LETTERS TO THE EDITOR

Skeletal malformations and polycystic kidney disease

The infant reported by Turco *et al*[1] in the journal has features consistent with Haas type polysyndactyly.[2] Rambaud-Cousson *et al*[3] reported a similar case with tibial agenesis from a family where at least six other subjects in three generations had hand and foot abnormalities but with normal tibiae. Haas type polysyndactyly typically presents with complete syndactyly of the fingers. Radiographs may show five metacarpals but there may be a larger number of terminal phalanges and nails. It would be important to have more details of the hand abnormalities in the case reported by Turcot *et al*.[1] Renal cysts have not been reported in Haas type polysyndactyly to my knowledge.

ROBIN M WINTER
Mothercare Department of Paediatric Genetics, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK.

1 Turco AE, Padovani EM, Chiaffoni GP, *et al.* Molecular genetic diagnosis of autosomal dominant polycystic kidney disease in a newborn with bilateral cystic kidneys detected prenatally and multiple skeletal malformations. *J Med Genet* 1993;**30**:419–22.
2 Haas SL. Bilateral complete syndactylism of all fingers. *Am J Surg* 1940;**50**:363–6.
3 Rambaud-Cousson A, Dudin AA, Zuaiter AS, Thalji A. Syndactyly type IV/hexadactyly of feet associated with unilateral absence of the tibia. *Am J Med Genet* 1991;**40**:144–5.

A report on CF carrier frequency among men with infertility owing to congenital absence of the vas deferens

It has previously been reported[1] that there is an abnormally high incidence of cystic fibrosis carriers among infertile men with congenital bilateral absence of the vas deferens. On the basis of this finding and the identification of three compound heterozygotes for CFTR mutations (D1270N and two cases of G576A each with ΔF508) within this group of 30 infertile men, it has been suggested that CAVD is a 'mild' form of CF with subclinical features, and that these patients would all eventually be shown to be compound heterozygotes for CF.[2]

After screening 35 men participating in a MESA (microscopic epididymal sperm aspiration) programme for cystic fibrosis carrier status, we found 57% were carriers of the most common mutation associated with CF (ΔF508), clearly much higher than the average CF carrier frequency of 4% in the general population. This value for ΔF508 is in agreement with similar studies from Dumur (1991) and unpublished data of Osborne and Santis (Royal Brompton Hospital, London, personal communication, 1993). Five of these men were later shown to be compound heterozygotes for the ΔF508 and R117H mutations. Based on DNA findings alone these men would have been predicted to have a mild form of cystic fibrosis.[3]

In most northern European countries (such as Denmark and Brittany), and in Israel where there is a founder effect, most CF chromosomes can be identified (97 to 99%).[4] However, in countries such as Italy and Spain only about 60 to 70% of CF chromosomes can be detected[5]; these figures suggest that there are many mild CF chromosomes yet to be identified, the most common of which may turn out to be R117H. It is likely that some of the less common mild mutations will be the 'other' alleles associated with milder forms of CF including CAVD. It is of interest to note that, conversely, there has been no association seen between the severity of CF and the absence of the vas deferens.[6]

Assisted conception via MESA and IVF for this group of infertile men should routinely be accompanied by screening of both partners for common CF mutations, including R117H. Follow up counselling and cascade screening for CF should be provided to couples where one partner is found to test positive.

In some cases ΔF508 and R117H compound heterozygotes present as CF with the full remit of mild CF clinical features; in other cases the only clinical phenotype indicative of CF is CAVD. Clearly, CFTR gene mutations determine the presence of CF, but the severity of disease can vary quite markedly possibly depending upon either the interaction of other genes or on environmental factors or chance. We propose that congenital absence of the vas deferens is a mild presentation of cystic fibrosis in many cases. It is possible that the difference between those affected more or less severely by the R117H mutation is because the mutation has occurred twice, once on a genetic background which expresses the partially functional CFTR gene at a high level to give mild disease (CAVD only), and once on a background which expresses at a low level to give pancreatic sufficient cystic fibrosis (as suggested by Amos and Cutting, Williamsburg CFF meeting, 1993). (It would be of interest to investigate male sibs of CAVD patients to determine whether any ΔF508/R117H compound heterozygotes have no presenting signs at all, and to study the parents of these cases to ensure that these cases are not mosaics and that the mutations are on different chromosomes.)

