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Kernoff P B A, Gruson R & Rizza C R. A variant of factor VIII related antigen. *Brit. J. Haematol.* **26**:435-40, 1974.
[Oxford Haemophilia Centre, Churchill Hospital, Oxford, England]

Using an antiserum prepared by immunizing a rabbit with human factor VIII concentrate, an atypical and probably functionally abnormal form of von Willebrand factor (factor VIII-related antigen) was identified in the plasma of a patient with variant von Willebrand's disease. [The *SCI*® indicates that this paper has been cited in over 125 publications.]

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The presence of a factor in normal and haemophilic plasmas that is lacking in plasmas obtained from patients with von Willebrand's disease (vWD) was deduced more than 25 years ago.[1] Quantitative or qualitative deficiencies of this von Willebrand factor (vWF) result in abnormalities of platelet function and blood coagulation, and an understanding of the pathogenesis of vWD has provided important insight into basic mechanisms of haemostasis.[2] vWF and the protein responsible for factor VIII coagulant activity (VIII:C) are now known to be biochemically and immunologically distinct. Previously, they were thought to be different components of a single molecule.

It first became possible to measure vWF antigen (otherwise known as factor VIII-related antigen; VIII:RAg) in the early 1970s, when Ted Zimmerman and his colleagues in Cleveland, using a heterologous antiserum raised against a factor VIII-containing fraction of normal plasma, developed a "rocket" electroimmunoassay that could be used to detect those antigens in normal and haemophilic plasmas that were reduced in plasmas obtained from patients with vWD.[3] They suggested that the assay detected nonfunctional forms of factor VIII in haemophiliacs–a misinterpretation that Zimmerman later conceded might have delayed advances in research into factor VIII:C for several years!

At that time, I was a junior clinical research fellow at the Oxford Haemophilia Centre, mainly engaged in studying adverse effects of transfusion therapy. I had developed an interest in inhibitors to factor VIII, and Zimmerman's paper provoked me to ask my supervisors, Rosemary Biggs and Charles Rizza, whether I could change my field of research activity to the immunology of factor VIII. With some initial reluctance, they agreed. With the help of Rizza and Rainer Gruson, who was visiting Oxford from Germany, I set about raising antisera to various factor VIII-related plasma components. We were able to show convincingly that factor VIII:C antigens and VIII:RAg were immunologically distinct, the latter probably representing the antigenic expression of vWF. In the course of studying plasmas from patients with less severe forms of vWD, we obtained odd results from one patient, subsequently described in our paper, that I initially attributed to artifacts caused by my lack of expertise in immunological techniques. Happily, I was persuaded otherwise, and the observations were confirmed in subsequent studies.

I think the paper is widely cited because it was the first description of variant vWD and therefore helped set in motion many studies carried out since that time that have elucidated the structural, functional, and immunological relationships between VIII:C and vWF and the role of the latter in haemostatic/thrombotic mechanisms.[2]

1. **Nilsson I M, Blomback M & von Francken I.** On an inherited autosomal hemorrhagic diathesis with antihemophilic globulin (AHG) deficiency and prolonged bleeding time. *Acta Med. Scand.* **159**:35-7, 1957. (Cited 310 times.)
2. **Holmberg L & Nilsson I M.** Von Willebrand disease. *Clin. Haematol.* **14**:461-88, 1985.
3. **Zimmerman T S, Ratnoff O D & Powell A E.** Immunologic differentiation of classic hemophilia (factor VIII deficiency) and von Willebrand's disease. *J. Clin. Invest.* **50**:244-54, 1971. (Cited 625 times.)