'The Duncan Guthrie Institute of Medical Genetics'

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THE DUNCAN GUTHRIE INSTITUTE

OF

MEDICAL GENETICS

The Institute houses the West of Scotland Regional Genetics Service, the University Department of Medical Genetics, and the Fraser of Allander Laboratories for Medical Genetics Research. It provides facilities for research into gene and chromosome abnormalities, and facilities for undergraduate and postgraduate teaching in medical genetics. The purpose of the work of the Institute is the prevention of handicap due to genetic disease and malformation, by the provision of comprehensive genetic services to a community of three million people in the West of Scotland.

The construction of the Institute was made possible by most generous grants from the National Fund for Research into Crippling Diseases (£150,000), and the Hugh Fraser Foundation (£100,000). The University contributed £69,000 and the balance of the total cost of construction (which amounted to £647,000) was provided by the Greater Glasgow Health Board. The Institute has been equipped by a grant of £303,000 from the Health Board, £58,000 from the University, and £80,000 from local industrialists and others through the "Action-80" Appeal by the National Fund for Research into Crippling Disease. The Institute is named after the distinguished founder of the National Fund, Dr. Duncan Guthrie.

The Institute is strategically placed at the south-west corner of the Yorkhill site, close to the Royal

Hospital for Sick Children and the Queen Mother's Hospital, and adjacent to the South Laboratory Block. It has four floors with a total floor area of about 12,000 square feet. The out-patient clinic, reception area and main cytogenetics and molecular genetics laboratories are situated on the ground floor. The lower ground floor has several specialised laboratories for cell culture, glass-ware preparation and sterilisation, cell-freezing laboratory and cell bank, media preparation, and computing services. The first floor contains the postgraduate research laboratory, biochemical genetics laboratories, genetic marker laboratory, cold room and administrative and other offices for medical and scientific staff. The Library, lecture theatre, genetic register and other offices are situated on the second floor.

The Architects and Services Engineers for the building project were the Scottish Health Service, CSA Building Division, the consultant quantity surveyors were Robert Mackintosh and Partners, the consultant structural engineers were Clarke, Nicholls and Marcell, and the main building Contractors were Melville, Dundas and Whitson Ltd.

HISTORY OF MEDICAL GENETICS RESEARCH IN GLASGOW

The early research work on sex chromatin and human chromosome aberrations in the late 1950's (in which a group led by Professor Bernard Lennox in the Glasgow University Pathology Department at the Western Infirmary played a significant part), initiated a world-wide interest and intense research in Medical Genetics which has continued unabated since then. Glasgow University were among the first to recognise this as an important area for development and established the first Lectureship in Medical Genetics outside London in 1961. There was some controversy at the time about which Department should hold the Lectureship . Although most of the research was

being done in the Pathology Department (Prof. D.F. Cappell), it was decided that as teaching in Medical Genetics had to be closely associated with classical genetics teaching, it should be under the wing of the Genetics Department (Prof. G. Pontecorvo, F.R.S.), until it became a discipline in its own right.

Among the interesting contributions made by the Glasgow group in those early days was the first use in 1956 of the buccal smear as a population screening tool for detecting sex chromosome aberrations. Unexpectedly high frequencies of Klinefelter's syndrome were found for the first time among sub-fertile males and among mentally-handicapped males. Investigation of these patients revealed that the cause of the sterility was a deficiency of germ cells which was present in childhood and thus untreatable. Very rarely, evidence of complete spermatogenesis (including a visible XY bivalent), was detected, and this paradox in individuals thought at the time to be sex-reversed females prompted an intense effort to determine their sex chromosome constitution. The earliest (unpublished) attempts at making chromosome preparations from bone marrow in patients with Klinefelter's syndrome, were made in Glasgow in 1957-58.

