



# The development of clinical genetics

Two important reports have recently been produced, one entirely on behalf of the Medical Research Council and the other jointly with the Department of Health and Social Security.<sup>1,2</sup> A Working Party of the Clinical Genetics Society has also been established to consider the constitution of Regional Genetic Advisory Centres. The present paper reviews these reports, which stem from the necessity to see the directions in which clinical genetics is likely to develop in the eighties, clinically, scientifically, and administratively.

## **Incidence of genetic factors in disease**

The first report reviews current research in human genetics, noting areas with potential for further development. Estimates of the incidence of diseases inherited in a Mendelian manner show considerable variation, partly depending on whether conditions such as familial hypercholesterolaemia or polycystic disease of the kidney are included. The report suggests that approximately 1% of all births have a single gene defect (autosomal dominant 0.7%, autosomal recessive 0.24%, and X linked 0.04%). The incidence of chromosome abnormalities is accepted as 0.5%. It assumes that, for congenital malformations, the genetic contribution is about half of the total incidence (2%), that is, 1%. When considering complex genetic traits, such as those involved in schizophrenia and diabetes, the estimate of 2% becomes less reliable. Nevertheless, despite these uncertainties, the burden that is being uncovered is far higher in Western countries than almost any other group of diseases except neoplasia. In particular, the emphasis in paediatrics is now shifting to diseases wholly or largely genetically determined, with the repercussions on the family as well as the statutory services being considerable. In adult medicine there has been a similar, though less dramatic, change of emphasis. Diseases such as duodenal ulcer and many of the degenerative disorders like ischaemic heart disease have a genetic component. Such multifactorial diseases should be explored so that predisposing factors can be identified and perhaps some modified. Areas of research expected to find general application in the future are then highlighted. From the field of molecular genetics, the identification of gene sequences by recombinant DNA techniques with the use of copy DNA probes is seen as offering

considerable potential, particularly in identifying the factors involved in the switch from fetal to adult haemoglobin. Somatic cell hybridisation has already produced an extending gene map, so that markers linked to specific diseases can be expected to provide further help in prenatal diagnosis or indicate susceptibility to disease. Earlier expectations of such linkages have not materialised however.

## **Cytogenetics**

A cytogenetics register is suggested but it seems unnecessary to duplicate that originally at the Johns Hopkins Hospital in Baltimore and now held at the University of Delaware.<sup>3</sup> A cell bank, similar to that at the Institute for Medical Research in Camden, New Jersey, while valuable, would be expensive to establish and maintain. The extent of its use is uncertain, but it would be particularly helpful in enzyme defects to keep cell lines from homozygous and heterozygous subjects for reference purposes. There would also be value in maintaining lines with structural rearrangements of the chromosomes so that testing for gene mapping could be repeated as required. Long term surveillance of subjects either with a chromosome anomaly or who have produced chromosomally unbalanced children or abortions might be worthwhile in a few centres. Sister chromatid exchange is regarded as a particularly promising technique, relevant to mutagenesis and probably carcinogenesis. In this field the two important, and probably interrelated, aspects of genetic change in the cancer cell itself and the inherited susceptibility to malignant disease require further study using biochemical as well as cytogenetic techniques.

## **Pressure on facilities**

The first report links to the second by referring to the implications of such research on the provision of service facilities.

Perhaps the most relevant comment is the extent to which the situation is changing as the service inevitably expands, both because of advances in scientific knowledge and because of increasing awareness by the public. The experience of Guy's Hospital,<sup>4</sup> in which the 'doubling time' for the number of referrals fell from 15 years to 2 years, highlights the way in which new methods, in this case principally prenatal diagnosis, radically alter the pattern of referrals and the consequent demand on

resources. It has been possible to meet some of these demands in varying ways, but it should be noted that over half of the consultant sessions at the time of the report were supplied by MRC or university personnel.

The present genetic services have developed on an ad hoc basis, largely as a result of the special interests of particular people. The support given, and the expertise acquired, by the colleagues in related disciplines, for example, obstetrics and paediatrics, profoundly affect the number and pattern of referrals, such as how many patients for amniocentesis are referred to the genetics clinic.

### Prenatal diagnosis

A Working Party of the Clinical Genetics Society<sup>5</sup> has estimated that in 1976 only one tenth of pregnancies at risk were examined. While this proportion is almost certainly higher now, some mothers would not wish to take advantage of the service. This is likely to be higher in groups where the risk is potential rather than in those where an affected child or sib has already been born. The present report accepts that facilities for prenatal diagnosis by amniocentesis are required for between 5% and 8% of all pregnancies. It endorses the view that there is a need for considerable expansion in this area which must be accompanied by adequate quality control.

