

# Immune Reactions in Liver Disease

Edited by

A L W F Eddleston

J C P Weber

Roger Williams

# IMMUNE REACTIONS IN LIVER DISEASE

*Edited by*

A L W F Eddleston

J C P Weber

Roger Williams

575



51757

IMMUNE REACTIONS

LIVER DISEASE

*First published 1979*

*Reprinted 1980*

Catalogue Number 21-0798-81

*Pitman Medical Publishing Co Ltd*  
P O Box 7, Tunbridge Wells,  
Kent, TN1 1XH, England

*Associated Companies*

UNITED KINGDOM  
Pitman Publishing Ltd, London  
Focal Press Ltd, London

CANADA  
Copp Clark Ltd, Toronto

USA  
Fearon Pitman Publishers Inc, California  
Focal Press Inc, New York

AUSTRALIA  
Pitman Publishing Pty Ltd, Carlton

NEW ZEALAND  
Pitman Publishing NZ Ltd, Wellington

© R Williams, A L W F Eddleston 1979

British Library Cataloguing in Publication Data

Immune reactions in liver disease.

1. Liver—Diseases—Immunological aspects—Congresses 2. Immune response—Congresses

I. Eddleston, A L W F II. Weber, J C P  
III. Williams, Roger, b. 1931  
616.3'62'0795 RC846

ISBN 0-272-79509-7

Printed and bound in Great Britain  
at The Pitman Press, Bath

PITMAN MEDICAL

## PARTICIPANTS

Alberti, A, University of Padova, Italy  
 Allison, AC, Northwick Park Hospital, Harrow, UK  
 Batchelor, JR, Blond Laboratories, Queen Victoria Hospital, East Grinstead, UK  
 Berg, P, Medizinische Universitätsklinik, Tübingen, Germany  
 Bernardi, M, University of Bologna, Italy  
 Berthowe, F, Hopital Herriot, Lyon, France  
 Bianchi, FB, University of Bologna, Italy  
 Calne, RY, University of Cambridge Clinical School, Cambridge, UK  
 Cannady, WG, Harvard Medical School, Boston, USA  
 Cantell, K, Central Public Health Laboratory, Helsinki, Finland  
 Chen, T, College of Medicine and Dentistry of New Jersey, Newark, USA  
 Chiarmonte, M, University of Padova, Padova, Italy  
 Chisari, FV, Scripps Clinic, La Jolla, USA  
 Cochrane, AMG, King's College Hospital, London, UK  
 Colombo, M, Mount Sinai School of Medicine, New York, USA  
 Davis, M, King's College Hospital, London, UK  
 de Groote, J, University of Leuven, Belgium  
 Desmyter, J, Rega Institute for Medical Research, Leuven, Belgium  
 Doniach, D, Middlesex Hospital, London, UK  
 Dubey, DP, Harvard Medical School, Boston, USA  
 Eddleston, ALWF, King's College Hospital, London, UK  
 Edginton, TS, Scripps Clinic, La Jolla, USA  
 El Sheikh, N, King's College Hospital, London, UK  
 Falchuk, KL, Harvard Medical School, Boston, USA  
 Fernandez, L, King's College Hospital, London, UK  
 Fitzpatrick, D, Harvard Medical School, Boston, USA  
 Galambos, JT, Emory University School of Medicine, Atlanta, USA  
 Galbraith, RM, King's College Hospital, London, UK  
 Gillette, JR, National Institutes of Health, Bethesda, USA  
 Good, RA, Memorial Sloan-Kettering Cancer Center, New York, USA  
 Guarriero-Bobylera, V, University of Bologna, Italy  
 Henning, H, University of Tübingen, Tübingen, Germany  
 Hodgson, HJF, Royal Postgraduate Medical School, London, UK  
 Holborow, EJ, The London Hospital Medical College, London, UK  
 Hütteroth, TH, Freie Universität, Berlin, Germany  
 Jain, S, Royal Free Hospital, London, UK  
 Jewell, D, Royal Free Hospital, London, UK  
 Kanagasundaram, N, College of Medicine and Dentistry of New Jersey, Newark, USA  
 Leevy, CM, College of Medicine and Dentistry of New Jersey, Newark, USA  
 Liebe, CS, Veterans Administration Hospital, New York, USA  
 McFarlane, IG, King's College Hospital, London, UK  
 Mackay, IR, The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia  
 MacSween, S, Harvard Medical School, Boston, USA  
 Matsumoto, K, College of Medicine and Dentistry of New Jersey, Newark, USA  
 Meyer zum Büschenfelde, KH, Freie Universität, Berlin, Germany  
 Miller, JO, Yale University School of Medicine, New Haven, USA  
 Moussouros, A, King's College Hospital, London, UK  
 Nielsen, JO, Copenhagen Kommunes Hvidovre Hospital, Denmark  
 Noreen, H, Harvard Medical School, Boston, USA  
 Paronetto, F, Mount Sinai School of Medicine, New York, USA

