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GENETIC FACTORS IN DRUG THERAPY: CLINICAL
AND MOLECULAR PHARMACOGENETICS
D A Price-Evans. (Pp 657; £120.00.) Cam-

Professor Price-Evans has taken on a for-
midable challenge in attempting a com-
prehensive single author text on pharma-
cogenetics. Nevertheless, he has proved
equal to the task and this impressive book
represents an exhaustive review of pub-
lications up to and including papers published
in 1992. Recent research in pharmacogenetics
has focused primarily on genetic poly-
morphisms of drug metabolism and a large
part of the book is devoted to the enzymes
involved and their genetic determinants. The
cytochromes P450 (CYPs) are dealt with, first,
since they represent the most important group
of drug metabolising enzymes. Two major
polymorphisms in this gene superfamily have
been identified, affecting CYP2D6 (the "de-
brisquine/sparetine" polymorphism) and
CYP2C19 (the "methenoxo" polymor-
phism). The list of drug substrates of
CYP2D6 is growing rapidly (presently about
40), many of them in widespread clinical use.
These chapters bring home the vast amount
of information that has been gained on the
molecular genetics, biochemistry, and sub-
strate selectivity of these enzymes. Clinical
data on population and ethnic aspects, phar-
camokinetics, and disease sus-
ceptibility in relation to phenotype and
genotype are also considered in depth. How-
ever, a more critical evaluation of the clinical
significance of the debrisoquine/sparetine
polymorphism could perhaps have been
expected. Most reports of unwanted drug effects
in one or other phenotype are from single
case studies, many of which have not been
substantiated. There is a similar exhaustive

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治ment of other drug metabolising enzymes
which show evidence of polymorphism, N-
Acetyltransferase, S-methyltransferase, and
pseudocholinesterase being the ones that have
received the most clinical attention.
It is good to see that the difficulties of inter-
preting pharmacogenetic data are covered,
an area that has often been ne-
glected. For example, distinguishing be-
 tween unimodality and bi- or trimodality in
population distributions is a fundamental problem in
pharmacogenetic studies of drug meta-
bolism and, in an Appendix, the author sum-
marises the main mathematical techniques
proposed for its solution.

The remainder of the book is devoted to a
discussion of adverse drug effects having an
inherited pharmacodynamic or receptor
basis. Well characterised disorders, such as
glucose-6-phosphate dehydrogenase
deficiency, the porphyrias, and malignant
hyperthermia, would be expected to be included
but the author has scoured published reports
for less well known adverse reactions that
may have a genetic basis. For example, in a
report of one patient described as a "green
man after indomethacin" it was suggested
that inhibition by this drug of a rare genetic
variant of biliverdin reductase caused his skin,
hair, and serum to turn green owing to the
accumulation of biliverdin. Unfortunately,
this was not followed up with family studies.

From this book it should be abundantly
clear to the reader that genetic variability
in pharmacokinetics and pharmacodynamics
has obvious implications for drug therapy,
but with a few exceptions this knowledge has
yet to be applied to clinical practice. The
debrisoquine/sparetine polymorphism is a
good example in that, although the phe-
nomenon was discovered 17 years ago, few
controlled prospective studies to evaluate its
clinical significance have been performed.
The recent emphasis on molecular genetics
needs to be augmented by a more determined
effort to define phenotypic differences in drug
response.

All chapters are clearly written and the text
and graphics layouts make the book easy to
read. It is also extremely well indexed. There
is a danger that, like all works of reference
covering an active research area, particularly
one in which molecular genetics has made
such an impact, this book could become out of