of the incidence of antibody to thyroglobulin. Furthermore, in so far as it has been possible to study the antigen content of human thyroid cells at a subcellular level, complement-fixing antigen and the antigen corresponding to the cytotoxic factor have been found to exist in parallel concentrations. Therefore it may reasonably be assumed that the cytotoxic and complement-fixing autoimmune systems are closely associated with each other and, indeed, are probably identical.

The rapidity of the cytotoxic effect *in vitro* is not in accord with the natural history of Hashimoto's or other forms of thyroid disease in which the factor has been found to occur in a high titre, and it is of interest that cells derived from human thyroid but which have not been subjected to trypsin are apparently uninfluenced by the presence in the nutrient medium of "cytotoxic" antibody.

A method is described whereby the lymphocytic infiltration characteristic of the Hashimoto goitre may be obtained in pure culture, and it is hoped that this may prove helpful in the attempt to clarify the relationship between humoral and cell-bound antibody.

It is a pleasure to acknowledge the support given to me in this work by Professor Sir Derrick Dunlop and Dr. James Robson. Professor John Bruce, Mr. J. R. Cameron, Mr. C. W. A. Falconer, Mr. D. McIntosh, and Professor M. F. A. Woodruff have kindly collaborated in providing thyroid tissue suitable for culture. I am grateful to Dr. L. G. Plaskett, of the Biochemistry Department, Edinburgh University, for doing the cell fractionation, to Dr. M. H. Robertson for collaborating in the tanned-cell haemagglutination tests, to Dr. A. R. Muir for help with the electron micrography, and to Dr. Paul Halberg, Miss Geraldine Walker, and Miss Laura Scarth for their invaluable assistance.

This work was made possible by a generous grant from the Medical Research Council.

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The Calouste Gulbenkian Foundation, Lisbon, has made a grant of £20,000 over three years to enable a committee to be set up to study the recruitment, training, and work of the staff in residential houses for those in need of care, and to publish its report.

DIAGNOSIS OF HODGKIN'S DISEASE BY LIVER BIOPSY

BY

M. MACLEOD, M.D., F.R.C.P.Ed.
Senior Lecturer in Medicine, University of Aberdeen

AND

A. L. STALKER, M.D.
Senior Lecturer in Pathology, University of Aberdeen

[WITH SPECIAL PLATE]

The histological diagnosis of Hodgkin's disease and the related reticuloses is usually made on biopsy of an enlarged superficial lymph-node. Though precise histological classification may be difficult, a clear indication of the nature of the disease process is usually obtained. Unfortunately, however, this is not always possible.

In the early stages superficial lymph-nodes may be unaffected or may show histological changes which are not conclusive (Goldman, 1940; Symmers, 1944, 1948; Jackson and Parker, 1947; Wintrobe, 1956). Not uncommonly the intrathoracic or intra-abdominal nodes are the first to become enlarged. Extranodal primary foci have been reported in almost every site and structure of the body. General features may be prominent with hepatic enlargement or splenomegaly, but without lymphadenopathy, while pyrexia, fatigue, and anaemia may simulate an infection or a "collagen disease." Haemolytic anaemia due to disordered reticulo-endothelial function may be slight or so severe that it dominates the clinical picture. In such circumstances difficulty in diagnosis is well known.

Series reports on the histological diagnoses revealed by aspiration biopsy of the liver occasionally include an isolated example of Hodgkin's disease or related reticulosis (Sherlock, 1945; Volwiler and Jones, 1947; Schiff, 1951; Tyor and Cayer, 1953). Hepatic enlargement, transient jaundice, biochemical evidence of liver involvement, and structural changes in the portal tracts are, in our experience, more common than textbook descriptions suggest. We have therefore used the aspiration biopsy technique in the investigation of suspected cases of Hodgkin's disease when the diagnosis could not be made by lymph-node biopsy. In each case the modified Gillman technique described by Terry (1949) was used.