Pattison, J, King's College Hospital, London, UK  
 Perlmann, P, Wenner-Gren Institute, Stockholm, Sweden  
 Popper, H, Mount Sinai School of Medicine, New York, USA  
 Preisig, R, University of Berne, Berne, Switzerland  
 Read, A, University of Bristol, Bristol, UK  
 Realdi, G, University of Padova, Italy  
 Redeker, AG, University of Southern California, Los Angeles, USA  
 Revillard, JP, Hôpital Herriot, Lyon, France  
 Roitt, IM, The Middlesex Hospital Medical School, London, UK  
 Scheuer, P, Royal Free Hospital, London, UK  
 Schuff-Werner, P, University of Tübingen, Tübingen, Germany  
 Scullard, G, King's College Hospital, London, UK  
 Sherlock, S, Royal Free Hospital, London, UK  
 Sullivan, S, King's College Hospital, London, UK  
 Talal, N, University of California School of Medicine, San Francisco, USA  
 Thomas, H, Royal Free Hospital, London, UK  
 Thomas London, W, The Institute for Cancer Research, Philadelphia, USA  
 Trepo, C, Hôpital Herriot, Lyon, France  
 Trey, C, Harvard Medical School, Boston, USA  
 Tsantoulas, DC, King's College Hospital, London, UK  
 Vergani, D, King's College Hospital, London, UK  
 Vernace, S, Mount Sinai School of Medicine, New York, USA  
 Vogten, AJM, Academisch Ziekenhuis Utrecht, Utrecht, The Netherlands  
 Walton, B, The London Hospital, London, UK  
 Wands, JR, The Massachusetts General Hospital, Boston, USA  
 Wansborough-Jones, M, King's College Hospital, London, UK  
 Wilkinson, S, King's College Hospital, London, UK  
 Williams, RM, Harvard Medical School, Boston, USA  
 Williams, Roger, King's College Hospital, London, UK  
 Wojcicka, B, King's College Hospital, London, UK  
 Wright, R, University of Southampton, Southampton, UK  
 Yunis, EJ, Harvard Medical School, Boston, USA  
 Zauli, D, University of Bologna, Italy  
 Zuckerman, AJ, London School of Hygiene and Tropical Medicine, London, UK

# CONTENTS

Introduction <i>Roger Williams</i>	1
---------------------------------------	---

## Part I – HBsAg NEGATIVE CHRONIC ACTIVE HEPATITIS

Immune Responses to the Liver-specific Membrane Lipoprotein <i>A L W F Eddleston</i>	2
Autoantibodies Against Liver Membrane Antigens in Chronic Active Liver Diseases <i>K H Meyer zum Büschenfelde, T H Hütteroth</i>	12
Cytotoxicity of Lymphocytes Against Autochthonous and Allogeneic Liver Cells in Patients with Chronic Hepatitis <i>F Paronetto, M Colombo, S Vernace</i>	21

### Panel Discussion

1. Results Confirmed? Liver Membrane Antibodies (LMA) <i>F B Bianchi, Danie'a Zauli, Valentina Guarriero-Bobyleva</i>	27
Lymphocyte Cytotoxicity to Autologous Hepatocytes <i>A J M Vogten</i>	28
2. The Nature of the Target Antigen Studies on the Liver Membrane Lipoprotein <i>K H Meyer zum Büschenfelde</i>	31
Characterisation of the Liver-specific Membrane Lipoprotein <i>I McFarlane</i>	36
A Newly-defined Liver Membrane Antigen <i>F Paronetto</i>	37
Results with LSP-coated Target Cells <i>A J M Vogten</i>	38
3. Nature of Immune Assault Further Fractionation of the Cytotoxic Cell Population <i>H Thomas</i>	40

