Integration of Human Genetic Studies in Clinical Medicine

A. M. O. VEALE, MB, MRACP, Professor of Human Genetics, and Honorary Director, MRC(N.Z.), Human Genetics Research Unit, University of Otago Medical School, Dunedin, New Zealand

In 1963, the Medical Research Council of New Zealand founded the Human Genetics Research Unit in the Otago University Medical School. From the beginning, the Unit has maintained a close liaison with clinical departments but especially with the Department of Medicine which provided accommodation for the Unit's activities. This article traces the development of the Unit's work since its establishment and shows how the clinical departments have come to make increasing use of the skills and facilities that have been fostered and developed within the Genetics Unit. An indication of the extent to which the work in medical genetics is expanding here is given by considering the staff establishment and its increases over recent years. From an initial staff of two (a medically qualified director and one technician) the present staff consists of two medical graduates, one biochemist, one cytogeneticist, five technicians and two clerical workers, all fully engaged in various aspects of the study of human genetics.

CYTOGENETICS
An important reason persuading clinicians of the need for a group interested and trained in medical genetics was the development of tissue culture techniques that lead to the recognition of chromosome abnormalities. From the beginning of the Dunedin Unit, this has been a major activity and all the usual techniques are available. The majority of chromosome investigations are from cultures of peripheral blood lymphocytes obtained from specimens of capillary or venous blood, but skin fibroblast and bone marrow techniques are available when indicated. Autoradiography of chromosomes using tritiated thymidine has also been used when more exact identification of the chromosomes involved in a particular abnormal karyotype is required.

Various attempts to present clinicians with a list of indications for chromosome analysis have proved fruitless because abnormal karyotypes are from time to time detected in individuals with a minimum of clinical signs. Con-
sequently the Unit continues to undertake chromosome analysis on a service basis from virtually all clinical referrals.

Table 1 sets out a summary of analyses done in the Unit during 1969 and 1970 indicating why the examination was requested and the number and types of abnormal karyotypes detected. Approximately one in every six investigations yielded a demonstrable chromosome abnormality, some of which were of particular interest. The detection of a hitherto undescribed translocation involving B and D group chromosomes in a girl with severe mental retardation resulted in the balanced carrier state being demonstrated.

| Referral                      | Normal | Failures | Abnormal Karyotypes         |
|-------------------------------|--------|----------|----------------------------|
| 1. Congenital defects         |        |          | 46, XX, C_6 inv.           |
| Parents                       | 53     | 6        | 46, Gq+                    |
| 2. Mental retardation         |        |          | 46, Gq-                    |
| Parents & siblings            | 44     | 6        | 46, Gp-                    |
| 3. Growth retardation         |        |          | Acentric fragment          |
| Parents                       | 11     | 2        |                            |
| 4. Psychopathic               |        |          |                            |
| 5. Mucopolysaccharidases      |        |          |                            |
| 6. Leukaemia                  |        |          |                            |
| 7. Cri du chat                |        |          |                            |
| Parents                       | 7      | 5        |                            |
| 8. Parents of Cp—             |        |          |                            |
| 9. Trisomy D                  |        |          |                            |
| Parents                       | 5      | 3        |                            |
| 10. Trisomy E                 |        | 1        |                            |
| Parents                       | 2      |          |                            |
| 11. Down’s syndrome           |        |          |                            |
| Parents and siblings          | 30     | 1        |                            |
| 12. Miscarriage               |        |          |                            |
| 13. Foetus                    |        |          |                            |
| 14. ? XO                      |        |          |                            |
| 15. XY gonadal dysgenesis     |        |          |                            |
| 16. ? XXX                     |        |          |                            |
| 17. ? XXY                     |        |          |                            |
| 18. ? XXY                     |        |          |                            |
| Parents                       | 19     | 3        |                            |
| 19. ? Male turner             |        |          |                            |
| 20. Unspecified               |        |          |                            |
|                               | 286    | 31       | 124                        |
| Total                         |        |          |                            |

Culture failures were due to faulting of the incubator thermostat (6), delayed arrival (5), unsatisfactory placental material (4), insufficient blood for a culture (1), and a faulty batch of phytohaemagglutinin (6). Four failed for unknown reasons. Five marrows were unsatisfactory.
in one parent and an apparently normal sibling (Veale et al., 1968). Advice concerning the risk of chromosomal imbalance among future offspring was given.

