

# This Week's Citation Classic

Blumberg B S, Alter H J & Visnich S. A "new" antigen in leukemia sera. J. *Amer. Med. Ass.* 191:541-6, 1965. [Institute for Cancer Research, Philadelphia, PA and NIH, Bethesda, MD]

Australia antigen was discovered during the course of a systematic study of the sera of transfused patients to detect precipitating iso-antibodies against antigens found in serum. This approach had previously led to the discovery of inherited antigenic specificities on the low density lipoproteins (the Ag system). The Australia antigen was identified in the serum of an Australian aborigine and the precipitating antibody in the serum of a transfused hemophilia patient. Australia antigen was found to be rare in normal Americans but common in patients with leukemia. It was also quite common in normal people from Africa, Asia, and Oceania and there was family clustering. On the basis of these findings, several hypotheses were made related to leukemia, viral agents, and the genetic control of the presence of Australia antigen, and these were tested in an extended series of studies over the next ten years. [The SC® indicates that this paper has been cited over 560 times since 1965.]

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"This paper is the first in which the term 'Australia antigen' is used, although the discovery had been briefly reported the previous year.<sup>1</sup> Australia antigen was subsequently found to be the surface antigen of the hepatitis B virus (HBsAg). Hepatitis B virus also appears to be an important factor in the development of primary cancer of the liver, a disease which is a serious public health problem in many parts of Africa and Asia. If these inferences are correct, then this would be an example of a common human cancer in whose pathogenesis a virus is involved. Further, it may be possible to use measures to prevent this disease and we have developed a vaccine currently being tested. In subsequent papers in this series the methods for detecting carriers of hepatitis B virus were detailed. This led to the now common practice of testing the blood of potential donors for the presence of Australia antigen.<sup>2</sup> The presence of the antigen indicates that the donors have a high probability of transmitting hepatitis. This paper describes the original phase of the work, in which a large amount of data was collected on stored sera from patients and normal in-

dividuals. The hypotheses derived from these observations were tested in a subsequent series of papers.<sup>3</sup> This paper set the pattern for the research for the next ten years.

"It now appears that hepatitis B virus has many unusual characteristics, so much so that it has been suggested that for heuristic reasons, it may be useful to consider it as a member of a special group of infectious agents which we later termed 'Icrons' (after the Institute for Cancer Research). We described the geographic distribution of the carrier state which appears to be, at least in part, under genetic control. We also suggested that the antigen was associated with a virus; in this case, the virus of leukemia. There is still reason to believe that there may be a connection between hepatitis B virus and the etiologic agent of some forms of leukemia. The relation of the antigen to transfusion was also cited in the paper.

"The work began at the National Institutes of Health and continued at the Institute for Cancer Research in Philadelphia. Harvey J. Alter, who subsequently went on to complete his training as a hematologist, had come to work in our laboratory on this project. He is now at the Blood Bank of the National Institutes of Health and is an important investigator in the hepatitis field. Sam Visnich was a former Navy flyer and a commercial airline pilot who has now returned to flying.

"This work was done during a period when funding for non-directed research was more available than at present. At the beginning of this investigation it was impossible to see where it would lead. We had confidence that it would be important, since basic patterns of the distribution of Australia antigen began to emerge; in particular, the clustering of antigen positive individuals in families, the sex differences and the consistently high frequencies in tropical or underdeveloped areas as compared to northern Europe and the United States.

"In the 1960s research support was readily available to pursue apparently esoteric problems, and, in this case, it led to a practical application. Our work has been cited on several occasions as an example of the unpredictable but practical advantages of fundamental research, and I hope that it will have a continued effect on scientific directors and Congress on the importance of non-directed investigations."

1. Blumberg B S. Polymorphisms of serum proteins and the development of isoprecipitins in transfused patients. *Bull NY Acad. Med.* 40:377-86. 1964.
2. Blumberg B S, Gerstley B J S, Hungerford D A, London W T & Sutnick A I. A serum antigen (Australia antigen) in Down's syndrome, leukemia and hepatitis. *Ann Intern. Med.* 66:924-31. 1967.
3. Blumberg B S. Australia antigen and the biology of hepatitis B. *Science* 197:17-25, 1977.