## Part II – HBsAg POSITIVE CHRONIC ACTIVE HEPATITIS

Immune Responses to Hepatitis B Virus Coded and Induced Antigens in Chronic Active Hepatitis <i>T S Edgington, F V Chisari</i>	44
---	----

Lymphocyte-cytotoxicity to HBsAg-coated Target Cells <i>M Wansbrough-Jones, G Scullard, N El Sheikh, A L W F Eddleston, Roger Williams</i>	61
---	----

Immune Complexes and Pathogenesis of Hepatitis B Virus Infections <i>C Trepo, J P Revillard, F Berthoux</i>	69
--	----

#### *Panel Discussion*

1. Results Confirmed? Results with HBsAg-coated Red Cells <i>A Alberti</i>	78
2. Nature of Target Antigens Mode of Replication of Hepatitis B Virus in Relation to Changes in Hepatocyte Membrane Antigens <i>A J Zuckerman</i>	79
HBsAg on Isolated Hepatocytes <i>A Alberti</i>	80
3. Role of Immune Complexes Immune Complexes and Immunoconglutinins <i>H Thomas</i>	81
Immune Complexes and Hepatocytes <i>G Realdi</i>	82
4. Nature of Immune Assault Nature of the Mononuclear Cells in the Infiltrates <i>D J Miller</i>	83
5. Effect of Blocking Factors Serum Blocking Factors <i>P Berg</i>	84
6. Comparison of HBsAg Positive and Negative Cases Clinical and Immunological Distinctions <i>R Wright</i>	86
The Histological Lesion <i>P Scheuer</i>	87

### **Part III - GENETIC PREDISPOSITION FOR CHRONIC ACTIVE HEPATITIS**

Genetic Studies in Chronic Active Hepatitis <i>I R Mackay</i>	89
Histocompatibility Antigens and Immune Responses <i>A L W F Eddleston, R M Galbraith, J R Batchelor, J Pattison, D Doniach, Roger Williams</i>	96
Family Studies of Patients with Chronic Liver Diseases <i>W Thomas London</i>	104



<b>HLA and DRw Antigens in Adult Patients with Chronic Active Hepatitis</b>	<b>110</b>
<i>E J Yunis, S Martin, R M Williams, K R Falchuk, C Trey, D P Dubey</i>	
<i>W G Cannady, D Fitzpatrick, H Noreen</i>	

#### **Panel Discussion**

<b>1. Results Confirmed?</b>	
<b>HLA and Persistent HBs Antigenaemia</b>	<b>113</b>
<i>M Chiarmonite</i>	
<b>Measles, Rubella and HLA</b>	<b>113</b>
<i>H Thomas</i>	
<b>2. Nature of Defect in HBsAg Positive Cases</b>	
<b>Factors Determining Progression from Acute to Chronic Hepatitis</b>	<b>115</b>
<i>J O Nielsen</i>	
<b>Factors Determining Progression from Acute to Chronic Hepatitis</b>	<b>116</b>
<i>P Berg</i>	
<b>3. Nature of Defect in HBsAg Negative Cases</b>	
<b>The Possible Nature of the HLA-linked Defect</b>	<b>117</b>
<i>J R Batchelor</i>	
<b>Alteration in Suppressor Cell Activity in Patients with Chronic Active Hepatitis</b>	<b>118</b>
<i>J R Wands, H J F Hodgson</i>	
<b>The Liver and Immune Tolerance</b>	<b>120</b>
<i>R Y Calne</i>	
<b>Heterogeneity Within the HBsAg Negative Group</b>	<b>121</b>
<i>D Doniach</i>	
<b>4. Environmental Triggers in HBsAg Negative Cases</b>	
<b>Significance of Migration Inhibition with HBsAg</b>	<b>122</b>
<i>A L W F Eddleston</i>	
<b>Clinical Observations on Initiating Illnesses</b>	<b>122</b>
<i>J O Nielsen</i>	

