- 1 Boat TF, Welsh MJ, Beaudet AL. Cystic fibrosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic basis of inherited disease*. New York: McGraw-Hill, 1989:2649-80.
- 2 Daigneault J, Aubin G, Simard F, De Braekeleer M. Genetic epidemiology of cystic fibrosis in Saguenay-Lac-St-Jean (Quebec, Canada). *Clin Genet* 1991;40:298-303.
- 3 Daigneault J, Aubin G, Simard F, De Braekeleer M. The incidence of cystic fibrosis in Saguenay-Lac-St-Jean (Quebec, Canada). *Hum Biol* 1992;64:115-19.
- 4 Rozen R, De Braekeleer M, Daigneault J, et al. Cystic fibrosis mutations in French Canadians: three mutations are relatively frequent in a Quebec population which has an elevated incidence of cystic fibrosis. *Am J Med Genet* 1992;42:360-4.
- 5 De Braekeleer M, Allard C, Leblanc JP, Simard F, Aubin G. Genotype-phenotype correlation in cystic fibrosis patients compound heterozygous for the A455E mutation. *Hum Genet* (in press).
- 6 De Braekeleer M, Daigneault J, Aubin G, et al. Phenotypic heterogeneity in CF sibs compound heterozygous for the G85E and 621+1G→T mutations. *Clin Genet* 1995;47:110-11.
- 7 De Braekeleer M, Simard F, Aubin G. Little phenotypic variability in three CF sibs compound heterozygous for the 621+1G→T and the 711+1G→T mutations. *Clin Genet* 1997;51:214-15.
- 8 De Braekeleer M, Allard C, Leblanc JP, Simard F, Aubin G. Genotype-phenotype correlation in five cystic fibrosis patients homozygous for the 621+1G→T mutation. *J Med Genet* 1997;34:788-9.

UK centres are not following the Royal College of Pathologists' recommendations for storage of Guthrie cards: a national policy is needed

Stored neonatal blood spots are a valuable source of DNA for retrospective diagnosis.¹ A recent working party of the Royal College of Pathologists recommended storage of neonatal screening test (Guthrie) cards for at least 20 years provided that no deterioration of the sample has occurred.² Our recent attempts to trace such cards convince us that a UK national policy and central funding for storage of Guthrie cards is necessary.

Mitochondrial encephalopathy with stroke-like episodes (MELAS) is frequently associated with a mitochondrial DNA point mutation A3243G.³ Segregation and proliferation of this mutation in different tissues is not well understood. Levels of the 3243 mutant in blood are usually lower than in muscle⁴ and cross sectional data suggest that the level of mutant in blood may fall with increasing age.⁵ There is concern that cases of MELAS may be missed if diagnosed using the polymerase chain reaction (PCR) on blood. Longitudinal studies are necessary to clarify this issue. We have initiated a European collaborative study using Guthrie cards to compare levels of the 3243 mutant mtDNA in blood at birth and at diagnosis, under the auspices of the European Neuromuscular Centre.

We identified 23 patients with MELAS born in the UK after 1970 and, with the informed consent of the patients or parents or both as appropriate, sought their Guthrie cards for quantitative assessment of mutant load at birth. It has been possible to locate only four cards, and one of these has been autoclaved (this destroys DNA). Hence, the failure rate was 87%, despite cooperation from repositories and great persistence. A telephone survey of the 25 UK neonatal screen-

ing laboratories showed marked variability in practice between regions. Two centres use serum for screening rather than blood spots, and one stores blood spots for five months only. Only 12 centres store cards for longer than 10 years, and the trend is towards shorter periods because of financial pressures.

We suggest that a national policy for storage of neonatal blood spots is needed and that this may require central funding. Centralisation of cards and records would be an advantage as families now move between regions frequently and do not always recall their previous addresses. Cards should be stored in such a way as to prevent cross contamination, particularly if PCR is to be used in analysis of the blood spot.¹

SHAMIMA RAHMAN

Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

ALAN EMERY

European Neuromuscular Centre, Baarne, The Netherlands

JOANNA POULTON

University Department of Paediatrics, John Radcliffe Hospital, Oxford OX3 9DU, UK

- 1 Gregerson N, Blakemore AIF, Winter V, et al. Specific diagnosis of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency in dried blood spots by a polymerase chain reaction (PCR) assay detecting a point-mutation (G985) in the MCAD gene. *Clin Chim Acta* 1991;203:23-4.
- 2 Royal College of Pathologists. *The retention and storage of pathological records and archives*. Report of the Working Party of the Royal College of Pathologists, February 1995.
- 3 Goto YI, Nonaka I, Horai S. A mutation in the tRNA^{Leu}(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature* 1990;348:651-3.
- 4 Ciafaloni E, Ricci E, Shanske S, et al. MELAS: clinical features, biochemistry and molecular genetics. *Ann Neurol* 1992;31:391-8.
- 5 Poulton J, Morten K. Noninvasive diagnosis of the MELAS syndrome from blood DNA. *Ann Neurol* 1993;34:116.

