Hepatology: a personal story

Roger Williams

ABSTRACT – When I first began my career in hepatology in October 1959, investigative and treatment measures for patients with liver disease were limited. It was not until the discovery of hepatitis B virus in 1967 and hepatitis C virus in 1989 that the specialty began to expand, particularly with the development of effective antiviral therapy. Phenomenal advances in the knowledge of immune reactions also led to advances in our understanding and treatment of autoimmune disorders affecting the liver and in the continued development of liver transplantation – a major success story. The new liver support devices are currently showing promise but on the negative side is the rising prevalence of alcohol-related liver disease and non-alcoholic fatty liver disease.

KEY WORDS: haemochromatosis, jaundice, liver failure support devices, portal hypertension, transplantation

This personal story of a lifetime career in hepatology dates back to 1 October 1959, the momentous day when I accompanied the late Professor Dame Sheila Sherlock to the Royal Free Hospital, London, as one of her two lecturers in the newly created Department of Medicine. At that time hepatitis B virus (HBV) had not been described, let alone hepatitis C virus (HCV) – can you imagine a liver clinic without a fatty liver? Bilirubin conjugation had recently been discovered and there was much interest in the various clinical syndromes of conjugated and unconjugated hyperbilirubinaemia. Working with Professor Barbara Billing, I was soon immersed in the intricacies of bilirubin clearance including the effects of the steroid whitewash that so intrigued clinicians at that time.

A quite different area of interest for me was in haemochromatosis. The favoured aetiology then, fiercely championed by McDonald in the USA, was of an acquired state consequent on alcohol excess. Together with Professor Peter Scheuer, lecturer in histopathology, we successfully showed iron storage of mild to moderate degree in liver biopsies from apparently healthy relatives. What a performance it would be to get that through ethics today! Minor increases in iron absorption were also found, again indicative of the heterozygous state and the now well-accepted recessive model of inheritance.

While in the USA, during 1964–5, on a Rockefeller Travelling Fellowship at the Columbia University College of Physicians and Surgeons, New York, I assisted Dr Bradley in his weekly liver catheter session at the old Belleview Hospital Downtown. After returning to the Royal Free this burgeoning interest in hepatic haemodynamics led me to work on new techniques for measuring blood flow through the spleen using radioxenon clearance. In big spleen disease of Africans, studied during a three-month Wellcome Trust Fellowship at the Makere University College, Uganda, and subsequently at King's College Hospital, London, in blood dyscrasias with splenomegaly, we were able to show substantial increases in splenic and portal blood flow sufficient to account for the occasional development of portal hypertension in these conditions. In parenchymal liver disorders, where the major factor in the portal hypertension is an increase in pre- or post-sinusoidal resistance, Professor Roberto Grossman and his group showed experimentally the importance of splanchnic vascular dilatation and an increased portal inflow in the development of collateral channels. Even more exciting is our current understanding of the chemical mediators involved. In cirrhosis there is a deficiency of the vasodilator substance nitric oxide adding a vasoconstrictor component whereas excess production within the splanchnic vasculature is the basis for the vasodilatation. Correcting the latter by the vasoconstrictor agent terlipressin (Glypressin®) has been of value in the treatment of functional renal failure – one of the many contributions to our understanding of the pathophysiology of portal hypertension and its complications to come from the Liver Unit of the Hospital Clinic, Barcelona. According to the unit's director, Professor Juan Rodes, and most gratifying to me, this was modelled on the King's Unit which, by 1972, was firmly established in new research laboratories built immediately above a dedicated ward for liver patients.

In the early 1970s, one of the more worthwhile advances in the treatment of liver disease was the introduction of endoscopic sclerotherapy for oesophageal varices. An overseas patient had for years attended appointments with Mr McNab, an ear, nose and throat surgeon based in Oxford, for injection of his varices and, with the encouraging results obtained by Professor Rogers in Belfast, I became

Roger Williams
CBE MD FRCP FRCS FRCPE FRACP FMedSci FRCPI(Hon) FACP(Hon), Director, Institute of Hepatology, University College London

Clin Med 2008;8:25–31

even more convinced that this was the way forward. The endoscopic technique was developed further by my surgical colleague, Mr John Dawson, using a flexible scope and the rest is well known, with its worldwide implementation and the later technical development of banding rather than injection of sclerosant. The use of propranolol prophylactically to lower portal pressure in cirrhosis, of which Professor Didier Lebrec from Paris was the leading proponent, added a further dimension to control oesophageal varices. Interestingly, the Pugh modifications of Child's Score were derived from an analysis of outcomes following oesophageal transections by Dr David Pugh, my houseman at that time, and Dr Iain Murray-Lyon, the senior registrar. The Child–Pugh Score does give an indication of the severity of portal hypertension and of important complications such as ascites and encephalopathy, unlike the model for end-stage liver disease (MELD) score recently developed in the USA and currently so favoured there.

