IMMUNOLOGY OF THE LIVER

Martin Smith
and
Roger Williams

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EDITORS' FOREWORD

Once involved in liver transplantation, it was perhaps not surprising that The Liver Unit at King's should also become interested in auto-immune liver disease. After an investigation of cell mediated responses during rejection, it became clear to us that such processes might also be involved in active chronic hepatitis and in primary biliary cirrhosis. There is also a high incidence of serum auto-antibodies in these conditions, but their exact role in pathogenesis has not so far been determined. The idea then began to grow of holding a meeting in which laboratory workers and clinicians with interests in this field would come together and discuss the basis of immune reactions in liver disease. To hold such a meeting seemed doubly important in view of the increasing use of immunosuppressive agents in the treatment of patients with apparently different clinical types of liver disease but which, according to current thinking, are attributable to auto-immunity.

The success of such a meeting depends so much on the ability of the chairmen and speakers and to them we express our sincere thanks. Dr. G. Dobias from Hungary, Dr. V. Pipitone from Italy and Dr. N. D. C. Finlayson from New York were unavoidably detained at the last moment but have allowed their papers to be published. Indeed, we are grateful to all those who came from overseas and we hope that this book represents a truly international account of auto-immune liver disease at the present time.

We are very much aware in publishing this symposium of the dangers of delay and we are most grateful to Heinemann's who have achieved such rapid publication. The meeting was generously sponsored by Beecham Research Laboratories and Mr. D. Goodchild, Liaison Officer, gave invaluable assistance. Many members of the Liver Unit helped in the organisation in different ways. It is not possible to mention them individually, except Dr. Adrian Eddleston who was responsible for a major share of the ideas and organization of the meeting.

Finally, without the untiring efforts of my personal secretary, Miss Margaret Skellern, and the Unit secretaries – Mrs. Jean Rowles and Miss Gillian McNay – the meeting and the publication of the proceedings would never have come to fruition.

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OPENING ADDRESS BY THE DEAN OF KING'S COLLEGE HOSPITAL MEDICAL SCHOOL – DR. D. I. WILLIAMS

At the end of January, 1860, an eminent physician was called to see a patient in South Wales. This was Sunday, January 29. On his way back he spent the night in Gloucester and while there he was seized with haematemesis and vomited three pints of blood. He did not rest but took the early train back to London and although feeling very ill he managed to see several patients. At 1 p.m. haematemesis violently came on again and prostrated him completely. Despite the attendances of five of his colleagues he died at 8 p.m. in his consulting room at the age of 50. He had been aware for at least a year of his inevitable doom; indeed, you can read all about it in Thackeray's "Roundabout Papers", where he is thinly disguised as "Mr. London". At the postmortem it was found that he had hypertrophic cirrhosis of the liver, the disease in fact sometimes called after him. Shortly before his death, he had collected a number of lectures which were later published. The last chapter in the book treats of "the therapeutical action of alcohol". "Some of you", he said, "would doubtless be surprised at seeing that a good deal of wine and brandy is administered to many of my patients". Some of you may think to salve your consciences when you hasten to agree with his statement that "alcohol possesses its stimulating property because it is a form of aliment, appropriate to the direct nourishment of the nervous system and its preservation, and its especial adaptation to this system gives it an immediate, exciting power superior to any other kind of food".

I may say, he stresses its value in very much divided doses. "Taken too much at one time, the patient will become more or less intoxicated or, in common language (he says), drunk." His potion is a most palatable mixture of Tinct. Canella,* brandy, syrup and water, and, judging by the accounts of the hospital, he prescribed it very often.

Now, this was a great teacher, a great physiologist and a great clinician. But his greatest contribution was to found this Hospital in 1839, and his statue, by Noble, was erected by colleagues, pupils and friends and now stands on Denmark Hill. His name was Professor Robert Bentley Todd, and our present Liver Unit, by chance rather than design, is in Todd Ward.