#### **Part IV – IMMUNE DAMAGE TO OTHER ORGANS AND CROSS-REACTING ANTIGENS**

<b>Introduction</b>	<b>124</b>
<i>E J Holborow</i>	
<b>Occult Liver Disease in Other Immunologically-mediated Conditions</b>	<b>125</b>
<i>R N M MacSween</i>	
<b>Renal Tubular Acidosis and Tamm-Horsfall Glycoprotein</b>	<b>135</b>
<i>I G McFarlane, D C Tsantoulas, A M G Cochrane, A L W F Eddleston,</i>	
<i>Roger Williams</i>	



Sicca Syndrome and Immune Responses to Bile and Salivary Antigens	144
<i>S Sullivan, I G McFarlane, B M Wojcicka, A L W F Eddleston, Roger Williams</i>	

#### **Panel Discussion**

1. Results Confirmed?	
The Clinical Spectrum of Disease in Other Organs in Chronic Active Hepatitis and Primary Biliary Cirrhosis	149
<i>I Mackay</i>	
Liver Involvement in Rheumatic Diseases	150
<i>L Fernandez</i>	
2. Nature of Antigens Involved	
Differences in Antimitochondrial Antibody Specificity in Different Diseases	152
<i>P Berg</i>	
Further Studies on the Mitochondrial Antigens	153
<i>D Dönisch</i>	
Separation and Characterisation of Bile Antigens	154
<i>B Wojcicka</i>	
Immune Complexes in Relation to Multisystem Involvement	156
<i>D Jewell</i>	
The Cellular Basis of Cytotoxicity for Kidney Cells in Renal Tubular Acidosis	157
<i>A M G Cochrane</i>	
Possible Mechanisms for Renal Tubular Acidosis	158
<i>S Wilkinson</i>	

#### **Part V – ALCOHOL-INDUCED LIVER DISEASE**

Direct Alcohol Hepatotoxicity	160
<i>C S Lieber</i>	
Alcoholic Hyalin and Immunologic Reactivity	195
<i>C M Leevy, N Kanagasundaram, K Matsumoto, T Chen</i>	
Autoimmune Reactions in Alcohol-induced Liver Disease	208
<i>A M G Cochrane, A Moussouros, A L W F Eddleston, Roger Williams</i>	

#### **Panel Discussion**

1. Results Confirmed?	
Comparison of Lymphocyte Cytotoxicity with Chang and Human Cell Lines	214
<i>H Thomas</i>	
Results with Rabbit Hepatocytes	215
<i>M Bernardi</i>	

<b>Immune Responses to Hyalin</b> <i>R N M MacSween</i>	215
<b>2. Mechanisms of Liver Damage</b>	
Fibrosis <i>H Popper</i>	220
The Role of Endotoxins <i>S Wilkinson</i>	222
<b>3. Genetic and Environmental Factors</b>	
Clues from Clinical Patterns of Disease <i>J T Galambos</i>	224
Influence of HLA Phenotype <i>M Davis</i>	225
HLA and Alcoholic Hepatitis <i>H Thomas</i>	226
<b>Part VI – DRUG-INDUCED LIVER DAMAGE</b>	
<b>The Role of Reactive Metabolites</b> <i>James R Gillette</i>	229
<b>Halothane Hepatitis – Toxicity and Immunity</b> <i>M Davis, D Vergani, A L W F Eddleston, Roger Williams</i>	235
<b>Immune Reactions to Drugs and Metabolites in Man</b> <i>P A Berg, P Schuff-Werner, H Henning</i>	247
<b>Panel Discussion</b>	
1. Results Confirmed?	259
2. Clues from Clinical Patterns Factors Promoting Halothane Damage <i>B Walton</i>	260
‘Toxicity’ or ‘Hypersensitivity’ <i>A Read</i>	261
Animal Models <i>R Preisig</i>	261
Microsomal Antibodies in Halothane Hepatitis <i>D Doniach</i>	262
3. Immune Mechanisms Comparison of Anti-LSP Responses in Predictable and Idiosyncratic Drug Reactions <i>D Jensen</i>	265
Immune Responses to LSP in Halothane Hepatitis <i>A J M Vogten</i>	266

## **Part VII – IMMUNOTHERAPY**

<b>Use of Interferons and Interferon Inducers in Chronic Hepatitis B</b> <i>J Desmyter</i>	268
---	-----

<b>Transfer Factor in HBsAg Positive Patients</b> <i>A G Redeker</i>	275
---	-----