The 1970s to 1990s saw phenomenal advances in our knowledge of immunological reactions in liver disease. Leading this on the unit was Professor Adrian Eddleston who had come to King's as my registrar in 1967. Peripheral blood lymphocytes from patients with active chronic hepatitis, as it was known then, were shown to 'kill' heterologous liver cells *in vitro*. The cytotoxic reactions involved a non thymus (T) cell subset (K cell) reacting together with serum autoantibodies against liver-specific lipoprotein in the liver cell membrane. It is a tribute to Adrian that many of the research fellows that came to work in the group, including Professors Alfredo Alberti and Mario Mondelli, went on to become leading workers in the field.

On the clinical front, Dr John Hegarty and Professor Philip Johnson defined the place of azathioprine in immunosuppressive drug regimes for autoimmune hepatitis. Professor James Neuberger initially worked on immune reactions in primary biliary cirrhosis (PBC) and devised a useful prognostic model for clinical use in a collaborative study in 1980 with the Department of Hepatology, Rigshospitalet Hospital, Copenhagen, and the Liver Unit in Barcelona. The same group also carried out a controlled trial of azathioprine in 1990 followed by a study of cyclosporine in PBC. The latter drug, in my view, represents the only agent found so far that can alter the natural history of the condition in the long term. The quite different view we now have of the natural history of this condition with many mild asymptomatic cases, we owe to the work of Professor Ollie James and his group at Newcastle where Dr David Jones's studies are giving a new insight into tolerance in PBC.

Immune reactions were also shown to be involved in idiosyncratic drug reaction including that of halothane, which was the subject of a long battle I had with the anaesthetists during the 1980s over its very existence. Dr Gerry Kenna was able to identify an antibody in the serum directed against a hepatocyte membrane surface antigen altered by a halothane metabolite, the relationship of this to chemical toxicity and genetic susceptibility being taken forward subsequently by Farrell and his colleagues in Australia.

In bringing at least a few of these immunological areas up to date, I should mention the work of the Institute of Hepatology at University College London (UCL), established after I left King's in October 1996. Using a novel tetramer technique, Professor Antonio Bertoletti was able to identify the relative components of specific and non-specific cytotoxic T cells in the intrahepatic and plasma compartments of patients with chronic HBV infection. Professor Diego Vergani has taken forward important observations on cross-sensitisation to bacterial antigens in PBC and Professor Nikolai Naoumov has continued to add to our knowledge of immune reactions in HBV and HCV infection. While mentioning these immunological heavyweights, it would be remiss of me not to refer to Professor Howard Thomas's work at St Mary's Hospital, and to Professor David Adams, who in this issue is considering interactions between liver and the gut, a fascinating area relevant to the pathogenesis of primary sclerosing cholangitis.

A very different area of endeavour in the King's Unit during the 1970s came from the formation of a multidisciplinary research group into alcohol-related liver disease led by Drs Michael Davis and John Saunders, working in conjunction with the Medical Research Council's Human Biochemical Genetic Unit and the alcohol addiction research unit at the Maudsley Hospital, London. Notable among the studies carried out are those on acute alcoholic hepatitis showing release of the inflammatory cytokine tumour necrosis factor (TNF) and those on the susceptibility to liver damage particularly in women. Whatever measures are devised to contain major lifestyle issues, for example rising levels of alcohol consumption, a progressive increase in mortality from cirrhosis, non-alcoholic fatty liver disease and the consequent rising levels of obesity, considerable expansion of the hepatology service in the UK is essential.[1,2]

Liver transplantation

The early days of liver transplantation were, to say the least, difficult. Professor Tom Starzl in Denver, USA, reported his first successful liver transplant in 1965 and it was at the spring meeting of the British Liver Club (now known as the British Association for the Study of the Liver) in 1968 that Professor Sir Roy Calne and I first talked about developing a collaborative programme between his unit in Cambridge and my own at King's. Our first patient in October of that year did marvellously for four months before developing an irreversible chronic rejection. In subsequent cases there were many problems relating to breakdown of the bile duct anastomosis and severe infections consequent on the high dose of corticosteroids used for immunosuppression. Indeed most of the transplant programmes set up around the world during the early 1970s ended in despair. Survival results only began to improve with the introduction of cyclosporine in 1979, the first results of which were presented by Starzl in 1983 at the Consensus Development Conference held at the National Institutes of Health, Bethesda, MD.[3] Thereafter, there was a steady increase in the number of patients transplanted. The subsequent decade saw the discovery and replacement of cyclosporine by tacrolimus, with which even chronic rejection could be reversed.