Testicular feminisation has been frequently described, but less well known is the familial syndrome of streak gonads and a normal male karyotype in phenotypic females. A family containing five affected persons in three related sibships was detected and investigated by members of the Unit in close collaboration with a distant department of endocrinology. The report (Espiner et al., 1970) describes how the diagnosis in two patients before puberty may allow some sequelae of this condition in the adult to be avoided by appropriate therapy.

A Unit survey of children with Down’s syndrome led to the recognition of a number of patients with enlargement of the short arms of D and G group chromosomes. Investigation of other relatives has shown that the condition segregates within families and is apparently unrelated to Down’s syndrome itself (Sands, 1968, 1969).

As well as the orthodox cytogenetic techniques already mentioned as a part of the Unit’s normal service, two relatively new techniques are being assessed and developed. The first of these relates to the recent work concerning ultraviolet fluorescent microscopy of chromosomes previously treated with certain antimalarial drugs or related compounds. The hope is that all pairs of chromosomes will exhibit characteristic fluorescent patterns so that each chromosome pair can be individually identified. The satisfactory development of such a technique applied to human chromosome analysis will, without doubt, be a major advance allowing the more ready identification of minor chromosomal rearrangements that may well produce serious clinical effects.

The second expanding field in tissue culture and cytogenetics brings these activities into a closer relationship with genetic counselling and biochemical genetics. Antenatal diagnosis of foetal chromosome abnormalities and biochemical disorders by the successful tissue culture of foetal cells in amniotic fluid removed early in pregnancy has been accomplished in many laboratories. In our Unit a number of successful amniotic fluid cultures have been achieved and the technique awaits a suitable clinical situation such as a mother who is a balanced translocation carrier of mongolism, or parents who are known to be heterozygous for a biochemical error detectable in the foetus.

GENETIC COUNSELLING

Soon after the establishment of the Unit, a Genetics Counselling Clinic was established at the Dunedin Public Hospital. This clinic is held weekly and
although very few referrals were made initially, interest is now considerable and the clinic continues to expand. An attempt is made to obtain complete family histories for nearly all referred cases. Often the information at the initial interview is incomplete and subsequent inquiries may be very extensive. Happily, patients are usually eager to assist and much family information has been accumulated.

It has been our practice to index all names, of all persons, in all family trees, in the Unit's files, making particular efforts to obtain and record the maiden names of married women. Occasionally, this policy has paid handsome dividends, enabling a tentative diagnosis of a genetic disease (when there is apparently a lack of affected relatives) to be made with certainty. This situation is particularly likely to occur in diseases with a delayed and variable age of onset such as Huntington's Chorea, which, contrary to popular opinion, is not excessively rare, and the belief that all affected persons trace their families to a not too remote ancestor in Norfolk is a mistaken one. At present, the Unit has 15 apparently unrelated New Zealand families in which the condition appears, with a total of several hundred relatives, many of whom are affected.

From time to time patients referred to the clinic for counselling have been astonished to find our records containing information about hitherto unknown but affected relatives; more rarely, the files have enabled a genetic diagnosis to be made in patients in whom an established genetic disease had not been suspected. For example, a patient about to be married sought advice concerning his future children as he had two sisters with idiopathic epilepsy.

| Referral re:                              | Number |
|------------------------------------------|--------|
| Dominant conditions                      | 7      |
| Recessive conditions                     | 10     |
| X-linked conditions                      | 2      |
| Familial disorders with obscure genetics | 2      |
| Congenital malformations                 | 16     |
| Mental retardation                       | 20     |
| Down's syndrome                          | 12     |
| Psychiatric conditions                   | 4      |
| ? sex chromosomes abnormality ? XXO, ? XXY, ? XXXY, etc. | 25 |
| Recurrent miscarriages                    | 2      |
| **TOTAL**                                | **100** |
Enquiry into his family yielded names already on file, and eventually a total of 14 relatives with adenoma sebaceum were revealed. This was undoubtedly the diagnosis in his sisters, and appropriate genetic advice was given to the patient.

A summary by broad categories of the last 100 patients referred for counselling to the genetics clinic is given in Table 2. It is not possible here to deal with the advice given in individual cases, or even in the broad categories of diagnoses given in the table, but both patients and referring doctors value the service given by the clinic. Many patients accept the offer of further counselling after the first visit. This allows them the opportunity to assimilate and discuss the advice already given and to return for a discussion of any new questions that have arisen. The clinic continues to be a source of many interesting and important genetic problems.

