have the care of patients as the prime objective for their work.

(3) "It will be essential that the evangelists of evidence remember that researchers have a duty of care towards their subjects, just as clinicians do towards their patients", writes Clarke. One of the reflections of the developed sense of duty of care by researchers towards research participants is the comprehensive and stringent system of Research Ethics Committees in which researchers, clinicians, and others are involved. All health workers have obligations both to the welfare of patients and to assessing continually the evidence on which their care decisions are based.

The greater the ethical, social, and psychological dilemmas associated with new developments in health care, the greater the need for relevant evidence to inform the decisions about whether, and how, to offer new services. Without this, decisions will, de facto, be made by those with purchasing, political, commercial, or medical power, decisions that will not necessarily be in patients' best interests.

## D409H/D409H genotype in Gaucher-like disease

We read with great interest the report by Chabas *et al*[1] on Spanish sibs with Gaucher disease linked with homozygous D409H (1342C) mutation presenting cardiovascular calcifications. However, they did not cite our article,[2] in which we delineated an unusual form of glucocerebrosidase deficiency on the basis of thorough clinicopathological investigations in three Japanese sibs. In fact, the unusual clinical manifestations of their juvenile Spanish patients[1] closely resembled those of our adult Japanese patients,[2] including fatal left sided valvular stenosis with calcification, corneal opacities, and supranuclear ophthalmoplegia. Also, communicating hydrocephalus, sensorineural deafness, and deformed toes were present in our Japanese sibs,[2] but common manifestations of Gaucher disease were less evident. This unique syndrome has been classified as "Gaucher-like disease (McKusick, MIM 231005)".[3] To determine whether both groups of patients share the same genotype and to establish the tightness of phenotype/genotype correlation in this syndrome, we tested for the D409H mutation of the glucocerebrosidase gene.

Genomic DNA was prepared from a frozen spleen taken at necropsy of patient 1 who died aged 44.[2] PCR based screening for the D409H mutation was performed as previously described.[4] A segment of the glucocerebrosidase gene spanning exons 9 to 11 was amplified using the oligonucleotide primer pair: 5'-ACCCCGAAGGAGGACCCAAT-3' (sense) and 5'-TGCCTCCTTGAGTAT CTGCT-3' (antisense). To avoid amplifing a pseudogene, PCR was performed for 25 cycles at 94°C for two minutes, at 53°C for three minutes, and at 72°C for three minutes. The resulting 825 bp product was digested with *Sty*I and the digests were resolved on 20% PAGE gel. As shown in fig 1, the proband's genotype was homozygous for the D409H mutation. None of the other mutations including L444P, N370S, P415R, F213I, 84GG, IVS2+1, and R463C were identified in our screening using previously

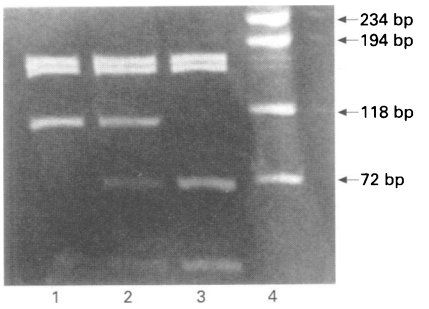


*Figure 1 Restriction site analysis of genomic DNA for the D409H mutation. An 825 bp fragment was amplified by PCR and digested with StyI. Lane 1, the proband; lane 2, heterozygote for D409H mutation; lane 3, normal control; lane 4, DNA size markers. The normal allele was digested to produce 37 bp, 65 bp, 156 bp, and 170 bp fragments. The D409H mutant allele was digested to produce 102 bp, 156 bp, and 170 bp fragments.*

reported methods.[4] Genotyping for the Pv1.1[5] and PKLR[6] polymorphism in our case showed the -/- and -/- genotype, respectively.