Involvement of Liver in Hodgkin's Disease

Material derived from two sources has been used in this analysis. Twenty-nine cases of Hodgkin's disease were studied post mortem. There was liver involvement in all but three cases. Tissue obtained by aspiration biopsy of the liver was available from 13 patients, in all of whom infiltration was observed in the biopsy specimen. Most of these specimens were obtained early in the disease as estimated from the onset of symptoms. From this material the following picture of the evolving pattern of liver involvement has been obtained.

Site of Infiltrate (Special Plate, Figs. 1 and 2).—The early infiltrate is in the portal space. If it becomes prominent it may encroach into the sinusoids.

Amount of Infiltrate.—In the early stages this is focal and affects only a few portal tracts. Serial biopsies taken later in the disease and necropsy material usually show more diffuse portal infiltration.

Character of Infiltrate (Special Plate, Fig. 3).—This is pleomorphic, comprising reticulum cells, plasma cells, round cells, polymorphonuclear leucocytes, and fibroblasts. The reticulum cells may be of an aberrant type, but usually fall short of the Reed–Sternberg pattern. As eosinophil leucocytes are often seen in biliary disease they do not here have their usual value in diagnosis. Fibrosis varies in amount and maturity from a few fine collagen fibres to a prominent and acellular sclerosis (Special Plate, Fig. 4). Occasionally the infiltrate has a folliculoid appearance with formation of giant cells suggesting sarcoidosis.

Associated Changes.—Sinusoidal congestion and fatty change of the liver cells are common. Iron pigment is often seen even in the absence of blood transfusion. A diffuse hyperplasia of the Küpffer cells is almost invariable, and syncytium-like masses of these cells may fill the sinusoids (Special Plate, Fig. 2). In the later stages of the disease there may be evidence of bile retention, apparently due to intrahepatic biliary stasis. Hyperplasia of bile ductules may be associated with portal fibrosis. In a few instances extramedullary foci of erythropoiesis have been seen.

Though these histological appearances are not always definitive, the pattern becomes progressively more distinctive and can be diagnostic.

Illustrative Cases

The salient features of 13 illustrative cases are given in the Table. The cases may be grouped according to their clinical presentation and the diagnostic problems which they raised.

Cases 1 and 2—General Features without Lymph-node Enlargement

Cases resembling a general infection often present diagnostic difficulty. Because of the coincidental mitral stenosis Case 1 particularly resembled bacterial endocarditis. The evolution of Case 2 simulated a collagen disease.

Cases 3–7—Prominent Intrathoracic Lymph-node Enlargement

In Cases 3, 4, and 5 biopsy of slightly or moderately enlarged superficial nodes was inconclusive, showing non-specific reactive hyperplasia only. In Cases 6 and 7 there was no superficial lymph-node enlargement.