Another notable event in the development of liver transplantation was the introduction in 1979 of brain stem criteria for death. These allowed retrieval of better functioning donor organs and the formulation in 1988 of the University of Wisconsin solution, giving preservation of the graft for up to 24 hours, which revolutionised the logistics of performing liver transplants. The donor graft could be safely brought back to the transplant centre, rather than the transplant team having to move to where the donor organ was being removed.

With near maximum figures for graft survival and function being reached (one-year survival 80–90% and 5–10-year survival of around 70%), more attention was directed towards the adverse effects of immunosuppressive drugs. As well as hypertension and nephrotoxicity with the calcineurin inhibitors, there is an increased frequency of diabetes along with hypercholesterolemia. Such metabolic disturbances account for the increased relative risk of ischaemic cardiac events in long-surviving patients. Fortunately the recent introduction of sirolimus provides an opportunity to avoid nephrotoxicity and, to a lesser extent, hypertension and diabetes.

Recurrence of the primary disease in the graft is inevitably for hepatologists, a fascinating event possibly providing new knowledge of underlying pathogenetic mechanisms. One of the earliest we recorded was that of PBC in 1970, although its occurrence was hotly disputed for many years afterwards. Usually mild in degree it could become more severe when cyclosporine was withdrawn, as befitting the effects of this drug in non-transplant setting. Similarly, recurrence of autoimmune hepatitis is often precipitated by withdrawal of corticosteroids. Hepatitis B virus recurrence is a more severe disease. Specific immunoglobulin was found to be highly effective when used prophylactically and has been only partly replaced by use of the new antiviral agents. Much more difficult to control is the almost universal recurrence of hepatitis C infection in the graft, with progression to cirrhosis in about a quarter of cases. It is no wonder that the histopathological contributions of Professor Bernard Portmann in these and many other diagnostic areas of hepatology brought him an international reputation.

The most serious challenge currently facing transplant programmes in the UK is the decreasing availability of cadaver organ donors. The number of deaths from road traffic accidents continues to fall, and the refusal rate by relatives of potential donors has increased to around 40% overall. Surgeons have been inventive in maximising the use of donor organs by splitting techniques so that two recipients can be treated from one graft. Some centres are also initiating programmes of non-heart-beating organ donation, though as with other marginal organs there is a higher incidence of primary non-function. Living donor liver transplantation is another approach that has found widespread adoption in the USA and mainland Europe. Right lobe donation carries a small risk to the donor (estimated mortality 0.24%) and the NHS has been slow in following this path, although the Edinburgh Unit has now started a programme. The unit for overseas patients at the Cromwell Hospital, London, which I set up in 1999, along with the surgical team from King's, has been very successful. Nevertheless, the preferred option must be to increase cadaver grafts.[4] The organ donation rate in Spain of 33.8 compared with 12.9 per million population in the UK, with corresponding liver transplant rates of 23.5 and 10.7 per million respectively (2006 figures), shows what can be done with appropriate statutory responsibilities and administrative procedures.

Acute liver failure and liver support devices

In the 1960s, reported mortality figures for acute liver failure (ALF) (often known as fulminant hepatic failure), whether occurring as a consequence of paracetamol overdose, viral hepatitis and idiosyncratic drug hepatotoxicity, were rarely less than 80–90%. With the establishment of a dedicated Liver Failure Unit at King's in 1973, the first of its kind in the UK, understanding of the condition grew. Survival rates began to improve and have now reached 60% in some aetiological groups. The availability of a large database allowed statistical analysis of prognostic factors by Dr O'Grady in 1989, and formed the basis of selection criteria for transplantation which remain in worldwide use today. In recent times the added effects of infection or rather of the systemic inflammatory response on potentiation of the hyperammonaemia and progression on encephalopathy in both ALF and in acute-on-chronic liver failure (ACLF) have come to the fore – a most fruitful area of continuing research by the Liver Failure Group in the Institute at UCL and by others internationally.

Liver support devices

It was soon realised that in addition to easily dialysable ammonia a whole range of endogenous substances were likely to be contributing to the toxaemia of liver failure. These include phenols, bile acids, digoxin-like substances, benzodiazepines and mercaptans, many of which are protein or lipid bound and led to trials of exchange transfusion and later of extracorporeal perfusion of isolated animals livers.[5] Encouraging improvements in encephalopathy were observed but overall survival was unaffected. A major breakthrough came in the early 1970s with the development of haemoperfusion columns containing the powerful adsorbent – activated charcoal. Initial clinical results were promising but again we were unable to show statistically significant improvements in survival. Nevertheless, absorbent columns are important components of devices based on bioreactors of cultured hepatocytes and in the most recent 'artificial' device developed in the University of Rostock – the molecular adsorbent recirculating system (MARS). In this, the patient's blood is dialysed against a high flux albumin impregnated membrane. Our studies at UCL, as well as those of other groups, have shown excellent removal of protein-bound toxic substances as well as correction of the disturbed pathophysiology of liver failure. An often striking improvement in encephalopathy was confirmed statistically in a major outcome study on ACLF reported in 2004.[6] Whether other devices based on albumin dialysis using a single pass technique or plasma fractionation have additional value remains to be established.