The prevalance of mutant alleles among Japanese patients with Gaucher disease seems to differ from that observed in affected subjects of Jewish and non-Jewish European ancestry.[4] By contrast, the phenotype of the D409H/D409H genotype appears to be identical in such diverse communities as the Spanish,[1] Japanese,[2] Arab,[7] and British/German.[8] Thus, there is a particularly tight pan-ethnic association between phenotype and genotype in this syndrome.

It was remarkable on re-evaluation of our postmorten examination that there was severe connective tissue involvement with a pattern resembling that of other lysosomal storage disorders, particularly the mucopolysaccharidoses (MPS); calcified aortic and mitral stenosis with marked fibrosis resulted from extensive pulmonary involvement, intimal fibrous thickening of the ascending aorta, and leptomeningeal thickening with marked perivascular fibrosis. Furthermore, ultrastructural studies disclosed proliferation of abundant vacuolated Gaucher cells resembling foam cells, in addition to classical Gaucher cells found only in the bone marrow.[2] These observations, together with the unusually severe "fibrotic changes" in connective tissue, indicate that an additional process is operating. Although we performed repeated urine screening spot tests for MPS,[2] assays of eight other kinds of lysosomal enzymes,[2] and extensive ultrastructual re-examinations, we could not detect any evidence of other coincidental lysosomal disorders, such as MPS and glycoprotein storage diseases.

As suggested by Mistry,[9] the recent discovery of metaxin,[10] a gene contiguous to both thrombospondin 3 and glucocerebrosidase, leads to the possibility of the presence of a contiguous gene syndrome in Gaucher-like disease. However, current investigations indicate no evidence for common metabolic relationships or for structural interactions between corresponding proteins of the metaxin and glucocerebrosidase genes in the human.[11] To elucidate the pathogenesis of unusual clinicopathological manifestations in this syndrome, further investigations for the peculiar connective tissue involvement associated with the unique genotype are required.

We gratefully acknowledge the contributions of Drs K Takahashi, R Okamura, M Naito, S Tsuji, S Kawasaki, and S Araki. Part of this work was supported by grants in aid for scientific research from the Ministry of Education, Science and Culture in Japan (05670563 to EU).

EIICHIRO UYAMA
MAKOTO UCHINO
*Department of Neurology, Kumamoto University School of Medicine, 1-1-1 Honjo, Kumamoto 860, Japan*

HIROYUKI IDA
YOSHIKATSU ETO
*Department of Pediatrics, The Jikei University School of Medicine, Tokyo, Japan*

MISAO OWADA
*Department of Pediatrics, Nihon University Surugadai Hospital, Tokyo, Japan*

1 Chabas A, Cormand B, Grinberg D, *et al.* Unusual expression of Gaucher's disease: cardiovascular calcifications in three sibs homozygous for the D409H mutation. *J Med Genet* 1995;**32**:740-2.
2 Uyama E, Takahashi K, Owada M, *et al.* Hydrocephalus, corneal opacities, deafness, valvular heart disease, deformed toes and leptomeningeal fibrous thickening in adult siblings: a new syndrome associated with β-glucocerebrosidase deficiency and a mosaic population of storage cells. *Acta Neurol Scand* 1992;**86**:407-20.
3 McKusick VA, Francomano CA, Antonarakis SE, Pearson PL. *Mendelian inheritance in man.* 11th ed. Baltimore: The Johns Hopkins University Press, 1994:411.
4 Ida H, Iwasawa K, Kawame H, Rennert OM, Maekawa K, Eto Y. Characteristics of gene mutations among 32 unrelated Japanese Gaucher disease patients: absence of the common Jewish 84GG and 1226G mutations. *Hum Genet* 1995;**95**:717-20.
5 Zimran A, Gelbart T, Beutler E. Linkage of the PvuII polymorphisum with the common Jewish mutation for Gaucher disease. *Am J Hum Genet* 1990;**46**:902-5.
6 Glenn D, Gelbart T, Beutler E. Tight linkage of pyruvate kinase (PKLR) and glucocerebrosidase (GBA) genes. *Hum Genet* 1994;**93**:635-8.
7 Abrahamov A, Elstein D, Gross-Tsur V, *et al.* Gaucher's disease variant characterized by progressive calcification of heart valves and unique genotype. *Lancet* 1995;**346**:1000-3.
8 Beutler E, Kattamis C, Sipe J, Lipson M. 1342C mutation in Gaucher's disease. *Lancet* 1995; **346**:1637.
9 Mistry PK. Genotype/phenotype correlations in Gaucher's disease. *Lancet* 1995;**346**:982-3.
10 Bornstein P, McKinney CE, LaMarca ME, *et al.* Metaxin, a gene contiguous to both thrombospondin 3 and glucocerebrosidase, is required for embryonic development in the mouse: implications for Gaucher disease. *Proc Natl Acad Sci USA* 1995;**92**:4547-51.
11 Long GL, Winfield S, Adolph KW, Ginns EI, Bornstein P. Structure and organization of the human metaxin gene (MTX) and pseudogene. *Genomics* 1996;**33**:177-84.

