

MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

November 13, 1969

AUSTRALIA ANTIGEN

Leading Candidate for Position of Hepatitis Virus

Patients receiving transfusions may develop precipitating antibodies against serum beta-lipoproteins. The antisera found in these patients were used to define a system of inherited antigenic specificities on the serum low-density beta-lipoproteins. This was termed the Ag system. A variety of specificities and alleles have been described.

1. An Isoprecipitation Reaction Distinguishing Human Serum-Protein Types. A. C. Allison and B. S. Blumberg. *Lancet* 1: No. 7178, 634, 1961.
2. Antigen Polymorphism of a Low-Density Beta-lipoprotein. Allotropy in Human Serum. B. S. Blumberg, S. Dray and J. C. Robinson. *Nature* 194: 656, 1962.
3. A Human Lipoprotein Polymorphism. B. S. Blumberg, D. Bernanke and A. C. Allison. *J. Clin. Invest.* 41: No. 10, 1936, 1962.
4. Inherited Antigenic Differences in Human Serum Beta Lipoproteins. A Second Antiserum. B. S. Blumberg and N. M. Riddell. *J. Clin. Invest.* 42: No. 6, 867, 1963.
5. Multiple Antigenic Specificities of Serum Lipoproteins Detected with Sera of Transfused Patients. B. S. Blumberg, H. J. Alter, N. M. Riddell and M. Erlandson. *Vox Sang.* 9: 128-145, 1964.
6. New Anti-Beta-Lipoprotein Sera in Transfused Children with Thalassemia. A. Vierucci, G. Morganti, D. Varone and L. Borgatti. *Vox Sang.* 11: 427-433, 1966.
7. A New Sensitive Method for Studying the Polymorphisms of the Human Low Density Lipoproteins. R. Butler and E. Brunner. *Vox Sang.* 11: 738-740, 1966.
8. The Ag-System. Comparison of Different Isoprecipitin Sera. Jan Hirschfeld. *Series Haematologica* I,1: 38-65, 1968.

Two sera obtained from multiply transfused hemophiliacs (one from Dallas) contained an antibody different from the lipoprotein precipitins. They reacted with only one serum in a panel of 24 against which they were tested. Since the reacting serum was that of an Australian aborigine, the antigen was given the geographic name "Australia antigen".

9. A "New" Antigen in Leukemia Sera. B. S. Blumberg, H. J. Alter and S. Visnich. *J.A.M.A.* 191: 541-546, 1965.

The antibody directed against Australia antigen is an IgG(7S) gamma globulin. Australia antigen is not identical with typical low or high density lipoprotein.

10. Further Studies on a "New" Human Isoprecipitin System (Australia Antigen). H. J. Alter and B. S. Blumberg. *Blood* 27: No. 3, 297, 1966.

Table 1  
AUSTRALIA ANTIGEN DISTRIBUTION IN PATIENTS AND CONTROLS

	No. Tested	Au positive	
		No.	%
Controls (nonhospitalized "normal")	2,412	2	0.1
Hospital patients, serial admissions	1,055	2	0.2
Liver disease			
Hepatitis, acute viral	125	25	20
Infectious mononucleosis	67	0	0
Laennec's cirrhosis	52	0	0
Other liver disease	15	0	0
Leukemia			
Acute myelogenous	51	7	14
Chronic myelogenous	63	0	0
Acute lymphocytic	89	11	12
Chronic lymphocytic	49	5	10
Hodgkin's disease	16	2	13
Down's syndrome (institutionalized)	257	75	29
Transfused anemia patients	144	5	3
Solid tumors	95	0	0
Various other diseases	1,414	0	0

11. A Serum Antigen (Australia Antigen) in Down's Syndrome, Leukemia, and Hepatitis, B. S. Blumberg, et al.  
Annals of Int. Med. 66: 924, 1967.
12. Hepatitis and Leukemia: Their Relation to Australia Antigen.  
B. S. Blumberg, A. I. Sutnick and W. T. London.  
Bull. N. Y. Acad. Med. 44: No. 12, 1566-1586, 1968.

