., the presence of the Diego factor among Oriental populations). But when differences in intelligence between populations are attributed to genetic factors, the lack of environmental equality and the remoteness of the measurement from relevant gene action should make us skeptical. However, an outright rejection of such suggestions is also not scientific even if such claims make us uncomfortable emotionally.

#### RESEARCH SUPPORT AND AREAS OF PRIORITY

Fairly clear signals have been given in Washington that the expansion of research activity which occurred at such a rapid rate in the past is coming to a standstill. At the same time, many authorities are becoming concerned about the delivery of health care. It would be a great tragedy if large proportions of the funds previously available for research now would be shifted to entirely applied areas. It may be worthwhile asking a broader question. Are there any principles which might be used in parcelling out the total funds available for research in all areas of science? At the present time

no firm long-term guidelines appear to exist. Depending upon the existence of pressure groups pushing one or the other fields, funds have been allocated without any concern for the real priorities of the future. Politicians can only look as far as the next election and therefore have a short horizon. The most vocal pressure group with the most spectacular type of performance, for example the space program, may attract a very large slice of the funds but, in fact, may be least important if the real priorities were considered (i.e., the big problems of our planet: nuclear war and the population explosion). While too rigid planning might be distasteful and dangerous because the unexpected discovery from unexpected quarters could be overlooked, the time has come when each field of science needs to take stock of its current status followed by a 10-year extrapolation. With this information at hand, scientific statesmen with no axe to grind for any particular field need to sit down and divide the existing pie.

I believe that under such a plan, the field of human and medical genetics would do rather well. Population research would get a fairly high priority. The interface of population genetics and population growth is one that requires much further work. Similarly, the area of reproductive genetics has significant potential to develop new contraceptive agents based on sound genetic principles. The study of aggression needs high priority, and human behavioral geneticists will participate heavily in this approach. Three areas touching on both ecology and genetics carry exciting practical and theoretical possibilities for the future. The first deals with environmental agents, such as X rays, and particularly chemicals as mutagenic agents. While as geneticists we are primarily interested in germ cell damage, somatic cell damage leading to malignancies is an important danger which can be analyzed by a variety of techniques in somatic cell genetics. The second area of environmental-genetic research deals with the interaction of specific genotypes with particular environmental agents. Pharmacogenetics is a central component of this type of investigation. Another interesting example is represented by the hyperlipoproteinemias. Such disorders may cause no harm with relative undernutrition, but when present in modern Western societies with relative overnutrition, may result in public health impairment in the form of atherosclerosis. The third broad area of environmental-genetic research is the interaction of the long-term relationship of different genotypes to the environment. Most of our genetic diseases are deleterious and presumably are kept in the population by mutation pressure. In other cases, selection undoubtedly has made certain genes reach relatively high frequencies. The total impact of various selective agents on the human gene pool is hardly understood and requires considerably more work.

Our society provides a relatively large amount of money for research. Much research on the interaction of heredity and environment offers potentially visible payoff in the near future. While research on diseases and traits that cannot be prevented should be done to discover basic principles and ultimate management, it will be easier to obtain funds for research on diseases which have a higher probability for prevention or treatment. We cannot all remain in ivory towers and disclaim public responsibility for the work we are doing. In each individual case a decision must be made whether to remain in the ivory tower (and I feel strongly that quite a few of us should remain) or whether to turn to some of the more applied areas. Unfortunately, the availability



of funds rather than a conscious decision will have a strong influence on future direction for many of us.

In summary, we can take pride in the strength and promise of our field. Human genetics already has illuminated many aspects of human health, disease, and behavior and is likely to continue to do so in the future. Human geneticists have the potential to contribute to the most urgent problems facing human survival: the prevention of nuclear war and the curbing of the population explosion. The human brain is the most precious possession of our species. To understand and control its workings remains our greatest challenge. I am sufficiently optimistic to believe that our scientific successors, be it in 1, 10, or 100 generations, will ultimately achieve this task. Once that goal has been reached, human culture—as the highest achievement of evolution—will flourish as never before. Men, women, and children all over the world will then be able to live a truly *human* existence in peace and in health. As human geneticists we may consider ourselves privileged to contribute to this vision.