Cyclopia and sirenomelia in a liveborn infant

Recently, Chen *et al*¹ published the case of a stillborn infant who presented with cebocephaly, alobar holoprosencephaly, spina bifida, and sirenomelia. We would like to describe a liveborn infant with cyclopia and sirenomelia, identified by the Spanish Collaborative Study of Congenital Malformations (ECEMC).^{2,3} This infant is similar to the one published by Chen *et al*,¹ although with a more severe form of clinical holoprosencephaly with cyclopia, absent nose with presence of a proboscis, and without any evidence of spina bifida.

In 1992, we participated in an epidemiological study in an international collaboration,⁴ providing data from the ECEMC to the study group. A picture of the case we are describing here in detail was published in the paper by Källén *et al*⁴ just to illustrate the title of that paper (The cyclops and the mermaid) but the case, which was included in the epidemiological analysis, was not described at all. In 1994, in a Letter to the Editor,⁵ we commented that we had observed a case with cyclopia and sirenomelia that may be a clinical representation of the so-called Monster of Ravenna, but the case was not described.

The infant was the product of the second pregnancy of a 29 year old mother and a non-consanguineous 33 year old father, both healthy. There was no family history of congenital malformations. The first preg-

nancy ended, a year earlier, in a normal male infant. In 1978, the proband was born spontaneously at 39 weeks of gestation after an uncomplicated pregnancy, apart from a respiratory tract infection during the first 15 days of gestation. The mother denied any exposure to known teratogens, including alcohol and tobacco. She also denied having had problems in conceiving. At birth, the infant's weight was 1600 g (<<3rd centile). The infant died at 15 minutes and had microcephaly, absent nose with presence of a proboscis, cyclopia, sirenomelia, and a clinical right forearm deficiency. No external genitalia or anus were visible. The umbilical cord contained only an artery and a vein. It was not possible to perform any radiological study, karyotype, or necropsy.

The prevalence of any type of holoprosencephaly in the series of 1 245 863 births monitored by the ECEMC between 1980 and 1996 is 0.83 per 10 000 births, while the prevalence of cyclopia and sirenomelia is 0.10 and 0.08 per 10 000 births, respectively. In an epidemiological study on the association of holoprosencephaly and caudal dysgenesis,⁶ we showed that both types of malformation tend to be preferentially associated. That is, both are associated in the same child with a frequency that is significantly higher than would be expected just by chance. However, the combination of the two most extreme forms of alteration of the cephalic and caudal part of the embryo, cyclopia and sirenomelia, is very infrequent. In fact, our case was identified among a total of 1 245 863 births. It appears that this case is the first one published with cyclopia and sirenomelia, bringing to three the total published cases with different degrees of holoprosencephaly and sirenomelia.^{1,7}

Cyclopia and sirenomelia are gross alterations of early blastogenesis. Thus, as Opitz postulated⁸ and we reported,³ the combination of the two conditions, which is lethal, is a polytypic response of the alteration of the primary field, mostly affecting the midline. We have also observed⁹ that mothers of infants with blastogenetic defects have a higher proportion of previous abortions that may mask the recurrence risk. However, we consider that in cases of holoprosencephaly (with different degrees of severity) and sirenomelia, in the absence of chromosomal abnormalities and maternal diabetes, the recurrence risk at birth should be very low.

We think that it is important to present this case in detail since, at present, it is the only one that has the two most severe forms of alteration of the cephalic and caudal part of the embryo (cyclopia and sirenomelia), and also because it was identified among a series of consecutive births, which allows the estimation of the birth prevalence of this entity.

This work was supported in part by a grant from "Fundación 1000 para la investigación sobre defectos congénitos" of Spain, and by a grant from Dirección General de Salud Pública, Ministerio de Sanidad y Consumo, Spain.

M L MARTÍNEZ-FRÍAS

ECEMC and Departamento de Farmacología, Facultad de Medicina, Universidad Complutense, 28040 Madrid, Spain

A GARCÍA

Servicio de Pediatría, Hospital General del Insalud, Guadalajara, Spain

E BERMEJO

ECEMC, Facultad de Medicina, Universidad Complutense, Madrid, Spain

- 1 Chen CP, Shih SL, Liu FF, Jan SW. Cebocephaly, alobar holoprosencephaly, spina bi-