**SPECIAL PROJECTS AND SURVEYS**

New Zealand has special advantages for investigating certain genetic problems on a population basis. The relatively homogeneous, medically well-documented and educated population, with central record keeping of hospital admissions under a socialised medical system, offers the opportunity of undertaking nationwide studies. The principal difficulty preventing a more vigorous pursuit of a number of such studies has been the lack of suitably trained and motivated workers. However, several surveys have already been undertaken with the help of workers from other disciplines.

A survey of children under six years of age with Down’s syndrome, paying special attention to the incidence of familial mongolism, translocations, mosaics, and the achievement of various developmental landmarks, was completed recently (Share and Veale, 1970). The incidence of clubfoot in Maoris is known to be nearly six times that in Europeans and a survey still being conducted has obtained information about its incidence in nearly 3,000 relatives of Maori children with this condition. Much valuable information about the strength of genetic factors in clubfoot is being obtained (Veale et al., 1966a). A survey into the incidence of leukaemia among the deceased relatives of index cases with chronic lymphocytic leukaemia has been made (Gunz and Veale, 1969). Although the incidence among the relatives was found to be much higher than in the population as a whole, the genetic interpretation of this finding remains obscure. Similar but much more extensive data is being collected in New South Wales and analysed here in the hope that the genetic position will be clarified.

Undergraduate and postgraduate students from the University medical and science faculties have from time to time undertaken thesis topics with a
predominant genetic component. Such work has been done in the Genetics Unit and has included theses on such subjects as the subtyping of haptoglobin variants, the timing and synchronisation of mitosis in tissue cultures, the familial incidence of rheumatoid arthritis, and segregation analysis in families with beta-lipoproteinaemia.

A number of genetic conditions are of particular interest to the Unit and affected families are actively sought with a view to obtaining a sufficient body of data to warrant more detailed study. Such conditions include familial intestinal polyposis and allied conditions (Veale et al., 1966b), osteogenesis imperfecta, Huntington’s Chorea, all forms of muscular dystrophy and retinoblastoma (Veale, 1969; Suckling et al., 1969, 1970). It is hoped that, eventually, separate registers of these and other conditions will contain most cases and families in New Zealand. The record system in the Unit is such that it could easily become a national archive of genetic abnormalities, and with that possible end in view practitioners are being encouraged to lodge information about genetic disease with the Unit.

**Genetic Linkage**

A particularly important aspect of centralised record keeping of genetically determined disorders is the prospect of accumulating enough data for genetic linkage investigations. Genetic linkage is of considerable theoretical interest for its own sake but there is no doubt that in the future, as more linkages are detected, it will come to play an increasing part in orthodox medical practice, affecting the advice given to families and patients at risk for certain genetically determined diseases. Linkage refers to the phenomenon of two different genetic traits having their respective gene loci located close together on one chromosome. This occurrence will be particularly important for those genetic diseases with a delayed age of onset or variable manifestation. A marker character such as a blood group, serum protein type or enzyme variant, whose genetic locus is close to that of the main character, will enable individuals at risk to be detected in some families before any signs of the main character have developed. This might allow appropriate treatment to be instituted or more definite advice given than is possible at present. Close linkage with the locus responsible for severe recessive traits would simplify the recognition of carriers among normal siblings of affected cases. Close linkage in a condition like familial intestinal polyposis would greatly simplify the management of affected families as those fated to develop the condition could be identified before symptoms or signs developed and those who had escaped inheriting the gene from their affected parent could be reassured and discharged from frequent medical surveillance.
INBORN ERRORS OF METABOLISM

