
A REPORT ON

INHERITED METABOLIC DISORDERS

-CLINICAL AND LABORATORY SERVICES

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MANAGEMENT SUMMARY

The Service, Clinical and Laboratory (Diagnostic and Screening) for Inherited Metabolic Disorders has been provided by Temple Street Children's Hospital, for 30 years.

The nature of the conditions dictates that specially trained personnel are needed at laboratory and clinical level to deal with this discipline.

The Laboratory equipment and expertise required are becoming more complex.

The numbers of individuals identified are increasing annually, and once a condition is identified the patient requires lifetime treatment. New conditions are being identified continuously, and more conditions previously undiagnosed are now being found to have a metabolic cause.

There is no metabolic service at any adult hospital to which patients could be referred as they get older. (International experience suggests that for a population of three or four million, only one centre can be justified).

YET

The level of approved staffing and facilities in the Laboratory are almost unchanged from the 1970's.

The Department of Health recently granted funding for an expansion of the clinical staff - a Dietitian, Doctor, ward area and second Consultant. This essential funding is allowing us to provide a basic service in an already overloaded and exacting clinical setting.

TSH is attempting to cope with this most complex and rapidly expanding area of medicine and will continue to need an increase in financial support from the Department of Health.
Introduction

The Children's Hospital Temple Street provides clinical and laboratory services for individuals with Inborn Errors of metabolism. (Inherited Metabolic Disorders).

This report shows the significance of these conditions for an Irish population.

It will show: 1. The present work load.

2. The present resources.

3. The present and projected needs.
1.1 WHAT ARE THEY?

Inherited metabolic Disorders differ from routine illness in that

(a) They are genetically endowed.

This means that several family members can be affected - there is a 1 in 4 risk at each conception or in some instances a 1 in 2 risk. They result from an enzyme deficiency and no "cures" are available. The problem or ill effects of it pass to the next generation.

(b) They cause problems varying from death to severe or mild mental handicap.

(c) They are life-long - a child identified with a metabolic problem will need treatment for life - the problem and the threat to life or intellect remains.

(d) They may go unrecognised as they have no specific physical features, are rare in general medical training terms, and will not be identified unless special biochemical tests are carried out which are not widely available.

(e) Treatment is available for some but not all conditions.

(f) All families can receive genetic counselling and therefore prevention is possible if given early enough.

(g) Early investigation and diagnosis is essential for families who want to avoid further similarly affected children.

(h) Early diagnosis is also essential where there is treatment available so that the treatment can begin before damage is done.

(i) Treatment has to be monitored by regular specific (non-routine) biochemical tests to maintain metabolic balance and good health for life.
(j) The identification of one family member may produce the "SNOWBALL" effect of detecting previously unidentified relatives. Conversely the loss of one individual from a treatment programme may produce several abnormal offspring in the next generation.
Incidence: The relative frequencies of genetic disorders are likely to go on increasing with time as presently unidentified causes of morbidity and mortality are recognised to be genetic in origin (Scriver 1984).

The incidence of identification of genetic disorders is increasing sharply - 10% of Paediatric admissions to University Hospitals in North America (1982); 40% of Paediatric admissions in Glasgow in 1988. Ireland has a higher incidence of the more commonly occurring defects.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ireland</th>
<th>U.K.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria</td>
<td>1 : 4,500</td>
<td>1 : 10,000</td>
</tr>
<tr>
<td>Galactosaemia</td>
<td>1 : 22,000</td>
<td>1 : 62,000 (est)</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>1 : 49,000</td>
<td>1 : 80,000 (est)</td>
</tr>
<tr>
<td>MSUD</td>
<td>1 : 110,000</td>
<td>1 : 250,000</td>
</tr>
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</table>

The above conditions affect amino acid and sugar metabolism but defects also occur affecting other pathways, but these do not occur at a rate which would justify national screening. Select or special group screening will have to be introduced in the future for conditions only gaining recognition now.

We have recently shown that the Irish travellers have a very high incidence of Galactosaemia (1 : 700) and of a rare condition called Glutaric Aciduria. The latter condition causes Cerebral Palsy and the identification, prevention, education and treatment of the itinerant families is essential to minimise the burden placed on the Health Service by these inherited disorders.
1.3

1) **Nature of Conditions:**

To identify one individual with an inherited disorder is to set in motion a process of family counselling, support, biochemical monitoring, nutritional education and specific illness management which will last for the duration of that individual's life. (Fig 1.) It will involve day to day adjustment of food based on blood levels of specific metabolites, where treatment is available in that form. In all cases genetic counselling is mandatory to ensure responsible reproduction.

