Blood Viscosity Induced Proteinuria

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Dear Sir,

In reporting on the effects of phlebotomy on the proteinuria of a patient with congenital cyanotic heart disease, de Jong et al. [1] not only extended an earlier observation [2] but also introduced the idea that increased postglomerular capillary resistance could be due to high blood viscosity. As the number of red cells is one of the major determinants of blood viscosity, it is not surprising that by reducing the number of red cells, phlebotomy reduces blood viscosity and thus causes a drop in postglomerular capillary resistance.

We have found [Simpson and Shand, unpubl.] in a patient with polycythemia rubra vera and associated high molecular weight proteinuria that successive phlebotomies not only lowered Hct but also resulted in a stepwise reduction in total urinary protein concentration and in the size of the largest urinary protein as determined by SDS-poly-acrylamide gel electrophoresis. These changes were predicted on the basis of my hypothesis that blood viscosity is an important factor in the mechanisms of proteinuria [3]. The reversible changes in glomerular function that are caused by increased blood viscosity associated with high Hct also occur when blood viscosity is raised because of changes in the red blood cell membrane which makes the cell less deformable. Such changes occur in diabetics with poor metabolic control [4]. In a preliminary report [5], temporary, reversible red cell rigidity resulting from high concentrations of plasma protein has been proposed as the cause of hyperproteinemic proteinuria in normal mice. Similar changes in red cell morphology have been reported [6] in climbers at high altitude. This observation raises the possibility that the edema of mountain sickness may be the consequence of hypoxia-induced reduction in red cell deformability which increases blood viscosity. In hyperproteinemic mice, despite the development of high molecular weight proteinuria 16 h after the first enhancement of plasma protein concentration [7], there appeared to be no permanent glomerular damage [8]. In contrast to the morphological changes in glomeruli described by de Jong et al. [1], only slight changes were seen at all levels of microscopy in the mice [8]. This difference in morphology was probably due to the length of time that the glomeruli had been subjected to insult in the polycythemic cyanotic patient. In the mice, less than 5% of glomeruli had Bowman's space and the proximal tubules filled with protein. But, as such changes were not seen during the posttreatment period, it was concluded that such conditions were reversible.

In the polycythemic situation, filtration-amplification of blood viscosity, together with the consequent thixotropic amplification of blood viscosity in the efferent arterioles [9], would be expected to lead to glomerular stasis and sclerosis. Evidence for such changes may occur in patients with congenital cyanotic heart disease, where atrophic glomeruli and widespread lesions possibly of ischemic origin, were described [10]. The authors also raised the possibility that localized increases in intravascular pressure might have caused the hyaline changes seen in afferent and efferent arterioles. For this reason it is surprising that the Jong et al. [1] did not report the presence of nonfunctional glomeruli. Those workers cited a paper by Hosfetter et al.

[11] to explain why glomerular enlargement and capillary dilation could lead to glomerular sclerosis. However, there are no data in that paper which would enable the mechanism of glomerular sclerosis to be explained. It seems more likely that the hemorrheologic consequences of filtration-amplification and thixotropic amplification of an already elevated blood viscosity would lead to intraglomerular stasis and eventually to sclerosis.

Proteinuria caused by increased blood viscosity disappears when blood viscosity is normalized. Depending upon the duration of the proteinuric episode, the increased concentration of filtered protein may induce changes in

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epithelial cell morphology as has been shown in albumin overload situations [8,12]. On the one hand, the potentially reversible nature of blood-viscosity-induced proteinuria places it in the category of the physiological proteinurias together with exercise and orthostatic proteinuria. On the other hand, there is little doubt that gross renal pathology will follow unless the blood viscosity is normalized. Thus there is no need to postulate a change in glomerular basement membrane as a necessary factor in proteinuria which in this case is more simply explained as a consequence of the elevated intraglomerular pressure required to maintain flow of viscous blood in postglomerular vessels. Blood-viscosity-induced proteinuria may be adduced as further evidence in support of the claim that glomerular basement membrane permeability is pressure dependent.

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