Garrod, Galton, and Clinical Medicine\textsuperscript{1,2}

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Received for Publication May 14, 1973

Human genetics must acknowledge many sources, but the earliest and perhaps most symbolic are Archibald Garrod and Francis Galton. I would like to begin with the contributions of these two men and what they stood for, because a look at human genetics in the context of the clinician suggests that it is strongly garrodian, but only weakly galtonian. On the other hand, there are strong pressures advancing the latter's viewpoint which may broaden the dimensions of the clinician's practice and which invite him to assume some responsibility for decisions about social issues arising out of the genetic causes of human differences.

GARROD AND GALTON

Garrod (1857–1936) was first of all a clinician, and an outstanding one. He was unique in his time for his knowledge of biology and biochemistry and for doing laboratory investigations. Everyone knows that he was the first to conceive the relationship between genes and enzymes which accounted for the variations he called inborn errors of metabolism. It is little known, however, that he extended his original insight to predict the molecular and genetical basis of variations of all functions under biochemical control; that is, all life functions, including physical appearance, responses to drugs, susceptibilities to disease, and even behavior. He thus outlined what later discoveries have attested; that each human being can be distinguished from all others by virtue of the possession of a unique set of protein molecules, and that the directions for this singularity are encoded in the genes. Garrod's view was that of a good clinician, inward looking, seeking the pathogenesis of nonadaptive differences in individual persons with a view to setting them right. In his later years he was especially interested in the genetic origin of susceptibility to disease or diatheses, suggesting that these, too, must have a molecular

\textsuperscript{1}Presented as the XV Grover F. Powers Lecture at Yale University School of Medicine, April 1973, and presented in part as the William McL. Wallace Lecture at Case Western Reserve School of Medicine, November 1971.

\textsuperscript{2}This work was supported by NIH grants HD 00004 and HD 00486.

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basis, and that the key to the solution of these diseases lay in understanding the interaction of genes and environment. Garrod was very much a medical man who saw things as a physician does.

Francis Galton (1822–1911), also an Englishman, had a different outlook. He was one of those extraordinary Victorian gentlemen whose financial independence allowed him to live a largely intellectual life. He was a first cousin of Charles Darwin and was strongly influenced by him. Originally a geographer and explorer, he turned in time to study the qualities and causes of individuality in the human species. His accomplishments were many. He was the first to appreciate the distinguishing qualities of finger prints; the first to use twins to partition the effects of heredity and experience; and the first to ascribe to heredity many intellectual, sensory, and behavioral properties. Measurement was his obsession. Observations were classified into quartiles, deciles, and the like, and the necessity to see the quantitative relationships of measurements between individuals caused him to invent the correlation and regression coefficients. In the main, he studied the inheritance of characters which are continuously distributed and which do not segregate, and he was interested in establishing the degree to which such traits are heritable. That is, unlike Garrod, whose object was to understand the molecular basis of heritable variation, Galton wished to know the average degree to which a character is inherited by the whole species. This preoccupation with species inheritance led him to suggest that humankind might be improved by differential reproduction and to invent the word eugenics to embody the idea. Thus, his view of heredity differs from that of Garrod in looking outward to consider the extent of variation in whole populations and to see the individual in his position in the distribution. It is not surprising that Galton's concepts engendered population genetics.

