Additional material is available on the ADC website (<http://www.archdischild.com/supplemental>)

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REFERENCES

- 1 Pushparajah K, Garvie D, Hickey A, *et al*. Managed Care Network for the assessment of cardiac problems in children in a district general hospital: a working model. *Arch Dis Child* 2006;91:892–5.
- 2 Paediatric and Congenital Cardiac Services Review report. Department of Health, December 2003. www.advisorybodies.doh.gov.uk/childcardiac/reports.htm.

Frequency of metabolic disorders

Frequency of metabolic disorders: more than one needle in the haystack

P J Lee, P Cook

Perspective on the paper by Sanderson *et al* (see page 896)

Since Archibald Garrod coined the term “inborn freaks of metabolism” after his classic studies on alkaptonuria, cystinuria and pentosuria a century ago,¹ clinicians have believed that these disorders are a rarity. Early progress was hampered by insensitive methods of detection, as well as a lack of awareness within the medical community as a whole. The successive application of chromatographic techniques, mass spectrometry, enzymology and, recently, molecular genetics has increased our ability to detect metabolic perturbations in symptomatic, and in asymptomatic, people. Despite possible diagnosis, nihilism persisted as few therapeutic interventions were available and many of those affected died early in childhood. Even with survival, quality of life was extremely poor.

Phenylketonuria (PKU) is a good example of how the application of new advances, diagnostically and therapeutically, can have a dramatic effect on outcome and therefore on expectations. PKU was first described by Følling in the 1930s. Biochemical diagnosis could be made on urine samples from infants with developmental and neurological problems. Two decades passed before Bickel showed that a phenylalanine-restricted diet could be given safely to affected children, although they remained severely impaired and dependent, with many of them institutionalised for life.² It required the development, by Robert Guthrie in the 1960s, of a cheap, sensitive and specific screening test that could be applied to large populations before a true effect on outcome could be shown.³ Since then,

further technological improvements have provided accurate, quantitative measurements of phenylalanine, and an explosion of phenylalanine-free nutritional products means that a newborn with PKU diagnosed today can expect a near-normal life. Management of PKU is certainly one of the success stories of 20th century medicine.

PKU is well known to paediatricians, but many other inherited metabolic diseases (IMDs) are not. *The metabolic and molecular bases of inherited disease* edited by Scriver *et al*⁴ lists so many IMDs that it has necessitated an existence on the internet rather than on paper. The use of laboratory techniques such as tandem mass spectrometry to measure acyl carnitines, gas chromatography–mass spectrometry to measure organic acids, tissue enzymatic tests to measure lysosomal, intermediary metabolic and respiratory chain enzymology, and molecular genetic testing mean that many of these disorders can be readily detected. Once a diagnosis is made, other family members at risk can be screened; appropriate genetic counselling about future pregnancies can be offered; and treatment, where available, can be introduced. The main question remains as to whether or not clinicians are sufficiently aware of the possible presentations to consider the diagnosis of an IMD. As these conditions have been considered to be rare, many clinicians will not have come across IMDs during their training or practice. In this issue, Sanderson *et al*⁵, in a careful retrospective review of one region in the UK, have shown that the frequency of these conditions may be

more common than was previously estimated: 1 in 800 live births rather than the often quoted 1 in 2500–5000.⁵ Although the population they studied has a high proportion of ethnic minority groups in which consanguinity is commonplace, their reliance on just a single regional specialist laboratory may mean that their prevalence figures are an underestimate. It is therefore reasonable to extrapolate their figures, suggesting roughly 800 new cases of IMD diagnosed each year in the UK.

This figure is not insignificant, as treatment for many of these conditions has improved considerably, increasing the survival rates and quality of life. Examples include enzyme replacement therapy for Gaucher's disease and other lysosomal storage diseases, with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione for tyrosinaemia type I, sodium benzoate and sodium phenylbutyrate nitrogen scavengers in urea cycle defects; overnight glucose pump feeds and uncooked cornstarch in hepatic glycogenoses; and organ transplantation such as bone marrow for leucodystrophies or liver transplantation for amino acidopathies. Preliminary data from the newborn screening trial for medium-chain acyl CoA dehydrogenase deficiency in the UK suggest that mortality and morbidity can virtually be eliminated. Without screening, 20% of patients are expected to die at presentation, and a further fifth may survive but with considerable neurological damage.⁶ Children diagnosed with IMDs are surviving, but more adults are now diagnosed with these disorders for the first time. The data of Sanderson *et al*'s⁵ suggest that more than a quarter of patients are diagnosed at >14 years of age, sometimes even as late as in the eighth decade. Doctors need to be aware of these disorders.

All of this has considerable implications for services to provide care for these patients and their families. A recent UK survey by the same group identified at least 10 000 children and adults with IMDs in contact with current specialist services in the UK.⁷ Using the old prevalence figures, the group estimated that at least 8000 other

patients are not known to these services. This could be because they are looked after in primary care or non-specialist services.⁸ Alternatively, they could be languishing without care or possibly have already died. Applying the West Midlands' prevalence figure would suggest that there are even more patients with these so-called "rare" disorders whose needs are not being met.

