On Being a Medical Geneticist

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BEING, I THINK, your youngest President, I cannot hope to use this occasion to give you the benefit of my mature wisdom, and in particular to match the scholarly and elegant presentation of my predecessor (Dunn, 1962). Neither am I willing to play the part of the brash iconoclast I was when I first got into human genetics and (fortunately) was too young for anyone to listen to me. It was suggested that I should call my talk "Ponderings of a Peripatetic Pediatrician," but the fact that I'm not a pediatrician spoils the alliteration. So I will air some thoughts that are either too trivial, or vague, or so completely unsupported by data, that I could not present them anywhere but in a Presidential address.

It's been a great year for genetics, saddened for us by the death of a former President of our Society, Madge Macklin, who played a pioneer role in introducing genetics to the medical fraternity, and whom we all loved for her energy, tenacity of purpose, humour, compassion, and the whimsical tirades with which she would castigate her male colleagues. She did a fine job and had a good time; may her memory remain as an inspiration for us all.

She would have enjoyed the excitement I'm sure we all feel at the dramatic progress that has occurred in genetics in the past year. In particular the "cracking" of the genetic code leaves me speechless with admiration, and I take pride in the fact that human geneticists played an important part in making this possible. Equally fascinating, although not so far advanced, is the analysis of "regulator" and "operator" genes and their control of gene activity. Here, too, human genetics is making contributions in an area which is basic to our understanding of differentiation and development, normal and abnormal. There is also some promise that the genetic code may be subject to controlled alteration, at least at the RNA level — a fascinating and frightening prospect, which, if it ever materializes, will place a tremendous responsibility on the medical geneticist.

Recent progress in human cytogenetics has consisted (necessarily, at this stage) mainly of documentation of relations between karyotype and phenotype, but a neat combination of the cytological and genetic approach has led to the intriguing concept of sex chromosome differentiation as a possible explanation of dosage compensation (Lyon, 1962). A number of groups are combining cytological and genetic observations to map the human chromosomes; the X chromosome map is well under way, and we now have a sex-linked blood group

Presidential address presented at the meeting of the American Society of Human Genetics, Corvallis, Oregon, August 30, 1962.

(Mann *et al.*, 1962) which has started quite a flurry of linkage studies. Mapping the autosomes is harder, but already there are some slight signs of progress. And there is progress on many other fronts, so rapid that one could spend all his time reading and still not keep up with it.

So Human Genetics is having a heyday. A heyday, incidentally, is "a time of greatest vitality, vigour and bloom, a season of ardor, joy, exuberant spirits, and *wildness*." Perhaps a certain amount of wildness is necessary in a period of exuberant growth — it certainly characterized the first such period in Human Genetics, after the rediscovery of the Mendelian laws, with the overenthusiastic attempts to jam the square blocks of pedigree data into the round holes of Mendelian segregation, and the naive hopes of human betterment that Mendelism brought to the Eugenicists.

In this second growth phase we again see examples of those who kick over the traces and go, half-cocked, off the deep end (just as this metaphor has done). Genetics has, indeed, lately acquired a tremendous boost in prestige and an aura of glamour, particularly among our medical colleagues who tend to attribute to it powers that border on the magical. Partly as a result of this, departments of Medical Genetics are springing up in medical schools all over the country (often staffed by personnel without very much training in genetics), enormous amounts of money are being granted for research, and enormous numbers of papers are being published in the name of genetics. As the volume goes up the quality goes down. When does the law of diminishing returns become a limiting factor?

I don't want to detract at all from the impressive accomplishments I have already mentioned. But let us not oversell ourselves, and let us protect the prestige of Human Genetics from jeopardy by unqualified people speaking irresponsibly in its name. It happened before, and it could happen again. Much genetic nonsense is still being written about race (*e.g.*, Putnam, 1961), people are still getting the data to fit Mendelian ratios by such errors as omitting to omit the proband, and still invoking reduced penetrance and other euphemisms for ignorance to account for deviations from Mendelian expectations that can better be accounted for by other mechanisms.