- fida, and sirenomelia in a stillbirth. *J Med Genet* 1997;34:252-5.
- 2 Martínez-Frías ML. Developmental field defects and associations: epidemiological evidence for their relationship. *Am J Med Genet* 1994;47:744-7.
 - 3 Martínez-Frías ML. Primary midline developmental field. I. Clinical and epidemiological characteristics. *Am J Med Genet* 1995;56:374-81.
 - 4 Källén B, Castilla EE, Lancaster PAL, *et al.* The cyclops and the mermaid: an epidemiological study of two types of rare malformations. *J Med Genet* 1992;29:30-5.
 - 5 Martínez-Frías ML. Another way to interpret the description of the Monster of Ravenna of the sixteenth century. *Am J Med Genet* 1994;49:362.
 - 6 Martínez-Frías ML, Bermejo E, García A, Galán E, Prieto L. Holoprosencephaly associated with caudal dysgenesis: a clinical-epidemiological analysis. *Am J Med Genet* 1994;53:46-51.
 - 7 Young ID, O'Reilly KM, Kendall CH. Etiological heterogeneity in sirenomelia. *Pediatr Pathol* 1986;5:31-43.
 - 8 Opitz JM. Blastogenesis and the "primary field" in human development. In: Opitz JM, ed. *Blastogenesis, normal and abnormal*. New York: Wiley-Liss for the National Foundation-March of Dimes, 1993:3-37.
 - 9 Martínez-Frías ML, Frías JL. Are blastogenetic anomalies sporadic? *Am J Med Genet* 1997;68:381-5.

BOOK REVIEW

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.)

Correcting the Blueprint of Life. An Historical Account of the Discovery of DNA Repair Mechanisms. Errol C Friedberg. (Pp 210; \$49.00.) Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press. 1997. ISBN 0-87969-507-2.

It is a salutary experience to open the index of a history book and find oneself cited (albeit only once, and then only in parenthesis), if for

no other reason than that it reinforces one's awareness of the passage of time. The events related in Errol Friedberg's book took place within living memory and the author deserves credit for eliciting for us the accounts of those who were responsible for them. The discoveries themselves are, of course, fascinating. While the need for living things to have means of dealing with the chemical and physical threats to their genomes is old hat to us, and the ways in which they achieve genomic stability and fidelity are not conceptually difficult today, this was not the case in the early days of DNA repair. It was first necessary to know the gene's composition, its structure (established by Dan Brown and Lord Alexander Todd in 1952), and its conformation (as shown by Watson, Crick, and Wilkins in 1954). Indeed there is a subtext to the story in that the giants in the field of molecular genetics (as it came to be known) were in general little interested in genomic repair and tended to regard such work as second rate, largely because it was often done in national laboratories established and maintained for the purposes of supporting atomic energy and weapons research. Yet DNA repair has contributed more than its fair share of major discoveries, excision repair, mismatch repair, and the SOS coordinated inducible response being the most exciting with implications that extend to modern clinical medicine. Even the classic work of Avery, McLeod, and McCarty in 1944 showing that genes are made of DNA was antedated by Hollaender and Emmons in 1941, who showed clearly that the wavelength of ultraviolet light that was most effective in inducing changes in genes coincided with the peak of absorption by nucleic acid.

Various controversies are dealt with as fairly as appears possible. It is understandable that Friedberg has no wish to disturb the amicable relations that he has with his colleagues. One senses, however, that there could be another even more entertaining history written that gave more prominence to the paranoias, suspicions, and personal animosities of the characters and showed them "warts and all".

While the field up to, say, 1970 is covered well, after that the coverage is selective. There is, for example, no more than a paragraph about the repair of ionising radiation induced double strand DNA breaks, despite the fact that the field is of major importance, and the commonality of mechanism with immunoglobulin gene rearrangement foreseen since around 1980 has been spectacularly demon-

strated in the last few years. Although there is a full and almost complete discussion of the inducible SOS system (lacking only an acknowledgement of the contribution of Peter Emmerson in Newcastle), there is no account of the discovery of the molecular mechanism by which mutations are made by the SOS gene products. Obviously, a second and updated edition will be needed before Friedberg himself retires.

One final thought in the reviewer's mind concerns the conceptual nature of the really significant advances described in this book. They were frequently made by bright people thinking beyond the confines of their field, often beyond what they were being paid to do, going out of their way to interact with other bright people who were needed for mental cross fertilisation. The advances were more often than not predictable only with hindsight. Rarely would they have been the subject of a successful grant application in today's world.

BRYN BRIDGES

NOTICE

Embryos, Genes, and Birth Defects

The Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust will hold a Short Course on "Embryos, Genes, and Birth Defects" on 5-7 May 1998. Course organisers: Professor Peter Thorgood and Professor Robin Winter. Speakers will include Steve Brown, Andrew Copp, Dian Donnai, Patrizia Ferretti, Ieuan Hughes, Robin Lovell-Badge, Willie Reardon, Peter Scambler, Cheryll Tickle, Veronica Van Heyningen. Themes to be covered: Research strategies, Mapping syndromes to genes, Use of dysmorphology databases, molecular genetic approaches, Transgenic technology, Teratology as an analytical tool, Developmental mechanisms, Analysis of birth defects of selected organ systems. Fee £175. For further information please contact: Courses and Conferences Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK. Tel: 0171 829 8692, fax: 0171 831 0488, e-mail: Courses@ich.ucl.ac.uk