IgA Nephropathy

L.O.		Simpson
B.I.		Shand
R.J.		Olds

Department of Pathology, University of Otago Medical School, Dunedin, New Zealand

L.O. Simpson, PhD, Department of Pathology, University of Otago Medical School, PO Box 913, Dunedin (New Zealand)

Dear Sir,

Recently the views expressed in 159 papers dealing with the cause, pathogenesis, and treatment of IgA nephropathy (IGAN) were reviewed [1]. The lack of a consistent relationship between the haematuria and proteinuria which occur in the disorder makes it unlikely that they have a common cause. It seems probable that the entry of red cells into the glomerular filtrate is post-glomerular, although this point is discussed rarely [2]. However, in subjects with IGAN the variability of the concentrations of the plasma globulins and the occurrence of IgA polymers make it likely that blood rheology may be altered sufficiently to play a causal role in their proteinuria. Proteinuria occurs as a consequence of increased intraglomerular pressure, and the higher the pressure the larger the proteins in urine [3]. Blood viscosity induced proteinuria (as in polycythemia) is a consequence of the haemoc-oncentrating effects of glomerular filtration on abnormally viscous blood [4]. In efferent arterioles the hyper-viscous blood will be resistant to flow. If there is an insufficient rise in pressure to restore the rate of blood flow to normal, stasis may develop and lead to glomerulosclerosis with deletion of the nephron. Alternatively, as a consequence of upstream vasodilation, blood flow may be restored, but the rise in intraglomerular pressure would result in proteinuria. Where blood viscosity was increased to a lesser degree (for example as a consequence of a rise in plasma protein concentration), blood flow problems would be determined by the relationship between viscosity and the size of the capillaries of the peritubular plexus and post-capillary venules. Consequently, in subjects with the same levels of plasma viscosity, but different-sized capillaries, one could be normal and the other proteinuric. Viscosity-impaired blood flow in the peritubular plexus may reduce the efficiency of tubular resorption sufficiently to contribute to the abnormality of the urine. However, the problems of flow in the microcirculation do not end in capillaries, as the rate of flow is lowest in post-capillary venules. For this reason the venules play a major role in determining peripheral resistance.

Therefore, it must be emphasized that, while it is possible to measure with precision and reproducibility the effects of IgA and other immunoglobulins on blood and plasma viscosity, such data refer only to one of the two major determinants of flow. At present, there are no practical means by which microvascular dimensions can be ascertained in vivo, and the lack of such information greatly reduces the predictive value of blood viscosity measurements. At the upper end of the scale, high blood viscosity would be associated with frank and possibly severe pathophysiological disorders, but in the middle of the viscosity range those at risk may be identifiable only by relatively minor symptoms such as oedema, fluid retention, and weight gain.

D'Amico et al. [5] reported on the status of 374 patients with IGAN and concluded that:

Obviously, other factors are responsible for the progression of the disease, but as yet they are unknown.' As the blood rheology of subjects with IGAN has not been investigated, it is possible that this is one of the '...other factors' in the disease. We wish to draw attention to the possibility that IGAN could be a renal manifestation of altered blood rheology, reliant upon the presence of small capillaries for its expression. If this is so, then the use of agents which improve blood rheology may provide an effective treatment option.

Changes in plasma concentration of IgA (or other globulins) or in the physical characteristics of the IgA molecule will alter plasma viscosity. Preston et al. [6] have pointed out that the asymmetry of the IgA molecule is responsible for equivalent concentrations of IgA being more viscous than IgG solutions. It is possible also that increased concentrations of immunoglobulins may influ-

254

Simpson/Shand/Olds

D'Amico, G.; Imbasciati, E.; Belgioioso, G.B di.; Bertoli, S.; Fogazzi, G.; Ferrario, F.; Fellin, G.; Ragni, A.; Colasanti, G.; Minetti, L.; Ponticelli, C: Idiopathic IgA mesangial nephropathy. Clinical and histological study of 374 patients. *Medicine* 64: 49–60 (1985).

Preston, F.E.; Cooke, K.B.; Foster, M.E.; Winfield, D.A.; Lee, D.: Myelomatosis and the hyperviscosity syndrome. *Br. J. Haematol.* 55:517–530(1978).