In cytogenetics the applications of the recent advances to clinical problems so far are minimal, being pretty well limited to the identification of high-recurrence-risk trisomies. Identification of sex chromosome aberrations, for instance, although it has increased our understanding a great deal, does not influence the clinical management of the patient in the great majority of cases. Most mongoloids can be diagnosed unequivocally on clinical grounds. Some, at least, of the doubtful ones turn out to be mosaics, and it will be helpful to learn how these develop, mentally, in comparison to the usual type. If, on the other hand, cell cultures show normal karyotypes in a suspected mongoloid, how can one be sure it *isn't* a mosaic?

Genetics has contributed a lot to our understanding of human disease, and particularly the inborn errors (although the greatest credit goes to the biochemist rather than the geneticist for these advances), but the specific situations where this knowledge can be directly helpful to the patient or his family include a fairly small proportion of the cases seen in medical practice. Stating, pontifically, at Medical Rounds from time to time, that "this disease has one

chance in four of recurring in subsequent sibs" still seems to impress some of my medical colleagues, but leaves a lot of problems unsolved for the patient. Probably because they are more difficult to analyze, the multifactorial diseases — familial, often common, but not fitting simple Mendelian segregations — have been rather neglected genetically, except for the attempt to fit them into Mendelian pattern by invoking penetrance, and so forth. There are signs of progress on this front, however, and I would like to mention in particular the work of Fraser Roberts and C. O. Carter who are finding evidence in several congenital malformations for a multifactorial pattern of inheritance (Carter, 1961; Roberts, 1962a), and in the case of congenital dislocation of the hip have made a beginning in identifying some of the specific elements in the system.

Let's admit that the DNA-RNA code isn't the whole answer. There are, no doubt, other systems that transmit genetic information (*e.g.*, the cell membrane) that may be very important in developmental processes. As Kacser (1960) pointed out, a computer contains a lot of information besides what's on the tape, and this information differs from computer to computer. It may well be the same with cells, and this would mean that not all familial, intrinsically determined diseases and defects will be traced to alterations in the DNA. The people who claim that a familial anatomical malformation is no different, in principle, than a deformed sickle cell hemoglobin molecule are, I think, oversimplifying the situation, and I doubt that anencephaly, for instance, will ever be identified as a molecular disease.

The present heyday of genetics raises other problems too. How many invitations to speak can you accept without seriously diminishing your working time? Of course we have a responsibility to educate, but there is a limit, or should be. I would suggest that from 50 to 95 per cent of the invitations to speak that we get are from groups who will not noticeably benefit from our donations of time and effort. There are too many medical societies, ladies' auxiliaries, radio commentators, student nurses' classes, physiotherapist associations, etc., who would like you to explain all about this wonderful new subject, genetics, in one hour, and most of us under such circumstances can succeed only in muddling such a group, to our mutual detriment. We could aid the cause of genetics by refusing most such invitations, on the ground that any group really interested in the subject will want to have more than one hour's exposure to it. In case you do have to accept, I would like to pass on a suggestion which can save a lot of time. You only need to have two slides for all such occasions. I use a slightly out-of-focus picture of the wiring diagram on my daughter's radio, and an equally blurred reproduction of a page from the Nova Scotia Tide Tables. This technique can also be used for papers given at scientific meetings when you are not quite sure of your results.

Another source of increasing demands on our time are the requests from medical journals to referee manuscripts with a genetic aspect. This can take a lot of time, but it needs to be done; too many journals do not have a geneticist on their list of referees. We should, whenever possible, take issue with editors who publish genetically false or nonsensical statements, and thus help to improve the reporting of genetic data in medical journals.

