investigation of these patients, incorporating both clinical and laboratory evidence.[3] It would be of great value to carry out a skeletal muscle biopsy on the patient described by Dr Albin, looking for histochemical and biochemical evidence of mitochondrial respiratory chain dysfunction. These investigations are often abnormal in patients with neurological abnormalities resulting from mtDNA disease, and the characteristic mosaic pattern of cytochrome c oxidase activity in muscle or a biochemical complex deficiency may provide clues as to the nature of the underlying genetic defect. It is often difficult to ascribe pathogenicity to a mtDNA mutation, particularly if the disease has an unusual phenotype.[3 11] Therefore, although the clinical evidence presented by Dr Albin is compatible with a mitochondrial disorder, the inference that the T4216C and G15257A nucleotide transitions are the primary aetiological factor responsible for Fuch's corneal dystrophy is unfounded.

PFC is a Wellcome Trust Research Fellow. RA is a MRC (UK) Research Fellow. NH is supported by the Wellcome Trust, The National Eye Institute (RO1 EY10758), and the John Sealy Memorial Endowment Fund.

PATRICK F CHINNERY
DOUGLASS M TURNBULL
Department of Neurology, The University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH, UK

NEIL HOWELL
Department of Radiation Oncology, University of Texas Medical Branch, Galveston, USA

RICHARD M ANDREWS
Department of Ophthalmology, The University of Newcastle upon Tyne, UK

1 Albin RL. Fuch's corneal dystrophy in a patient with mitochondrial DNA mutations. *J Med Genet* 1998;**35**:258-9.
2 Chinnery PF, Turnbull DM. Mitochondrial medicine. *Q J Med* 1997;**90**:657-66.
3 Chinnery PF, Turnbull DM. The clinical features, investigation and management of patients with mitochondrial DNA defects. *J Neurol Neurosurg Psychiatry* 1997;**63**:559-63.
4 Howell N. Leber hereditary optic neuropathy: how do mitochondrial DNA mutations cause degeneration of the optic nerve? *J Bioenerget Biomemb* 1997;**29**:165-73.
5 McCartney MD, Robertson DP, Wood TO, McLaughlin BJ. ATPase pump site density in human dysfunctional corneal epithelium. *Invest Ophthalmol Vis Sci* 1987;**28**:1955-62.
6 Johns DR. The other genome: mitochondrial DNA and disease. *Nat Med* 1996;**2**:1065-8.
7 Pineros O, Cohen EJ, Rapuano CJ, Laibson PR. Long-term results after penetrating keratoplasty for Fuchs' endothelial dystrophy. *Arch Ophthalmol* 1996;**114**:15-18.
8 Howell N, Kubacka I, Halvorson S, Howell B, McCullough DA, Mackey D. Phylogenetic analysis of the mitochondrial genomes from Leber hereditary optic neuropathy pedigrees. *Genetics* 1995;**140**:285-302.
9 Torroni A, Petrozzi M, D'Urbano L, *et al.* Haplotype and phylogenetic analyses suggest that one European-specific mtDNA background plays a role in the expression of Leber hereditary optic neuropathy by increasing the penetrance of the primary mutations 11778 and 14484. *Am J Hum Genet* 1997;**60**:1107-21.
10 Howell N. Primary LHON mutations: trying to separate "fruyt" from "chaf". *Clin Neurosci* 1994;**2**:130-7.
11 Schon EA, Bonilla E, DiMauro S. Mitochondrial DNA mutations and pathogenesis. *J Bioenerget Biomemb* 1997;**29**:131-49.

"Cataplexy" in Coffin-Lowry syndrome

Crow *et al*[1] reported an unusual, non-epileptic, cataplexy-like phenomenon in three males with Coffin-Lowry syndrome (CLS). The authors also provided evidence of neuromuscular dysfunction as part of the phenotype by showing abnormalities on muscle ultrasound in four gene carriers, and they commented on our observation of marked distal muscle wasting in two affected brothers, aged 15 and 14 years at the time of our report.[2] In that report, we described the frequent occurrence of generalised epileptic seizures without pathognomonic epileptic elements on EEG after the age of 6 years. We had occasion to follow these CLS brothers up to their sudden death at the age of 32 and 34 years, respectively. During this follow up it became evident that the "epileptic episodes" were episodes of sudden, non-epileptic collapses with atonia; as in case 1 reported by Crow *et al*,[1] these episodes were precipitated by a loud noise or excitement. The frequency and severity of these drop attacks worsened with age and was correlated with a further progression of the peripheral muscle wasting and of a severe thoracolumbar torsion scoliosis, which finally resulted in acute cardiorespiratory failure.

