GENETIC PROGNOSIS*

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I have employed the title 'Genetic prognosis' in its widest sense: it may be taken to indicate a prospective view, in terms of genetic aberration, of the individual or of mankind in general; it implies an interest in prevention, which may be purely passive or active; it embraces many aspects of genetic investigation and counselling, and plays upon the theme of eugenics.

The substance of my theme impinges directly upon a collocation of the 3 time elements in the biologic picture.[10] On the largest scale is evolution, with Man the result of a long line of ancestors and himself the potential ancestor of a long line of descendants. On the intermediate canvas is painted the life-history of an individual as such. On the shortest time-scale are events at the physiologic or dynamic intracellular level. The science of genetics pervades all 3 time strata and acts as a link between them.

Man, the phenotype, is the as yet imperfect product of hereditary factors conditioned by evolution and mutation, on the one hand, and by influences arising from the immediate multiform environment, on the other. The last few decades have been coloured by significant victories in the battle against Man's ambient circumstances. The control of infectious diseases and advances in surgery, to name but two, have served to give relative emphasis to the remaining enemy in the field — the danger of genetic disorder. Furthermore, our genetic constitution may, in fact, be subjected to deterioration owing to this relaxation in natural selection, which is intensified by the artificial increase in ionizing radiation. Finally, improved methods of detection and diagnosis have directly focussed attention on the importance of the genetic component. In this regard, progress in cytogenetics since 1956 and in biochemistry over the last 15 years, have not only provided us with a wider vista and a more solid point of vantage, but have also enabled us to elevate human genetics from the esoteric realms of conceptual thinking to those of eclectic, concrete formulation and application.

Man's evolution depends upon his heredity. The well-being of the ordinary family unit devolves upon the scientific acumen of the physician. The picture on the intermediate time canvas is therefore determined, to a large extent, by the doctor. His function at the interpersonal level also influences the future, so that it is, in addition, the gene changes over the centuries which are becoming the responsibility and concern of medical science. It is apparent that our immediate destiny will be conditioned, not by genetic change, but by determinants in the phenomenal social environment.

I have alluded briefly to the significance of genetics in the field of medicine and its implications for human evolution. It is thus surprising to look back to Sheldon Reed's statement in 1955[5] when he said: 'About the only practical use for human genetics is in counselling'. Almost a decade later we see the convergence of the frontiers of many disciplines occurring at the common intersection of genetics. Medicine has undergone a metamorphosis in outlook, from the macroscopic, through the microscopic to the molecular, and in studying the very particles of life we have gained understanding of various disease processes, invasive bacterial life, and immuno-chemical reactions. We ride today a swelling tidal wave, which may well sweep over and change the contours of human life as we know it.

GENETIC COUNSELLING

With regard to the counsellor, these very developments in cytologic and biochemical genetics have altered the milieu in which he acts, in as much as his prognostications change in emphasis from passive empiricism to definitive understanding in terms of enzyme blocks, protein derangements or cytopathogenetics. In addition to mere advice, he is able to thrust back further the barriers of uncertainty and to detect heterozygotes and late-onset cases. The arena in which he moves, therefore, has widened perimeters, and the fight is carried to a more elemental level. Consequent on discovery of cause comes discovery of correction, and in these instances the very concept of eugenics as such almost fades in the bright light of molecular therapy. Thus, far from being an inactive adviser, the counsellor, as I see it, converts to the status of active moderator.

The number of people who are in need of genetic advice is fairly small. Most often they are prompted to enquire because an abnormal child has been born. This is unfortunate, since ideally, counselling should be premarital when, in the case of heterozygote carriers, the courtship to marriage equation can be favourably influenced. As advice is bound to be given (and accepted), the situation is best handled by those with knowledge of the subject. One of the aims of the Clinical Genetics Unit in Johannesburg is to provide just this service.

The order of frequency and the nature of counselling requests to this Unit over the last 9 months are given in Table I. The problems are varied and various and provide for interest at the personal level: A young woman who is on the threshold of marriage, discovers that her fiance's

TABLE I. SOME INDICATIONS FOR COUNSELLING

1. Mental defect and mongolism.
2. The psychoses: Manic depressive psychosis and schizophrenia.
3. Huntington's chorea.
4. Essential hypercholesterolaemia and ischaemic heart disease.
5. Twinning.
6. Congenital heart disease.
7. Miscellaneous: Porphyria.
   Peutz syndrome.
   Tylosis.
   Marfan syndrome.
   Hereditary ataxia.
   Retinitis pigmentosa.
   Fibrocystic disease of the pancreas.
   Myopathy.