A further danger of the genetic heyday arises from the large sums of money

being poured into genetic research these days. I am, naturally, very much in favour of good salaries for geneticists, and adequate funds to support research which often requires funds for expensive equipment, field trips, diagnostic tests, and so forth. But there is a danger of becoming over-equipped. Just as our children are supplied with so many realistic toys, television sets and supervised play periods that they don't seem to use their imaginations any more, we may tend to get so busy using our expensive machines, simply because they are there, programming data so they will fit a computer, filling out application forms to get more money to buy more machines, writing progress reports, and rushing around the country (on expense accounts) seeing how other people are using their machines, that we lose sight of the basic problems, and no longer take time to sit down and think. Yet Crick (1961) made his splendid attack on the code in a room borrowed for a few months from a Zoology museum, and Lejeune (1959) found the mongoloid trisomy in an attic laboratory equipped with one cock for serum, an incubator and an obsolete microscope. He had an idea (one of many) and time to work it out.

One of the most important demands that the heyday is making on us, as geneticists, is to provide training for the rapidly increasing number of people who need it, and this means providing properly trained teachers to do the training.

How, then, should a medical geneticist be trained? Obviously he should have a solid grounding in mathematics, biochemistry, basic genetics, human genetics, and cytology, as well as a medical degree, preferably with a medical specialty such as hematology, neurology or pediatrics. He should be able to relate well to people, have enough psychiatric training to handle the emotional aspects of counseling, and be a good teacher. A working knowledge of anthropology and sociology is desirable. And furthermore, he must live long enough to get all this training and still have a few years left to practice his profession!

The fact is that those who call themselves medical geneticists (or at least work in departments of Medical Genetics) have a wide variety of talents and training, and this is all to the good. Those with degrees in both genetics and medicine can enjoy the prestige of being regarded as geneticists among their medical colleagues, and as physicians among their geneticist confreres, but are kept from becoming unduly conceited by the realization that they are not really expert in either specialty, since each is a full-time job. Some medical geneticists have Ph.D.'s in basic genetics and have gotten into the medical end of it by a variety of routes other than through medicine. Medical schools are rapidly losing their prejudices against non-medical specialists, and lack of a medical degree is no longer a serious handicap to work in Medical Genetics, provided the worker is honest and critical (as he ought to be in any scientific field), and does not oversimplify or underrate the medical aspects of the condition he is studying. Many non-M.D.'s are doing first-class work on the genetics of disease and have the full respect and trust of their medical colleagues. The plant cytogeneticists in particular are having a ball, because of their excellent cytological training, and the fact that they have known for years about many of the things the medical people are astonished to discover in man.

If one extrapolates the present trends it looks as if much of what is now

called genetics may be incorporated into the other disciplines over the next few decades. The teaching of DNA and RNA metabolism and the genetic control of protein synthesis is being taken over more and more by the biochemists. The microbiologists are rapidly moving in on microbial genetics, and it looks as if Departments of Bacteriology may well take over the bulk of teaching and research in this area. The embryologists aren't moving in quite so fast, but eventually they may well take over many areas of developmental genetics. The anthropologists may very well incorporate some aspects of population genetics into their research and teaching. So what's left for genetics, and in particular Medical Genetics?

For one thing there is the special methodology and mathematical background of Human Genetics. So far I haven't seen any signs of anyone taking this over. There is still plenty of need for intelligent, thorough, pedigree-collecting to delineate modes of inheritance more precisely, establish recurrence risks, extend linkage maps, and in general provide the basic material on which so much of our genetic knowledge is based. Much of cytogenetics is likely to remain with us, although hematology and pathology laboratories may well take over much of the diagnostic screening. And, of course, there is genetic counseling.

It is often said that counseling should be done by the patient's personal physician, who, therefore, ought to be adequately trained in at least the basic principles of genetics. This may be somewhat impractical. There are, of course, lots of cases where the pattern of inheritance is clear, and precise predictions of recurrence risk can be established with a minimum of genetic knowledge. But there are complications, such as mutation, reduced penetrance, phenocopies and genetic heterogeneity, that can make even apparently simple cases tricky. Furthermore, there are a great many conditions showing simple Mendelian inheritance that are not generally recognized as such, and the relevant literature is usually not readily available to the average physician. There are no good compendia available that list recurrence risks, and indeed some among us feel that there should not be one, because it may lead the physician who consults it to oversimplify his counseling. (I will argue that it is better for him to oversimplify reliable risk rates than falsify them, as he may do otherwise, but that is a matter of opinion.) In any case the average physician, usually being human, is likely to forget his Mendelian principles after a few years out of school, unless he is using them, and Fraser Roberts (1962b) has estimated that the frequency of cases needing expert genetic counseling would work out at about one case a year for the average general practice. (I suspect this is an underestimate, but not grossly so.) Furthermore, an increasing number of people in this civilization do not have a family physician, and in the usual clinic the doctor has little time to take an adequate family history or to interpret recurrence risks adequately to the patient.

