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IgA Nephropathy: Introduction

It is now forty years since Jean Berger's original description of a group of patients whose renal biopsy was characterised by diffuse mesangial deposition of IgA. At some stages called 'Berger's Disease' this is the entity now universally known as 'IgA nephropathy'. It is our pleasure in this volume of Seminars in Nephrology to present an assessment of our current understanding of IgA nephropathy [IgAN] with contributions from those who are at the leading edge of this field.

In many ways progress in IgAN has been slow over the last forty years; this most common of glomerular diseases is yielding its secrets rather reluctantly. But in our judgement, work in many aspects of IgAN is now gaining real momentum; new information and new concepts are emerging and coalescing to enable us to think more clearly about the origins, manifestations, and implications of this clinical entity. The topics we have selected for this volume reflect those points of change, and are reviewed by those who are among the most powerful contributors to the progress we are now seeing.

The early clinical perception of IgAN as a benign entity characterised by self-limiting visible haematuria was soon replaced by an understanding that in many instances it is a slowly progressive condition, and by virtue of its prevalence an important cause of end-stage renal disease. We have continued to develop this understanding through the careful study of large patient populations, as we work towards the goal of refining prognosis for individual patients. The careful and prolonged observation of patient cohorts is exemplified by the work of Francois Berthoux and colleagues which they here summarise alongside the work of others in adult patients with IgAN. Rosanna Coppo complements this by reviewing our current understanding of the clinical course of IgAN in children. Another element assisting precise prognosis for individuals with IgAN is the combined interpretation of histopathological findings on renal biopsy in the context of the clinical scenario. David Philibert and his colleagues have contributed a lucid analysis based on case studies of the clinical opportunities which come from thoughtful review of clinical and pathological information.

We have chosen in this volume not to focus on Henoch-Schönlein purpura, in which IgAN occurs in association with an IgA-mediated small vessel vasculitis. But the issue of "secondary" IgAN, in which the renal lesion appears to be a consequence of significant extrarenal disease, remains an area of uncertainty. Shideh Pouria and Jonathan Barratt review the most commonly appreciated forms of secondary IgAN, those associated with chronic liver disease and chronic bowel disease. They also critically review the basis on which other disease associations with IgAN are proposed, indicating that these may often be adjuvants modifying the clinical phenotype in patients who already have primary IgAN rather than themselves the disease initiator.

In this volume we have chosen not to devote extensive space to the question of therapeutic strategies for IgAN, not least because they were so well reviewed in the 2004 Seminars in Nephrology volume on IgAN edited by Mark Haas. However in one area, the use of immunosuppressive therapy in IgAN, some new evidence has emerged since 2004, and this remains the most contentious issue of clinical practice in IgAN. Jürgen Floege and Frank Eitner provide a lucid review of the rationale behind immunosuppressive approaches and of evidence for their use in the context of modern non-immune management of chronic glomerular diseases such as IgAN. Rosanna Coppo also provides an

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analysis of the specific evidence of therapeutic strategies in children with IgAN.

We have chosen to commit the remainder of this volume to studies on the pathogenesis of IgAN. This reflects our accelerating knowledge; but the distinct emphases of the remaining contributions also demonstrate that we have yet to integrate some very interesting strands into a single coherent view of the pathogenesis of IgAN. This should not surprise us. The clinical and pathological heterogeneity of IgAN, let alone its racial and ethnic variations, have always suggested that this may not in due time prove to be a single disease entity. We define IgAN merely by the presence of mesangial IgA deposition and it has always been improbable that this is the consequence of a single pathogenic defect or that the subsequent extent of renal injury would have a single provoking element. Nevertheless we believe that the range of hypotheses and research strategies exemplified in this volume are all bringing critical insights.

As Stephen Hsu points out, racial and ethnic variations in the apparent prevalence of IgAN strongly suggest a role for genetic factors influencing pathogenesis and clinical phenotype, yet there as been disappointing progress in the identification of such factors. The limitations of case-control genetic association studies are now better appreciated with new understanding of the haplotype block structure of the human genome, and he shows how emerging data from human familial IgAN as well as murine models are providing a basis for an understanding of genetic susceptibility both to the development of IgAN and its subsequent clinical phenotypes.

The characteristic clinical association of exacerbations of IgAN with mucosal infection has always pointed to dysregulation of mucosal immunity and of the mucosa-marrow axis as likely contributors to the pathogenesis of IgAN. Beatrijs Oortwijn and her colleagues review evidence for secretory IgA involvement in human IgAN, including its role in activating complement; while Yusuke Suzuki and Yasuhiko Tomino demonstrate the increasingly powerful insights into IgA immune system dysregulation which are emerging from the study of murine models.

Alterations in IgA glycosylation have received considerable attention over the last decade as a key factor promoting formation of pathogenic IgA-immune complexes and mesangial IgA deposition, and also a mediator of subsequent pathogenic interactions with inflammatory effector mechanisms. Jan Novak and his colleagues review the increasingly powerful evidence that this physicochemical abnormality of the IgA molecule plays a pivotal role in pathogenesis.

IgA interacts with a variety of cell surface receptors, and variations in such interactions with receptors both in the kidney, the liver and on circulating inflammatory cells, may influence both the initiation and progression of IgAN. Ivan Moura and his colleagues review this topic and present evidence in particular that the transferrin receptor may contribute to mesangial cell activation by enhanced interaction with abnormally glycosylated IgA, and that the Fcα receptor, FcαRI, may have a role in pathogenesis - both through classical receptor mediated induction of inflammatory processes, and also because the soluble form of FcαRI may contribute to the formation of IgA immune complexes.

Fundamental differences in the biology of the IgA system between humans and rodents have hampered IgAN research over the last two decades since extrapolation of findings from animal models to human IgAN has been very uncertain. The studies of Moura, Suzuki and their colleagues demonstrate that animal research in IgAN is now beginning to come of age with the development of models which can answer carefully posed questions relevant to the pathogenesis of human disease.

The varied hypotheses presented in these articles do not yet readily coalesce into a single understanding of the pathogenesis of IgAN. This is not unexpected, since the heterogeneity of the clinical and pathological phenotypes of IgAN leads us to the expectation that multiple pathogenic pathways all leading to mesangial IgA deposition and glomerular injury will eventually emerge. But the convergence of our

thinking will also need more time; research in this field is at the lively stage where there is sufficient background information to encourage energetic hypothesis generation, but critical testing of these hypotheses is challenging, and needs to find its own internal consistency before we are rewarded with a more integrated understanding of disease mechanisms in IgAN.

We are extremely grateful to our friends and colleagues who have so willingly agreed to make their contributions to this edition of Seminars in Nephrology, and we are confident that it provides an excellent summary of the contemporary 'state of the art'.

John Feehally, DM, FRCP
Jonathan Barratt, PhD, MRCP
Guest Editors
Department of Inflammation,
Infection & Immunity
University of Leicester and
John Walls Renal Unit
University Hospitals of Leicester
Leicester, UK