MODERN MEDICAL GENETICS

It might be supposed that with so favorable a start human or medical genetics would have flourished from the beginning, but it did not and probably could not, having as it did to await the development of the theory of the gene, of cytogenetics, and of mechanisms of gene action. Even the discovery and elucidation of inborn errors could not proceed until the invention of appropriate biochemical techniques, and in any case babies with severe metabolic errors must have died early of infections, and multiple deaths in infancy in families must have been a commonplace event not easily assignable to any genetic cause. So genetics developed outside the medical school and hospital in botanical and zoological laboratories, and the earliest devotees of human genetics were mainly scientists to whom the biology of man was not a primary interest. Genetics must be, therefore, the only scientific discipline to be imposed upon medical education and practice from without. Biochemistry, physiology, microbiology, and even molecular biology, have been for the most part lodged in schools of medicine, and new developments have always been passed on to current crops of students. Not so with genetics, which is a recent arrival. Figure 1 shows, for example, that it was not until the early 60's that the number of papers listed in the Index Medicus under such headings as human genetics, chromosomes, and human heredity surpassed the number devoted to hernias. This surge in research effort was the result of the discovery of a way to look at human chromosomes, of biochemical techniques to assay enzymes and other proteins, and to study their physical properties, and of the means to separate and measure metabolites in body fluids. These biochemical feats must delight Sir Archibald's shade.
Figure 2 shows the exponential rate of discovery of enzyme deficiencies which qualify as inborn errors in the garrodian sense. There appears to be no letup, and theory suggests that, barring a meanness of spirit at the Office of Management and Budget, there should be none for a long time. Further, for many of the loci specifying the mutants which cause those inborn errors more than one variant allele has been discovered (1). Some of these multiple allelic systems are surprisingly large; the hemoglobins number over 100, the G6PD's over 80, and several others number in excess of 10, and some of these have been shown to account for the variability in severity and symptoms of disease. The discovery of the cause of a disease usually suggests what to do about it and clinicians have responded to this proliferation of genetic disorders by designing treatments which alter the environment in such a way as to nullify the adverse effects of the mutant genes;

![Figure 1](image1.png)

**Fig. 1.** Research in human genetics did not exceed that devoted to hernias before the early 1960's. Human heredity, ○; hernia, x.

![Figure 2](image2.png)

**Fig. 2.** Discovery of new inborn errors of metabolism is proceeding exponentially.
A GREAT DEAL MORE IS KNOWN TODAY ABOUT INBORN ERRORS THAN WAS KNOWN TO SIR ARCHIBALD GARROD

|                  | Garrod’s inborn errors of metabolism | 3rd Edition of “Metabolic Basis of Inherited Disease” |
|------------------|--------------------------------------|-----------------------------------------------------|
| Date of publication | 1909 | 1972 |
| Weight | 300 g | 2400 g |
| Contributors | 1 | 93 |
| Chapters | 6 | 74 |
| References | 248 | 14,690 |
| Ref/chapt | 41.3 | 198.5 |
| Pages | 168 | 1778 |
| Surface area (sq in) | 9300 | 137,795 |
| Words/page | 235 | 900–1000 |
| Index pages | 11 | 41 |
| Index items | 600 | 7075 |
| Cost | $2.50 | $45.00 |
| Cost/g of book | 0.90¢ | 1.87¢ |

I have emphasized the metabolic side of human genetics because of its obvious connection with Garrod, but as everyone knows, there has been an equal expansion of knowledge of chromosomal abnormality and of other aspects of clinical genetics. A glance at the editions of “The Metabolic Basis of Inherited Diseases,” as well as at McKusick’s catalogues of mendelian traits, tells the story (2, 3). Perhaps it is even better revealed by a comparison, shown in Table 1, of the third edition of “The Metabolic Basis of Inherited Diseases” and Garrod’s “Inborn Errors of Metabolism” (4). All of this is in the traditional medical vein. The diseases may be rare, their names unpronounceable, and the pathways and metabolites impossible to memorize, but none of this strains in any way the conventional affinity between the doctor and his patient. It is sufficient for the clinician to think of the mutant gene or the abnormal chromosome as a causative agent, conceptually similar to a microorganism whose ill effects must be neutralized when possible by environmental manipulation. If definitive treatment is not possible, physicians are accustomed to providing symptomatic relief as well as other forms of support.