So a medical geneticist, in the most appropriate sense, should be one who is capable of teaching elementary genetics of a kind and at a level suitable for medical students, of supervising the training of graduate students and others who wish to do research in the genetics of human disease, and of acting as a consultant in cases referred for genetic counseling.

In December 1961, the World Health Organization called a meeting of an Expert Committee on Human Genetics to prepare a report on the Teaching of Genetics in the Undergraduate Medical Curriculum and in Postgraduate Training (WHO, 1962). The report can be obtained from Columbia University Press in New York, or the WHO in Geneva. Although the strength of the recommendations of the report was modified somewhat in view of the varying economic and political conditions in different parts of the world, it will be good ammunition for those of us who think genetics doesn't occupy enough space in our medical school curricula. After an introductory section on the value of genetics in the medical sciences, the report discusses undergraduate and postgraduate training, and I would like to summarize what it says about this.

The student entering medical school should already have a thorough grounding in biology including elementary genetics. This is, of course, not always so. In the preclinical years of medicine he should have a short course reviewing basic genetics and introducing the special methodology of Human Genetics. This should take a minimum of 15-20 hours, *providing there has been satisfactory teaching previously*. If not, the course should be lengthened proportionately. The timing would vary with the local conditions. At the University of British Columbia, for instance, the students enter a four year course in Medicine after completing the Bachelor's degree. At the request of several Departments, particularly Biochemistry and Bacteriology, who want the students to have this background for their own teaching, the lectures on basic genetic principles are given in the first year. Principles relating more specifically to Human Genetics are presented early in second year, when the students are becoming more familiar with the concepts of disease and will shortly begin to deal with patients. Incidentally, the Committee almost unanimously agreed that it was didactically good to introduce the course by a description of DNA, RNA and their role in controlling protein synthesis, rather than with Mendelism. This material is not only exciting, but if well grasped provides a logical basis for understanding the concept of the gene, dominance and recessiveness and the disappearing distinction between them, and the role of the gene in disease.

The concepts of expressivity and penetrance seem to be difficult for the medical man to grasp; here it helps to point out that measles, for instance, produces a variable clinical picture in different patients, just as a gene may do, and that the concept of reduced penetrance is very much like the concept of subclinical disease. Population genetics often presents an obstacle to the medical student who for some reason seems to develop a phobia for mathematical abstractions once he enters medical school, but with a little thought the basic concepts can be developed from first principles without writing q^2 on the board even once! Microbial genetics should be included, if not dealt with in microbiology. A laboratory period or practical session is highly desirable, and could include determination of blood groups and color blindness (single gene differences), PTC taste threshold (single gene difference with modifiers giving a bimodal distribution) and a quantitative trait (normal distribution). The sex ratio in families of male and female students, respectively, can be used to illustrate the bias caused by inclusion of the proband. This can be done effectively in class, too, by having a number of male (or female) students state the

total number of boys and girls in their sibships, including themselves, and then omitting the probands to approach the expected 50:50 ratio. There can be microscopic demonstrations of sex chromatin and karyotypes, blood smears of hereditary anemias, and demonstration of simple biochemical phenotypes such as electrophoretic separation of hemoglobins. Patients with hereditary diseases and their pedigrees can be presented, and (as is done at Sao Paulo, for instance) groups of students can each take an inherited condition, work up a case and prepare a short report and literature review. This takes space and a lot of the instructor's time; few of us are able to do this at present, but it is something to aim at.