# BOOK REVIEWS

If you wish to order or require further information regarding the titles reviewed here, please write to or telephone the BMJ Bookshop, PO Box 295, London WC1H 9JR. Tel 0171 383 6244. Fax 0171 383 6662. Books are supplied post free in the UK and for BFPO addresses. Overseas customers should add 15% for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank or by credit card (Mastercard, Visa, or American Express) stating card number, expiry date, and full name. (The price and availability are occasionally subject to revision by the Publishers.)

**Neurology of Hereditary Metabolic Disorders of Children**. G Lyon, R D Adams, E H Kolodny. (Pp 379; $75.00.) New York: McGraw-Hill. 1996. ISBN 0-07-000389-0.

There is a need for a book on hereditary metabolic disease of childhood which is user friendly, not too large to pick up, not in two volumes, and written primarily for the clinician. This book fulfils all of these criteria. It has even been printed on acid free paper (could it be more user friendly?), and although the book will not fit neatly into your pocket (it is fairly comprehensive) it will not concuss you either when it falls off the shelf.

The authors, who are well respected clinicians in the field, have taken the unusual stance in deciding not to describe disorders according to their chemistry. The chapters are not entitled "organic acid disorders" or those of "purine and pyrimidine defects" but are subdivided according to age of onset and this is just how a clinician would begin to think. The first chapter, therefore, deals with disorders presenting in the neonatal period, and then it proceeds through early infantile onset, late infantile, into childhood and adolescence. This does necessitate some degree of repetition. The discussion of Krabbe's disease, for instance, which might present in any of those age groups, is dealt with in various chapters, but this does not seem to matter as the infantile onset disease is so different from that appearing in childhood. Laboratory tests, and the latest genetic linkage information, are well covered. The primary defect in Smith-Lemli-Opitz syndrome is mentioned and prenatal diagnosis has not been neglected.

What is particularly pleasing is that the authors bring their own clinical practice with sentences like "to an experienced neurologist intention myoclonus ... alway conveys the idea of hereditary metabolic disease", and the text is full of tips. They are not frightened to say "in our experience there are five major troublesome areas", and these are listed in point form and discussed.

Another outstanding feature is the line drawings indicating the clinical course and life profile of well known diseases showing when different clinical features appear in the course of deterioration. There is also a helpful perspective in that the authors are prepared to be fairly dogmatic. They would state "in some metabolic encephalopathies seizures are obligatory signs", and the reader knows they are in the hands of experts and would take heed. This book should be read, and I mean read, by all paediatric neurologists of whatever age. This reviewer remembers many years ago, when a senior registrar in neurology in Cape Town, being visited, and suitably put in his place by the now, I take it, very senior author of this book (RDA), and being astounded by his erudition. He and his co-authors are still imparting erudition with enthusiasm.