POPULATION GENETICS

It would be a mistake to suppose that human genetics is concerned wholly, or even mainly, with the detection and description of new genetic disorders and with their biochemical elucidation and treatment. The fact that chromosomes segregate and genes assort themselves independently allows us to predict their distribution in families and in populations, and geneticists have worked out mathematical statements of those distributions in various mating systems and under environmental conditions favorable or unfavorable for their spread. The theories of population genetics were worked out in the 1920’s and 30’s, but they have had to wait until now to be tested because of a lack of traits to provide the empirical data to support or contradict them. This deficit is being made up by the discovery of variant protein molecules of all kinds, whose distribution in families attests to their genetic origins. Some of these are the defective molecules which account for the inborn errors,
while others, although structurally unique, cause no apparent physiological difference. Some of the genes specifying these molecules, called polymorphic genes, are common in the population, reaching frequencies of more than 1%, while others are restricted to particular families. Probably a majority of the gene loci show genetic polymorphism, enough at least so that about 20% of the loci of each human being are heterozygous for alleles determining alternative forms of the corresponding proteins (5). The search for these variants goes forward so that what is being begun is a tabulation of the genetic quality of man.

The result of all this is the recognition that the human species is as variable as any other and more variable than had been suspected, and questions are being asked whether genes with frequencies in the population of 1 or 2% or more are so common because they are adaptively favorable, or because although selectively neutral they have accumulated at random (6).

The relationship of this aspect of genetics to medicine in the distant future is easy to project. One might extract from a culture of cells derived from an early fetus a catalogue of gene products which would give strong indications of future developmental directions, allowing the physician to map the future, if any, for that fetus. This possibility is not open to us now, may never be, and as outlined may be morally undesirable. In any case, we need not worry about the remote future, the question for now is whether population genetics has something for clinical medicine of the present and near future.

I think it is reasonable to say that clinicians are generally ignorant of population genetics and do not see its relationship to their patients. One reason for this is that many investigations have gone on outside the purview of clinical medicine. Many of the investigators are nonmedical and even those with medical training are seldom working in clinical departments. Nor is a great deal of the work published in such a way as to attract the attention of clinicians, least of all those in practice. A recently published and comprehensive book entitled “The Genetics of Human Populations” lists over 700 references (6). Of these, only 28, or 4%, were to journals which might be read or glanced through by practicing physicians. A further 10% were to journals such as Science, Nature, The Proceedings of the National Academy of Sciences, Proceedings of the Royal Society, and Scientific American, journals which clinical investigators would look at, but would read selectively. About 18% of the references were to books, of which only a few would even be seen by clinicians or clinical investigators let alone be read, and of the rest, most were to genetics journals and transactions of congresses and symposia which would be likely to be scanned only by the handful of clinicians interested especially in genetics.

A second reason has to do with the nature of physicians, the exigencies of practice as they see them, and their view of their role in medicine. The doctor is concerned largely with the immediate complaints of patients; deals with the diseases of individual persons, not of society or of any other statistical unit; lacks much interest in the theoretical or in that which cannot be put to immediate use; and always requires strong empirical evidence to cause him to move.

Population genetics is still theoretical, strongly mathematical, and still insufficiently buttressed by empirical data. Its concern is primarily biological but it is also strongly social and evolutionary and has lately engendered public musings about the uses of genetics for the improvement of the human race. In short, it is a galtonian view and it has led to new looks at eugenics, mainly by molecular
biologists and geneticists. It is not surprising that it should be geneticists who discuss eugenics. Their view of human life is unlike that of the physician; their thinking is more abstract, theoretical, and experimental. Their view of man is evolutionary. They see him in relation to other forms of life, as a species with a past and an uncertain future. They have recently witnessed, or participated in, the discovery of fundamental truths about genetics and life, and they suggest that the new principles which apply generally to all living things ought to be used to improve man's welfare and to give constructive direction to his evolution.

**POPULATION GENETICS AND CLINICAL MEDICINE**

We have seen how readily the clinician has absorbed the lessons of Garrod; the imposition of a galtonian stamp on clinical medicine is another matter.

Genetic counseling, antenatal diagnosis after amniocentesis, and population screening for genetic disease are all going on in one form or another and represent the present interface between clinical medicine and population genetics. Each of these can be seen in the narrow context of individual patient care, but each has also wide social implications which have not been systematically studied or even faced, and which tend to enlarge the doctor's responsibilities. These are mainly measures of negative eugenics, and beyond these are measures of positive eugenics for which neither the people nor the medical profession are ready, but which suggest the capabilities science will offer and which can be devoted to human welfare if we are ever wise enough and judicious enough to decide whether to use them or to reject them.