So, what services currently exist? The UK metabolic services review⁷ has shown that 11 centres look after at least 100 children with IMDs, but only five of them look after ≥ 500 . Nine centres see ≥ 100 adult patients, but only two see ≥ 500 . Indeed, many adults are still cared for in paediatric services, but transition arrangements are limited and the healthcare personnel in each service vary considerably. Ideally, paediatricians, dietitians and clinical nurse specialists should link up with their adult internal medicine counterparts, with clinical services underpinned by comprehensive laboratory and genetic support. Clinical psychology involvement in services is conspicuous by its absence, despite neuropsychometry being the most important outcome measure for many of these conditions. Some regions, particularly the northwest and London, are well catered for, but others, such as the southwest and the south coast, have a dearth of specialists.

Doctors treating adults need to be aware of these conditions so that a diagnosis may be made; also, as paediatric patients increasingly survive into adulthood, an expansion of metabolic services for adult patients is required. Examples of this already exist in other disciplines of medicine—for example, adult congenital heart disease⁹ and cystic fibrosis.¹⁰ Metabolic medicine should not fall into the trap of reinventing the wheel. Much can be learnt from other specialties, and emphasis needs to be placed on the transition from childhood to adolescence to adulthood. Paradigms of transitional care have been well established for diabetes mellitus for several years. The aim should not just be keeping patients alive but enabling them to fully integrate into society.¹¹

To run age-appropriate, comprehensive services, adequately trained personnel are required.¹² Paediatric metabolic training is available only in two centres within the UK at present (three training posts). Recently, adult metabolic medicine training, under the auspices of the

Royal Colleges of Physicians and Pathologists, has been introduced with the aim of considering the needs of the adolescent and adult population.¹³ Indeed, the estimated 3500 adult patients with an IMD not attending any metabolic clinic⁷ and the substantial rise in year-on-year activity in established centres suggest that the provision of services needs to occur rapidly for fear of losing even more patients to follow-up.

Clinicians cannot function in this specialty without adequate laboratory provision, including out-of-hours interpretative services. Currently, in some parts of the country, this relies on the goodwill of people. To facilitate the training and development needs of laboratory scientists, a National Metabolic Biochemistry Laboratory Network was recently established and the Department of Health for England agreed to fund higher specialist trainee and trainer posts dedicated to inherited metabolic clinical biochemistry. But comprehensive metabolic services are doomed without supporting expert dietetic services. Unfortunately, no formal training in IMDs for dietitians exists: a 3-day course every 2 years as part of an MSc is all that is available at the moment in the UK. Skills in the dietary management of IMD are mainly gained from workplace experience. As the paediatric specialty has grown, there are more dietitians working single handed in departments where there is little or no previous experience in IMD. Experience is generally available only in the major metabolic centres and dietitians at these centres provide advice, on an informal basis, to other dietitians for whom IMD management is not considered a specialty. Of major concern is the paucity of dietitians trained to deal with adult patients with IMD who are currently managed by paediatric dietitians at paediatric hospitals.

In many ways, the community with IMD is a victim of its own success. Improved diagnosis has shown that the incidence of these diseases is much higher than was previously thought, and with improved treatment these patients are now frequently surviving into adulthood. This is likely to increase further with the introduction of expanded newborn screening for fatty acid oxidation defects, organic acidemias and aminoacidopathies over the next few years.¹⁴ Once the domain of a small band of dedicated enthusiasts,

demand has now outstripped this model of care. There are numerous motivated patient groups, and with their political help, the community with IMD needs to develop a comprehensive, national service that covers the needs of all patients. A multidisciplinary National Inherited Metabolic Disease Board is being established to consider all these issues by setting standards of care and working closely with specialist commissioners.

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REFERENCES

- 1 Garrod AE. The incidence of alkaptonuria: a study in chemical individuality. *Lancet* 1902;**2**:1616–20.
- 2 Bickel H, Gerrard J, Hickmans EM. Influence of phenylalanine intake on phenylketonuria. *Lancet* 1953;**2**:812–13.
- 3 Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics* 1963;**32**:338–43.
- 4 Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic and molecular bases of inherited disease*, 8th edn. New York: McGraw-Hill, 2001.
- 5 Sanderson S, Green A, Preece M, et al. The frequency of inherited metabolic disorders in the West Midlands, United Kingdom. *Arch Dis Child* 2006;**91**:896–9.
- 6 Pollitt RJ, Leonard JV. Prospective surveillance study of medium chain acyl CoA dehydrogenase deficiency in the UK. *Arch Dis Child* 1998;**79**:116–19.
- 7 Burton H, Sanderson S, Shortland G, et al. Needs assessment and review of services for people with inherited metabolic disease in the United Kingdom. *J Inher Metab Dis* 2006 (in press).
- 8 Lee P, Leonard J. Textbook of endocrinology. *BMJ* 1994;**308**:1512.
- 9 Reid GJ, Irvine MJ, McCrindle BW, et al. Prevalence and correlates of successful transfer to adult health care among a cohort of young adults with complex congenital heart defects. *Pediatrics* 2004;**113**:197–205.
- 10 Jackson R, Pencharz PB. Transition of care between paediatric and adult gastroenterology. Cystic fibrosis. *Best Pract Res Clin Gastroenterol* 2003;**17**:213–35.
- 11 McDonagh JE, Viner RM. Lost in transition? Between paediatric and adult service. *BMJ* 2006;**332**:435–6.
- 12 Viner R. Transition from paediatric to adult care. Bridging the gaps or passing the buck? *Arch Dis Child* 1999;**81**:271–5.
- 13 Shenkin PA. Training in metabolic medicine. *Clin Med* 2001;**1**:392.
- 14 Wilcken B. Newborn screening for inborn errors of metabolism—clinical effectiveness. *J Inher Metab Dis* 2006;**29**:336–9.