Following the establishment of the Lectureship in the Genetics Department, there was a productive period of research on human chromosomes and their aberrations. The first observations were made on satellite association and the behaviour of nucleolar chromosomes in mitosis and meiosis, and considerable progress was made with defining

the nature and extent of chromosomal variation. Papers on true hermaphroditism, the XXXY syndrome, the triple-X syndrome, Klinefelter's syndrome and Turner's syndrome, led to a unified hypothesis to explain the pathogenesis of malformations in the sex chromosome disorders on the basis of abnormal dosage of the X-Y pairing segment; the main evidence for incomplete inactivation of the X chromosome came from these karyotype-phenotype correlations, as did the evidence for X-Y interchange as the cause of sex reversal in XX males. During this period the group also worked on human gene mapping using linkage of genetic markers with chromosomal polymorphisms, on the genetics of multiple self-healing squamous epithelioma, on the meiotic analysis of chromosome aberrations, and were one of the first to report on the results of prenatal chromosome analysis in the U.K.

Since his appointment, the lecturer in Medical Genetics had provided genetic counselling and chromosome diagnosis to patients referred by consultants and general practitioners, as part of a research programme. By 1964, the demands for these services were far exceeding the resources of the Genetics Department in Church Street. In 1965, with the kind support of Professor J.H. Hutchison, a Chromosome Diagnostic Service was established at the Royal Hospital for Sick Children by the Western Regional Hospital Board. Temporary laboratory and clinic accommodation was provided at the Queen Mother's Hospital, and the Lecturer was appointed Senior Lecturer (and honorary consultant in medical paediatrics), a post held jointly

in the Departments of Genetics and Child Health. Five years later the laboratories moved to new accommodation for medical genetics in the South Laboratory Block at Yorkhill, and this provided facilities for amniotic cell culture for prenatal diagnosis. A second Lectureship in Medical Genetics was established in 1971 and in 1973 Glasgow University established a Chair of Medical Genetics. The Medical Genetics group continued to work in the sixth floor laboratories of the Genetics Department in Church Street, and at Yorkhill, where additional temporary laboratories were provided until the Duncan Guthrie Institute was completed in 1980.

In the past ten years the major research effort of the group has been in human gene mapping and in the development of prenatal screening. A particularly productive part of the gene mapping work has been the use of gene dosage in chromosome aberrations, and in 1973 the group achieved the first human gene assignment by this method (red cell acid phosphatase locus to the distal part of the short arm of chromosome 2). A number of other assignments followed, including the particularly satisfying assignment in 1976 of the ABO blood group locus to chromosome 9 at band 9q34. Currently the techniques of interspecific somatic cell hybridisation and molecular genetics are being developed for gene mapping, with the recent successful regional localisation of the alpha-globin and immunoglobulin light chain genes by *in situ* hybridisation. This work has been done in collaboration with Professor Bob Williamson of St. Mary's Hospital Medical

School, and Dr. Sue Malcolm of Queen Elizabeth College, London.

The work in prenatal diagnosis which started in 1967 was occupied, firstly, with developing techniques for amniotic cell culture and fetal chromosome analysis, and when suitable methods became available, for the prenatal diagnosis of metabolic disorders, particularly the mucopolysaccharidoses. Following Brock and Sutcliffe's discovery of the use of amniotic alphafetoprotein in the prenatal diagnosis of spina bifida in 1972, a pilot scheme was developed for prenatal screening for neural tube defects. This scheme has now become incorporated into the routine genetic services provided to all families in the West of Scotland.

Much of the research undertaken over the years has been possible only with the close collaboration of many other Departments at Glasgow, particularly the Departments of Pathology, Pathological Biochemistry, Child Health and Obstetrics. Two recent collaborative projects deserve special mention in view of their successful application to practical problems. One project was set up in 1979 in collaboration with the late Dr. John Stevenson and the Inborn Errors Screening Laboratory at Stobhill Hospital, and with Dr. John Radcliffe of the Department of Biochemistry at Glasgow Royal Infirmary, to develop a programme for neonatal screening for congenital hypothyroidism which is an important cause of handicap in children. A very satisfactory screening test to detect abnormal levels of thyroid-stimulating hormone on dried

blood spots, is now being applied to all newborn children in Scotland, so that those with early thyroid deficiency can be detected and treated in time to prevent irreversible brain damage. The second project is a joint project with Dr. Bryan Young of the Beatson Institute for Cancer Research which has led to the development of a very promising method for the automated analysis of chromosome aberrations by fluorescent-activated chromosome sorting. With appropriate development this technique should lead not only to a more economic means of screening for chromosome abnormalities, but also to the recognition of defects presently beyond the resolution of the microscope.