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father has Huntington's chorea and she wants to know what chance there is of her beloved developing the dread disease, and furthermore what risk there is to the children of their marriage. A man sustains a myocardial infarction at the unusual age of 30 years and is informed that he has a disturbance of his blood fats — he wonders whether his two daughters, who have cutaneous xanthomata, will also develop early heart disease. A normal couple have produced two mentally retarded children — dare they try for a third time and with whom does the fault lie? The cardiologist diagnoses congenital pulmonic stenosis in twin boys and refers them to the Clinic for proof of monozygosity.

Useful advice of a practical or psychologic nature can always be provided. The risk usually has to be given in terms of odds, which is accepted and understood by most people. No attempt is made to influence parents as to whether they should or should not have children. The average estimate given by the counsellor is frequently lower than that suspected by the family and is therefore in itself reassuring.

When inheritance is simple, the odds can be specifically stated. When the genetics become really involved and obscure, then the chances are usually so small that one has very little to worry about. For such conditions, empiric risk figures based on family and population occurrence are available in the literature. As a comparative index, it is salutary to note that the possibility of any random pregnancy resulting in a serious congenital defect is about 1 in 40.[9] One should inform about the relative and absolute risks involved. For instance, empiric risk tables may indicate that a disease is 25 times as likely to manifest in children of a given couple than in the rest of the population. However, if the population risk is 1 in 1,000, then the actual risk is rather minor, being only 2·5%.

Genetic counselling must be formulated on the basis of 3 cornerstones:[7]

1. Diagnosis.

2. The family tree.

3. Knowledge of the pertinent genetic literature.

1. Diagnosis

Definitive diagnosis is a prerequisite for any prognostication. In this regard the counsellor straddles many specialities and requires liaison with many different departments. Thus, the cytologist is called upon to state whether a translocation-type of mongolism is present or not, the psychiatrist to advise on the nature of the psychosis, the biochemist to confirm the presence of porphyria. A patient with muscular dystrophy must be carefully assessed by the neurologist, for if the disease is of the facio-scapulo-humeral type, a dominant mechanism is at fault, if of the Duchenne type, it is likely to be sex-linked.

The elucidation of the problem may be very specialized indeed as portrayed by the case of a mentally and physically retarded patient. Here the paediatrician favoured cretinism and was correct. However, cretinism is a state with a broad aetiologic basis, and the pin-pointing of the inherited biochemical defect in iodine metabolism required the services of the endocrinologist and radioactive isotopes.

2. The Family History

The family tree provides the adviser with a pattern of inheritance. This pattern gains significance especially when alternate modes of transmission operate. In retinitis pigmentosa, for example, the aberrant gene may rarely behave as a dominant, or it may be sex-linked or, most commonly, it is recessive. In other words, the same phenotypic disease can be perpetuated in 3 different ways, and in such instances the family tree of a blind individual can offer the solution.

3. The Background of the Literature

Advice should not be based on text-book information alone. On the other hand, only very rarely can the family history be taken as sufficient guide — ideally this history should be interpreted in terms of what is relevant in the literature.

Illustrations

It is propitious at this point to give illustrations under the following headings:

(*i*) Recessive defects
(*ii*) Dominant inheritance
(*iii*) Partly genetic conditions
(*iv*) Chromosomal aberration
(*v*) Sex-linked inheritance

(*i*) *Recessive defects.* The simply inherited recessive traits include fibrocystic disease of the pancreas, Werdnig-Hoffman's disease, albinism, gargoylism and phenylketonuria.