*Genetic Counseling*

Genetic counseling has two purposes. One of these is to give interested persons a discussion of the genetic aspects of their problem including odds for or against particular reproductive outcomes. The second is to provide such support as may be derived from advice about contraception, adoption, and the use of social agencies, as well as to try to resolve the emotional turmoil engendered by the burden of genetic diseases and the damage to self-esteem which may result from learning that one is the possessor of genes capable of bringing harm to one's children. Much of this is old stuff for physicians, who give supportive help every day, but the recitation of odds is still approached with diffidence by some doctors, and, if the genetics of the condition is obscure, many prefer to send the patient to a genetics clinic. Even this wariness about genetics is a matter which education might solve, since it is in the conventional doctor–patient context; but what of the patient's relatives whose risks can be calculated with precision and who do not happen to be in the doctor's practice? Whose duty, if anyone's, is it to tell the sisters of a woman who has a hemophilic child and who has been shown to be a heterozygote, that they are at risk? And what about the mother's female first cousins, who have a one-eighth chance of having the mutant too? Some physicians assume some responsibility, others don't; some parents warn their relatives, others don't, but surely there is some social obligation here to all the members of the family. Some geneticists have proposed to deal with this question by means of computerized registries (7). Each new family is entered in the registry, including all of the relatives. If desirable, these data can be linked with such other information already public property as birth and death records, census material, and the like. In this way, people at risk can be discovered who are utterly unaware of their jeopardy. Should they be told,
and who should do the telling, and who shall give them appropriate counseling, and to what doctor will they be sent in the end? Such methods need to be studied and may or may not become the rule, but whatever mode of dealing with families is settled upon, some kind of violence will have been done to the conventional doctor–patient relationship.

A review of the literature of genetic counseling reveals differences in the goals of counseling (8). Most counselors see this service in the orthodox light of providing a patient or parent with the wherewithal to make intelligent choices about further reproduction, but some see it as a means of reducing the number of defective persons in the population; to these latter it is an eugenic measure. For the former, success must be measured by the patient's or parent's own statement that knowing the risks and the potential burden they made a choice—either way, while to the latter success is inversely proportional to the number of children born after counseling. No one knows how many practicing doctors are now doing genetic counseling, or among those who do, how many preserve neutrality with regard to the counsellee's reproductive decisions, or how many are directive. Nor do we know the outcomes of counseling by all counselors, so we cannot judge to what degree counseling may be reducing the numbers of persons with genetic disease, or even if it is, whether it is the risks or the burden which is decisive in the choice not to reproduce (9).

Amniocentesis and Antenatal Diagnosis

Physicians are generally more comfortable in telling patients of something they can do rather than warning against the hazards of action, so urging antenatal testing and abortion of affected fetuses is very much in the traditional medical vein. On the other hand, selective abortion is at least a novel idea to doctors whose primary aim is to protect and support life. More foreign to ordinary practice is the idea of pressing this possibility on people who have not asked for it. Even more out of the usual is the request for a baby of a given sex; obviously a normal fetus of the unwanted sex is to be aborted. Should amniocentesis become a routine procedure during every pregnancy, it could become an instrument of population control, or at least for the control of sex determination. Etzioni has reviewed the possible consequences of control of sex determination as an example of the impact on the whole society of the use by physicians of a medical technique designed to fulfill the requirements of single patients (10). The results are not particularly alarming, but have widespread social effects not envisioned in the rationales for sex choice each time it is carried out.