The treatable disorders mainly require daily, life-long adherence to synthetic diets. These need biochemical monitoring weekly or monthly in the stable phase, and daily monitoring during unstable periods e.g. infection or growth. The treatments are synthetic and fraught with dangers e.g. deficiencies, unless monitored closely. Abnormal constituents (metabolites) accumulate with infection, fluctuations in growth and intake of protein (egg, fish, cheese, bread, meat not permitted).

Teaching the diets and encouraging adherence to distasteful foods is time consuming and labour intensive. Genetic counselling is included in the educational process. The time taken for each family to learn the difficult lifestyle varies from 1 - 2 hours daily for the initial week and 1 - 2 hours per week thereafter. (Fig 2).

The present staffing does not allow us to identify, locate, document, and teach the families with these disorders.

In addition some of these conditions which were heretofore untreatable are now responding to bone marrow transplants or the application of principles used in conditions like PKU e.g. Mucopolysaccharidoses and Adrenoleucodystrophy (ALD) - Lorenzo's Oil. The monitoring and documentation of post transplant patients and children on Lorenzo's Oil is extremely time consuming.

The early application of all of these treatments is essential to a successful outcome which puts a major burden on clinical staff, already working at full capacity, to identify, arrange, coordinate and document the complex detail required in each case. Failure to achieve this may result in an untreatable handicap and subsequent litigation.
Fig. 2.

**TIME STUDY = ESTIMATE OF TIME SPENT TEACHING PARENTS AND CHILDREN BASIC PRINCIPLES AND PRACTICAL MANAGEMENT OF TREATMENT.**

<table>
<thead>
<tr>
<th>Numbers</th>
<th>Total</th>
<th>Average Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU</td>
<td>Others</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Doctor Pat Group</th>
<th>Average Hrs</th>
<th>Total Hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dietn.</td>
<td>Hrs</td>
<td>Hrs Yr Age</td>
</tr>
<tr>
<td>0 - 3 Yrs</td>
<td>42</td>
<td>150</td>
<td>192</td>
</tr>
<tr>
<td>3 - 8 Yrs</td>
<td>93</td>
<td>124</td>
<td>217</td>
</tr>
<tr>
<td>9 - 14 Yrs</td>
<td>95</td>
<td>65</td>
<td>160</td>
</tr>
<tr>
<td>15 - 25 Yrs</td>
<td>138</td>
<td>70</td>
<td>208</td>
</tr>
<tr>
<td>25+ Yrs</td>
<td>53</td>
<td>10</td>
<td>63</td>
</tr>
<tr>
<td>Adult Pregnant adult</td>
<td>26</td>
<td>4 hours / preg</td>
<td>104</td>
</tr>
</tbody>
</table>

Plus Phone 15 mins./year/patient = 200 hrs

Total Hours = 3168 hrs = 396 days*
(Approximately 230 days = average working year)

* Hours spent teaching diets and genetics
Other work not included.
1.4

FAILURE TO PROVIDE GOOD TREATMENT

Failure to comply results in mental handicap, blindness, dependency or death. The public health implications are great – for the future. One fertile woman (off diet) can be responsible for numerous handicapped offspring. One teenager who rebels and goes off diet may become dependent (institutionalized) and also produce abnormal children.

1. Mental retardation arises from untreated P.K.U. – current costs of maintaining a person in a mental institution are estimated at £12,000 to £22,000 per year.

2. Failure to continue treatment of P.K.U. in adults may result in a 20-point drop in I.Q. – this can mean institutionalization for some. Acute neurological problems have occurred in individuals who come off diets e.g. Ataxia, Epilepsy, and Quadriplegics Thompson A.J., Smith I., et al. Neurological deterioration in young adults with phenylketonuria. The Lancet 1990; 336: 602 –605

3. Fertile females with these conditions give birth to babies with microcephaly and major structural defects unless on treatment at conception and during pregnancy – it has been estimated that the retarded offspring of these women will replace their mothers in mental institutions unless treatment is provided. This clinic has identified 18 women who have delivered 23 microcephalic infants from a total of 44 pregnancies. Fig 5(a), 5(b).