In April 1966, the New Zealand Government Health Department started a screening programme of New Zealand newborns for phenylketonuria by means of the Guthrie Bacterial Inhibition test. This programme was gradually taken over by the Genetics Unit and from 1st January 1969 all babies in New Zealand have been tested in this laboratory for elevations of blood phenylalanine. In addition, samples are received regularly from some of the babies born in Australian New Guinea, the British Solomon Islands, Fiji, Western Samoa, American Samoa, Niue Island, Guam and three of the Health Districts of the United Nations Trust Territory of Micronesia, namely, Saipan, Majuro and Yap. During 1969, 60,878 New Zealand babies and 3,996 babies from Pacific Island countries and territories were tested. An additional 3,271 specimens were received from older patients. The majority of these were under investigation for mental deficiency or suspected metabolic disease. During 1969, the tests used were four Guthrie bacterial inhibition tests designed to measure levels of phenylalanine, methionine, leucine, and tyrosine, with a view to detecting cases of phenylketonuria, homocystinuria, maple syrup Urine Disease, and hereditary tyrosinaemia respectively. A total of 2,789 elevations above the 'threshold of action' were detected, and requests sent to the practitioners in charge of the patients for repeat specimens to be obtained in order that the initial elevation could be confirmed or otherwise. A total of 2,312 second specimens was received and retested, reports being sent to the individual doctor in each case. The majority of these elevations consisted of raised tyrosine levels as a result of transient neonatal tyrosinaemia.

A total of 159 phenylalanine elevations at 4 mg per cent or more were detected among New Zealand newborns. On further investigation, these cases yielded five cases of classical and one of atypical phenylketonuria. One case of homocystinuria in a newborn baby was also diagnosed during 1969. All these cases are under careful paediatric surveillance, and the appropriate dietetic treatment has been instituted.

In 1970, there was an extension of the screening programme to include four additional tests for genetic diseases. The first of these was another bacterial inhibition test to measure the level of blood histidine to detect cases of histidinaemia. Four newborn babies with this condition have been detected since the test was introduced and an additional case has been found among the older siblings of an index case. The next test introduced at the beginning of 1970 was an enzyme test for arginosuccinic acid lyase deficiency which, if present, leads to arginosuccinic aciduria, a serious condition in newborn infants. No cases of this disease have been detected. The third test was a modification of the Beutler enzyme test for the galactose 1-phosphate uridyl transferase
deficiency that is present in galactosaemia. One New Zealand newborn with galactosaemia has been detected by this technique but, unfortunately, the baby died at 11 days in spite of the institution of a galactose-free diet. A previous sibling of this family born in 1969 also died from galactosaemia but the diagnosis was made only in retrospect by examination of the liver histology from specimens taken at the post-mortem examination. The previous sibling had become known to the screening programme as a result of a generalised aminoacidaemia complicating the undiagnosed galactosaemia. This family has been very carefully investigated and quantitative enzyme estimations on the parents have confirmed that each parent is a heterozygote for galactosaemia and the normal gene for the transferase enzyme. The mother of these two children is now pregnant again and a galactose-free diet was instituted early in the pregnancy. The Beutler test has also enabled the Unit to detect a number of children with reduced enzyme activity in whom subsequent investigations have confirmed that some are double heterozygotes for the galactosaemia/Duarte genes; others are simple heterozygotes for the galactosaemia normal genes, and the rest have shown delayed maturation of the enzyme pathway. The final test to be introduced into the screening programme during 1970 was a test for $C_1$ esterase inhibitor deficiency, the metabolic defect present in

Table 3. Result of New Zealand ‘inborn error’ screening programme

| Newborn blood specimens, 1969/70:          |          |
|-------------------------------------------|----------|
| Classical phenylketonuria                | 8        |
| Atypical phenylketonuria                  | 1        |
| Homocystinuria                            | 1        |
| Histidinaemia                             | 4        |
| Galactosaemia                             | 2        |
| Intermittent Maple Syrup Urine Disease    | 1        |
|                                          |          |
| Newborns tested                           | 121,833  |
| Non-newborns tested                       | 2,753    |

| Urine specimens, 1970:                     |          |
|-------------------------------------------|----------|
| Heterozygous cystinuria                   | 3        |
| Prolinemia                                | 1        |
| Hyperglycinaemia                           | 1        |
| Phenylketonuria                            | 2*       |
| Lowe’s syndrome                            | 1*       |
|                                          |          |
| Urines tested                             | 3,000    |

*Previously known cases.

hereditary angioneurotic oedema. So far, no newborns with this condition have been found but a number of families have been investigated and affected members detected. An accurate titration of the amount of $C_1$ esterase inhibitor present is possible from specimens of the patients’ serum.
During 1970, a total of 60,955 New Zealand and 9,820 Pacific Island newborns were tested. The results obtained from the four additional tests have already been mentioned, and in addition three cases of classical phenylketonuria were detected. A total of 1,924 infants were re-investigated because of initial elevations or abnormal test results. A summary of results is given in Table 3.