Simpson, L.O.; Shand, B.I.: The implications of the changes in the nature of the urinary proteins which occur in albumin overload-induced proteinuria in normal mice. *Br. J. exp. Path.* 64: 6–14(1983).

Simpson, L.O.; Shand, B.I.: Morphological changes in the kidneys of mice with proteinuria induced by albumin overload. *Br. J. exp. Path.* (54):396–402 (1983).

Terry, R.; Hawkins, D.R.; Church, E.H.; Whipple, G.H.: Proteinuria related to hyperproteinemia in dogs following plasma given parenterally, *J. exp. Med.* 87:561–573 (1948).

Berger, J.; Yaneva, H.; Nabarra, N.; Barbanel, C: Recurrence of mesangial deposition of IgA after renal transplantation. *Kidney int.* 7:232–241(1975).

Cameron, J.S.; Turner, D.R.: Recurrent glomerulonephritis in allografted kidneys. *Clin. Nephrol.* 7:47–54 (1977).

Hogg, R.J.; Silva, F.: A multicenter study of IgA nephropathy in children. A report of the Southwest Pediatric Study Group. *Kidney int.* 22:643–652 (1982).

Clarkson, A.R.; Woodroffe, A.J.; Bannister, K.M.; Lomax-Smith, J.D.; Aarons, I.: The syndrome of IgA nephropathy. *Clin. Nephrol.* 27:7–14(1984).

Hattori, S.; Karashima, S.; Furase, A.; Terashima, T.; Hiramatsu, M.; Murakami, M.; Matsuda, I.: Clinicopathological correlation of IgA nephropathy in children. *Am. J. Nephrol.* 5: 182–189 (1985).

Simpson, L.O.; Olds, R.J.; Hunter, J.A.: Changes in rheological properties of blood in cigarette smokers taking Efamol: a pilot study. *Proc. Univ. Otago med. School* 62:122–123 (1984).

Soma, M.; Manku, M.S.; Horrobin, D.F.: The effects of hydrogenated coconut oil, sunflower oil and evening primrose oil on development of hypertension and sodium handling in spontaneously hypertensive rats. *Can. J. Physiol. Pharmacol.* 63: 325–330(1985).

ence blood rheology through an effect on red cell deformability. Reports of studies on hyperproteinemic proteinuria in animals [7–9] show the effects of increased plasma protein concentration on renal function. The possibility that IGAN is a consequence of altered blood c

rheology is supported by observations on the fate of kidneys grafted from or into subjects with IGAN. Normal kidneys develop the mesangial deposits of IgA which are characteristic of IGAN when grafted into patients with IgA-related renal failure [10,11], but donor kidneys with IgA mesangial deposits lose those deposits when transplanted into patients without IGAN.

According to D'Amico [1] 'there is no proven therapy for IgA nephropathy', and similar opinions have been expressed by others [12–14]. But if altered blood rheology is involved in the pathogenesis of IGAN, then regimens aimed at improving blood rheology may provide a treatment option. Drugs such as cinnarizine, flunarizine, Hydergine, the hydroxyethylrutosides, and pentoxifylline are considered to improve microcirculatory blood flow through their effects on blood rheology. Oil of evening primrose (Efamol) as a dietary supplement improved blood rheology in cigarette smokers [15] and prevented the development of hypertension in spontaneously hypertensive rats [16].¹⁴

Because of raised levels of plasma IgA and/or the presence of IgA polymers, there is a high probability that blood rheology will be abnormal in patients with IGAN, a disorder in which conventional treatment has been reported as being ineffective. However, there are good theoretical grounds to support a suggestion that agents which improve blood rheology could be beneficial in patients with IGAN.

References

D'Amico, G.: Idiopathic IgA mesangial nephropathy. *Nephron* 47:1–13 (1985).

Kupor, L.E.; Mullins, J.D.; McPhaul, J.J.: Immunopathologic findings in idiopathic renal hematuria. *Archs. intern. Med.* 755: 1204–1211 (1975).

Simpson

L.O.: Glomerular permeability: an alternative to the pore theory. *Lancet* ii: 251–252 (1981).

Simpson

L.O.: Blood viscosity induced proteinuria. *Nephron* 56:280–281 (1984).