Antenatal diagnosis and selective abortion can be used to reduce significantly the incidence of genetic diseases only if the people and matings at risk in the population can be identified; that is, families who could have, but have not yet had, affected babies must be included (11). If this were to be done, and it should be stated that it is not yet certain for how many diseases it ought to be done, it would require all physicians, but perhaps particularly general practitioners, obstetricians, and pediatricians, to ensure that their patients were screened for many genes, a list of which is likely to increase year by year. It should be noted that this must be a cooperative venture for the doctors, since, as with all public health measures, the success of this one depends upon affecting a maximum proportion of the population. Incidentally, any dysgenetic effects of these tactics are likely to be minimal (11).
Mass Screening

Mass screening is a distinct departure from conventional episodic medical care and very much of a piece with the new ideas of community medicine. But the scope of screening for genetic characters can be broader than that envisioned in any current medical care program. That is, there are several objectives, running all the way from the discovery of persons with treatable diseases to finding persons who are not themselves at risk for anything but who carry genes which, given an appropriate mating, could put an unborn offspring at risk for an untreated condition. It is doubtful that practitioners devote much thought to screening for genetic disease, since state and city health departments usually administer the screening for PKU and other inborn errors. Mass screening for Tay–Sachs disease and sickle cell disease and trait, however, have had much recent exposure in the public and medical media drawing attention to screening, so that there is some chance that such screening for a diverse list of conditions will go forward, involving practitioners, whether they think about it or not. As this list of genetic susceptibilities increases, as undoubtedly it will, some mechanisms will be required to counsel the large numbers of possessors of such genes and to help them to live with them. This could be done by health departments in some way, but would be better handled by clinicians accustomed to giving medical care. Perhaps group sessions or family meetings would be the way. Certainly ancillary medical personnel experienced in counseling and in home visiting have been proved useful (12). In addition, mechanisms for the education of the public and of persons shown to be carriers or otherwise affected will be required. The conditions now being screened do not in the aggregate affect a very large proportion of the population, but if it becomes possible and is judged desirable to screen for genetic susceptibility for such frequent disorders as diabetes, psychoses, hypertension, some forms of cancer, and the like, then a practitioner lacking some appropriate mechanism to deal with the numbers would be hard put to keep up with it all.

Positive Eugenics

Although positive eugenic measures (summarized in Table 2) are even less congenial to medical practice, they should be mentioned here both because they have been the subject of articles in the public press and because their proponents are, for the most part, nonmedical scientists with strong beliefs in social improvement. But they seem to me to have little practical significance for the clinician of the moment. Everyone agrees that direct manipulation of genes, however desirable, will not be done soon. The various forms of reproductive manipulation are perhaps more feasible, but raise more immediate questions of ethics and social acceptability, but even in the unlikely event that they are judged acceptable, they would have

| **TABLE 2** |
| **Measures of Positive Eugenics** |
| Addition, subtraction, repair of genes in germ cell lines |
| Reproductive manipulation, in vitro fertilization |
| Cloning |
| Parthenogenesis |
| Germinal selection |
| Selective mating |
| Artificial insemination |
little effect on the genetic quality of the human race. As for germinal selection, or the means to improve human quality by selective reproduction of persons with desirable genes, this too must await a day when we have some idea of which genes are desirable, which combinations are desirable, and what environments are required to bring out their beneficial effects. It might be possible also in that distant future to persuade people to mate for genetic rather than emotional reasons, but for the moment, even leaving aside our inability to select the "best" mating, germinal selection surely must be at the bottom of the list of reasons, not so say impulses, which cause people to mate.

There is a sizeable literature on these eugenic measures consisting of papers, transactions of symposia, and a few books. Table 3 lists the symposia by their rather resounding, even apocalyptic titles, and shows that the bulk of the participants and authors have been nonmedical persons; indeed, in only one session have the medical out-numbered the nonmedical (13–22). In addition, a review of the literature revealed that of 45 authors of 53 papers written on these subjects between 1959 and 1972, only 18 of the authors, or about one third, were medical (23–75). Some of the nonmedical authors and many of the nonmedical participants in the symposia were clergymen, philosophers, or lawyers, and that is as it should be; the future of man is too important to be left to physicians, but the heavy non-medical preponderance is due to the geneticists, who in the galtonian manner hope to put our knowledge of genetics to work in the interest of man, or to make sure that such knowledge is not misused. These exercises, then, were a means of bringing eugenic possibilities to the attention of the scientific community and to the public with the idea of starting some debate. Medical authors and participants in the symposia, on the other hand, true to their traditions do not see the immediate applications, especially of the more outré of these suggestions, and in any case are wary of schemes for the improvement of man and so tended to draw the discussion around to the uses and misuses of antenatal diagnosis, screening, and counseling.