While cytogenetic laboratories capable of producing reliable results rapidly will be available in all areas, this is not practical for metabolic disorders. About 120 families per year are thought to require this service and some centralisation is essential. Positive advantages that ensue, in addition to optimum use of resources, include depth of experience in a particular assay. It is therefore recommended that only two laboratories should be responsible for each disorder. However, care should be taken to avoid monopolies. Funding must allow for growth and the development of new technology. The discovery of a particular inborn error in a centre remote from the responsible laboratory often provides the impetus there to develop the appropriate assay. Such local initiative and interest should not be stifled. Furthermore, the whole pattern may change radically with new advances, if, for example, a test for the prenatal diagnosis or detection of heterozygotes for a common disorder such as cystic fibrosis were to be found.

Fetoscopy is still under evaluation and a note of caution is rightly sounded. It is potentially valuable, particularly for obtaining fetal blood, and the difficulties should be overcome with advances in techniques or methodology. Screening of the maternal serum for  $\alpha$ -fetoprotein is being extended

to the whole of the country and newer assays are being developed, for example, amniotic acetylcholinesterase. Ultrasonography also has its supporters who point out that conditions other than neural tube defects, such as short limbed dwarfism, can be identified by this technique, and the result is immediately available for the patient.

The stress involved in waiting for the results of prenatal diagnosis is considerable. Farrant,<sup>6</sup> Harris *et al.*,<sup>7</sup> and Laurence and Morris<sup>8</sup> have all emphasised the extreme anxiety engendered even when mothers are told beforehand that "no news is good news". The pressures on the average antenatal clinic are not conducive to a full understanding by the mother of the medical issues involved in prenatal diagnosis, nor to dealing with the emotional problems which may arise.

### Perinatal pathology

Absence of accurate pathological reports on perinatal deaths, stillbirths, and abortion material often leaves the genetic counsellor in considerable difficulties because the lack of precision in diagnosis leads to inability to estimate the risk reliably. This area requires much more support, but even now steps can be taken to improve the present service.<sup>9</sup>

### Population screening

Population screening is of more limited value, except in the neonate for inborn errors of metabolism such as phenylketonuria. The most pressing need, as emphasised in a recent editorial in the *British Medical Journal*, is the early detection of hypothyroidism by TSH assay.<sup>10</sup> The schemes already started in several areas need to be extended to the whole country. An increasing service load must be anticipated. Certain ethnic groups may also require screening for carriers of recessively inherited diseases, for example, haemoglobinopathies and thalassaemias. Such surveys, if they are to succeed, require the most careful organisation and sensitive handling of the families.<sup>11</sup>

### Research projects

In their brief review of research, this second report concludes that the evidence does not suggest that financial constraint has been a limiting factor but rather the paucity of good projects. This seems to be a rather dubious statement when so often applications, whose preparation is so time-consuming, have to be made to several sources before funding is eventually obtained. Inevitably the presentation of new projects is inhibited.

The report recommends 20 areas in which research in relation to prenatal diagnosis and genetic counselling should be undertaken. Some depend on exploitation of current techniques, like ultrasonography, while others require the development of new ones, for example, induction of gene activity in amniotic cells. Perhaps the most important of all is in the field of operational research, so that the best service may be offered and the knowledge gained fully exploited to the greatest advantage of the patient. The report comments particularly on monitoring the service, but a major difficulty is defining the service as it exists and as it should be. The Working Group recommends that the Health Departments should finance not only this type of operational research but others included in their 'top twenty' which can be classified as primarily health service research.

The place of genetic registers has already been considered in the Journal.<sup>12</sup> At the very least a register of local families is essential for the satisfactory functioning of a genetic service.

