LETTERS TO
THE EDITOR

Skeletal malformations and
cystic kidney disease

The infant reported by Turcot et al. in the
journal has features consistent with Haas type
polyendocrinopathy.1 Rambaud-Cousson et al.2
reported a similar case with bilateral agenesis
from the kidneys and six other organs affected in
three generations had hand and foot anomalies
but with normal titbitae. Haas type polyendocrinopathy typically presents with com-
plete 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 polyendocrinopathy to my
knowledge.

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1 Turco AE, Padovani EM, Chiannoni GP, et al. Molecular genetic diagnosis of autosomal

dominant polyendocrinopathic cystic kidney disease in a new-

born with bilateral cystic kidneys and affected prenatally


3 Rambaud-Cousson A, Dusin A, Zanier AS, Thali A. Syndactyly type IV hexadactyly of

feet associated with unilateral absence of the


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

It has previously been reported3 that there is
an abnormally high incidence of cystic fibrosis
among infertility men with congenital bilateral
absence of the vas deferens. On the basis of this
finding, we identified the frequency of three
compound heterozygotes for CFTR muta-
tions (D1270N and two cases of G576A each
with AF508) within this group of congenital men
and found that all cases had CAVD and a mild
form of CF with subclinical features, and that
these patients would all eventually be shown to
be compound heterozygous for CF.

After screening 35 men participating in a
MESA (microscopic epididymal sperm aspira-
tion) programme for cystic fibrosis carrier
status, we found 57% were carriers of the most
common mutation associated with CF
(AF508), clearly much higher than the average
CF carrier frequency of 4% in the general
population. This value for AF508 is in agree-
ment with similar studies from Dumur (1991) and
unpublished data of Osborne and Santis
(1980). Royal Brompton Hospital, London, personal
communication, 1993. Five of these men were
later shown to be compound heterozygotes for
the AF508 and R117H mutations. Based on
DNA findings alone these men would have been
detected to have a mild form of cystic fibrosis.

Most northern European countries (such as
England and in Israel with a founder effect,
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, to date, there has been
no association seen between the severity of
CF and the absence of the vas deferens.6

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

In some cases AF508 and R117H compound
heterozygotes present as CF with the full
remitt 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 fibro-
sis in many cases. It is possible that the dif-
ference between those affected more or less
severely by this phenotype is because the
mutation has occurred twice, once on a genetic
background which expresses the partially
functional CFTR gene, at a low level to give
mild CAVD (only), and once on a background
which expresses at a low level to give
pancreatic sufficient cystic fibrosis (as
suggested by Garrod from his observations, London,
William'sburg CFF meeting, 1993). (It would be
of interest to investigate male sibs of CAVD
patients to determine whether any AF508; R117H
compound heterozygotes have no pre-
senting 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 popu-
lation of British CAVD patients confirm those
of several other groups in Europe and Amer-
ica, and that this distinct set of infertility 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 elec-
etrophysiology, pancreatic sufficiency, and pul-
monary function. These data would allow cor-
grelation of genotype with phenotype for mild
mutations. The further study of the CFTR
sequence in cases of CAVD may also help to
identify new 'mild' CF mutations.

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1 Dumur V, Gervais R, Rigot M, et al. Abnormal distribution of CF (delta)F508 allele in azoz-
 spermic men with congenital displacement of the epididymis and infertility. Lancet 1990;
336:512.

2 Angiuolo A, Oates RD, Amon JA, et al. Congen-
 ital bilateral absence of the vas deferens: a

determination of pancreatic function in

4 Scriver CR, Fujisawa TM. Cystic fibrosis geno-
types and views on screening between both
genital and extragenital related. Am J Hum

of 14 CF mutations in 54 families in five South
European populations. Hum Genet 1991;87:737-42.


BOOK REVIEW

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the Publishers.)

Archibald Garrod—and the Individu-
ality of Man. Alexander G Bean.
(Pp 227; £35.00.) ISBN 0 19 2621459. Oxford: Clar-

The concept of inborn errors of metabolism
is now so widely accepted as to be common-
place, but Garrod's medical signal was that
metabolic processes proceed in a stepwise
fashion, each step being genetically con-
trolled. It is therefore by interest how long it
took for this concept, first enunciated by Archibald Garrod in his Croonian Lectures in
1908, to be accepted. For ex-
ample, 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 interpret-
ing his family data, and involvement with Genetics, perhaps, as Bean suggests, because he didn't wish to become embroiled in the controversy then raging between Biometricians (for example, Wel-
don) and the Mendelians (for example, Bates-
on). 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,
who were not well versed in these new ideas on "bio-
chemical individuality". His cause would not
have been helped by his emphasizing the
"medical" aspects of these diseases. Disease
which most physicians would never have seen
but appreciated the signifi-
cance of Garrod's findings.

This addresses all these issues in this
detailed biography as well as presenting a
clear picture of a truly scientific physician.
What is most striking is the medical scientist for a
father, an encouraging home life, and an
enviable education, coupled with his intellect
and perseverance, he was assured an aca-
demic life.

He was essentially what we would now
refer to as a chemical pathologist. But he always
remained oriented toward clinical
diseases, even if he avoided ward responsi-
bilities 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
bouts of depression. He died of coronary thrombosis in 1936 at the age of 78.

This is a well researched and scholarly
biography by a writer of considerable
eminence. It deserves to be widely read for: “...only in the context of biochemical individuality can human disease be understood”.

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