There are no signs of damage to the endothelium, and there have shown that intense production of vWFAg occurs in the many new vessels occurring in the inflammatory infiltrates (figure). The figure also shows the presence of vWFAg as a slight immunoperoxidase staining in endothelium cells. This staining pattern is not different from the pattern seen in normal temporal arteries or in biopsy specimens from patients with polymyalgia rheumatica and normal levels of vWFAg. As similar microvascular abnormalities (the introduction of many new vessels) are present in most of the diseases with increased vWFAg mentioned above, the reliability of raised levels of vWFAg in these diseases, including Sjögren’s syndrome, as a marker of endothelial damage should be reconsidered.

**Author’s reply:** Elling et al propose that raised circulating levels of von Willebrand factor antigen (vWFAg) reflect not endothelial cell damage but production by endothelial cells in newly growing microvasculature, challenging existing dogma. In support of this hypothesis they offer an immunohistological photograph from a patient with temporal arthritis taken from a previous publication which examined temporal artery biopsy specimens from patients with arthritis temporals, polymyalgia rheumatica, and other diseases. They found raised serum vWFAg and intense vWFAg staining in new vessels in the lamina elastica only in patients with arthritis temporals, but offer no mechanism or evidence that these are ‘new’ vessels. Could it be that the intense staining seen in the elastic lamina is because these endothelial cells are damaged? From the photograph it is difficult to tell if all or part of the intense staining for vWFAg is from intact cells, disrupted cells, or from vWFAg in the general connective tissue stroma.

I am surprised that Elling et al suggest that endothelial damage cannot explain why increased concentrations of vWFAg are present in such varied diseases as proliferative glomerulonephritis, diabetes mellitus, systemic sclerosis, Sjögren’s syndrome, and arteritis temporals, as endothelial damage in these diseases is not a common denominator. Other workers, such as Cioppo et al, have expressed an opposite view, stating that vessel injury is a common feature of scleroderma, glomerulonephritis, diabetes mellitus, Behçet’s syndrome, systemic lupus erythematosus, rheumatoid arthritis, and vasculitis in general. There seems to be little disagreement about the presence of raised vWFAg in a large number of conditions, some of which may be characterised by histological evidence of injury to the vasculature. However, the exact mechanism, in many cases, is unclear. Raised vWFAg is common in the acute phase response, but it would be surprising if there was evidence of damaged endothelium in this condition. It may be that in this case endothelial cells are merely ‘activated’ or ‘stimulated’ to produce vWFAg in expectation of a more severe insult (i.e. septicaemia or infection) that should damage the endothelium. Further increases in vWFAg may be the product of increased synthesis by actively growing cells in the capillary beds, the adventitia, or elsewhere. If this were true then one would need to explain why there should be an extra growth of endothelial cells, or upregulated production from a resting cell. Perhaps existing cells are being damaged, possibly to the point of cell death, by disease process, such as the combined effects of immune complexes and complement in vasculitis or ketoacidosis in diabetes.

Probably the ultimate proof of injury/damage would be an electron micrograph study of the endothelium in human disease. Such work would need to show a damaged endothelial cell with absent or depleted Weibel-Palade bodies (typical storage sites of vWF), ideally with immunocytochemistry for cytoplasmic vWFAg, alongside plasma levels of vWFAg. Another approach may be to look at vWFAg mRNA from in vivo ‘damaged’ and ‘normal’ endothelial cells—but these data would not provide information about vWFAg in Weibel-Palade bodies.

Until such data are easily obtained then the hypothesis that raised vWFAg is produced by injured endothelial cells in vivo may never be completely accepted. Yet despite this there remains a wealth of clinical and non-clinical data from many different diseases which all support the hypothesis. Convincing competing hypotheses would need to take account of all these findings.

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