4. Cataracts and ovarian damage are being identified in patients with Galactosaemia whose mothers were not on diet during pregnancy.

5. Mental retardation, cerebral palsy and life-long dependency may result from any of the other conditions.
PREGNANCIES IN PKU
INCREASE IN PREGNANCIES INVOLVING MANAGEMENT OF FOETAL NUTRITION

Fig. 5(a)
Cost of Institutional Care.

Current patient numbers = 800

Cost in Institution £18,000 - £22,000 per annum

£18,000 × 550 = £9,900,000 per annum

Without treatment and taking the lower cost of institutionalized care (£18,000) and assuming that some patients will not need to be institutionalized the conservative estimation of saving per annum is approximately 6 million pounds.

In addition, approximately forty patients with moderate to severe handicap are maintained on diets for metabolic conditions at present. This enables them to be managed in the community and saves on institutional care.
GROWTH IN DEMANDS ON THE SERVICE

The improvement in medical technology means that specific enzyme defects can be identified now and therefore:

1) treatment may be available

2) prevention is possible e.g. by treatment and/or genetic counselling

Recent advances have led to a break-through in the cause of coma, "cot death" or "near miss" cases (metabolic causes may be responsible for as high as 12.5%). Several family members at risk can be identified and saved from cerebral palsy or death. The investigation is expensive and time-consuming, and requires gas chromatography and mass spectrometry with specialized Laboratory training for the personnel involved. Newer methodologies using high Performance Liquid Chromatography and polymerase chain reactions (PCR) are now used to identify family members and cases - we have to send all samples to the UK or Holland at present.

The delay in making these diagnoses means that we have to keep a child safe from cot-death or "near-miss" while waiting weeks or months for a specific diagnosis. This imposes a great burden on families and medical staff if the pathway with the inherited defect is not clearly known.
2. NEW BORN SCREENING

2.1 Numbers Screened & Detected

Numbers: Since screening was established in 1965 the programme has expanded to include 5 treatable conditions.

8,445,975 tests on 1,689,195 million infants. (February 1993).

721 have been identified with treatable conditions.

The 721 contribute to the numbers attending for treatment - thus preventing institutional care.

2.2

Work Involved:

Blood samples from every baby born in this country are tested for 5 different conditions - the PKU test being the best known of these. The work is manual and labour intensive.

A positive case has to be recalled and the diagnosis proven using other laboratory techniques.

All data has to be documented for medical and medico - legal purposes.
3. Acute Metabolic Diagnostic & Monitoring Laboratory Service

This section of the Laboratory carries out specialised tests which are not routinely requested, in contrast to the routine biochemistry laboratory where there is a 70% stat turn over and automated work predominates. (Fig 3)

3.1 All tests carried out in this section require specialised skill and training - one test may require 5 hours for one person to carry out. See Fig 4 (a), (b)

3.2 This section is responsible for diagnosis and monitoring and must be available 24 hrs/day. It provides service for all other hospitals in amino acids, galactose, etc.

3.3 Special tests not available in Ireland are dispatched via this laboratory. The material to be tested has to be handled in a specific manner (liquid nitrogen or cold or room temp) and dispatched, documented and labelled by the trained staff. The increase in this area has put great stress on Laboratory staff.

3.4 Storage facilities for samples of skin, tissue, blood and urine which need specialized handling are inadequate.

Needed: One standard fridge 18 cubic feet
        One standard freezer 10 cubic feet.

3.5 As seen from Fig.3, the Inherited Metabolic Laboratory work now exceeds the routine work.
Fig. 3.
Fig. 4. Based on Welcan Units
Quantitative Amino Acid Analysis
Users - 1990

Diagnostic Tests (11157)

Monitoring Tests (11526)

Figure 4(a)
Qualitative Amino Acid Analysis
Users - 1990

Blood Analysis
Test Nos.(3668)

Urine Analysis
Test Nos.(16764)

Figure 4(b)
Fig. 6.
CLINICAL TREATMENT AND INVESTIGATION.

4.1

CLINICAL UNIT: WORK

The work carried out by the Unit may be categorised as follows:

* 1. Stabilisation and establishment on treatment of new patients identified by the newborn Screening Programme (16 to 20 new patients per year).

