superfrequency of a given phenotype in health and disease with
the inherent consequence of conflicting results.

have centred on phenotypic studies comparing the fre-
ocality-determined pharmacogenetic polymorphisms in rheumatology,
back-up evidence of genotyping. Until recently, studies
and disease become difficult to interpret without the
Essentially the two methods should complement one
otype as reference. However, it remains that it is the
become possible and geneticists have adopted the gen-
methods is most appropriate for clinical investigations
mined by direct genotyping of extracted DNA and
olism of S-carboxymethyl-L-cysteine (SCMC). This
phenotypic data alone can be highlighted by the metab-
phenotypic polymorphisms and RA [3, 4] and
and sodium aurothiomalate [11-14]. The danger
continues to be disagreement over fundamental issues
of sulphoxidation status [10]. A number of reports have
between poor sulphoxidation of this mucolytic agent
phenotypic observations since genotypic studies (by breeding experiments)
drug acetylation polymorphisms and RA [3, 4] and
and idiopathic SLE [5, 6]. A clearer association exists
between acetylator phenotype and adverse drug reac-
tions [7] or drug-induced lupus [8]. More recently, the
polymorphic form of the enzyme N-acetyltransferase
(p-NAT, NAT-2) has been gene sequenced [9] and will
allow a clearer picture of any association (or lack thereof) between acetylation and rheumatic disease.

The problem of defining a genetic polymorphism on
phenotypic data alone can be highlighted by the metabol-
ism of S-carboxymethyl-L-cysteine (SCMC). This
compound has been used as a pharmacogenetic probe of
polysulphidation status [10]. A number of reports have
appeared in the literature showing an association
between poor sulphoxidation of this mucolytic agent
and development of RA and toxicity to β-penicillam-
mine and sodium aurothiomalate [11-14]. The danger
here is that contrary to a previous investigation [10],
sulphoxidation of this compound has not been proven
to be genetically determined and the weight of current
opinion supports a non-genetic control over the metabol-
ism of SCMC [15, 16]. The metabolite previously
thought to be a sulphoxide of the probe compound has
now been shown to be S-carboxymethylthio-L-cys-
teine, a mixed disulphide [17, 18]. It appears that
patients with RA may exhibit a defect in sulphur
metabolism, as shown by an increase in plasma and SF cysteine concentration and a corresponding decrease in sulphate levels [19]. This has been attributed to a genetic or disease-related suppression of the enzyme cysteine dioxygenase however this enzyme is highly specific for L-cysteine and SCMC is not a substrate [20], thus any genetic polymorphisms of this enzyme are unlikely to affect the metabolism of SCMC.

A well-characterized enzyme displaying a definite pharmacogenetic polymorphism is CYP2D6, a cytochrome P450, involved in the metabolism of debrisoquine and many other drugs and xenobiotics [21]. A recent study has shown no difference in the distribution of debrisoquine hydroxylation genotypes in patients with RA compared to normal controls, although there was a tendency for patients to have a reduced frequency of the mutant allele, CYP2D6D. A number of genotypic homozygous extensive metabolizers (EMs) of debrisoquine were found to phenocopy as heterozygous EMs, this was caused by concomitant administration of dextropropoxyphene, a non-substrate inhibitor of CYP2D6 [22]. This may have implications in patients undergoing polypharmacy being treated with, for example, dextropropoxyphene and the antidepressant amitriptyline, a not uncommon combination. Amitriptyline is a pro-drug requiring activation to nortriptyline by N-demethylation via CYP2D6, inhibition of the enzyme leads to lower levels of the active metabolite and thus reduced efficacy. Additional problems may occur if the beta blockers metoprolol or timolol are added to the treatment regimen since both of these are substrates for CYP2D6, also [21].

Whilst the concept of a direct link between predisposition to rheumatic disease and a defect in drug metabolism is too simplistic to assume, a similar proposal to a hypothesis between abnormal drug metabolism and tendency to develop ulcerative colitis [23] becomes quite attractive. Here it is postulated that a pharmacogenetic defect in a given metabolic pathway gives rise to a toxic reactive metabolite, this subsequently undergoes phase two metabolism and the conjugate is excreted in the bile. Colonic bacteria may then regenerate the reactive metabolite the concentration of which would increase as it descended the colon. Once a toxic concentration is reached within the lumen, the colonic epithelium may break down exposing bacterial antigens to the mucosal immune system.

The use of pharmacogenetics to predict either a predisposition to a given disease or to predict drug toxicity has to be done with care. Without the use of genotyping any definite link with a genetic polymorphism must remain speculative though without phenotyping to take into consideration the expression of the gene, genotyping becomes clinically redundant. Concomitant administration of other agents and exposure to xenobiotics must be carefully controlled wherever possible.

Pharmacogenetics in both the genetic and metabolic senses does have a role in rheumatology providing sweeping generalizations are not made and wild claims avoided. A dislike of cauliflower and coconut has been reported in healthy poor metabolizers of dextromethorphan (a CYP2D6 substrate) whilst extensive metabolizers have a dislike of cabbage and spinach [24]. Could there be a link therefore between a preference for baked beans and vanilla ice cream and development of rheumatic disease? Somehow I do not think so!

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REFERENCES


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**ANNOUNCEMENTS AND CALENDAR FOR 1995**

**March** 2-3 Clinical Immunology Course, Birmingham.

**April** 5-7 BSR AGM: Glasgow.

**May** 17-19 Advanced Course, London.

**June** 29-30 Spine Course, Cambridge.

**July** 23-26 Rehabilitation Course, Leeds.

**September** 1 Closing date Margaret Holroyd Prize.

**September** 13-15 Heberden Round—Dr T. Hothersall, Keele University.

**September** 15 Closing date Non-Clinical Bursary.

**September** 21-22 EMG Course, Oxford.

**October** 11-13 Paediatric Rheumatology.

**October** 27 Closing date for 1996 Michael Mason Prize.

**November** 2-3 Core Course, Portsmouth.

**November** 25 Closing date for 1996 Senior Registrar Travelling Fellowship.

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