Over the last 25 years we have had the opportunity to examine 20 other CLS males. In one of these patients the same type of sudden, non-epileptic attacks were noted from the age of 4 years. When walking this CLS boy suddenly dropped, always in a forward position, hurting himself. No epileptic discharges have ever been noted on repeated 24 hour EEG monitoring. Also, a progressive thoracolumbar scoliosis was noted in this boy, and after the experience in the two brothers we decided to operate on the scoliosis at the age of 14 years with satisfactory correction and stabilisation of the curvature. On that occasion a muscle biopsy was performed with normal results. Much to our surprise, the frequent episodes of sudden and reversible loss of muscle tone have completely disappeared after the scoliosis fusion.

In conclusion, our experience in CLS males confirms that "cataplexy" is not rare in this XLMR syndrome, as we observed it in three of 22 male patients. The aetiology and pathogenesis of this sudden collapse phenomenon remains unclear. In this perspective, it is of interest to note that these cataplexy-like symptoms increased in frequency and severity in the two brothers, together with progression of the torsion scoliosis and muscle wasting. In contrast, the collapse symptoms disappeared completely in the third male after surgical correction of the scoliosis.

JEAN-PIERRE FRYNS
ERIC SMEETS
Centre for Human Genetics, University of Leuven, Herestraat 49, B-3000 Leuven, Belgium

1 Crow YJ, Zuberi SM, McWilliam R, *et al.* "Cataplexy" and muscle ultrasound abnormalities in Coffin-Lowry syndrome. *J Med Genet* 1998;**35**:94-8.
2 Fryns JP, Vinken L, Van den Berghe H. The Coffin syndrome. *Hum Genet* 1977;**36**:271-6.

Autoclaving Guthrie cards does not prevent their use in PCR reactions!

Doctors Rahman, Emery, and Poulton (*J Med Genet* 1998;**35**:263) point out their problems in obtaining neonatal screening dried blood spots or Guthrie cards from patients with the MELAS 3243 mutation. They comment that of the four cards they were able to obtain, one had been autoclaved. This, they claim, destroys the DNA.

Dried blood spot cards are commonly autoclaved or steamed before performing the bacterial inhibition assay for phenylalanine in screening for phenylketonuria (PKU).[1] We have used such blood spots for analysis of the common mutations for medium chain acyl CoA dehydrogenase deficiency (MCADD), hereditary fructose intolerance, and the NARP 8993 mutation. One has also been successfully used for identification purposes by DNA fingerprinting. In a study of autoclaved blood spots from 5014 neonates in the West Midlands Region[2] for the common MCADD mutation, a failure rate of PCR of only 0.3% was obtained.[3]

Hence there is no reason to believe autoclaving per se substantially contributes to a poor PCR. In fact it may be that denaturing contaminating protein by autoclaving may help to reduce the amount of protein carried over during extraction and hence reduce the risk of PCR failure. However, we fully support the authors' suggestions for central funding for the storage of this important medical resource.

R G F GRAY
S K HALL
West Midlands Regional Laboratory for Neonatal Screening and Inherited Metabolic Disorders, The Birmingham Children's Hospital NHS Trust, Ladywood Middleway, Ladywood, Birmingham B16 8ET, UK

1 Guthrie R, Susi A. A simple method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics* 1963;**32**:334-8.
2 Seddon HR, Green A, Gray RFG, *et al.* Regional variations in medium chain acyl COA dehydrogenase deficiency. *Lancet* 1995;**345**:135-6.
3 Seddon HR, Gray G, Pollitt RJ, *et al.* Population screening for the common G985 mutation causing medium chain acyl-COA dehydrogenase deficiency with Eu-labeled oligonucleotides and the DELFIA sytem. *Clin Chem* 1997;**43**:436-42.

