

## Personal Opinion

### No common final pathogenetic pathway in haemolytic uraemic syndromes

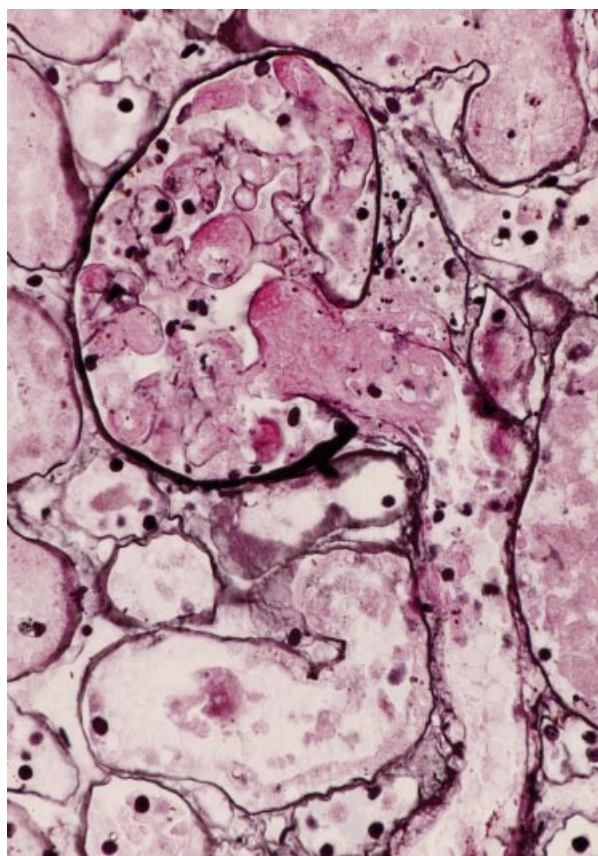
C. Mark Taylor, Alexander J. Howie<sup>1</sup> and Julie M. Williams

Department of Nephrology, The Birmingham Children's Hospital and <sup>1</sup>Department of Pathology, University of Birmingham, Birmingham, UK

There is a long standing and widely held view that the many sub-forms of the haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) share a common final pathogenetic pathway. This was expressed recently in a review article in this journal [1]. This is an assumption which deserves to be challenged. It appears to be based on the concept that the histological hallmark of these syndromes, thrombotic microangiopathy (TMA), is a single entity. There is growing evidence that it is not.

Symmers originally used the term TMA to describe thrombi occurring in an arteriolar distribution, particularly at the junction between arteriole and capillary, in the absence of vasculitis [2]. Later, Habib found such lesions in infants with HUS and subsequently described different patterns of TMA, expanding the term to cover all of them. One form, remaining close to Symmers' description, consisted of lesions at the arteriole with or without extension into the glomerular capillaries. In a second type, thrombosis was confined to the glomerulus, with endothelial swelling and amorphous material in the subendothelial space. The third form affected larger arteries as well as arterioles, and glomeruli appeared ischaemic. Various correlations were made between the histological sub-types and the clinical features of patients, and an extensive and valuable summary of this work appeared in 1992 [3]. In brief, arterial lesions were more often associated with severe hypertension and adverse outcome, while glomerular thrombosis alone was more favourable, as long as there was no co-existing extensive renal cortical necrosis [4]. Others have reinforced this view.

While the histological sub-type of TMA could be related to prognosis, early studies were not in a position to match this to the clinical groups discernable today. For example, much of this work was performed before the mid-1980s, the time when the commonest single cause of HUS became recognized, i.e. infection by verocytotoxin (shiga-like toxin)-producing *Escherichia coli* (VTEC). This precluded histological definition in



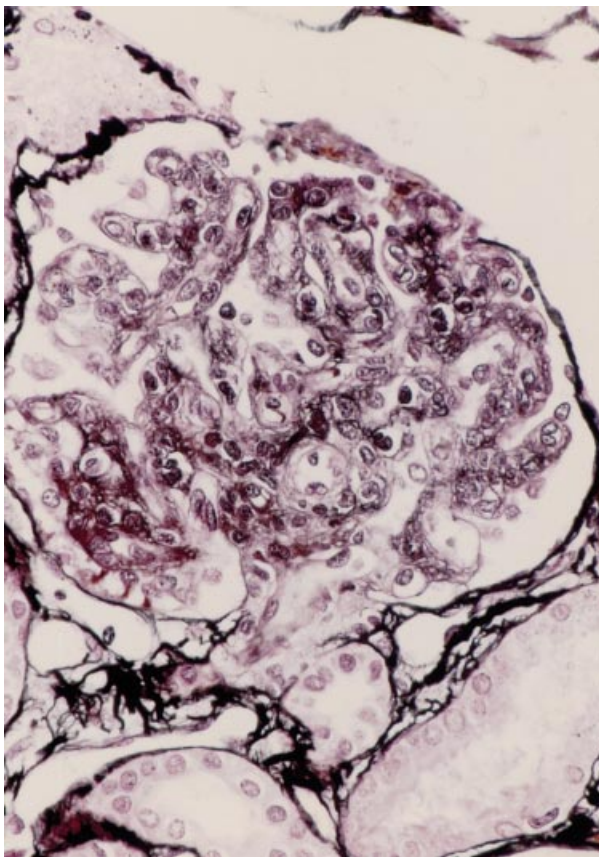
**Fig. 1.** Necrotic kidney from a child with VTEC-induced HUS. A glomerulus is distended by thromboses, with a thrombus in the afferent arteriole. Periodic acid-methenamine silver (PAAg).