Phenylketonuria is the paradigm of a genetically determined enzyme block. Of the children of a heterozygote union, 25% will suffer absence or hypofunction of the enzyme phenylalanine hydroxylase. In these cases there follows failure of conversion of the essential amino acid phenylalanine to tyrosine. This block in metabolism cannot be directly equated to the mental disturbance, but early postnatal therapy using a phenylalanine-low diet produces a happy outcome. More exciting for the prognosticator is the fact that phenotypically normal heterozygotes can be detected by means of the phenylalanine-load test. After a standard dose of 100 mg./kg. body weight of the amino acid, plasma-phenylalanine levels are determined at 1, 2 and 4 hours. At each period the heterozygotes have levels about twice those of normal controls. The implication for eugenic counselling is that carriers can be found and followed and possibly dissuaded from marrying. Should two such heterozygotes bear children, we can be in at the birth, with therapy at hand. J. B. S. Haldane foresaw the time when we would all know what harmful genes we possessed. He relates, in a light moment, the story of a young man who attends a dance and becomes enamoured of a beautiful young woman. While dancing, and before falling quite in love with her, he whispers in her ear: 'I am a heterozygote for amaurotic familial idiocy'!

It is worth noting, *en passant,* that the geneticist in his endeavours to help mankind, is probably increasing the number of outwardly normal *homozygotes* for phenylketonuria in the population.

(*ii*) *Dominant inheritance.* In simple dominant inheritance, such as Huntington's chorea, craniofacial dysostosis, peroneal muscular atrophy, epiloia and achondroplasia, the

risks are in general bad: 1 in 2 for a child of a parent suffering from the disease. Huntington's chorea has been intensively studied in the Republic by Dr. Gordon K. Klintworth,[11] about 160 cases having been documented. Although it is a severe disorder, it evades extinction by manifesting only late in life. We desperately need to know more about gene action so that we can foretell precisely which children of an affected parent will develop the disease and which will remain normal. Epiloia presents, perhaps, a more oblique problem because there is a high mutation rate (about a quarter to a half of all cases seen are due to mutation in a parent[7]) and very variable expressivity.

(*iii*) *Partly genetic conditions.* The partly genetic conditions comprise the major central nervous system malformations, non-specific oligophrenia, harelip, cleft-palate, and some types of epilepsy. As mentioned earlier, the outlook for subsequent children in this group is good. Thus the risk of recurrence for further children following the birth of one child with say, anencephaly, spina bifida or harelip, is about 1 in 25; it is about 1 in 30 after the birth of an oligophrenic and about 1 in 40 for the usual type of epilepsy. The recurrence rate of congenital heart disease is likewise very low. However, after the birth of 2 children with, for example, a central nervous system defect, the chance of recurrence is nearer 1 in 7.[8] This contrasts with simple inheritance, where the ratio remains the same for each new birth, no matter how many children have previously been affected.

(*iv*) *Chromosomal aberration.* Mongolian idiocy, or congenital acromicria, has provided the first example of autosomal aneuploidy in Man. Essentially 2 mechanisms underlie its production: (*a*) Non-disjunction and (*b*) translocation.

(*a*) Non-disjunction is the common type. During meiosis two *homologous* chromosomes (probably No. 21), instead of separating and each migrating to its own pole, stick together and move to the same daughter cell. The result is classical Down's syndrome or trisomy 21.

Non-disjunction occurring during *mitosis* results in a mosaic of normal and trisomy 21 cells, and here only certain mongoloid features are apparent.

(*b*) Translocation of chromosomes is less common but more important. It involves the breakage of non-homologous chromosomes (one of which is number 21) and an exchange of fragments between them — a reciprocal translocation. Noteworthy is the production of a carrier state (with a diploid number of 45, but full complement of genetic material), thus providing means of perpetuation of mongolism through many generations.

Several translocation types have been reported. In all there is a virtual trisomy 21, since the greater part of chromosome 21 is attached to one or other chromosome and results in a normal diploid number of 46.

There is an increased risk of producing a second mongoloid child if this sort of mechanism is operative *via* the carrier karyotype in a parent.

From the practical point of counselling (and in the absence of cytogenetic aids) parents who have had one mongol child and have no other close relatives affected, run a risk of the order of 1 - 2%.[2]

(*v*) *Sex linkage.* Sex-linked genes are very regular in their transmission. With haemophilia, therefore, there is a 1 in 4 chance that a son will be affected and a 1 in 4 chance that a daughter will be a carrier. Again, it would be valuable if the female carrier could be clearly delineated. In familial haemophilia, workers in Denmark[6] have advocated puncture of the uterus in the 4th month of pregnancy. Cytologic examination is carried out on a small amount of amniotic fluid. If the majority of cells are chromatin negative, the mother is informed that she has a male foetus with a risk of 1 in 2 of its being affected. Pregnancy may then be terminated. It is beyond the scope of this paper to discuss the justification of interrupting pregnancy in conductors of haemophilia or in any other severe heritable disease.