As a part of the investigation of families in which abnormal babies have been detected, quantitative enzyme investigations have been undertaken on other family members and, where appropriate, amino acid load tests have been administered both to the patients and to parents in order to throw light on the response of known heterozygotes to the stress situation. In this more exact work, estimations of amino acid levels are done on a Beckman 120C amino acid analyser.

As an adjunct to the programme for detecting metabolic errors from the dried bloodspot specimens, a survey has started of urine specimens collected on filter paper cards. These cards are obtained from babies in the Otago and Southland provinces, aged 6 to 12 weeks, and are subjected to a number of chemical tests as well as a routine one-way amino acid chromatogram and a two-way chromatogram if further investigation is indicated. So far, over 2,000 babies have been tested in this way, and three children are at present under further investigation. Two of these are suspected of being heterozygous for cystinuria and the third is probably a case of prolinaemia. As a part of this programme, urine specimens were also obtained from 780 patients in a hospital for the mentally retarded but, apart from confirming known cases of phenylketonuria and one case of the oculo-cerebro-renal syndrome of Lowe, the only unsuspected abnormalities detected were one apparent heterozygote for cystinuria and one possible case of hyperglycaemia.

Routine tests on one neonatal blood specimen resulted in the diagnosis of atypical maple syrup urine disease. Close liaison is maintained with the physician in charge of this patient, measuring blood and urine levels of the branch chain amino acids and the response of the patient to changes in his dietary management. The Unit also receives regular specimens from the one newborn detected with homocystinuria, and a number of patients with phenylketonuria who are under dietary control.

The considerable number of tests now performed would not be possible without some degree of automation. All screening tests (bacterial inhibition and enzyme tests) are done on 1/2-inch paper discs cut from 1-inch blood spots on the special filter paper specimen cards (Fig. 1). Four spots are punched simultaneously by a punch index machine (Fig. 2) which automatically places each spot in a different test situation. An account of the laboratory
Fig. 1. Filter paper specimen card received from newborn babies. The specimen circles are 0.5 inch in diameter. Directions about collecting the specimen are printed on the reverse side.
organisation has been given by Houston and Veale (1971). Two of these machines enable the large number of specimens to be processed in a very short time.

**CONCLUSION**

Although many interesting aspects of human genetics may not impinge at all on the main stream of clinical medicine, the experience in Dunedin indicates that it is possible for a human genetics unit to function fruitfully and in a mutually stimulating way with clinical departments. It has not been possible in this account to cover other than superficially all the various activities and contributions made by the Unit and its staff. However, it is true to say that there is scarcely a branch of clinical medicine in which a medical geneticist
cannot, at one time or another, make significant and useful contributions to the diagnosis and management of patients and their families.

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Towards an American Way of Life

In mild weather, feather beds should never be used; and, in winter, those who keep fire in their rooms, and those who live in the south, should not sleep on them. A hard bed, of curled hair, straw, husks of Indian corn, or long moss, is much to be preferred, as promoting the density and strength of the muscles, and hardening the skin. Persons who have been lodged on hard beds from their infancy, greatly prefer them. What are called ‘weakly’ children should sleep on no others. Mechanical pressure is the natural stimulus of the skin and muscles; and cannot be with-held at night, without detracting from their firmness and vigor. The rule should be, to resort to feathers only for warmth; and under all circumstances which admit of that, in an adequate degree without them, they should be dispensed with. This rule, rigidly observed, would banish them entirely from the southern zone of the Valley, and limit them to the winter in the middle and northern.

The extensive, and especially the summer, use of feather beds, in the Valley, may be traced back to the practice of our English ancestors; for family customs, not less than nursery tales, are traditional. But, in Great Britain, the summers are proverbially cool; and, hence, what may there be very well, may be prejudicial here. It is necessary, however, that we should lodge warm. To sleep cold is exceedingly injurious to health; for it is natural, that is physiological, for the perspiration, sensible or insensible, to flow freely while we are asleep. Repose, silence, and the absence of mental emotion, favor it; and if it be suppressed by cold, injury to health ensues.

(From Daniel Drake’s Principal Diseases of North America, 1850.)