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.)

Genetic Disorders and Pregnancy Outcome. Editors L D Platt, R Koch, F de la Cruz. (£55.00, $98.00.) London: Parthenon Publishing. 1997. ISBN 1-85070-721-9.

Many clinicians who deal with high risk obstetrics or have specialised in maternal-fetal medicine, obstetric physicians, and geneticists will welcome a book on the approach to management of people with genetic disorders who intend to have

catalytic activities, are even less well studied for their in vivo effects.

RON TRENT

The Yeast Two-Hybrid System. Editors Paul L Bartel, Stanley Fields. New York: Oxford University Press. 1997. ISBN 0-19-510938-4.

It is now difficult to open a life science journal without reading at least one paper with the sentence "a yeast two hybrid screen was performed..." so the arrival of this attractively produced book caused a stir in my laboratory. It is written by the people who developed the system. Late one afternoon in 1987, Stanley Fields (then a new assistant professor at SUNY in a small laboratory working on an obscure aspect of yeast pheromone responses) suddenly realised that he could use two different hybrid proteins, one containing a DNA binding domain and the other a transcription activation domain, to detect protein-protein interactions. He immediately recognised that it might be feasible to use the system to search cDNA libraries to find novel protein partners. It is ironic that a seed grant proposal written later that same year was rated by the review panel as "having no possibilities for commercial development" and the research was eventually supported by Procter and Gamble. Eleven years later Fields and his colleagues must feel entitled to a quiet glow of vindication as they survey the honour roll of proteins pulled out of yeast two hybrid screens. For example, in working out cell cycle checkpoint control during the early 1990s, the CDK inhibitors p16,18, p19, p21, and p27 were all discovered by different groups using the system.

Many people will buy the book for the three early chapters which describe the nuts and bolts of manipulating yeast and performing a basic library screen. Each of these chapters is devoted to one of three different systems that have been developed by different groups over the years. The protocols are clear and sufficiently detailed to allow someone who has never worked with yeast to perform a two hybrid screen (chapter 3 is an improved and more detailed version of a much photocopied protocol which our laboratory has used successfully over the past three years). We have found that the scientists who developed the system are generous with their time and reagents and this impression is reinforced by the list of laboratory web pages, e-mail addresses, telephone and fax numbers at the end of chapter 4. These first four chapters justify the price of the book. I also enjoyed the clear description of the ingenious reverse two hybrid system for mapping critical residues in protein-protein interactions and will use the protocols presented here, which seem straightforward. A chapter on constructing activation domain-fusion libraries did not provide much more information than can be obtained from Maniatis. Other chapters are more descriptive or speculative; there are reviews of ligand-receptor interactions, cell cycle and signal transduction pathways which, although well written, cannot provide more than an overview in the space assigned to them, and I was disappointed that the one hybrid system which holds great promise for detecting DNA binding proteins was only given a brief space. The possibility of using the yeast two hybrid system to generate massive whole genome protein interaction connectivity networks in the "post-genomic future of the 21st century" is discussed in a very readable chapter; it sounds like science fiction, but given the achievments of the yeast community in the last decade, I wouldn't be surprised if they pull it off.

LUKE HUGHES-DAVIES

Genetics. A Molecular Approach. 3rd edition. T A Brown. (£27.50.) London: Chapman and Hall. 1998. ISBN 412 798700.

The field of molecular genetics is vast and complex with its own extensive vocabulary and it is hard for a novice to approach it without feeling daunted. However, an understanding of genetics is now essential for most undergraduate and postgraduate science and medical students. This well written book will be welcomed by both newcomers and experienced geneticists as well as those who teach the subject to undergraduates.