DISCUSSION

One has considered some of the important modes of genetic transmission and their application at the individual level in terms of counselling. In addition, the solution of problems of a psycho-social nature is incumbent upon the counsellor. Parents of a deformed child often feel lonely and may wonder why they have suffered the visitation of evil. Did something go wrong during conception or pregnancy? Is the husband or wife to blame? Are they paying for the sins of *their* parents. Feelings of guilt or shame are common and lead to what I have termed 'the ostrich-with-its-head-in-the-sand attitude'. For such people will either conceal information or prevent full examination of an affected child, in the belief that if the doctor discovers nothing, then nothing serious is wrong with that child. Such a state of affairs is exemplified by a family we have studied with Peutz syndrome.[1] The father had undergone 3 laparotomies for intestinal polyposis. His young daughter showed typical buccal mucous membrane pigmentation and suffered from abdominal cramps. The parents refused to allow barium-meal examination: for if X-rays were done, polyps would be found and she would have the disease; if X-rays were not done, polyps would not be found and consequently she would not have the disease!

As Waddington[10] has pointed out, the greatest defect of modern science as a general philosophy is its exaggerated atomism. Perhaps my concluding remarks may reflect that Man has indeed placed himself inexorably in a sheerly mechanistic universe. It has been claimed that the discovery of insulin was dysgenic in that it permitted those with the deleterious gene to survive and reproduce, whereas this may not formerly have been possible. With medicine advancing progressively against the factors of natural selection, Man will eventually be carrying a greater number of 'bad' genes than formerly.

We have considered aspects of imminent import in the physician-patient set-up. Any comment on prognosis must, however, *vis-a-vis* the diabetic dilemma, for example, be concerned with human ecology as a whole. The genetic counsellor may not only be required to advise and treat the affected ones, but to direct the course of the normal. Sir Julian Huxley created a medico-social furore when he propounded the view (in his recent Galton lecture on eugenics[3]) that positive eugenics should be advanced to the point where enlightened couples would utilize artificial

insemination with the sperms of an admired donor. Ultimately selected sperm would be combined with donor ova and be foster-mothered. A wide range of preferred sperm and ova could be chosen from, so creating a diversity of excellence in the race as a whole. This seems to be quite a rational, albeit visionary, concept to entertain, and certain thoughts are provoked: Firstly, rather complex tests may be required in order to sort out the preferred beings, who will be future propagators of mankind. The question of what types of humans we require not only embraces the destiny of our race, but also involves an insight we probably do not possess. Perhaps the unintelligent dustman is as valuable to our social structure as the mathematical genius. Secondly, the problem of the ubiquitous heterozygote comes to mind. To avoid ugly homozygosity will necessitate a complete knowledge of the individual genetic constitution, which we are unable to assess at present. Finally, the wasteland of social prejudice will have to be traversed and the icy glaciers of ethics, legality and religion, negotiated. As Sir Julian pointed out, changes in outlook have been dramatic even in his life-time, and there is no reason to suppose that further changes will not be tolerated in future. Sir Julian's thesis does offer a positive solution, however, and envisages not a superior being but a diversely well-above-average population.

While one is thus indulging in the pink dream of tomorrow, it is possible to conceive that it will not be all-important what sperm blends with what ovum. It may well be that our knowledge of gene action will be precise enough for the genetic destiny of the fertilized ovum to be favourably influenced by scientific means. However, until the central problems of the genetic code are successfully tackled, and we see more clearly how the substance of life is transmitted and how we are chemically and phenotypically moulded, until these things are known, our approach to genetic prognosis will remain as empirical as was organic chemistry before the advent of structural formulae! Nevertheless, we as scientists have in fact just entered this exciting and electrifying era of new developments and where we must now accept the *burden* of genetic prognosis — for the towering mushroom of altering atoms is our own doing, and medicine, that reaps so well the field of human natural selection, is our own creation.

Even at that remote time when our appreciation of human heredity becomes complete, caution will be required in its application. The aim may well have to be in the nature of Galton's good average — 'a compromise between the maximal vigour of the phenotypic population and its maximal potentialities for the future'.[4]

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