WHAT IS THE PATHOGENESIS OF FAMILIAL GOUTY NEPHROPATHY?

J. Stewart Cameron * Fernando Moro ** and H. Anne Simmonds +

+ Purine Research Laboratory and * Renal Unit
Guy's Campus UMDS, London, UK

Familial juvenile gouty nephropathy (FJGN: McCusick 16200) was first noted by Duncan and Dixon in 1960 (1). We first observed the condition in 1968-72 (2), and by 1990 18 papers describing 38 affected kindreds containing 130 affected individuals had been described (3), plus three new kindreds described more recently (4-7). We are also aware of a number of unpublished kindreds, from some of whom material has been available to us for study. The purpose of this communication is to summarise what information we have accumulated; to speculate from these data, published and unpublished, as to what the pathogenesis of FJGN may be; and to suggest further studies which may illuminate the problem in the future.

Clinical features of FJGN which require explanation

The characteristics of FJGN are now well-established: hyperuricaemia and consequent gout arise in young individuals irrespective of sex because of a low fractional excretion of urate, FEur. Renal failure has appeared in 78 of 130 affected individuals in the available kindreds (leading to end stage disease in 32), but the finding that the low FEur and consequent hyperuricaemia can occur before the appearance either of renal dysfunction or of gout (5-7) suggests that this is a prior event. Purine enzymes are normal and renal urate excretion (UVur) within normal limits. Secondary hypertension may be found (in 13 of 38 kindreds), but is usually a late event, appearing in those with renal dysfunction. Onset is usually in childhood, adolescence, or early adult life, and renal failure usually appears between 20 and 40 years of age. Untreated hypertension of course may accelerate the entrance to renal failure. Until and if gout appears in one or more members, the condition may be missed and a diagnosis of a "familial nephritis" made (5).

The disease is familial, inheritance following a dominant pattern, (consecutive generations affected, 78 males and 32 females). One kindred was reported as being consistent with an X-linked inheritance (8), but it is notoriously difficult to prove or exclude this in small studies. Male to male transmission was present in several kindreds studied by us and other workers (e.g. ref 4), which together with abundant affected females makes a simple dominant inheritance certain in the majority of families.

What is the relationship between the hyperuricaemia and the renal failure? Clearly we can relate the hypertension to the renal failure, and the clinical gout to the hyperuricaemia. But how do the renal failure and the
low FEur/hyperuricemia relate? One obvious possibility is that the renal
disease might be a form of urate nephropathy. However, a number of
observations exclude his possibility, even though allopurinol may slow or
prevent progression (see Moro et al. 6, this volume).

First, prolonged hyperuricaemia of itself, although an independent risk
factor for vascular disease, does not lead to renal dysfunction in the
presence of a normal FEur in (for example) idiopathic symptomless
hyperuricaemia (9), hereditary fructose intolerance or PRPP synthetase
overactivity observed over 10 years or more (Simmonds, unpublished); in
HGPRT deficiency of course, the massive renal excretion of urate/uric acid
may lead to massive crystal nephropathy. However, in FJGN the UVur has been
observed to be within normal limits in all cases, and in the kidneys
studied in the 44 renal biopsies and 6 autopsies known to us, no or only
occasional urate crystals have been noted. Thus it seems impossible that
the non-specific interstitial nephropathy seen in FJGN with renal failure
is the result of urate deposition nephropathy.

Could the low FE ur damage the tubules in some way through an increased
transstubular flux of urate? We do not know what, in functional detail,
underlies the decreased fractional excretion, and it would be worth doing
pharmacologic studies using probenecid/benzbromarone and pyrazinamide; but
the detailed interpretation of such data in terms of secretion and
reabsorption is now heavily criticised. However, given present models of
urate handling in the mammalian tubule (see Weiner, this volume) it seems
likely that some defect in a proximal tubular secretory mechanism is at
fault, suggesting that FJGN may be the human analogue of the inherited
gouty chicken, in which a defect in a basolateral urate transporter has
been described (10).

What is the nature of the defect in proximal tubular urate secretion?
The most likely explanation is that there is a defect in the gene coding
for one of the anion transporters in the proximal tubular epithelium,
either in the basolateral or the brush border membranes. Since none of
these have yet been cloned the search for candidate genes (in which are
presently engaged) is difficult, and non-specific search techniques must be
used. Whether a single mutation, or many different mutations, might be
present in the gene can only be speculated at the moment; however it is
relevant that many mutations at the same site have been discovered in
genetic disorders of other transporters (e.g. in cystic fibrosis) which can
lead to phenotypically identical disease. Also, even at the level of
pharmacologic studies, the inherited defect leading to isolated
hyperuricosuria shows great diversity between the rather small numbers of
kindreds studied (11,12). Therefore, we might predict both genetic and
phenotypic diversity to underlie the low FEur of FJGN. Of interest to
subsequent discussion, hypouricaemia with reduced tubular absorption can
be acquired, following the appearance of some product from malignant tissue
(13).

The renal failure might arise as a direct consequence of this genetic
alteration, as outlined above, even if we do not understand the mechanism;
but it might also result from a concurrently inherited (but structurally
separate) gene which in some other way determines the appearance of renal
failure from interstitial nephritis. Inherited interstitial nephritis may
occur in the kd.kd mouse (14) and in man, in many of whom cystic changes
occur, as they do in the mice (15). The finding of medullary cysts in 7
patients with FJGN (4 at autopsy and 3 by biopsy) as occurs also in the
mice, should not lead to a diagnosis of nephronophthisis (uraemic medullary
cystic disease) (16). In addition this condition usually shows an autosomal
recessive inheritance.