the numerically most important group. Furthermore, it was only at the beginning of that decade that a prodromal illness of diarrhoea was shown to have prognostic significance, allowing a broad interim classification into diarrhoea-associated (D+) and non-diarrhoeal forms [5]. In Europe and the Americas, there is a close association between D+HUS and VTEC infection in children. On the other hand, non-diarrhoeal HUS in adults or children is a heterogeneous collection of rare diseases. Only a minority of patients

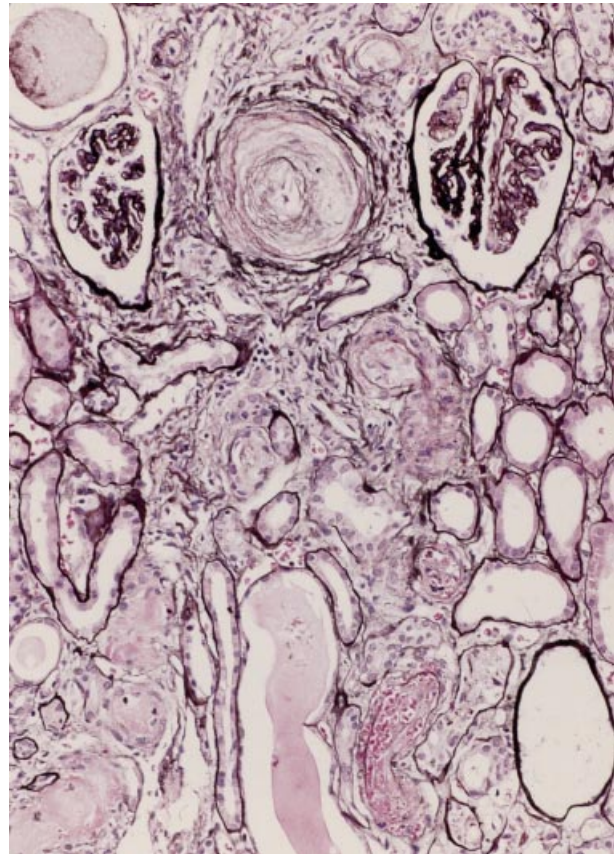
Correspondence and offprint requests to: Dr C. M. Taylor, Department of Nephrology, The Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NH, UK.

falling into this category can be defined further, for example into inherited disorders of complement regulation, or associated with specific drugs such as quinine. This continues to pose a problem in making clinico-pathological correlations. Rarity reduces single centre studies to case reports or small series collected over long periods, and meta-analysis based on these is difficult because descriptive terms used by different authors may lack precision. Multicentre collaboration is therefore needed to match histology to well-defined larger clinical groups.

In spite of these restrictions, different pathological appearances are emerging. In VTEC-induced HUS in children there are glomerular thromboses [6–8]. Arterial thromboses do occur but are uncommon and appear to be a proximal extension of the glomerular lesion (Figure 1). These features are not seen in familial HUS with complement factor H deficiency, in which glomeruli show mesangial increase and double basement membranes [9,10] (Figure 2). There is no evidence of development of double glomerular basement membranes either acutely or up to 5 years after an attack of VTEC-induced HUS [11]. Most adults with non-diarrhoeal HUS have loose mucoid intimal thickening in small arteries with fibrinoid necrosis of arterioles resembling the changes seen in systemic sclerosis and accelerated hypertension [12] (Figure 3). In TTP,



**Fig. 2.** Glomerulus in a biopsy specimen from a child with HUS associated with familial factor H deficiency. Several capillary loops have double basement membranes. PAAg.