<b>Immunostimulants in Treatment of HBs Antigen Positive Chronic Active Liver Disease</b> <i>H C Thomas</i>	281
--	-----

<b>Choosing an Immunosuppressive Regime</b> <i>Roger Williams</i>	288
--	-----

### **Panel Discussion**

<b>1. Results Confirmed?</b> <b>Transfer Factor for HBsAg Negative Chronic Active Hepatitis</b> <i>M Wansbrough-Jones, R M Galbraith</i>	297
--	-----

<b>Transfer Factor in HBsAg Positive Chronic Active Hepatitis</b> <i>S Jain</i>	298
--	-----

<b>Interferon: Its Effects on Viral Replication and on the Immune Response</b> <i>G Scullard, A-J Zuckerman, K Cantell</i>	298
---	-----

<b>Interferon in Acute Hepatitis</b> <i>J de Groote</i>	299
--	-----

<b>Interferon and Its Use in Chronic Active Hepatitis</b> <i>R Wright</i>	300
--	-----

<b>2. Today's Therapy</b> <b>Immunosuppressive Drugs in the Treatment of Alcoholic Liver Disease</b> <i>C Leevy</i>	302
---	-----

<b>Immunosuppressive Drugs in Fulminant Hepatitis</b> <i>A G Redeker</i>	303
---	-----

<b>HBsAg Positive and HBsAg Negative Chronic Active Hepatitis: Differences in Therapeutic Requirement and Response</b> <i>S Sherlock</i>	304
---	-----

<b>Immunosuppressive Therapy in HBsAg Positive and Negative Chronic Active Hepatitis</b> <i>K H Meyer zum Büschenfelde</i>	305
---	-----

<b>Use of Immune Markers of Disease Activity in Planning Therapy</b> <i>P Berg</i>	310
---	-----

## INTRODUCTION

*Roger Williams*

It is about eight years since our last meeting on immune reactions in liver disease. Some of you who were at that meeting will know only too well what an enormous amount has been added to our knowledge since then. We would not be able to cover it all in this book, and we have therefore tried to identify certain main areas of importance. Active chronic hepatitis is at the centre of the stage, but in alcoholic liver disease and hepatic drug reactions there is undoubtedly, at least in some patients, an autoimmune component. The scope too has been widened by the finding of a relationship to certain histocompatibility antigens and familial influences are also more clearly apparent. We hope that our discussions here will give some perspective to these new areas of knowledge.

There are three questions too, to which I hope we will address ourselves in this book, even if we may not be able to answer them exactly as yet.

1. Can we ever prove that autoimmunity is damaging to the liver in man?
2. Can we relate the defects in immunoregulation to a genetic background?
3. Can specific immunotherapy for the abnormalities found be developed?

## IMMUNE RESPONSES TO THE LIVER-SPECIFIC MEMBRANE LIPOPROTEIN

*A L W F Eddleston*

In this presentation, I shall review some of the evidence that our group and others have obtained relating to the role of immunity to a liver-specific membrane lipoprotein in the pathogenesis of chronic active hepatitis. Our interest in this unusual antigen was entirely due to Professor Deborah Doniach who pointed out the importance of the work of Professor Meyer zum Buschenfelde and his colleagues at the end of the 1960s. He had discovered two liver-specific antigens in the supernatant of a human liver homogenate and had partially separated them by column chromatography [1]. Immunofluorescent studies indicated that one was found in the cytoplasm of hepatocytes while the other was an unstable high molecular weight lipoprotein derived from the hepatocyte surface membrane [2]. Antisera to these antigens were prepared in rabbits, and of considerable importance was the finding that these immunised animals developed inflammatory lesions in the liver [3], akin to those of chronic aggressive hepatitis in man (Figure 1). After prolonged immunisation, some of the animals progressed to cirrhosis [4], another characteristic of the human disease. At this time the membrane lipoprotein could not be prepared in a stable purified form but Meyer zum Buschenfelde and his colleagues were able to show that immunisation with the cytoplasmic antigen alone was relatively ineffective in inducing the liver damage [3], thus implicating the membrane lipoprotein in the pathogenesis of the experimental lesion.

We began to look for immune responses to the liver membrane lipoprotein (LSP) in patients with chronic active hepatitis in 1970 after first purifying the relevant antigen. This difficult task was undertaken first by Dr Joanna Miller [5] and later by Dr Ian McFarlane who has since gone on to explore the structure and properties of LSP [6].