Before 1839, King's College – that is, King's College, London, not the Hospital – had medical students but no hospital: Todd was the power behind the foundation of the new Hospital, close to Lincoln's Inn Fields, alongside the graveyard of St. Clement Dane's Church and adjacent to the slaughterhouse of Butchers, Row. "Its locality is fine", the *Medical Times* said, "shambles on one side and a churchyard on the other – butchers within and without, prayers for the living and for the dead". In 1864 a second hospital was built on the old site, where W. H. Smith's are now, and in 1913 we came out to Denmark Hill. In 1909 the Medical School became a School of Medicine of the University of London.

In 1845 there was published a book on "Diseases of the Liver" by George Budd, like Todd, a Fellow of the Royal Society, and herein he describes the case of a man who died in King's in February, 1844, with "inflammation of the hepatic vein". Curiously, he too says, "The patient had for many years been in the habit of drinking enormous quantities of gin", and it was to this that Budd

* Wild cinnamon.

attributed the inflammation. In 1912, another great man, Samuel Kinnier Wilson, wrote on progressive lenticular degeneration – 'Wilson's Disease', and he came on the staff of this hospital in 1919. On a personal note, may I say that I had the honour of being his house physician, but this was later, in 1937.

This exciting meeting arises, therefore, almost as a natural progression in the study of liver disease at this hepatophilic Hospital. But not quite so. It has arisen, really, on the initiative of my colleague and namesake, Dr. Roger Williams, who gets all my cheques while I get his bills, who conceived the idea and who has worked so hard to bring it into the world, and it is up to the rest of you to give life to this conception. On behalf of the Medical School, I am therefore very happy to welcome you to this meeting, and I hope you will enjoy it.

The Dean then repeated the welcome in German, Italian, Spanish, French, Australian and American.

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CLINICAL SPECTRUM OF AUTO-IMMUNE LIVER DISEASE

A. E. Read

Over the past twenty years, those interested in liver disease have gradually accepted the idea that certain chronic liver disorders may represent either partially or completely the effects of auto-immune damage. In opening this symposium, it is my task to review with you the clinical features of the diseases which have come under auto-immune "suspicion", admitting that, on the one hand, there is really no clear proof that any one of these diseases is of auto-immune aetiology and on the other, it is equally possible that I shall leave out some disorders which will later turn out to be clearly of this aetiology. However, I propose to start by reviewing the features of so-called "Primary auto-immune" disease, that is, auto-immune disease where specific organ antibodies are found and where these antibodies are thought to cause damage to the target organ. These have been reviewed very ably by Dr. Doniach (1970) recently and some of the features that she has set out are shown in Table 1. Primary auto-immune

Table 1

Features of Primary Auto-immune Diease

(Doniach 1970)

(1) No known cause
(2) Female preponderance
(3) Protracted course
(4) Appropriate serum antibodies
(5) Histology shows immune hyperactivity
(6) Familial aggregation
(7) Association with other auto-immune conditions
(8) Variable clinical picture.

disease has no known cause, often a female preponderance and a protracted course; there are appropriate specific serum antibodies, the histology shows immune hyperactivity, there is often familial aggregation of cases, there is an association with other auto-immune conditions, and lastly, the clinical picture is sometimes variable.

HEPATIC DISEASES FULFILLING CRITERIA OF PRIMARY AUTO-IMMUNE DISORDERS

Now let us see what diseases might fit into this pattern, or a similar sort of pattern, when we are dealing with the liver. Table 2 shows those conditions where auto-immunity may, in the light of present knowledge, have a part to play in hepatic damage. Firstly, active chronic hepatitis – known by a wide variety of names, most of them stressing some clinical or pathological feature of the disease. Secondly, primary biliary cirrhosis and thirdly, a rare syndrome for which I have found no name, first adequately described by Craig, Schiff and Boone in 1955, in which chronic liver disease exists in an environment of auto-immune disease affecting the adrenal gland, the parathyroid, etc. Some of these cases are

Table 2

Clinical spectrum of auto-immune liver disease

(1) Active Chronic Hepatitis.

Lupoid hepatitis
Waldenström's active chronic hepatitis
Plasma cell hepatitis
Juvenile cirrhosis.