MICHAEL BARAITSER

**An Introduction to Recombinant DNA in Medicine**. 2nd edition. A E H Emery, S Malcolm. (Pp 206; £14.95.) Chichester: John Wiley. 1995. ISBN 0-471-93984-6.

The authors' stated aim is to "provide an introduction to the subject of recombinant DNA technology for those whose interests are perhaps more medically orientated ... (giving) a simple outline of the general principles of DNA technology and some of the ways in which it can be applied".

In writing this illustrative rather than comprehensive text, they have been broadly successful in fulfilling this aim. To distil the essence of a subject is more difficult than merely recording every last detail.

The first part of the book summarises the structure and function of DNA, DNA technology, and gene mapping, structure, and function. Although some sections are astonishingly brief (for example, that on protein translation), the text is clearly written and conveys concepts and strategies rather than being overloaded with nomenclature. However, some of the diagrams are unclear; for example, the one to explain Sanger sequencing is confusing. In addition, the majority of the first chapter could be dropped without loss; most of the information is duplicated elsewhere.

The next two chapters deal with the molecular pathology of disease. Firstly, the principles of single gene disorders are discussed, with particular focus on the haemoglobinopathies, followed in the subsequent chapter with examples of the causation of common diseases such as diabetes. A highlight of the book is the section on cancer genetics, an excellent summary of the field.

Prevention of genetic disease through prenatal diagnosis is covered well and uses Duchenne muscular dystrophy to illustrate the range of methods available. The last major chapter alludes to some of the treatment options, again, a very neat summary.

Overall, this short book is a good starting point for someone who wishes to introduce themselves to molecular medicine, and it should entice them to read further.

FIONA NORWOOD

**Human Molecular Genetics**. Editor Kenneth W Adolph. (Pp 500; $85.00.) New York: Academic Press. 1996. ISBN 0-12-044310-4.

There are now a large number of books available which describe the theory and techniques of molecular genetics, many of which include protocols for the experimental techniques. This book is the eighth volume of a series of such books describing methods in molecular genetics, and deals in particular with human molecular genetics. It is a comprehensive book dealing with many newer techniques and covers a wide range of subjects from gene mapping and mutation detection to transcription, RNA editing, signal transduction, and the use of the mouse as a model system. It is aimed at providing practical experimental advice for experienced scientists and achieves this well.

This is a useful addition to the body of publications and is well thought out. There are 26 chapters separated into seven sections: mutation detection in human genes; gene mapping, cloning, and sequencing; transcription, promoters, transcription factors, mRNA, RNA editing, ribozymes, antisense RNA; genome recombination, amplification; receptors, signal transduction; the mouse as a model system for human molecular genetics. Each chapter covers a different technique and includes a brief explanation and detailed protocols. The techniques described are dealt with very well and in enough detail to allow the reader to attempt the techniques based on the information given. Many topics are covered but there are, however, some omissions. In the section entitled gene mapping, cloning, and sequencing, for example, there are chapters describing direct cDNA selection, subtraction cDNA cloning, and fluorescent differential display but no mention is made of exon trapping.

As an introduction to the techniques some of the chapters are excellent and provide the background information necessary to understand and interpret results, but the book covers such a wide range of techniques that it is unlikely that one person would want to read every chapter in detail. The format is rather dry and the book would not be a good teaching aid, but for the experienced scientist would be a good reference text. I am not sure I would rush out to buy a copy but would find it helpful to refer to occasionally and would be glad to find a copy in the genetics department library.

DOROTHY TRUMP

# NOTICE

**38th Annual Short Course in Medical and Experimental Mammalian Genetics**

This course will be held on 14-25 July 1997 at The Jackson Laboratory in Bar Harbor, Maine, USA. For further information contact: 1997 Courses and Meetings, The Jackson Laboratory, tel: (207) 288-6262; fax: (207) 288-6080; Email: education-@aretha.jax.org; URL: http://www.jax.org.