The effects of this debate on medical practice, if any, are not clear and may not be clear for a long time, but whatever else it does, it should help to direct the medical view to genetic issues of wide social concern not now seen to be in

| Title of symposium                        | Participants |
|-------------------------------------------|--------------|
| Evolution and Man's Progress              | Nonmedical   |
|                                          | Medical      |
|                                          | Total        |
|                                          | Reference    |
| The Control of Human Heredity and Evolution | 9            |
| Biology and the Future of Man             | 7            |
| The Future of Man                         | 19           |
| Genetics and the Future of Man            | 7            |
| Who Shall Live                            | 6            |
| Changing Mores of Biomedical Research     | 7            |
| Genetic Engineering                       | 6            |
| The New Genetics and the Future of Man    | 9            |
| Ethical Issues in Human Genetics          | 16           |
|                                          | 94           |
|                                          | 96           |
|                                          | 129          |
| (Percent)                                | (72.9)       |
|                                          | (27.1)       |
|                                          | (100.0)      |
its province. A good example is the mutagenic effects of a variety of agents in common use. Edwards has pointed out that those technological advances which have made life generally safe and more comfortable paradoxically have added to the hazards of intrauterine life by exposing the embryo to drugs, chemicals, pollutants, radiation, and the like, all of which can be both teratogenic and mutagenic (76). The mutagenic properties of these agents have received little or no attention from physicians, but geneticists have been active in working out systems for testing mutagenicity and pressing for recognition of the problem by appropriate government agencies (77, 78).

THE FUTURE

If, in fact, clinicians are insufficiently galtonian in knowledge and uses of genetics, what should be done about it? What is needed is first, some conceptual treatment of population genetics which puts it into the context of medical practice, a frame of reference congenial to a physician whose time and energies are taken up with patient care; and secondly, places to center research and teaching which will have access to patients, families, and populations.

A Context for Teaching

As for the conceptual approach, what is required is to show that knowledge of the genetic structure of the population is conjunctive to clinical medicine, that mating systems, the distributions of genes in families and in larger groups, their frequencies, the causes of their equilibria, and their ebb and flow are all of importance to the clinician. We must translate the selective value of genes into clinical terms and try to discover the significance of the polymorphisms. We must impress the clinician that each patient is shaped by the concatenation of genes which are his by random chance and that all human variations, including onset, extent, severity, and duration of disease are likely significantly to be influenced by those genes.

It might be argued that there are insufficient empirical data to link genetics to medicine except in the sense of cause of disease; a deficiency which will leave physicians unimpressed since they are usually interested only in that which is of practical use in coping with their patients. But screening for inborn errors in this country and abroad has established frequencies for a number of diseases, and for the relevant genes and their carrier states, and other studies give frequency figures for several chromosome abnormalities as well. In addition, there must be 50–60 loci for which there are alleles with frequencies of over 1%, and while the selective qualities and functional implications of few of these common genes are known, some examples suggesting what is in store are coming to light (5, 79).

One such example is the locus specifying the α, trypsin inhibitor protein. In all there are 19 known alleles, of which four, including the Z and S alleles, have been found in Scandinavian and U.S. populations in frequencies in excess of 1% (80–83). The Z allele in homozygotes causes a deficiency of the inhibitor which is associated with severe emphysema of early onset or with cirrhosis, both of infancy and adult life. In addition, there are suggestions that other genotypes, especially ZSs, are associated with the emphysema of smoking, although the evidence on this is conflicting. But such uncertainty, given the small numbers of persons studied, is precisely what one should expect. To begin with, there are 190 possible genotypes, and even if it were possible to grade these with regard to tendency to
emphysema, given exactly the same environment, actual outcomes in each separate individual must depend upon exposure to pollutants and infections, as well as the number and quality of cigarettes and the duration of the habit. Nor can we ignore the modifying effects of other genes, each of which may be representative of some equally elaborate allelic system. For example, since the cause of the emphysema is thought to consist of attack on elastic fibers by uninhibited proteases, variability in onset and extent of disease could be due to functional differences of alleles for both proteases and elastins. In fact, the condition is simpler than this because only three or four of the alleles are as frequent as 1 or 2%, so perhaps only 10 genotypes are of much numerical importance. Still, the 19 alleles currently known have been discovered after study of only a few thousand persons and the history of the hemoglobin and G6PD loci suggests that many more alleles, some of which may be as nonadaptive as Z, remain to be discovered.