Starting with DNA rather than Mendel, the author tells the story of genetics in three parts. In part 1, he explains the structure of DNA and the chemical nature of the gene with chapters describing control of gene expression and DNA replication, mutation, repair, and recombination. In part 2, genes are put into the context of genomes, both prokaryotic and eukaryotic, with an excellent chapter describing the structure of the human genome including gene families and pseudogenes, extragenic DNA, and polymorphisms. Part 3 describes patterns of inheritance with sections on Mendel's experiments and their subsequent molecular explanations, genetic linkage, the human genome mapping project, and an overview of the techniques currently used in the molecular biology laboratory. An historical context is maintained throughout the book with descriptions of landmark experiments such as those used by Hershey and Chase in the 1950s to show that genetic material is DNA and not protein.

The text is clear, succinct, and liberally illustrated and no new term is introduced without being defined and listed in the extensive glossary. The author is clearly an experienced teacher of his subject and has written a book which is both readable and informative. I would have no hesitation in recommending this book to anyone needing a thorough grounding in molecular genetics.

JULIA RANKIN

The Calculation of Genetic Risks: Worked Examples in DNA Diagnostics. 2nd edition. Peter J Bridge. (£34.50.) Baltimore: The Johns Hopkins University Press. 1998. ISBN 0-8018-5744-9.

Apart from a few exceptional people, I think that geneticists, whether clinical or in the molecular diagnostic laboratory, are not particularly mathematically inclined. Indeed, I am fairly certain that there are many, including me, who develop a curious form of mental fugue when faced with the more complex risk calculations that we sometimes come across in clinical genetic practice. Peter Bridge's book is written for us. The main aim of the book is to provide the reader with the skills required to formulate sensible risk calculations, and it takes a very practical approach, building from problems which use only pedigree information to increasingly complex problems incorporating biochemical and molecular genetic information. The problems are not abstract; service geneticists could expect to meet very similar ones on a regular basis. The particular beauty of this book lies in its comprehensibility. Rather than inflicting difficult equations on us, the author instead uses clarity of ideas and expression, and emphasises general principles. My one criticism is the lack of "self-test" problem sections at the end of each chapter, which would allow readers to really test their new understanding. However, I would unhesitatingly recommend this book to clinical geneticists, molecular geneticists in diagnostic laboratories, and to anyone who wants to have a good grounding in the principles of risk calculation for genetic disease.

EVAN REID

NOTICES

British Human Genetics Conference

The British Human Genetics Conference will be held on 28-30 September 1998 at the University of York, England. There will be special sessions on: Practical approaches to methylation and imprinting; FISH: present and future; Predictive testing protocols - who benefits; The genetics of human behaviour; Human evolution; Joint symposium on multiple endocrine neoplasia with the Cancer Family Study Group, as well as plenary sessions. The Carter Lecture will be given by Professor Ken Kidd on "Evolution of modern humans". Further information from Professor Peter Farndon, British Society for Human Genetics, Clinical Genetics Unit, Birmingham Women's Hospital, Edgbaston, Birmingham B15 2TG, UK. Tel/fax: 0121 627 2634, e-mail: bshg@bham.ac.uk http://www.bham.ac.uk/bshg

The National Registry for Ichthyosis and Related Disorders

The purpose of this NIH supported registry is to improve methods of diagnosis, promote the search for basic defects, and develop more effective methods of treatment/prevention of the inherited scaling skin disorders. Affected people are asked to enrol through their local dermatologists. All contact information is kept confidential. Persons with ichthyoses (except ichthyosis vulgaris), erythrokeratodermas, Darier disease, Hailey-Hailey disease, palmar-plantar keratodermas, pachyonychia congenita, extensive epidermal naevi, and related disorders are eligible for enrolment. The Registry offers a means of "empowerment" for affected people and family members. It enables skin biologists, pharmacologists, and other investigators to share information about ongoing and future research with this well characterised group having specific diagnoses. For information please contact us at: The National Registry for Ichthyosis and Related Disorders, Box 356524, Seattle, WA 98195-6524, USA. Tel: 1-800-595-1265 or 1-206-616-3179, e-mail: ichreg@u.washington.edu or visit our web site at http://weber.u.washington.edu/~geoff/ichthyosis.registry/

Philip Fleckman, MD, Principle Investigator
Geoffrey Hamill, RN, Registry Coordinator