The method of purification consists essentially of a series of gel chromatography columns through which the supernatant of a human liver homogenate is passed [6]. The membrane lipoprotein appears in the void volume on chromato-

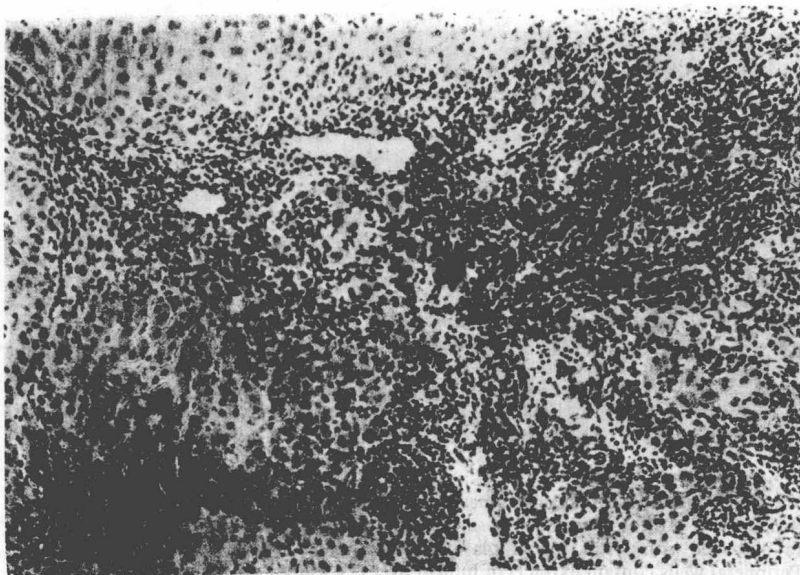


Figure 1 The histological features of chronic aggressive hepatitis induced in the liver of a rabbit by multiple injections of human liver-specific antigens.  
(By courtesy of Professor Meyer zum Büschenfelde)

graphy over Sepharose 4B indicating an apparent molecular weight of greater than 20 million but, since hydrophobic molecules behave abnormally in gel chromatography, this estimate may not be accurate. Dr-McFarlane has prepared the apoprotein by treatment with sodium deoxycholate and this is included in Sepharose 4B, producing a single peak [6]. Unfortunately the immunological reactivity is lost after this treatment [6].

The organ specificity of LSP has been confirmed by immunodiffusion (Figure 2). Polyvalent antiserum raised in guinea pigs against a crude preparation of LSP (the first peak from Sephadex G-100) and absorbed with normal human plasma gave two lines on immunodiffusion against liver homogenate (Figure 2a). One of these appeared to be liver-specific, the other showed complete identity with a line obtained against kidney, spleen, adrenal, thyroid and submaxillary gland homogenates. This second line was distinct from another line obtained against an adrenal homogenate. After further absorption of the polyvalent antiserum with purified freeze dried LSP the liver-specific line disappeared while the other reaction with the liver homogenate and those with all the other organ extracts were not affected (Figure 2b). The same antiserum showed surface immunofluorescence when incubated with isolated rabbit hepatocytes, a phenomenon which was not observed when the antiserum was first absorbed with LSP [6].

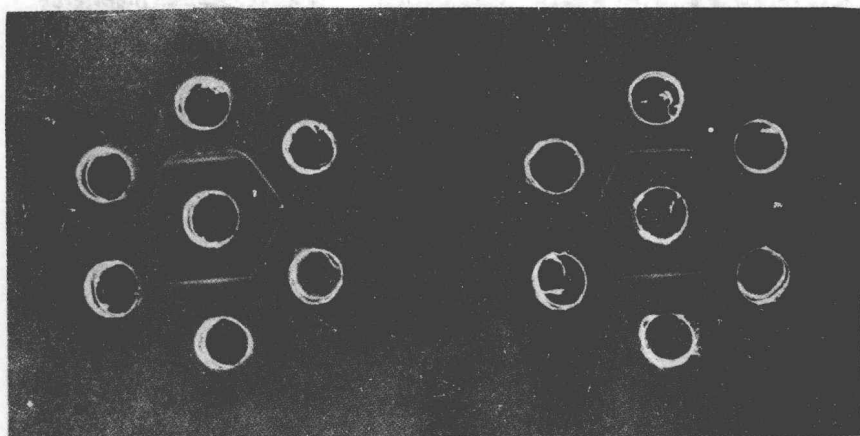


Figure 2 Immunodiffusion using guinea pig antiserum in centre wells raised against the Sephadex G-100 first peak of the supernatant of a human liver homogenate: (a) absorbed with normal human plasma and (b) further absorbed with purified LSP. Peripheral wells contain extracts of human liver (1), kidney (2), spleen (3), adrenal (4), thyroid (5), and submaxillary gland (6). (From McFarlane 1977 [6])