We have shown that our findings in a population of British CAVD patients confirm those of several other groups in Europe and America, and that this distinct set of infertile males has a raised risk of having a mild form of CF. Further analysis of these patients should be carried out to evaluate whether they have other cystic fibrosis phenotypes, including clinical features such as chloride channel electrophysiology, pancreatic sufficiency, and pulmonary function. These data would allow correlation of genotype with phenotype for mild mutations. The further study of the CFTR gene sequence in cases of CAVD may also help to identify new 'mild' CF mutations.

CAROLYN WILLIAMS
EDWARD S MAYALL
ROBERT WILLIAMSON
North West Thames Regional DNA Laboratory, Department of Biochemistry and Molecular Genetics, St Mary's Hospital Medical School, Imperial College London, London W2 1PG.

ANTHONY HIRSH
HELEN COOKSON
Hallam Medical Centre, 77 Hallam Street, London W1N 5LR.

1 Dumur V, Gervais R, Rigot JM, *et al.* Abnormal distribution of CF (delta)F508 allele in azoospermic men with congenital dysplasia of the epididymis and vas deferens. *Lancet* 1990; **336**:512.
2 Anguiano A, Oates RD, Amon JA, *et al.* Congenital bilateral absence of the vas deferens: a primarily genital form of cystic fibrosis. *JAMA* 1992;**267**:1794–7.
3 Kristidis P, Bozon D, Corey M, *et al.* Genetic determination of exocrine pancreatic function in cystic fibrosis. *Am J Hum Genet* 1992;**50**:1178–84.
4 Scriver CR, Fujiwara TM. Cystic fibrosis genotypes and views on screening are both heterogeneous and population related. *Am J Hum Genet* 1992;**51**:943–50.
5 Nunes V, Gasparini P, Novelli G, *et al.* Analysis of 14 cystic fibrosis mutations in five South European populations. *Hum Genet* 1991;**87**:737–8.
6 Heaton ND, Pryor JP. Vasa aplasia and cystic fibrosis. *Br J Urol* 1990;**66**:538–40.

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 071 383 6244. Fax 071 383 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.)

Archibald Garrod—and the Individuality of Man. Alexander G Bearn. (Pp 227; £35.00.) ISBN 0 19 2621459. Oxford: Clarendon Press. 1993.

The concept of inborn errors of metabolism is now so widely accepted as to be commonplace. All medical students appreciate that metabolic processes proceed in a stepwise fashion, each step being genetically controlled. It is therefore astonishing to learn how long it took for this concept, first enunciated by Archibald Garrod in his Croonian Lectures in 1908, to be accepted. For example, Haldane was writing on biochemical genetics at the time and may well have heard of Garrod's work but he does not refer to it until some 30 years later! It is difficult to understand why this should have been so. Despite enlisting Bateson's help in interpreting his family data, Garrod never became involved with Genetics, perhaps, as Bearn suggests, because he didn't wish to become embroiled in the controversy then raging between Biometricians (for example, Weldon) and the Mendelians (for example, Bateson). But for whatever reason, by excluding himself from the genetic world this may not have helped. On the other hand, the medical profession, to which Garrod firmly belonged, was unreceptive to these new ideas on 'biochemical individuality'. His cause would not have been helped by his emphasising the principles as exemplified by alkaptonuria, a disease which most physicians would never have seen let alone appreciate the significance of Garrod's findings.

Bearn addresses all these issues in this detailed biography as well as presenting a clear picture of a truly scientific physician. With a distinguished medical scientist for a father, an encouraging home life, and an enviable education, coupled with his intellect and perseverance, he was assured an academic life.

He was essentially what we would now refer to as a chemical pathologist. But he always remained orientated toward clinical problems, even if he avoided ward responsibilities as much as possible! He was a founder of the Association of Physicians and later became Regius Professor of Medicine at Oxford. But his life was sad. He lost two sons in the First World War and the third in the influenza pandemic of 1919. In later life he was dogged by ill health and increasing blindness. He died of a coronary thrombosis in 1936 at the age of 78.

This is a well researched and scholarly biography by a writer who is himself an eminent physician-scientist. It deserves to be widely read for "... only in the context of biochemical individuality can human disease be understood".

ALAN EMERY