Concluding remarks

With the current pace of technological advance, one can safely predict that our understanding of liver disorders and their treatment will continue to improve. Advances in ultrasound, computed tomography, and magnetic resonance imaging, of which space has not allowed consideration, are already enabling the detection of small hepatocellular cancers at the stage when local ablation techniques can give long-term survival. The use of stem cells to enhance regeneration and remodelling of the liver may be but a pious hope but there is already evidence from Professor John Iredale that the breakdown of fibrosis is a feasible proposition.

Enabling clinicians to work alongside scientists with multidisciplinary skills in dedicated centres will continue to be the most effective way of enhancing knowledge and expertise in the specialty, a view from which I have never deviated.

Acknowledgements

The advances in research and clinical care touched on in this personal story have involved many medical and surgical colleagues, scientific and technical staff as well as a succession of outstanding research fellows. To those mentioned in the text and to all the others, I can but express admiration for their efforts. Finding funding for research is a never-ending battle and the support of the Medical Research Council, Wellcome Trust, Department of Health, Foundation for Liver Research, other charities and private benefactors is gratefully acknowledged. My thanks also to Ms Enda O'Sullivan, Editorial Assistant, who was a great help in bringing this paper together.

References

For references relating to research over the period 1966–1991 please refer to: The Liver Unit, King's College Hospital. 25th anniversary report 1966–1991. *Gut* 1991 Suppl:S1–S128.

1 Williams R. Global challenges in liver disease. *Hepatology* 2006;44:521–6.
2 Williams R. Services for liver disease in the United Kingdom. *BMJ* 2005;331:858–9.
3 Williams R. Learning and new discovery with cyclosporine in the Cambridge-King's Programme: a personal view. *Transplant Proc* 2004;36(2 Suppl): S261–S266.
4 Williams R, Alisa AA, Karani JB *et al.* Adult-to-adult living donor liver transplant: UK experience. *Eur J Gastroenterol Hepatol* 2003;15:7–14.
5 Williams R. The elusive goal of liver support – quest for the Holy Grail. *Clin Med* 2006;6:482–7.
6 Hassanein T, Tofteng F, Brown Jr RS *et al.* Efficacy of albumin dialysis (MARS) in patients with cirrhosis and advanced grades of hepatic encephalopathy: a prospective, controlled, randomized multicenter trial. *Hepatology* 2004;40:S726A.

CURRENT KEY DEVELOPMENTS

Mucosal lymphocytes in the pathogenesis of the hepatic complications of inflammatory bowel disease

David H Adams FRCP
Professor of Hepatology, Liver Research Group, Medical Research Council Centre for Immune Regulation, University of Birmingham Medical School

Email: d.h.adams@bham.ac.uk

Inflammatory bowel disease (IBD) is associated with extra-intestinal manifestations which occur either at the same time as bowel inflammation (joint, skin and eye) or run an independent course (autoimmune hepatitis and primary sclerosing cholangitis (PSC)). It has been suggested that eye, skin and joint manifestations are driven by the trapping of gut-derived effector cells in capillaries in these sites; however, this cannot explain the liver diseases that develop when bowel inflammation is quiescent or even after colectomy.[1,2] This led us to propose that long-lived memory lymphocytes that arise as a consequence of bowel inflammation express homing receptors that direct their subsequent migration not only to the gut but also the liver.[3] Such cells could recirculate between the liver and gut without causing damage for many years but if they subsequently encounter an antigen in the liver this could result in their activation and the promotion of tissue damage and disease. This could explain how a patient can develop liver disease many years after their IBD has become quiescent. In order to prove the hypothesis we needed to:

- demonstrate that lymphocytes in the liver of patients with PSC were originally activated in the gut
- provide a mechanism to explain how these cells are recruited to the liver
- show that they are critical for disease pathogenesis.

Over the last nine years we have answered the first two questions and thus the hypothesis is still valid.[4]

When lymphocytes are activated by dendritic cells (DC) in gut-associated lymphoid tissues (GALT) they are not only programmed to respond to antigen but are also imprinted with a homing phenotype which directs their subsequent trafficking back to the gut.[5] After antigen has been cleared, a population of long-lived memory cells remain that retain gut tropism and thereby provide immune surveillance against the same pathogen entering the gut in the future. The molecular basis of this tissue-specific homing has recently been elucidated. Lymphocytes are recruited into tissues from the blood by sequential interactions with adhesion molecules and chemotactic cytokines called chemokines presented on the endothelium lining the vessels in the target tissue. Adhesion molecules allow lymphocytes with an appropriate receptor to recognise and bind the endothelium and chemokines can then direct migration through the endothelium