There is strong circumstantial evidence for a link between idiopathic childhood nephrotic syndrome, a clinical entity synonymous with the renal biopsy appearances of minimal change nephropathy (so-called because histological examination of the kidney in this condition shows no evidence of glomerular inflammation) and a disturbance of the cytokine balance in the immune system. In particular, there are reasons to suspect a predominance of ‘type 2’ cytokine responses, i.e. those involving the cytokines interleukins (IL) 4 and 13, and their respective receptors IL4R and IL13R. Evidence for this includes a high level of circulating IgE [1–3], persistence of IgG4 when other IgG subclasses are suppressed [4], a strong association with a personal or family history of atopy or allergy [5,6] and direct demonstration of high levels of type 2 cytokine production by cells from individuals with idiopathic nephrotic syndrome [7,8]. Since idiopathic nephrotic syndrome is most common in children, and since some of the associated immunological features are also present in family members, it is reasonable to assume that there are immunogenetic predisposing factors. Study of genes of the major histocompatibility complex shows only relatively weak associations [9]. Another set of candidate genes are those encoding the type 2 cytokines themselves and their respective receptors. We have previously reported in Clinical Science [10] that we found no evidence of any association between polymorphisms of IL4 or IL4R and childhood nephrotic syndrome. Elsewhere [11], we have reported a similar lack of association with a promoter polymorphism in the IL13 gene. These results are confirmed and extended by the work of Tenbrock et al. [12] in this issue of Clinical Science. They analysed polymorphisms of the high affinity IgE receptor, IL4R and IL13 in 84 children with idiopathic nephrotic syndrome, also providing information on the presence or absence of atopy. They report differences in allele frequencies of the various polymorphisms between atopic and non-atopic children with nephrotic syndrome, although these did not reach statistical significance. In addition, they analysed the clinical course (frequency of relapse, steroid-dependence etc.) and reported no effect of the polymorphisms on outcome.

Where does this leave us? It seems that polymorphisms in the genes encoding type 2 cytokines and their receptors are not useful predictors of susceptibility to, or the clinical course of, idiopathic nephrotic syndrome. Whether they are useful in understanding the predisposition to atopy itself, or other atopy-related diseases such as asthma, remains controversial [13]. Many questions remain. For most cytokine gene polymorphisms, there is no proof of functional significance. Polymorphisms in the gene promoter or other regulatory regions of the gene may affect transcriptional activity, for example by affecting the binding of transcription factors. This was suggested by an early study on the human IL4 gene in which Song et al. [14] reported that one polymorphism resulting in a single base change in the IL4 promoter had a marked effect on transcriptional activity. However, subsequent studies including our own [10] failed to identify this polymorphism in population studies and it is now believed that the original finding was an artefact due to the use of transformed cell lines by Song et al. [14]. Polymorphisms within the coding sequence of a gene may alter the encoded amino acid sequence in such a way that the function of the resulting protein is altered. This ‘gain of function’ was suggested by Hershey et al. [15] for a polymorphism in the IL4 receptor which was associated with enhanced signalling by the receptor. For many cytokine gene polymorphisms, functional significance has been implied, usually by studies showing an association with altered cytokine production in vitro. For example, a single nucleotide polymorphism (SNP) at position –1082 of the human IL10 promoter has been extensively studied, with the presence of a guanine (G) at this site called a ‘high producer’ genotype since one early study reported higher levels of IL10 production by peripheral blood cells from individuals with G at this position [16]. However, subsequent studies [17,18], including detailed functional analysis using reporter-gene assays in which the effect of this single base change can be studied using site-directed mutagenesis, have suggested that adenine (A) at position –1082 can have greater transcriptional activity than G, and that there are marked variations according to cell type and stimulus used. Clearly the effects of SNPs in cytokine genes are not as simple as has been sometimes assumed. Indeed, the whole subject of SNPs, single gene association studies, candidate gene studies etc. may be usurped by advances in technology and methodology [19]. Greater sophistication in our ability to study these genetic effects on complex phenotypic traits such as nephrotic syndrome will be welcome, as we seek to unravel the pathogenetic complexities of these conditions.

Sadly, so far these immunogenetic studies have not substantially improved our understanding of nephrotic syndrome. Nephrologists must acknowledge that available treatments, although often effective, remain crude and non-specific. There has been a shift of emphasis in
recent years in the study of idiopathic nephrotic syndrome, with increasing appreciation that a particular cell in the glomerulus, the glomerular epithelial cell or podocyte, is the cell whose dysfunction leads to the clinical syndrome [20,21]. Whether the immune disturbance associated with nephrotic syndrome results directly or indirectly in podocyte dysfunction, and which of these phenomena are primary, remain open questions. It will be essential to bring together these twin threads: the cytokine imbalance (with its possible genetic predictors) and the podocyte disruption, which leads to proteinuria, if we are to improve our understanding of this important clinical problem, and improve the treatment and prognosis for our patients.

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