#### Australia Antigen Associated With Hepatitis

Australia antigen has been detected in sera of patients considered to have acute infectious hepatitis and serum hepatitis.

13. Australia Antigen and Acute Viral Hepatitis. W. T. London, A. J. Sutnick, and B. S. Blumberg. Annals of Int. Med. 70: No. 1, 55, 1969
14. Hepatitis Antigen: Correlation with Disease and Infectivity of Blood-Donors. D. J. Gocke and N. B. Kavey. Lancet pp 1055, 31 May 1969.
15. Australia Antigen in Acute and Chronic Liver Disease. R. Wright, R. W. McCollum and G. Klatskin. Lancet, Vol. II, No. 7612, 19 July 1969.
16. Hepatitis-Associated Antigen in Chronic Liver Disease. R. A. Fox, S. P. Niazi, S. Sherlock. Lancet, pp 609, 20 Sept. 1969.

17. Virus-like Particles in Sera of Patients with Infectious and Serum Hepatitis. R. J. Hirschman, N. R. Shulman, L. F. Barker, and K. O. Smith. J.A.M.A. 208: No. 9, 1667, 1969.

TABLE 2  
AUSTRALIA ANTIGEN AND HEPATITIS

	Ref. 13		Ref. 14		Ref. 15		Ref. 16		Ref. 17	
	No. Tested	Au Positive	No. Tested	Au Positive	No. Tested	Au Positive	No. Tested	Au Positive	No. Tested	Au Positive
Acute viral hepatitis	125	25	77	49	88	46	17	5		
Infectious hepatitis	84	11	15	7	12	3			a. 39 b. 112	2 18
Serum hepatitis (post-transfusion)	41	14	48	36	43	21			a.** 24 b. 62	2 46
Unknown virus			14	6	33	22				

\* Occasional samples

\*\* Weekly samples prospective.

Australia antigen has been identified with long incubation hepatitis infection at the Willowbrook State School. The long incubation virus tentatively considered equivalent to SH virus. The virus can transmit disease when administered parenterally or orally.

18. Infectious Hepatitis: Evidence for Two Distinctive Clinical, Epidemiological, and Immunological Types of Infection. S. Krugman, J. P. Giles, and J. Hammond. J.A.M.A. 200: No. 5, 365, 1967.
19. Viral Hepatitis: Relation of Australia/SH Antigen to the Willowbrook MS-2 Strain. J. P. Giles, R. W. McCollum, L. W. Berndtson, Jr., and S. Krugman. N. Eng. J. Med. 281: No. 3, 119, 1969.

Some feel that Australia antigen is related specifically to long incubation hepatitis (SH). The major arguments are a) association of Australia antigen with long incubation hepatitis; b) SH antigen and Australia antigen are identical immunologically by agar diffusion; c) Australia antigen present in high proportion of patients with parenterally transmitted hepatitis (transfusion, addicts); d) Australia antigen not found in spontaneous childhood hepatitis.

Proponents of this view consider that long incubation virus was transmitted by mouth in patients with antigen positive hepatitis who have not received parenteral injections.

20. An Antigen Detected in the Blood During the Incubation Period of Serum Hepatitis. A. M. Prince. Natl. Acad. Sciences 60: No. 3, pp 814, July 1968.
21. Relation of Australia and SH Antigens. A. M. Prince. Lancet 2: Pt. 1, pp 462, August 24, 1968.
22. Immunologic Distinction between Serum and Infectious Hepatitis. R. L. Hargrove, G. H. Jeffries, and A. M. Prince. J. Clin. Invest. 48: 35a, 1969.
23. The Serum Hepatitis Related Antigen (SH) in Illicit Drug Users. C. E. Cherubin, R. Leslie Hargrove and A. M. Prince. J. Clin. Research 17: 367, 1969.
24. Immunologic Distinction between I.H. and S.H. A. M. Prince. New Eng. J. Medicine 281: No. 3, 163, 1969.