(2) Primary biliary cirrhosis.

Chronic non-suppurative destructive cholangitis.

(3) Craig-Schiff-Boone Syndrome (1955).

Chronic hepatitis, hypoparathyroidism.
Addison's disease. Moniliasis.

(4) ? Cryptogenic cirrhosis.

(5) Liver disease in collagen diseases

(a) Systemic sclerosis
(b) Rheumatoid arthritis – Felty's Syndrome
(c) Sjögren's syndrome, etc.

complicated by systemic Candida infections. Fourthly, it is possible that some cases of cryptogenic cirrhosis, of the sort commonly seen in this country, belong to this group. Lastly, one must look for evidence of liver disease in the collagen disorders as the latter are already suspected of an auto-immune aetiology, and it is therefore reasonable to examine these cases for evidence of liver involvement. The ones that have been particularly investigated are systemic sclerosis, rheumatoid arthritis with Felty's syndrome, and Sjögren's syndrome.

ACTIVE CHRONIC HEPATITIS

This is a disease of great interest, one which has an international flavour (Table 3), for various features have been described from various parts of the

Table 3

Landmarks in the history of A.C.H.

(1) 1948 (Australia) Wood *et al.* "*Chronic Infectious Hepatitis*".
(2) 1950 (Sweden) Waldenström. *Age Sex.*
(3) 1950 (U.S.A.) Kunkel. *Serum proteins.*
(4) 1955 (Australia) Joske and King, *LE cell.*
(5) 1956 (U.S.A.) Bearn *et al. Generalised Disease.*
1957 (Australia) Gajdusek. *Immunology.*
(6) 1960 (U.S.A.) Page & Good. *Histology.*
(7) 1963 (England) Read *et al. Multiorgan involvement.*
(8) 1965 (England) Johnson *et al. S. M. Antibody.*

world. In Australia, this was thought to be chronic infectious hepatitis by Wood *et al.* (1948). Waldenström (1950) pointed out the particular age and sex incidence, the serum protein changes were described by Kunkel and Labby (1950). Joske and King (1955) in Australia first showed that some patients have an LE cell phenomenon, hence one of its alternative names, lupoid hepatitis. In the United States (Bearn *et al.* 1956) and England (Read *et al.* 1963), it was realised that this was a multisystem disease and not just one confined to the liver. Gajdusek (1958) in Australia found nonspecific antibodies in the serum and Page and Good (1960) were particularly interested in the plasma cell infiltrate in the liver. Lastly, the smooth muscle antibody was described by Johnson *et al.* (1965) in a fair percentage of patients with this disease, whereas it was not found in patients with disseminated lupus.

There are two particularly interesting facets to this disease:

Multisystem involvement

Firstly, many organs apart from the liver may be involved. I do not propose to give you a comprehensive list of the conditions that can occur, but joint and skin involvement, disorders of the lungs, gut disease, particularly ulcerative colitis, valvular heart disease, various types of glomerular and tubular renal lesions, endocrine disorders and blood disease, are well recognised. The important thing is that evidence of organ involvement may precede that in the liver. I should also remind you of the systemic manifestations more recently described. In the kidney, one should mention renal tubular acidosis; in the lungs one might mention fibrosing alveolitis (Turner Warwick, 1968), and perhaps also pulmonary hypertension (Cohen and Mendelow, 1965), as being the most recent additions to the crime sheet.

Prognosis

The second interesting factor about this disease concerns the prognosis. When we looked some years ago, at a series of 82 cases with respect to the prognosis, dividing patients into males and females, and also into those who had received corticosteroids – because this was the only form of therapy known at the time – and those who had not, we found very little evidence of a beneficial effect of corticosteroids on the mortality. The average expectation of life in both groups seemed to be of the order of three and a half years. There were, however, a number of cases, mostly female, and often those who had not been treated with corticosteroid drugs, in which there was an extremely long survival, where apparently the liver cell lesion gradually burnt itself out. Recently Page *et al.* (1969) have reported their results of immunosuppressive therapy with 6-mercaptopurine and corticosteroids and point out that they have a twelve-year survival of almost 30 per cent. So perhaps there is a variability, either natural or due to therapy, of the survival of patients with this disease. I would like to mention two examples of this, to show how variable the disease may be.