Table Showing Salient Features in 13 *Illustrative Cases of Hodgkin's Disease*

Case No.	Age and Sex	Presenting Features		Serum Analysis		Results of Liver Biopsy			Remarks
		General	Superficial Lymph-nodes	Bilirubin (mg./100 ml.)	Alkaline Phosphatase (K.-A.Units)	Pleomorphic Portal Infiltrate	Küpffer-cell Activity	Comments	
1	33 M	Pyrexia, lassitude, dyspnoea, anaemia, mitral stenosis, liver+, spleen+	Not enlarged	0·8	13	+++	+	Haemosiderosis, early fibroblastic activity	Rapid course. Died 8 months after biopsy. Diagnosis confirmed at necropsy
2	65 M	Pyrexia, fatigue, weight loss, ankle oedema, peripheral neuritis, neutropenia, liver+	,, ,,	0·4	38	++	+	See Special Plate, Fig. 1	Developed transient jaundice. Died 7 months after biopsy. No necropsy
3	42 M	Pyrexia, lassitude, cough, right sciatic pain, enlarged hilar nodes, pulmonary infiltration, liver+, spleen+	Cervical-node biopsy inconclusive	0·2	28	+++	++	Portal infiltrate mainly reticulum cells; early fibroblastic activity	Developed terminal jaundice. Died 6 months after liver biopsy. Diagnosis confirmed at necropsy
4	30 M	Pyrexia, cough, dyspnoea, enlarged mediastinal nodes, liver+, spleen+	Axillary-node biopsy inconclusive	0·9	37	++	++	See Special Plate, Fig. 3	Diagnosis confirmed by later node biopsy Episodes of jaundice Died 15 months after liver biopsy. No necropsy
5	49 M	Fatigue, dyspnoea, pruritus, enlarged mediastinal nodes, liver+, spleen+	Cervical-node biopsy showed reactive hyperplasia of "sarcoid pattern"	0·4	31	++	++	Giant-cell forms and fibroblastic activity. See Special Plate, Fig. 4	Diagnosis confirmed by later node biopsy. Died 12 months after liver biopsy. No necropsy
6	37 M	Pyrexia, lassitude, enlarged mediastinal nodes, liver+, spleen+	Not enlarged	0·2	23	+	++		Diagnosis confirmed at necropsy 6 months after liver biopsy
7	35 M	No symptoms, enlarged hilar nodes on chest radiograph; pyrexia and dyspnoea later, with liver+	,, ,,	0·3	19	+	++	Mainly reticulum-cell infiltrate; early fibroblastic activity	Under treatment 1 year after liver biopsy
8	69 F	Fatigue, weight loss, anorexia, massive splenomegaly, liver+	Not enlarged	0·4	40	+	+		Diagnosis confirmed at necropsy 3 months after liver biopsy. Spleen weight 3,500 g.
9	55 F	Acute haemolytic anaemia, liver+, spleen++	Not enlarged	2·0	83	++	++	Haemosiderosis, extramedullary erythropoiesis. See Special Plate, Fig. 2	Diagnosis confirmed at splenectomy Died 1 year later. No necropsy
10	51 F	Chronic haemolytic anaemia, dyspnoea, ankle oedema, liver+, spleen++	,, ,,	1·6	25	+	++		Diagnosis confirmed at necropsy 3 years later. Obstructive jaundice latterly
11	50 M	Onset with enlarged cervical nodes; later pruritus, dyspnoea, obstructive jaundice, liver+	Cervical-node biopsy diagnostic of Hodgkin's disease	—	37	++	+	Notable fibroblastic activity; residual biliary stasis	Biopsy performed in investigation of jaundice
12	25 M	Enlarged axillary nodes at routine examination; transient jaundice 1 year later, liver+	Axillary-node biopsy diagnostic of Hodgkin's disease	0·5	25	++	+	Fibroblastic activity; biliary stasis	,, ,, ,,
13	33 M	Lassitude, chest pains, dyspnoea, chills; later pyrexia	Cervical-node biopsy showed non-specific changes but ? atypical sarcoid	0·3	12	(1) ++ (2) +	+ ++	First liver biopsy suggested sarcoidosis. Second liver biopsy showed pleomorphic pattern	Diagnosis of Hodgkin's disease confirmed at further node biopsy 2 years after second liver biopsy

Case 8—Massive Splenomegaly

Splenomegaly is found at some stage in almost every case. Occasionally, as in this instance, it overshadows all other features. Similar cases, not diagnosed until necropsy, have been described (Mellon, 1916; Krumbhaar, 1931; Isaacson *et al.*, 1947).

Cases 9 and 10—Haemolytic Anaemia

The association of Hodgkin's disease and haemolytic anaemia is well established (Dacie, 1954). Haemolysis may be so slight that it is detectable only by careful studies of red-cell survival, or so severe that it dominates the clinical picture (Scott, 1949). Case 9 is an example of an acute haemolytic process, while Case 10 is of more chronic nature with terminal intrahepatic biliary stasis.