THE WEST OF SCOTLAND REGIONAL GENETICS SERVICE

The genetics service which started in a small room in the Queen Mother's Hospital in 1965 is being developed into a comprehensive clinical and laboratory service to the six Area Health Boards of the West of Scotland (Greater Glasgow, Argyll and Clyde, Lanarkshire, Ayrshire and Arran, Dumfries and Galloway and Forth). The region has a total population of 2.9 million with over 36,000 births annually. Two morning clinics are held each week, and an additional joint Paediatric Neurology/Genetic Clinic is held six times a year. Clinics are held every six weeks at Bellshill Maternity Hospital in Lanarkshire. An analysis of the clinical work of the Medical Genetics Department in 1980 indicates the extent to which genetic services are currently used, and their value in the reduction of handicapping disorders in children.

For example, in 1980 -

- nearly 500 new families were seen at the Genetics Clinic for diagnosis and genetic advice. Each family may contain several affected members and other relatives requiring genetic counselling. With such advice many couples are now able to plan sensibly for future healthy children, not only by avoiding pregnancy when the risks are high, but also by being reassured and encouraged to have healthy children when the risks are low. At least four times as many families require similar help each year, and with improved facilities, it is hoped to reach additional families.
- Over 1200 mothers at risk of severe fetal abnormality were able to have their pregnancies tested (by amniocentesis) at the medical genetics laboratories so as to be given the option of stopping affected pregnancies and trying for a healthy child at another time. 92% could be reassured by the test. In the 91 terminations, the diagnosis of spina bifida and related abnormalities was made in 79 and the diagnosis of a chromosome abnormality in 12. This is equivalent to a 56% reduction in all neural tube defects among the 36,000 births in the West of Scotland.
- 71.4% of all pregnancies in the West of Scotland in 1980 had maternal serum screening (between 16-20 weeks) for open neural tube defects by the Medical Genetics Department. 100% of anencephalic fetuses and 80% of spina bifida fetuses were detected by the screening test and this was the major factor in the 56% reduction in neural tube

defects noted above.

- 1436 chromosome analyses were performed in children and others suspected of having a chromosomal syndrome. 263 bone marrow samples were analysed for specific chromosome defects in patients with leukaemia and other related disorders. 241 tissue samples were set up in cell culture for chromosome analysis or for the diagnosis of metabolic disorders. There is an increasing demand for these specialised diagnostic laboratory services each year, as the number of genetic disorders which are diagnosable by biochemical and other techniques increases.

These results must be regarded as a preliminary attempt to introduce genetics into local health services. The full benefits of a comprehensive genetic service will only be realised when the facilities of the Duncan Guthrie Institute are fully operational and the necessary staff can be employed.

TEACHING OF MEDICAL GENETICS

Significant disability due to congenital malformation and genetic disease occurs in about 5% of the liveborn population and important questions about diagnosis, treatment and recurrence of these disorders are raised by the parents and families of such patients. The provision of comprehensive genetic services requires that all medical graduates and other health professionals including health visitors, midwives and nurses, should be sufficiently instructed in medical genetics to answer straight forward questions on genetics, and to know when to refer more complex genetic problems to the Regional Genetics Service.

The numbers of families with such problems are too great for all to be referred for specialist advice.