In the clinical years there are many opportunities we shouldn't miss to demonstrate the application of genetic principles to human disease in the clinics and at ward rounds, in collaboration with the various clinical departments. At the University of British Columbia, for instance, the final year students have five three-hour sessions in which cases of genetically determined diseases are presented, and discussed by a clinician, geneticist and other appropriate specialists. Thus the genetic aspects of the disease are presented as an integral part of the medical problem.

Postgraduate training in Medical Genetics can be considered at three levels — as part of the regular training in the various medical and surgical specialties, as more advanced training for those who wish to use genetics as an adjunct to their research and practice but do not wish to make it a full-time occupation, and as advanced training to qualify candidates for full-time research and teaching in Medical Genetics. I have time to mention only the last of these. A well-trained teacher and practitioner of Medical Genetics should be conversant with the genetics of man, of course, but also, to some degree, of other animals and of micro-organisms. He should be as familiar as possible with the tools of modern biological research. The report recommends that in those countries where the profession of a specialty is controlled, Medical Genetics should eventually be placed in the same position as are other specialties, and qualification as a specialist in Medical Genetics should be governed in the same way. (I am comforted by the thought that when this happens in Canada I shall either have retired, or as with other new specialties, I may be admitted as a charter member without examination.) A program, now in operation at Western Reserve, is outlined as a suitable course model, although not, of course, the only one. Finally, the Committee recommended that "in order to maintain a satisfactory teaching program in genetics, it would be highly desirable, as trained personnel become available, to have a chair or department of Medical Genetics at each medical school, with a staff to participate in the teaching and to create interest by their research activities." A word to the wise is sufficient. Go and see your Dean!

One thing the report did not discuss was the proper training for genetic counseling. The reason is obvious; once the statistical recurrence risk is established, counseling becomes an individual matter, and the approach depends largely on the counselor's personality and the situation at hand. How can you teach a person patience, wisdom, and compassion? Some aspects of medical school training can help to nourish these qualities, if they are there, and they

can grow with experience, if the counselor allows them to. It is held by some that psychiatric training is an asset in this regard, but apart from a brief exposure in medical school this is difficult for most of us to get. So about all we can do is try to be continually aware of the counselee as a person, and to maintain, humbly, a balance between scientific objectivity and sympathetic sensitivity. I am repeatedly struck by the profound impacts that a mutant gene can have on a family. There is no time to dwell on this, but I would like to mention one case I have been following for the past two years, which is often on my mind. A 27-year old girl came for advice because her mother and five of her six sisters all suffered from what she described as a "muscular wasting disease." Three of the sisters had already died from it, and her mother was severely crippled and barely able to walk. The girl, Sheila, suspected that this might be an inherited disease and was naturally worried about her chances of getting it or transmitting it to her children. She had avoided any prospects of marriage for this reason. Repeated efforts to find out what the disease was had been fruitless. Her family doctor, for instance, had told her flatly that it was not her concern and to forget about it. (Why?) I offered to look into it and made an appointment for another interview in three months time. After considerable correspondence, and some difficulty in getting release of information from certain hospitals, it became clear that the disease was Huntington's chorea, and there was evidence of dominant inheritance through the mother's father who had died, supposedly unaffected, at age 34, of alcoholism.

So Sheila had a little less than a 50:50 chance of developing it herself. What should I tell her? Apparently her physician thought it best she should not know, and I wondered myself whether I would want to know if I were in the same position. One geneticist I talked to about this stated definitely that he would prefer not to know. But Sheila was an intelligent girl who had been trying hard to find out. I felt her spirit was sturdy, and that she would never be satisfied just to go on wondering. So, in the course of almost a full morning, I described the situation to her. She was visibly shaken, but courageous.

We discussed the early signs, the possible value of an EEG, and many other things, including the relation of God to a situation like this. A month later she wrote me a letter thanking me for telling her, saying that although it was rough at first, it was certainly best to know the score, and very sweetly adding how difficult it must have been for me to tell her (which it certainly was). The following year she came in again "just to talk," but it was soon clear that she was worried about the early signs of the disease, and especially a little twitching of the muscle of her right arm. There is no doubt that fear of a disease can produce symptoms. Imagine what it is like to know, from watching a loved one develop the disease, exactly what the early signs are, and to wonder, with each minor memory lapse, each slip of the tongue, each accidental stumble, whether this is it. I referred Sheila to a neuropsychiatrist who specialized in organic brain disease, and after a thorough examination, completely negative, she was reassured and her twitches disappeared.