The first is a patient who initially presented at the age of 12, with liver cell jaundice. Because this lasted a number of weeks she was investigated surgically and the diagnosis of active chronic hepatitis was made at laparotomy and biopsy. She was treated at that stage with corticosteroid drugs. At the age of 19 she had a Coombs positive haemolytic anaemia; at 22 she developed alopecia and also at 22 she had Stevens-Johnson syndrome of considerable severity due to drug-sensitivity. At the same age she had a splenectomy because the corticosteroid drugs failed to control completely her haemolytic anaemia – she also had severe arthralgia; at 24 she had at least two attacks of staphylococcal septicaemia, but by the age of 26, that is fourteen years later, she is well working perhaps rather

inappropriately as a barmaid, and with a barium swallow showing no varices! So after 14 years, perhaps because of treatment, perhaps despite it, the patient, with all these multiple vicissitudes, is well.

Contrast this with the second patient: a female aged 61 who in 1964 developed two-weeks jaundice and was found to have LE cells in her serum and was given corticosteroids. In 1966 she had splenomegaly and, two and a half years from the beginning, she had a haematemesis which led to her death, despite ligation of varices. At autopsy there was a fully developed macronodular cirrhosis of the liver and portal vein thrombosis.

These then are the extremes of the disease and this is one of the problems that worries me: how one tells what is going to happen to an individual patient. Various investigators have suggested that patients with an acute onset, with LE cells in the blood, and with multiple organ involvement are likely to do well with treatment. But then others have put forward exactly the same findings as indices of a poor prognosis. Personally, I find the age of great importance and I think, on the whole, that the younger patient with this syndrome does much better than the older one.

PRIMARY BILIARY CIRRHOSIS

This again is a disease which may be of auto-immune aetiology and I wonder if we could consider Dr. Doniach's requirements for a primary auto-immune disease and see how they fit this condition.

Indeed, this is a disease of unknown cause with a female preponderance and a protracted course. One observer at least has found specific antibodies (Paronetto *et al.* 1964) but many people have only found nonspecific serum antibodies. The histological picture is of immune hyperactivity, both in the liver and in the draining lymph node; there is a familial aggregation of cases and of antibody changes. There is a variable clinical picture in some of these patients but until recently I had not thought that this was a disease which was associated with other auto-immune conditions. I refer to the recent paper by Reynolds *et al* (1970), where they said "Is this a new syndrome?" They were describing five female patients, all with a positive mitochondrial antibody test, with the combination of systemic sclerosis, primary biliary cirrhosis and hereditary telangiectasia. I would remind you that systemic sclerosis is a disease in which clinicians have felt that auto-immunity might be important, and here it is allied with a genetically determined disease of the blood vessels (hereditary telangiectasia). Quite how these fit together is difficult to say but at least here was a disease occurring with primary biliary cirrhosis, so perhaps primary biliary cirrhosis is a multi-organ disease.

CRAIG-SCHIFF-BOONE SYNDROME

Now perhaps I could discuss an extreme rarity: I refer to the cases of multiple immunological endocrine disease, some of which have been accompanied by liver disorder. The history of this is quite interesting. In 1955, Reissner and Ellsworth described a number of patients with idiopathic hypoparathyroidism and pernicious anaemia. Some of these patients also had idiopathic Addison's disease and Candida infection. In 1931, Rowntree and Snell had already described 20 cases of non-tuberculous Addison's disease occurring with pernicious anaemia and they pointed out that some of these patients had Monilial infection and idiopathic hypoparathyroidism. Then Leonard (1946) gave the first suggestion that liver involvement occurred in patients with Addison's disease and hypoparathyroidism. We have two patients, a brother and sister, with this syndrome, under the care of Professor Bruce Perry and more recently, of my colleague Dr. Martin Hartog. I would like to show you their clinical histories because I think these are of interest.