In Glasgow, medical undergraduates receive teaching in medical genetics in their first and fourth years. The first year students have 10 lectures on the principles of human genetics during the medical biology course; in addition, each student has 15 hours of practical work which includes human chromosome analysis, blood grouping and making Drosophila crosses. In IVth year, a course of 11 lectures on the application of genetics to clinical medicine is given and this is examined in a compulsory class examination. Fourth year students have an opportunity to attend the Genetics Clinic and take part in the discussion of clinical cases.

Undergraduates taking a Genetics degree in the Faculty of Science are given a series of 10 hours of lectures and tutorials on human genetics and related topics in the Advanced Ordinary Course, and a further series of 10 lectures in the honours year. A significant proportion of these students are employed in the Health Service following graduation and it is important that they have some appreciation of the contribution of genetics to medicine. The Department also contributes to other courses in the Faculty of Science.

Many informal lectures and tutorials are given to nurses and midwives in training, and to health visitors and others as part of the Department's contribution to postgraduate teaching. The Department currently takes 1-3 postgraduate students annually to work for a higher degree (Ph.D. or M.Sc.) in human genetics. 1-2 honours students undertake

research projects each year.

RESEARCH SUPPORT

The research work of the Department of Medical Genetics has been supported in the past by the National Institutes of Health, U.S.A., the Medical Research Council, the British Empire Cancer Campaign and the Scottish Hospitals Endowments Research Trust. Current grant-aided projects are:

(i) "In situ hybridisation in human gene localisation."

Joint project with Queen Elizabeth College, London, supported by M.R.C. grant of £41.000. A paper reporting the precise localisation of the gene for β-globin is published and another on α-globin is in preparation. A recent discovery has been the gene localisation for immunoglobulin light chains. The work is considered valuable as it demonstrates, for the first time, that single copy genes can be localised using radioactive DNA probes cloned in bacteria and hybridised to human chromosome preparations.

(ii) "Intrachromosomal identification of structural genes using molecular hybridisation techniques in inter-specific cell hybrids."

Supported by a grant of £21,543 from the National Fund for Research into Crippling Diseases. Again, genetic engineering techniques are being used to map the α-globin genes (and 3 other genes) on chromosome 16 in man-mouse hybrids.

(iii) "Neonatal Screeening for Congenital Hypothyroidism."

Joint project with Department of Bacteriology

(Stobhill), and Department of Biochemistry (Glasgow Royal Infirmary), supported by £57,714 from S.H.H.D. A national programme of TSH screening has been set up for Scotland. So far, 24 affected babies have been detected and treated in the 85,000 infants screened to date.

(iv) "The Application of DNA Recombinant Technology to the Detection of Genetic Abnormalities in Fetal Cells." Supported by a grant of £20,264 from the National Fund for Research into Crippling Diseases.
Methods are being established for the diagnosis of genetic disorders by direct analysis of DNA. The technique involves determining genetic linkage with DNA restriction cleavage site polymorphisms. Human globin genes and chromosome specific DNA cloned in bacteria are used as probes.

(v) "The Identification of Chromosome Aberrations and Polymorphisms Using Fluorescent Activated Chromosome Sorting." This collaborative venture with the Beatson Institute for Cancer Research (Dr. John Paul), has been awarded an M.R.C. Partnership Award for 1981-83.

A substantial part of the research work undertaken by the Department continues without the support of grant-awarding agencies, some being projects undertaken by individual staff members, postgraduate students and honours students and this work is supported by University Departmental funds. Other projects, including those associated with the prenatal screening programme, fall into the category of developmental research as they seek to improve the service currently offered to our patients. This work is supported by the Health Board

and by a research fund to which local donors may contribute. Current projects include:-

- Evaluation of amniotic acetylcholinesterase levels as a prenatal test for open neural tube defects.
- Mapping the Xg blood group and other genes located in the non-inactivated segment of the human X.
- Hair root steroid sulphatase assay as a simple diagnostic test for X-linked ichthyosis, placental sulphatase deficiency and X chromosome aneuploidy.
- Maternal serum AFP levels as an indicator of placental insufficiency and fetal complications of pregnancy.
- Studies on the pathogenesis of fetal neural tube defects, Meckel's syndrome and exomphalos.
- The use of isoelectric focussing of CF protein in serum in the diagnosis of cystic fibrosis, and the assay of amniotic MUGB reactive proteases in the prenatal diagnosis of this disorder.