Other examples exist. Association of the H-La antigens with many diseases, usually malignant or of autoimmune origin, have been detected (84, 85). These antigens are the products of a complex locus with many alleles, most of which are very frequent in the population. Diseases such as Hodgkin's and other lymphomas, psoriasis, ankylosing spondylitis, glomerulonephritis, lupus erythematosus, and others have been found to show variable, but some very strong, associations to certain antigens and genes. The reasons for these relationships remain a mystery, but whatever they are, they are clues to the susceptibility of some persons and resistance of others, genetic markers of a sort. Another interesting example is given by the acetyl transferase locus. Two very common alleles specify enzyme molecules which differ in the rate at which many metabolites are acetylated. A recent paper reporting observations on the efficacy of phenelzine as a treatment for neurotic depression revealed that the drug was successful if the patient was a fast acetylator, but failed to work nearly as well for the slow acetylators (86).

Recognition of the influence of genes controlling variations in blood lipid levels on the development of atherosclerosis and coronary artery disease is just beginning (87, 88). Genetic causes of variations in such other risk factors as obesity, hypertension, diabetes, and physiological responses to smoking are not known, but it is an entirely safe bet that they exist and that in time a person's status with regard to the probability of having a heart attack in some part of life will be established by the possession of particular alleles at several, or more likely many, loci.

I referred previously to the polymorphic loci whose constellations contain two or more common alleles. The metabolic effects of most of these genes is unknown, and the population geneticists cannot conclude on theoretical grounds whether they have accumulated in the population for selective reasons or by random drift. Intuition would suggest both, and that in any case they are the source of much human variation. The examples just cited suggest as much and hint that the polymorphic genes play some part in common disorders whose origins are thought to be multifactorial; that is, due to the action of several genes in particular environments. Since these diseases are common, as opposed to the rare inborn errors of metabolism, the genes which predispose to them must be common, and what other reservoir exists than the polymorphic loci (89)?

Places for Research and Teaching

Impressive progress in teaching genetics in medical schools has been made. Of 96 schools whose 1972 catalogues were available to me, 47, or about 52%, list
TABLE 4

DEPARTMENTS OF GENETICS AND DERMATOLOGY IN AMERICAN MEDICAL SCHOOLS

| Department | Division | Neither | Total |
|------------|----------|---------|-------|
|            | No. | %     | No. | %     | No. | %     | No. | %     |
| Genetics   | 19  | 17.1  | 28  | 25.2  | 64  | 57.7  | 111 | 100.0 |
| Dermatology* | 35  | 33.1  | 41  | 38.2  | 30  | 28.3  | 106 | 100.0 |

* Five two-year schools had no clinical departments.

TABLE 5

NATIONAL INSTITUTES OF HEALTH RESEARCH SUPPORT FOR AMERICAN MEDICAL SCHOOLS DIVIDED ACCORDING TO WHETHER THEY HAVE DEPARTMENTS AND DIVISIONS OF GENETICS

| Number of schools | Percent of all schools | NIH support* | Percent of NIH support for all schools |
|-------------------|------------------------|---------------|---------------------------------------|
| Departments       | 19                     | 18.3          | 228.8                                 | 37.8                                   |
| Divisions         | 28                     | 26.9          | 198.3                                 | 32.7                                   |
| Neither           | 57                     | 54.8          | 179.0                                 | 29.5                                   |
| Total             | 104                    | 100.0         | 606.1                                 | 100.0                                  |

* Millions of dollars for year 1971.