Over this period she had looked further into her family situation, and found that two of her first cousins were developing suspicious symptoms. She described the tragic personality changes that had occurred in her mother and

aunts, who became pathologically suspicious, terribly stubborn, and subject to frightful temper tantrums. The husbands of all four married aunts had deserted their wives, because life was such hell living with them. Only Sheila's father had stood by his wife, and she didn't know how long he would last. Furthermore, almost all the daughters of her four affected married aunts had married before they were twenty, in order to get away from their homes as soon as possible, with the dysgenic result that they will probably have more children than they otherwise would have.

This summer Sheila came in for another chat. Her mother can hardly walk, her speech is unintelligible, and she is terribly difficult to live with, but not crippled enough to be hospitalized. Sheila said she was enjoying life, outside the home, but then she burst out and said what a block this has been to her all her life, how bitterly she has fought it, how her father had brought her up to be strong ("All the Giffords are strong, and you're a Gifford, not a Pearson," he would say); how she is always thinking about it. "I hate this thing," she said. "I hate what it does to the person who has it and to everyone around her, and what it's done to me." She would like to marry and have children, but she's not a gambler — and even if she found a man who would be willing to adopt his children, she feared what she would do to him if she developed the disease. This is a great tragedy, because Sheila is the sort of person who would make a good wife and mother — and perhaps she doesn't carry the gene at all. I've told you about her to emphasize how much can be involved in the question of a mutant gene besides the statistical fact of a 50:50 segregation. What Sheila needed was moral support. Others need more practical aid. Let us not be content with providing risk rates and sympathy. There are cases that need to be referred to a gynecologist, others to a priest, others to a psychiatrist, and others to a social service worker or clinic that can ensure a regular family follow-up.

Counseling has its lighter moments too — for instance, the young Scots girl married to a Greek man whose first baby was born with an unusual combination of malformations. I still don't know exactly what it is, but the father's brother, who had married a relative, had had two similarly affected children. I discussed the recurrence risk with her as well as I could in our state of ignorance, and made a note in the chart that I would like to know the outcome of future pregnancies. Last year the hospital called to say there was a new baby, and would I come and examine it. She was beautifully normal, so I went in to congratulate the mother. While chatting with her, I became aware that she did not seem at all surprised that the baby was normal, but had a complacent look about her and an underlying gleam of amusement in her eye. On impulse I asked her if she had any secrets to tell me. She laughed and said "I think you already know." This is one method of coping with genetic problems which is, from a practical point of view, comparable to AID — artificial insemination donor. I call it NID — natural insemination donor, who, in this case, had been carefully chosen to resemble the husband in his physical features!

So there are many aspects of being a Medical Geneticist — discouraging, frustrating, bewildering, amusing, exciting, rewarding, and always challenging. It's a good job.

ADDENDUM

It would be a nice tradition for each President to make some sort of bequest to forward the work of the Society. The following contribution is therefore presented in readiness for the day when it will be possible to change the genetic constitution of man by DNA transformation. If the Society is on its toes it will patent the process, corner the market on human DNA, and conduct a vigorous advertising campaign, which will of course require a jingle for the TV commercial. This one is sung to the tune of "Smiles."

There are genes that make you happy
There are genes that make you blue[1]
There are genes that tell you who's your father[2]
And how you'll rate on your I.Q.
There are genes that make your blood clot quickly
And genes that tell how much you'll weigh[3]
But if you don't like the genes you're born with
TRY A.S.H.G. D.N.A.[4]

[1]Congenital methemoglobinemia, for instance.
[2]Poetic license; actually, of course, they can usually only tell who's *not* your father.
[3]If you don't make a pig of yourself.
[4]Copyright pending.

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