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This Week's Citation Classic

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. [Inst. for Cancer Research, Fox Chase, Philadelphia, PA]

This is the first paper in which it was stated that Australia antigen (Au) was the hepatitis virus. This subsequently led to the identification of the hepatitis B virus (HBV), the development of methods for the diagnosis of hepatitis B, the prevention of post-transfusion hepatitis, the control of hepatitis in high risk environments, a vaccine against hepatitis B, and the recognition of the role of HBV in the causation of primary hepatocellular carcinoma (PHC).[1] [The *SCI*® indicates that this paper has been cited in over 480 publications since 1967.]

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"Australia antigen (Au) was discovered in 1963, and described in 1964[2] and 1965.[3] It was present in many normal people particularly in the tropics. It was also found in leukemia patients. We hypothesized that some individuals had a trait, possibly inherited, which made them susceptible to leukemia and also *to* having persistent Au in their blood. We tested individuals who had a high likelihood of developing leukemia, including patients with Down's syndrome (DS). The hypothesis predicted a high frequency of Au in high risk groups. This prediction was fulfilled for DS. During the course of the study on DS, we found that one patient had developed Au in the period he was under observation. During this period he had also developed hepatitis. This led to a systematic study of patients with hepatitis and in this paper, we reported an increased frequency of Au. We concluded, 'Most of the disease associations could be explained by the association of Au(1) with a virus, as suggested in our previous publications. The discovery of the frequent occurrence of Au(1) in patients with virus hepatitis raises the possibility that the agent present in some cases of this disease may be Australia antigen or be responsible for its presence. The presence of Australia antigen in the thalassemia and hemophilia patients could be due to virus introduced by transfusions.'

"We continued to study ideas generated by earlier findings. Family studies showed that susceptibility to developing the carrier state for hepatitis B virus (HBV) was under genetic control. Recent studies indicate that HBV DNA is integrated into host DNA in carriers and in patients with chronic liver disease and primary cancer of the liver. Could a viral gene introduced in this manner be transmitted from generation to generation and explain the apparent Mendelian segregation we detected?[1]

"We found a striking difference in the age distribution of carriers and inferred that younger people are more likely to become carriers. We now believe that this is related to the differentiation of liver cells.[4] The role of maternal infection which is now known to make a major contribution to the carrier pool in many populations was first discussed in this paper. Vaccine programs are now based in large part on the vaccination of infants to prevent the development of carriers. We also questioned why DS patients are more susceptible to persistent infection than others. This led to studies on host immune differences which determine whether an infected individual will become a carrier with an increased risk of chronic liver disease or develop protective antibody. These studies also led to the finding that carriers have higher levels of serum iron and ferritin and lower levels of transferrin and a model of the pathogenesis of chronic liver disease and primary hepatocellular carcinoma (PHC).[5]

"The frequent citation of this paper may be a result of its having been the first published association of Au to what is now known to be HBV. We subsequently prepared a more extensive paper on the relation of Au to HBV, but it was rejected. The editors were reluctant to publish a paper asserting that the hepatitis virus had been found, and required additional studies and publications to have this concept accepted.

"London, Sutnick, and I continued to work on hepatitis. Gerstley continued in medical teaching and patient care. Sutnick became dean of the Medical College of Pennsylvania. Hungerford recently retired because of medical disability. This work eventually resulted in the award in 1976 of the Nobel prize and other recognitions."

1. **Blumberg B S.** Australia antigen and the biology of hepatitis B. *Science* **197**:17-25, 1977.
2. ..... Polymorphisms of serum proteins and the development of isoprecipitins in transfused patients. *Bull. NY Acad. Med.* **40**:377-86, 1964.
[The *SCI* indicates that this paper has been cited in over 205 publications since 1964.]
3. **Blumberg B S, Alter H J & Visnich S.** A "new" antigen in leukemia sera. *J. Amer. Med. Assn.* **191:**541-6, 1965.
[Citation Classic. *Current Contents/Life Sciences* **22**(51): 14. 17 December 1979.]
4. **Blumberg B S & London W T.** Hepatitis B virus: pathogenesis and prevention of primary cancer of the liver. *Cancer* **50**:2657-65, 1982.
5. **Lustbader E D, Hann H W L & Blumberg B S**. Serum ferritin as a predictor of host response to hepatitis B virus infection. *Science.* In press, 1983.