required courses in genetics, 70% list electives, and a total of 78% have either or both. This enterprise is given status and visibility in 19 schools which list departments of genetics in the AAMC directory, while 28 more list divisions (90). These data are set out in Table 4 and are contrasted with the number of departments of dermatology. This is in no sense an invidious comparison, but perhaps suggests that, although genetics is fairly widely recognized as a valuable point of view, its importance to clinical medicine has yet to be fully grasped. Indeed, the evidence is that genetics is regarded as a basic science. Most of the required courses listed are given in the first or second year of medical school—emphasis on the first, and as Table 5 shows, the departments, and to a lesser degree the divisions, are to be found in schools which are strongly research oriented, and do not appear in schools more concerned with teaching future practitioners than with training investigators and providing an atmosphere favorable for research (91). It is notable also that while all schools with a department of genetics give a required course in genetics, as do three-fourths of those with divisions, only a third of the remaining schools list a required course. What these data seem to be showing is that at a time when genetics is becoming less a matter of rare and complicated inborn errors and more a matter of everyday concern to clinicians and practitioners, there is some question whether the medical schools are ready to embrace the change.

Everyone would agree that departments and divisions of genetics are ideal places for research into all aspects of human genetics, including theoretical population genetics, and as a source of stimulus and teaching. But these institutions may not be ideal for the research and teaching appropriate for the kind of clinical population genetics which seems to be emerging today. A perfect site for these operations might be the departments of family practice, community medicine, or as some "out of it" schools still call them, departments of preventive medicine. These institutions are oriented toward families and to the population, are interested in health as well
as illness, are accustomed to taking health care to the patient, family, and community, think epidemiologically, and do just the kind of research which needs to be done to evaluate and improve screening and counseling. Screening, antenatal diagnosis, and genetic counseling raise many questions of impact, efficacy, compliance, and even of ethics, which should be studied with the same kind of rigorous testing of ideas, of experimental design, and of planning that is given to laboratory research. Geneticists and clinicians, in general, have not worked with the methods of health education, medical sociology, and epidemiology and need the guidance of experts. Furthermore, these departments of community and preventive medicine also have the advantage of ubiquity. Medical programs in the population genetics vein must be widespread to be successful. That is, to reduce significantly the incidence of mongolism, all obstetricians should know about the effectiveness of antenatal diagnosis and most should cooperate. Table 6 reveals that most medical schools do have departments of community or preventive medicine and that these do not greatly overlap with those having departments and divisions of genetics. The table reveals that schools which emphasize genetics tend either to leave preventive medicine to their schools of public health, which are not necessarily in close collaboration, or not to bother with it at all, while those which emphasize family practice, community, and preventive medicine often lack departments or divisions of genetics. This stresses the major flaw in this plan—these departments have everything favorable to its success but genetics. This is suggested by a survey of 18 well-known and widely read texts on these subjects, all published since 1960 (92–109). Only one half had any reference to genetics at all, and most of those that did treated it in a perfunctory, absent-minded way.

The remedy for this deficiency, I do not know. If screening and antenatal diagnosis continue to proliferate and the need for widespread counseling increases, it may be that teachers of family practice, community medicine, and preventive medicine will see their responsibilities and will take them up. To this end it should be the role of medical geneticists to emphasize the effects of gene segregation on all aspects of variation among the members of those social groups which are the objects of study by those who profess community and preventive medicine; namely, the family and the population.

### SUMMARY

It seems almost as if the concern for genes and chromosomes as causes of disease has paradoxically obscured the evolutionary aspects of genetics, its predictive qualities, its social applications, and its role in describing the sources of variation of human development and life. Full appreciation by physicians of these qualities

| Department of community medicine | Has dept. | No dept. | Total |
|---------------------------------|-----------|---------|-------|
| Departments of genetics         | 9         | 10      | 19    |
| Division of genetics            | 19        | 9       | 28    |
| Neither department nor division | 50        | 7       | 57    |
| Total                           | 78        | 26      | 104   |

**TABLE 6**

American Medical Schools That Have Departments or Divisions of Genetics Tend Not To Have Departments of Community Medicine, Family Practice, or Preventive Medicine
would be likely to modify the traditional doctor–patient relationship by introducing a societal outlook not now commonly expressed.

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