Australia antigen positive sera obtained from patients with (a) parenterally transmitted and nonparenterally-transmitted hepatitis; (b) Down's syndrome with anicteric or icteric hepatitis; (c) leukemia; (d) known carrier status and from chimpanzees and a gibbon contain particles about 200 A identified by electron microscopy. The particles agglutinate in the presence of antibody derived from rabbits immunized with Australia antigen-positive sera.

Reference 17 (See above)

25. Particles associated with Australia Antigen in the Sera of Patients with Leukaemia, Down's Syndrome and Hepatitis. M. E. Bayer, B. S. Blumberg, B. Werner. Nature 218: No. 5146, pp. 1057-1059, June 15, 1968.
26. Immune electron Microscopy of the Australia-SH (serum hepatitis) Antigen. J. D. Almeida, A. J. Zuckerman, P. E. Taylor and A. P. Waterson. Microbios 1: No. 2, 117-123, 1969.

27. Production of Antibody Against "Australia Antigen" in Rabbits. L. Melartin and B. S. Blumberg. Nature 210: No. 5043, pp. 1340-1341, June 25, 1966.

Australia antigen has also been detected in:

- a) Nuclei of liver cells of patients post transfusion and non-parenterally transmitted hepatitis.
28. Australia Antigen detected in the Nuclei of Liver Cells of Patients with Viral Hepatitis by the Fluorescent Antibody Technique. I. Millman, V. Zavatone, B. J. S. Gerstley, B. S. Blumberg. Nature, 222: 181-184, 1969.
- b) Stool and urine obtained from patients with acute viral hepatitis.
- c) A soft shell clam (*mercinaria mercinaria*) taken from an estuary known from bacterial studies to be polluted.
29. Australia Antigen and Viral Hepatitis. R. M. H. Kater, C. Y. Kim, and C. S. Davidson. J. Infectious Diseases 120: 391, 1969.
- d) A freeze-dried icterogenic pool of serum collected in 1944.
- e) Serum of an asymptomatic carrier 20 years after his blood was demonstrated to have transmitted hepatitis to a donor. Current serum was shown to contain 200 A particles.
30. Persistence of the Serum Hepatitis (SH-Australia) Antigen for Many Years. A. J. Zuckerman and P. E. Taylor. Nature, 223: 81-82, 1969.
- f) Bank blood, the administration of which was followed by hepatitis.
31. Hepatitis Antigen. Detection of Infectious Blood Donors. D. J. Gocke, H. B. Greenberg and N. B. Kavey. Lancet, August 2, 1969, pp. 248-249.

TABLE 3  
AUSTRALIA ANTIGEN IN VARIOUS TYPES OF LIVER DISEASE

	Ref. 15		Ref. 14		Ref. 32		Ref. 16	
	No. Tested	Au Positive	No. Tested	Au Positive	No. Tested	Au Positive	No. Tested	Au Positive
Prolonged viral hepatitis ( 4 mos.)	29	11	5	0			7	3
Unresolved classic hepatitis	14	7						
Subacute hepatic necrosis progressing to post- hepatic cirrhosis	15	4						
Chronic persistent hepatitis							19	0
Chronic active hepatitis	24	6			31	3	32	0
Inactive postnecrotic cirrhosis cryptogenic cirrhosis	26	1*					49	1
Other hepatic diseases	222	2						
Primary biliary cirrhosis	44	0					39	0
Laennec cirrhosis, Alcoholic	57	1*	10	0			31	0
Drug hepatitis	23	0	5	0			8	0
Biliary Obstruction	35	1*	1	0				
Neoplasms	11	0	3	0			33 <sup>†</sup>	2
Infectious mononucleosis	6	0	12	0				
Miscellaneous	46	0	5	0				
Controls	135	0	162	2*				

