

This Week's Citation Classic

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Almeida J D & Waterson A P. Immune complexes in hepatitis. *Lancet* 2:983-6, 1969.
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Serum from three cases positive for hepatitis B antigen were examined in the electron microscope (E/M). The subjects were: a silent carrier, a chronic hepatitis, and a fatal case of fulminant hepatitis. In each instance the distribution of the antigen differed in the E/M. These appearances were related to the presence or absence of antibody and a theory was proposed that the effect of HBAg was immune mediated. [The SC[®] indicates that this paper has been cited over 310 times since 1969.]

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"This paper is a prime example of being in the right place at the right time. The place was the Royal Postgraduate Medical School, London, and the time was just a year after the Australian antigen, later to become the hepatitis B antigen (HBAg), was first visualised in the electron microscope. A.P. Waterson was, and still is, the head of the virology department there and we had managed to enter the virological side of the hepatitis B story at an early stage mainly through the even earlier interest of A.J. Zuckerman. At that time there were none of the present-day sophisticated methods for the detection of HBsAg. The antigen was recognised serologically by immuno-diffusion or counter immunoelectrophoresis, or visually by negative staining in the E/M. As might be

imagined we looked in the E/M at anything that might potentially be hepatitis B, and in so doing recognised that the antigen was usually randomly distributed but on occasion it was clumped. My own long-term interest and study throughout the years has been the use of negative staining to visualise the interaction of virus-antigen and antibody. It was therefore natural to consider that the change in distribution seen in different specimens was due to the presence or absence of immune complexes. At this point serendipity entered and, looking back, it seems almost unbelievable that the three cases described occurred almost simultaneously. They were: a silent carrier known to have been positive for HBAg for 20 years; a tragic fatal case of hepatitis in a young nurse; and a long standing chronic hepatitis. The antigen had obviously been harmless in the carrier, fatal in the nurse, and had produced chronic disease in the last subject. The micrographs from the three cases turned up in one batch and, to use a hackneyed English expression, the penny dropped!

"It seemed that the antigen itself did not do the damage without an immune response being mounted against it. This was so exciting that what happened next can only be described as reprehensible. We published on a series of three! However, it appears that this was the right thing to do; more data would almost certainly have muddied the picture, and made the theory less attractive. If there is a moral to this story it is that journals should occasionally take a chance by publishing papers that, although based on observations, also contain a certain amount of surmise, which is exactly what *Lancet* did for us.

"Why has this paper been cited? It came at a time when hepatitis B antigen was very new; in the paper it is still referred to as Australia-serum hepatitis antigen (Au-SH). It is therefore one of the earliest papers to suggest that hepatitis B antigen was God's gift not just to virologists, but to immunologists as well."