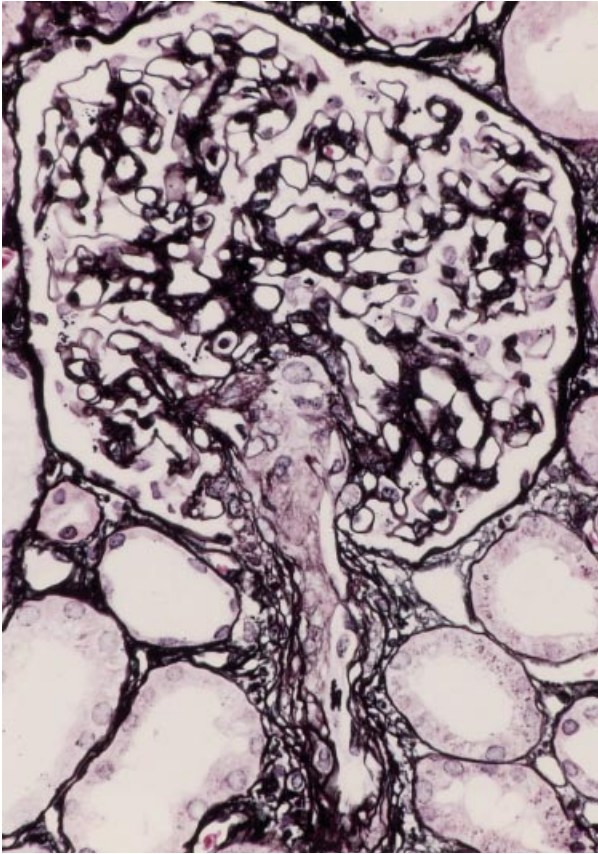


**Fig. 3.** Cortex in a biopsy specimen from an adult with HUS. Interlobar arteries have loose concentric intimal thickening. Glomeruli are shrunken due to ischaemia. PAAg.

the characteristic abnormality is thrombosis confined to an arteriole at the glomerular hilum, and glomerular thrombosis is uncommon [12] (Figure 4).

It seems most unlikely that these different patterns are part of a single process distanced only by severity or duration. Almost certainly they represent separate end-points, and thus separate processes. This being the case, the assumption of a common final pathway becomes untenable. Present evidence leads us to consider HUS as a collection of specific diseases. Each one needs to be understood in terms of its aetiology, pathogenesis, prognosis and response to therapy.

The last point acquires clinical importance. If there is no final common pathway there is unlikely to be a single cover-all treatment. Treatments need to be tested in clearly defined specific diseases or groups. For example, there is a consensus view that plasma exchange can reverse some forms of TTP and atypical, non-diarrhoeal HUS. However, in a recent literature review of HUS management [13], no effective, evidence-based primary treatment could be identified for D+ or VTEC-induced HUS. This included plasma therapy. Better understanding of disease mechanisms and therapeutic options for HUS and TTP is a realistic target, and laying to rest the myth that these conditions



**Fig. 4.** Glomerulus in a biopsy specimen from an adult with TTP. There is a thrombus in an arteriole at the hilum. PAAg.

have interchangeable pathogenetic features should help to accelerate the process.

## References

1. Kulzer P, Wanner C. Thrombotic microangiopathy: a challenge with uncertain outcome. *Nephrol Dial Transplant* 1998; 13: 2154–2160
2. Symmers WSC. Thrombotic microangiopathic haemolytic anaemia (thrombotic microangiopathy). *Br Med J* 1952; 2: 897–903
3. Habib R. Pathology of the hemolytic uremic syndrome. In: Kaplan BS, Trompeter RS Moake JL, eds. *Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura*. Marcel Dekker, New York: 1992: 315–353
4. Thoenes W, John HD. Endotheliotropic (haemolytic) nephroangiopathy and its various manifestations: thrombotic microangiopathy, primary malignant nephro-sclerosis, haemolytic uraemic syndrome. *Klin Wochenschr* 1980; 58: 173–184
5. Dolislager D, Tune B. The hemolytic uremic syndrome. Spectrum of severity and significance of prodrome. *Am J Dis Child* 1978; 131: 55–58
6. Richardson SE, Karmali MA, Becker LE, Smith CR. The histopathology of the hemolytic uremic syndrome associated with verocytotoxin-producing *Escherichia coli* infections. *Human Pathol* 1988; 19: 1102–1108
7. Inward CD, Howie AJ, Fitzpatrick MM, Raafat F, Milford DV, Taylor CM. Renal histopathology in fatal cases of diarrhoea-associated haemolytic uraemic syndrome. *Pediatr Nephrol* 1997; 11: 556–559
8. Renaud C, Niaudet P, Gagnadoux MF, Broyer M, Habib R. Haemolytic uraemic syndrome: prognostic features in children over 3 years of age. *Pediatr Nephrol* 1995; 9: 24–29
9. Ohali M, Shalev H, Schlesinger M *et al.* Hypocomplementemic autosomal recessive hemolytic uremic syndrome with decreased factor H. *Pediatr Nephrol* 1998; 12: 619–624
10. Warwicker P, Donne RL, Goodship JA *et al.* Familial relapsing haemolytic uraemic syndrome and complement factor H deficiency. *Nephrol Dial Transplant*, submitted
11. Moghal NE, Ferreira MAS, Howie AJ, Milford DV, Raafat F, Taylor CM. The late histological findings in diarrhea-associated hemolytic uremic syndrome. *J Pediatr* 1998; 133: 220–223
12. Heptinstall RM. *Pathology of the Kidney* 4th edn. Little Brown, Boston: 1992: 1172–1199
13. Taylor CM, Milford DV. Haemolytic uraemic syndrome. *Clin Paediatr* 1997; 5: 575–593