### **Medical (clinical) geneticists**

The report rightly emphasises the key role of the clinical geneticist with involvement in the planning and monitoring of the service as a whole. Training, teaching, and advising on screening are other major responsibilities. The Working Group stresses the importance of keeping up to date with new developments in view of the rapid expansion of the field, including research and the direction of trainees and other staff. These responsibilities demand skills and personal qualities of a high order, such that perhaps they are rather daunting. What aspects of the role, and therefore the training, of the medical (clinical) geneticist should be emphasised? Have views of his function altered since it was last discussed here?<sup>13</sup> There is general agreement that he should be a clinician whose initial training should normally be that of any intending paediatrician or physician. Subsequently, his experience will be primarily in clinical genetics, though some laboratory work, particularly in cytogenetics, is essential. The question arises therefore as to whether he should seek sufficient experience to enable him to be responsible for a laboratory. Many of the present generation of medical geneticists developed of necessity considerable expertise in laboratory work, but the past should not be taken as a guide for the future. The next generation should be trained primarily as clinicians. While some may wish to undertake further training in laboratory work, the majority should develop further their clinical skills and expand their

experience. The suggestion has also been made that the clinical geneticist should share his time equally between his own field and routine clinical work, for example, paediatrics. Among the difficulties that arise are whether he would be regarded as second class in either or both fields and how realistic it is to expect a senior registrar to complete enough extra training so that he can compete on equal terms with his peers. There is also the very real practical problem as to whether an appointee who shared his time between two rather different fields would be able to resolve the conflicting claims that would inevitably arise from time to time. While it might be possible in a well staffed academic department of medicine or paediatrics, it is not feasible for National Health Service appointments. Furthermore, there are so many challenging opportunities in the field of clinical genetics that a wholehearted commitment to the specialty is essential.

The Working Group next recommends that for a region of, say, 3 million the equivalent of at least 22 NHS funded consultant clinical geneticist sessions per week should be available, largely for counselling. It must however be emphasised that much of the counselling in a clear-cut situation, for example, cystic fibrosis or haemophilia, should normally be carried out by the clinician responsible for that family. The importance of, and the work involved in, establishing a diagnosis have not been stressed sufficiently. Nor is a post devoted solely to counselling likely to attract the right calibre of clinician. Diagnosis can be difficult and Berry *et al*<sup>14</sup> have recently made a strong plea for a national reference centre for dysmorphology syndromes. Many are so rare that such a service would be invaluable to a much wider range of specialists than merely the clinical geneticists.

The rather optimistic suggestion is made that each region should have one consultant in each major specialty, for example, dermatology, to advise on genetic problems. It is much more realistic to suggest a similar service nationwide and this is already beginning to emerge.

### **University and health service**

Some of these services, clinical and laboratory, are, and must continue to be, provided by university personnel. The report comments on the continuing difficulty which arises when new developments are pioneered by university departments and the NHS subsequently finds difficulty in supporting them. While such transfer of financial responsibility to the NHS should be facilitated, it is in many ways inevitable, as well as highly desirable, that the closest

co-operation should exist from the initiation of a new project to its acceptance as a service commitment.

### Facilities for the future

In regard to services for prenatal diagnosis, the report considers that facilities must be provided for ultrasonography and for amniotic cell culture laboratories with appropriate staff. Training in counselling is required both by health visitors and midwives and by obstetricians, who also need experience in the technical aspects of amniocentesis.

However, a major weakness of this report, particularly since the DHSS was involved, is that no attempt is made to provide a proper estimate of the service implications.

However, another Working Party set up by the Clinical Genetics Society is currently preparing a report on Regional Genetic Advisory Centres (J S Fitzsimmons, 1980, personal communication). The aim is a commendable effort to produce a yardstick against which present services can be measured. They recommend that one Regional Genetic Advisory Centre should be established for each Regional Health Authority and financed by that authority. This will usually be in the teaching centre. Close contact with, and preferably proximity to, the clinical specialties, especially paediatrics and obstetrics, is essential. Like the other two reports, they strongly recommend that an Advisory Committee on Genetic Services should be established and also that it should become part of the statutory advisory structure of the Health Service. Their proposed staffing is more detailed and therefore apparently more generous. Inevitably, such levels would only be reached by gradual growth. For a region of  $1\frac{1}{2}$  to 3 million population there should be two consultant medical geneticists, a senior registrar or medical assistant, and two research assistants or registrars. A nursing sister and a health visitor, both full-time, are recommended, and possibly a social worker. Medical genetics generates much more secretarial work than many specialties, for example, tracking down notes of other members of the family. They therefore recommend two personal secretaries and a higher clerical officer. The latter's duties should include receptionist, since families are to be seen in the centre, and particularly responsibility for the genetic register. The latter would also require a computer programme operator. Two counselling rooms, a waiting area, and a library/seminar room bring their estimate of office space up to 2700 square feet to provide the clinical services for an established centre.

