

Gocke D J, Hsu K, Morgan C, Bombardieri S, Lockshin M & Christian C L.  
Association between polyarteritis and Australia antigen. *Lancet* 2:1149-53, 1970.  
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This paper describes the association of polyarteritis nodosa with hepatitis B virus infection. It was the first clear demonstration in man of a systemic vasculitis induced by an immunologic reaction to a virus. This provided long-sought evidence for the idea that an infectious agent may initiate the complex immunopathologic events seen in a connective tissue disorder of previously unknown etiology. [The SCI® indicates that this paper has been cited in over 410 publications since 1970.]

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The finding described in this paper was really another example of serendipity in science. In the late 1960s at the Columbia-Presbyterian Medical Center in New York City, my lab was intensely involved in studies of posttransfusion hepatitis in which we prospectively followed recipients of donor blood containing the "Australia antigen" (now called hepatitis B surface antigen or HBsAg). These studies eventually proved the infectivity of such blood and led to prohibition of its transfusion. However, in the midst of these studies, a patient who had received a unit of antigen-positive blood developed unexplained fever three weeks after transfusion. Before our eyes, a syndrome of skin rash, mild hepatitis, and peripheral neuropathy evolved. Then an explosive nephritis with severe hypertension and congestive heart failure supervened. The serum—which was HBsAg-negative prior to transfusion—was now found to be HBsAg-positive. Biopsy of several tissues revealed vasculitis with fibrinoid necrosis in small- and medium-sized arterioles typical of polyarteritis nodosa. This combination of events occur-

ring in conjunction with recent hepatitis B infection prompted a search for immune complexes composed of hepatitis B viral (HBV) antigen and antibody. Sure enough, complexes containing HBsAg, homologous antibody, and complement components were readily found in the serum and localized in sites of vascular injury. Subsequently, we studied 10 other patients with polyarteritis and found 3 more whose serum was HBsAg-positive. At first we wondered whether these findings might represent only an epiphenomenon in which viral antigen, globulin, and complement were deposited non-specifically at sites of vascular injury. However, appropriate control patients failed to reveal HBsAg-antibody complexes in their serum or tissues, and the association of HBV infection with polyarteritis was much greater than could be accounted for on the basis of coincidence alone. Subsequently, these observations were amply confirmed by ourselves and others. In addition, this finding was extended to the elucidation of other HBV-related immune-complex phenomena. For example, the serum sickness-like prodrome that occurs in 15-20 percent of patients with acute hepatitis B has been shown to be due to circulating complexes composed of HBsAg, antibody, and complement. Also, some cases of glomerulonephritis in both adults and children have been shown to have immune complexes of HBV antigens and antibody in the glomerular lesions. This area has been recently reviewed.<sup>1,2</sup>

This article is frequently cited because it provided the first hard evidence in man to support the idea that an infectious agent can initiate a complex of immunopathologic events that account for the pathogenesis of a connective tissue disorder of previously unknown etiology. Such a mechanism was known to exist in certain experimental situations and had long been sought in man. The possibility that other agents operating by a similar mechanism may account for other disorders provides an intriguing line for further research.

1. Gocke D J. Systemic manifestations of viral liver disease. (Gitnick G L, ed.) *Current hepatology*. Boston: Houghton Mifflin, 1980. Vol. 1, p. 229-41.
2. .... Systemic manifestations of viral liver disease. (Gitnick G L, ed.) *Current hepatology*. New York: Wiley, 1982. Vol. 2, p. 273-88.