The Department collaborates in a number of multi-centre studies, e.g., EUROCAT project on congenital abnormalities and twins (an EEC Concerted Action Project), and the U.K. Collaborative Study on Alphafetoprotein.

OUR GENEROUS BENEFACTORS

Reference has already been made to the most generous grant of £150,000 from the National Fund for Research into Crippling Diseases which initiated the venture to find suitable accommodation for Medical Genetics in Glasgow. The award was made in 1975 to the Medical Genetics Group to promote a centre for research into the prevention of crippling

disease in general, and in support of a project aimed at reducing the birth prevalence of spina bifida and chromosome aberrations in particular. Inflation, and an early error in estimating the cost of constructing the building, led to a decision to reduce the laboratory and other accommodation to two-thirds of the original plan. However, thanks to the timely intervention of the Trustees of the Hugh Fraser Foundation who generously contributed £100,000, the original concept was rescued and the laboratories reinstated as the Fraser of Allander Laboratories for Medical Genetics Research.

When the time came for the new building to be equipped, further generous support was received from our benefactors. The W.A. Cargill Charitable Trust gave £1,000 to start our medical genetics reference library. Major items of laboratory equipment including a biological safety cabinet (£3,693), research microscopes (£9,263), environmental chamber (£8,394), radiochromatogram scanner (£8,050), scanning microdensitometer (£13,500), electrophoresis apparatus (£812), luminometer (£2,253), Slit Lamp (£1,665), computing equipment (£13,100), and a grant towards the library (£2,000) were made through the "Action '80" Appeal, a special Scottish project of Action Research for the Crippled Child, whose Committee is chaired by the Marquis of Bute. The other members of the "Action 80" Committee who have generously given much of their time to our cause are Mr. A. Baker, Mr. J. Caldwell, Mr. A.K. Denholm (Project Manager), Mrs. Edward Denny, Mr. D.C. Smail, Mr. J.T.F. Simpson, Mr. J.D. Whyte and Mr. R.T. Richardson.

Some of the responders to the Appeal are listed below but, unfortunately, space does not permit the inclusion of all the names of the hundreds of kind donors who have contributed to Action Research for the Crippled Child in support of the Duncan Guthrie Institute.

The staff of the Institute appreciate that their research in the prevention of handicap would be impossible without the strong support of our generous donors, and hope that the results of the work being done in the Institute will always justify such generosity. We regard our work as a joint venture between those who are priviledged to work in the field and those who are able to support us, and we hope that our donors have a similar feeling of being involved in a worthwhile joint endeavour.

LIST OF CONTRIBUTORS TO "ACTION 80"

	DONATION
The Gamma Trust	£ 2,500
Wilforge Foundation Ltd.	2,000
Miss E.C. Hendry's Charitable Trust	10,000
Garfield Weston Foundation	1,000
Commonweal Fund, The Trades House of Glasgow	1,000
Broom Church Youth Fellowship	1,000
Merchants House	1,000
The Gannochy Trust	1,550
Applecross Trust	3,000
The W.A. Cargill Fund	1,000
Hiram Walker Charitable Trust	1,000
Western Recreation Trust	1,000
I.C.L. Discretionary Trust	1,100
Peter Coates Trust	1,000

STAFF OF THE DUNCAN GUTHRIE INSTITUTE OF MEDICAL GENETICS

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Mrs. Barbara Pawlowska, Department of Genetics, Psychoneurological Institute, Warsaw, Poland.

Dr. Nicos Strintzis, Genetics Laboratory, Alexandra Hospital, Athens.

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