\* Multiple transfusions

† Hepatoma

32. Australia Antigen in Chronic Active Liver Disease with Cirrhosis. C. L. Gitnick, G. J. Gleich, L. J. Schoenfield, A. H. Baggenstoss, A. I. Sutnick, B. S. Blumberg, W. T. London, W. H. J. Summerskill. Lancet, pp. 285-288, August 9, 1969.
33. The Role of Serum Hepatitis Virus in Chronic Liver Disease. A. M. Prince, R. L. Hargrove and G. H. Jeffries. (Abstract) J. Clin. Res. 17: 461, 1969.

## OTHER CONDITIONS ASSOCIATED WITH HIGH INCIDENCE OF AUSTRALIA ANTIGEN IN SERUM

### Down's Syndrome

Patients with Down's syndrome in large institutions where likelihood of endemic hepatitis is great have a high incidence of Australia antigen. Postulated this may be related to a susceptibility factor in association with Down's syndrome.

See References 11 and 12.

34. Anicteric Hepatitis Associated with Australia Antigen. Occurrence in Patients with Down's Syndrome. A. I. Sutnick, et al. J.A.M.A. 205: No. 10, 670, 1968.

### Leukemia

See References 11 and 12

35. Leukemia and Australia Antigen. A. I. Sutnick, W. T. London, and B. S. Blumberg. (Abstract) Proc. of Amer. Assoc. for Cancer Research. pp 90, 1969.

### Leprosy

Patients with lepromatous leprosy have high incidence of Australia antigen, whereas patients with tuberculoid leprosy do not.

36. Association between Lepromatous Leprosy and Australia Antigen. B. S. Blumberg et al. Lancet, 2: pp. 173-176, July 22, 1967.

Patients with lepromatous leprosy have impairment of delayed tissue hypersensitivity.

37. Impaired Delayed Hypersensitivity in Patients with Lepromatous Leprosy. D. S. Waldorf, J. N. Sheagren, J. R. Trautman and J. B. Block. Lancet, 2: Pt. 2, pp. 773-775, October 8, 1966.

### Patients Undergoing Chronic Hemodialysis

In those units with well studied hepatitis outbreaks in patients and staff, Australia antigen tends to persist in sera of patients. It has been postulated that persistence of antigen is related to impaired immunologic responsiveness of patients with chronic uremia.

38. S. H. Antigen in Haemodialysis-Associated Hepatitis. G. C. Turner, G. B. B. White. Lancet 11: No. 7612, pp. 121-125, July 19, 1969.

39. An Epidemic of Hepatitis in a Chronic-Hemodialysis Unit: Australia Antigen and Differences in Host Response. W. T. London, et al. New Eng. J. Medicine 281: 571-578, 1969.

#### Certain Populations

Unusually high incidence of Australia antigen found in a number of nonhospitalized "normal" populations.

See Reference 12.

40. Family Studies of a Human Serum Isoantigen System (Australia Antigen). B. S. Blumberg, L. Melartin, R. A. Guinto, and B. Werner. Amer. J. Human Genetics 18: No. 6, 594-608, 1966.

#### Methodology

Newer technical refinements suggest that antigenic differences exist among samples of Australia antigen. Antibodies directed at different antigenic determinants, and procedures such as complement fixation tests have detected a significantly higher incidence of reactions in suspected hepatitis carriers.

41. Additional Specificities of Australia Antigen and the Possible Identification of Hepatitis Carriers. C. Levene and B. S. Blumberg. Nature 221: 195-196, 1969.
42. Virus-like Antigen, Antibody, and Antigen-Antibody Complexes in Hepatitis Measured by Complement Fixation. N. R. Shulman and L. F. Barker. Science 165: 304-306, 1969.
43. A Complement-Fixation Test for Measuring Australia Antigen and Antibody. R. H. Purcell, et al. J. of Infectious Diseases 120: No. 3, 383-386, 1969.