

This Week's Citation Classic

Doniach D, Roitt I M, Walker J G & Sherlock S. Tissue antibodies in primary biliary cirrhosis, active chronic (lupoid) hepatitis, cryptogenic cirrhosis and other liver diseases and their clinical implications.
Clin. Exp. Immunol. 1 : 237-62, 1966

The finding of mitochondrial antibodies in the serum of almost all cases of primary biliary cirrhosis and in very few patients having other clinically similar disorders, made it possible to avoid unnecessary and harmful laparotomies by a correct preoperative diagnosis of the 'autoimmune' cases. [The SC[®] indicates that this paper has been cited 235 times since 1966.]

Deborah Doniach
Department of Immunology
The Middlesex Hospital Medical School
London W1 England

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"This paper contained the fullest account of the serological studies which led to the identification of mitochondrial antibodies, and the realization of their importance in the differential diagnosis of chronic liver diseases. The work was a direct extension of the initial discovery by Ivan Roitt and myself in 1956 that human lymphoid thyroiditis was an 'autoimmune' disorder, when we found precipitins to normal thyroglobulin in the sera of patients with Hashimoto goitres.¹ This was soon followed by the detection of adrenal antibodies in Addison's disease with 'idiopathic' adrenal atrophy, and of gastric autoimmunity in pernicious anaemia. These two conditions were known to occur in clinical association with chronic thyroiditis.

"Autoimmune mechanisms had been suspected in hepatic cirrhosis since the beginning of the century when the complement fixation reaction (CFT) was first discovered. This was found to be positive to high titres in certain cases of cirrhosis when liver extracts were used as antigens.

"In the early 1960s we had acquired our first ultraviolet microscope and had mastered the art of immunofluorescence, the method developed by Albert Coons, which has contributed more than any other to unravelling the mysteries of organ and tissue antibodies.

We then felt that we ought to look for evidence of autoimmunity in liver diseases. We approached the distinguished hepatologist, Prof. Sheila Sherlock, and asked her to send us the sera of cases likely to belong to the autoimmune group. Her young resident at the time was Geoffrey Walker, who is now a consultant and much loved teacher in clinical gastroenterology. He was the go-between for us autoimmunologists. We worked together for several years and spent many hours puzzling over the data described in the cited paper. It proved impossible to demonstrate liver-specific antibodies at that time but instead, when the results on over 200 cases were decoded, we found that a defined immunofluorescence pattern, which we identified as mitochondrial, was seen mostly in middle aged women with a disease in which there is a progressive destruction of the small bile ductules inside the liver, giving rise to an obstructive jaundice difficult to distinguish from that produced by lesions affecting the larger extrahepatic ducts, for which surgery is mandatory. The anti-mitochondrial-antibody (AMA) test has now been adopted worldwide as one of the essential diagnostic parameters for this and related diseases. Later Peter Berg, now Professor of Clinical Immunology in Tubingen, joined our research team and contributed important studies relating to the location and nature of the mitochondrial antigens. He is now expanding this work in many fruitful directions. "I was always an endocrinologist at heart and in the past four years I have had the good fortune to train another gifted autoimmunologist, Dr. Franco Bottazzo, whose work led to the discovery of pancreatic islet-cell antibodies in 'insulin-dependent' diabetes mellitus,² a disease more common and causing even more suffering than hepatic cirrhosis. If this 'autoimmune' marker allows us to predict the onset of the disease in predisposed families this will be ample reward for my 30 years spent in trying to fathom the causes of human ailments."

1. Doniach D & Roitt I M. 'Autoimmune thyroid disease' in *Textbook of immunopathology*. (Miescher P A & Muller-Eberhard H J. ed.) Vol. II, 2nd edition, Grune & Stratton N.Y., 1976, p. 715-735.
2. Doniach D & Bottazzo G F. Autoimmunity and the endocrine pancreas in *Pathobiology Annual* Vol. 7 (Iochim H L. ed.) Appleton-Century-Crofts N.Y., 1977, p. 327-346.