Turning to genetic laboratory services, there is still considerable discussion as to the level of staffing and the accommodation required, but this too is likely to

be more than that available in many regions. For example, the demand for prenatal diagnosis, so expensive of time, is increasing steadily.

The need for close liaison between the Genetic Advisory Centre and the laboratories, particularly cytogenetic, is obvious. Ideally, they should also be in close proximity but the constraints imposed by buildings may preclude this.

However, the relationship between the laboratory staff and the medical geneticists could present problems. The key role of the latter has been emphasised already. Potential difficulties might be avoided if it were recognised that the medical geneticist is not so much the apex of a pyramid but rather at the centre of a circle of supporting services, cognisant of the activities of the spokes. Clearly, he himself will have a major involvement in only one or two of the spokes, which might be cytogenetic, but would more probably be in a clinical area.

Basic information on the extent and availability of genetic services, both clinical and laboratory, is still inadequate. The figures given for staffing in the MRC/DHSS report are out of date and even then were probably not completely reliable. This itself requires correction as one form of operational research. Nevertheless, it is quite certain that the scale of services currently available falls far short of what is necessary. While it may be argued that terms such as cost/benefit analysis and effectiveness should never be used in reference to human life, these principles are inevitably involved, especially when funds are limited, only their use may not be recognised. Because of the increasing burden of disease which is genetically determined or related, proper use of resources demands that increased funds, separately allocated, are made available throughout the country. Despite the current financial constraints, much planning should be carried out now regarding the provision of the necessary staff and accommodation, making due allowance for developments and changes of emphasis. Then, as soon as possible, steady expansion of the service can occur into a Genetic Advisory Centre, not merely in name, but in place and function. Such a Genetic Advisory Centre will then be the focal point for referral of all problems in the region relating to medical genetics. Because of the needs of the patients and their families, there is urgency about the provision of such centres. Implementation of these reports is essential for the further development of genetic services in this country.

A W JOHNSTON  
Ward 8,  
Woodend General Hospital,  
Aberdeen AB9 2YS.

References

- <sup>1</sup> Medical Research Council. *Review of clinical genetics*. London: MRC, 1978.
- <sup>2</sup> Medical Research Council/Department of Health and Social Security. *Joint Working Group on genetic counselling and service implications of clinical genetics research*. London: MRC, 1979.
- <sup>3</sup> Borgaonkar DS. *Chromosomal variation in man*. 3rd ed. New York: Liss, 1980.
- <sup>4</sup> Polani PE, Alberman E, Alexander BJ, *et al*. Sixteen years' experience of counselling, diagnosis, and prenatal detection in one genetic centre: progress, results, and problems. *J Med Genet* 1979;**16**:166-75.
- <sup>5</sup> Clinical Genetics Society Working Party. *The provision of services for the prenatal diagnosis of fetal abnormality in the United Kingdom*. Bull Eugen Soc Suppl, 1978.
- <sup>6</sup> Farrant W. *Br Med J* 1980;**281**:452.
- <sup>7</sup> Harris R, Read AP, Donnai D, Donnai P. Stress after amniocentesis for high serum alpha-fetoprotein concentrations. *Br Med J* 1980;**281**:807.
- <sup>8</sup> Laurence KM, Morris J. The effect of the introduction of prenatal diagnosis on the reproductive history of women at increased risk from neural tube defects. *Prenatal Diagnosis* 1981;**1**:51-60.
- <sup>9</sup> Rushton DI. Fetal and perinatal pathology. *R Coll Pathol Bull* 1980;**31**:11-2.
- <sup>10</sup> Editorial. Screening for congenital hypothyroidism. *Br Med J* 1980;**281**:1.
- <sup>11</sup> Editorial. Population screening for carriers of recessively inherited disorders. *Lancet* 1980;**ii**:680-1.
- <sup>12</sup> Emery AEH, Brough C, Crawford M, Harper P, Harris R, Oakshott G. A report on genetic Registers. *J Med Genet* 1978;**15**:435-42.
- <sup>13</sup> Johnston AW. Training of medical geneticists. *J Med Genet* 1978;**15**:260-1.
- <sup>14</sup> Berry C, Cree J, Mann T. Aarskog's syndrome. *Arch Dis Child* 1980;**55**:706-10.

Requests for reprints to Dr A W Johnston, Ward 8, Woodend General Hospital, Aberdeen AB9 2YS.