* 2. Monitoring of treatment and nutritional balance for children and adults - weekly, or in acute cases daily, blood tests, followed by nutritional adjustments as indicated.


* 4. Investigation of possible metabolic causes in Sudden Infant Death and near misses.

* 5. Investigation of possible metabolic causes in patients having cerebral palsy and / or retardation, referred by institutions (adults and children).

* 6. Monitoring of biochemical control in individuals with these disorders while in-patients in adult hospitals.

* 7. Intensive care of acutely ill patients during critical episodes. In-patient management requires meticulous attention to detail - calorie intake, synthetic food, blood glucose, trace metal, amino acid monitoring.


* 9. Management of pregnancies in affected mothers - an increasing workload (Fig. 5(a,b)).

10. Education of patients and their families, health workers, teachers.

11. Support for families in adjusting to the difficulties of coping with life-long conditions, and bereavement counselling.

12. Genetic counselling for families with these defects.


* Indicates clinical situation which necessitates Laboratory monitoring.
4.2

THE FUTURE FOR THE CLINICAL METABOLIC UNIT

The higher incidence of Inherited Metabolic Disorders in Ireland—twice that in other developed countries—gives rise to a major public health problem, which has to be managed as efficiently as possible with the resources available. The Unit at Temple St. handles significantly larger numbers than any comparable unit in Western Europe or the United States, and it does this with less staff, and with limited ancillary support.

The ever-increasing numbers of patients and complexity of conditions means that the unit cannot continue to function with present staff. (See graph) Fig 5.

The effectiveness of the unit in its preventative role is dependent on the following factors:

4.2 (1). An increase in staff:

(a) Social worker and

(b) Psychologist to interface with families and Community Health workers.

(c) A second secretary (full-time) to help document and coordinate this complex, multi detailed discipline. (of medico-legal and economic importance).

(d) The current rate of increase indicates that a further Consultant and Dietitian will be required in the near future.

4.2 (2). The availability of specialised laboratory service on a 24-hour basis for diagnosis and prompt adjustment of treatment. The service currently available is not adequate for the demands of this specialty.
**PROPOSED STAFF NO'S.**

### CLINICAL

<table>
<thead>
<tr>
<th>Position</th>
<th>Existing</th>
<th>Additional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>3</td>
<td>1 Consultant 1/2 Registrar, 1 Consultant 1/2 Registrar</td>
</tr>
<tr>
<td>Paramedical</td>
<td>4</td>
<td>2 Dietitian, 1 Psychologist, 1 Social Worker</td>
</tr>
<tr>
<td>Secretary</td>
<td>1</td>
<td>1 Secretary</td>
</tr>
</tbody>
</table>

The Registrar to be a full time Clinical Assistant

### LABORATORY

<table>
<thead>
<tr>
<th>Position</th>
<th>Existing</th>
<th>Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Pathology</td>
<td>1 Consultant (7 Sessions)</td>
<td>2 Technicians to cater for the increased laboratory workload from a new Consultant.</td>
</tr>
<tr>
<td>Metabolic Screening</td>
<td>2 Technician, 2 Typists, 0.5 Locum Cover</td>
<td>3 Technicians to do tests currently sent to England.</td>
</tr>
<tr>
<td>Metabolic Laboratory</td>
<td>4 Biochemist/Technician, 1/2 Porter</td>
<td>For 6 beds 15 nurses are required.</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. CONCLUSION.

The cost to the country of failing to provide an adequate laboratory and clinical service for the individuals with Inherited Metabolic Disorders is large (6 million - 11 million pounds) in economic and human terms (handicap, cerebral palsy, blindness, death).

The preventative nature of this work is obvious. It is also time-consuming, labour intensive, demands sub-specialty training and is not catered for in general training of nurses and Doctors. The laboratory needs are enormous, as the clinical needs are labour intensive.

Once identified all patients are looked after in this Unit (unlike Cystic Fibrosis where the patient goes to adult physician) in conjunction with local adult Physician.

The present clinical and laboratory facilities are severely stressed and are having great difficulty coping with the increasing demand.

The staffing in both areas needs to be updated and expanded to deal with modern demands.

e.g. increase in staff for clinical unit - special nurses for inpatients; psychologist; medical social worker, and second secretary.

An increase in staff for laboratory - specifically trained personnel to devote full time to special procedures.