### Cellular Immunity to LSP

We first looked at cellular immune reactions to this antigen using the leucocyte migration test, and found that 11 of 16 patients with chronic active hepatitis showed evidence of sensitisation to LSP [5]. The number of patients who could be studied was limited at this stage because the lipoprotein antigen was only stable in solution for two or three days. Thus the discovery by Dr McFarlane that stability could be extended for up to two years by the addition of Imm EDTA to the Tris HCl buffer system [6] represented a major practical advance. Further studies using the leucocyte migration test showed that sensitisation to LSP was an almost universal finding in cases of untreated chronic active hepatitis while in those cases treated with prednisone with or without azathioprine the incidence of migration inhibition was lower, particularly in those with satisfactory biochemical control of disease activity (Table I).

TABLE I Cellular Immune Response to LSP in Chronic Active Hepatitis and the Effect of Immunosuppressive Therapy

	Number tested	Inhibition of leucocyte migration with LSP as antigen
Untreated	14	13 (93%)
Treated: with high serum bilirubin	23	16 (70%)
Treated: with normal serum bilirubin	21	9 (43%).





microwells [7]. Peripheral blood lymphocytes were then added in the ratio of 400 to one and after 48 hours incubation at 37°C the remaining adherent hepatocytes were counted. Lymphocytes from all of 15 patients with untreated chronic active hepatitis have shown significantly increased cytotoxicity as have those from 21 of 25 treated cases whose liver biopsy still showed piecemeal necrosis of periportal hepatocytes (Figure 3). Addition of 0.5 µg of purified LSP to the incubation wells specifically inhibited the cytotoxic reaction indicating that LSP was the principal target antigen on the liver cell membrane [7].

Cytotoxic lymphocytes have been detected less frequently in treated patients whose liver biopsy no longer showed evidence of disease activity, only four of 17 showing significant lymphocyte cytotoxicity for the isolated hepatocytes (Figure 3). In fact, this assay has proved to be superior to other immunological and biochemical tests in predicting the disease activity as assessed histologically [8].

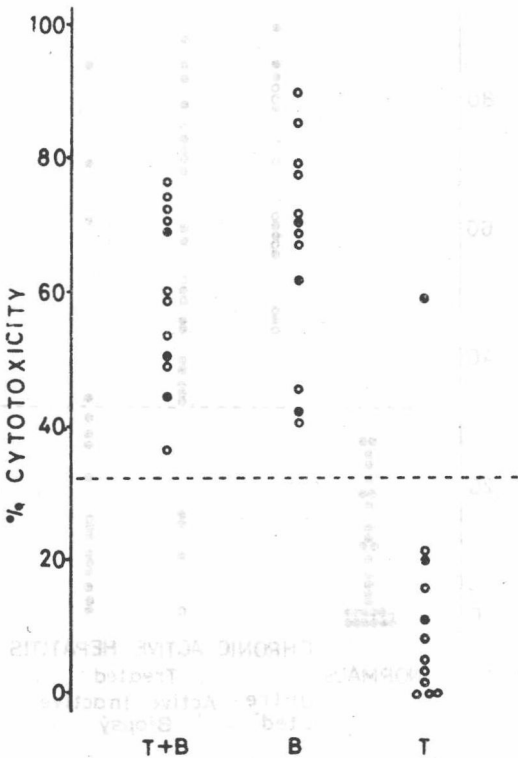


Figure 4 Effect of removal of T cells (B cell enriched fraction) or of B and K cells (T cell enriched fraction) on lymphocyte cytotoxicity to isolated hepatocytes. The lymphocytes were from the peripheral blood of patients with uncontrolled or untreated chronic active hepatitis. (From Cochrane et al 1976 [9]).