Cases 11 and 12—Investigation of Jaundice

Transient jaundice is common in Hodgkin's disease (Symmers, 1948), and many factors probably contribute to its development (Sherlock, 1958). Levitan *et al.* (1961) have recently reviewed the subject, stressing the need for liver biopsy in its investigation. The diagnosis in Cases 11 and 12 had already been made by lymph-node biopsy. In both obstructive jaundice developed. Investigation included liver biopsy, which showed portal fibrosis and slight intrahepatic biliary stasis. This is a common cause of jaundice in Hodgkin's disease. The view that jaundice is due to extrahepatic biliary obstruction by enlarged lymph-nodes cannot, in our experience, be sustained.

Case 13—Atypical Sarcoidosis

This case shows the evolution of Hodgkin's disease through a histological picture resembling sarcoidosis. A similar tendency was seen in Cases 5 and 12. Jackson and Parker (1947) have described this, but its occurrence is not sufficiently well known and has not been previously described in the liver.

Discussion

In our series of over 300 aspiration biopsies of the liver many have been performed in the investigation of unexplained pyrexia, hepatomegaly, or intrathoracic lymph-node enlargement, and not in the investigation of intrinsic liver disease. Many other diseases share this form of presentation with Hodgkin's disease, and liver biopsy can be of great value in revealing their true nature.

The chance of obtaining a sample of liver tissue showing the features of Hodgkin's disease depends upon the stage of the illness. In most cases the disease is initially restricted to superficial lymph-nodes and becomes generalized some years later. In these cases liver biopsy is both unnecessary and unlikely to be of diagnostic value. When deep structures are primarily affected there may be no symptoms until the condition is generalized and the liver is involved. It is in this group, in which a diagnosis is often difficult to establish, that the liver is most likely to be infiltrated.

Ross *et al.* (1956) have shown that a normal or only slightly raised serum bilirubin level with increased alkaline phosphatase activity is common in chronic infiltrative disease of the liver. We have found this biochemical pattern to indicate that liver biopsy is likely to be helpful.

It is now established that aspiration biopsy of the liver is without risk or discomfort to the patient if the essential precautions are observed. The particular technique adopted is less important than experience in its use. In the interpretation of these liver samples the pathologist must be familiar with the wide range of conditions in which infiltration and Küpffer-cell activity occur in the liver, and the value of his opinion on the interpretation of the changes in biopsy specimens will increase with his experience. Close co-operation between the clinician and the pathologist is invaluable.

It is submitted that aspiration biopsy of the liver is a useful investigation in cases of Hodgkin's disease in which a diagnosis cannot be made by superficial lymph-node biopsy, and that it may often assist in the elucidation of other diseases presenting with similar general features.

Summary

Involvement of the liver in Hodgkin's disease is common, and is usually present when general features of the illness appear. The histological changes evolve to a distinctive pattern which can be diagnostic.

In 11 cases of Hodgkin's disease in which the diagnosis could not be established by examination of a superficial lymph-node, aspiration biopsy of the liver gave valuable information. These cases presented difficult diagnostic problems; some had general features suggesting systemic infection or a collagen disease, while others had primary involvement of deep nodes, hepatosplenomegaly, or haemolytic anaemia.

Liver biopsy was also helpful in the investigation of two cases of obstructive jaundice due to intrahepatic cholestasis occurring in the later stages of the disease.

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"A hitherto unknown collection of twentieth-century French paintings and drawings, including works by Picasso, Juan Gris, Leger, Lurcat, Marcoussis, Masson, Derain, Gleizes, Metzinger, and Herbin, is to be sold by auction in Jersey on May 29. The pictures are the collection of the late John Wardell Power a millionaire who was once a doctor in Australia. His bequest of £800,000 to Sydney University to form a faculty of fine arts was announced a few weeks ago, more than 18 years after his death in Jersey in 1943. The proceeds of the sale of the Power collection will go to the Imperial Cancer Research Fund. The collection came to light after the death of Mrs. Power last autumn. The works are believed to have been collected by Dr. Power when he was living in Paris. Dr. Power himself gained distinction as an artist. His widow bequeathed 140 of his paintings which remained in her possession to Sydney University. They will shortly be placed on permanent exhibition there. The sale will be the first of modern art to take place in Jersey." (*Guardian*, May 5.)

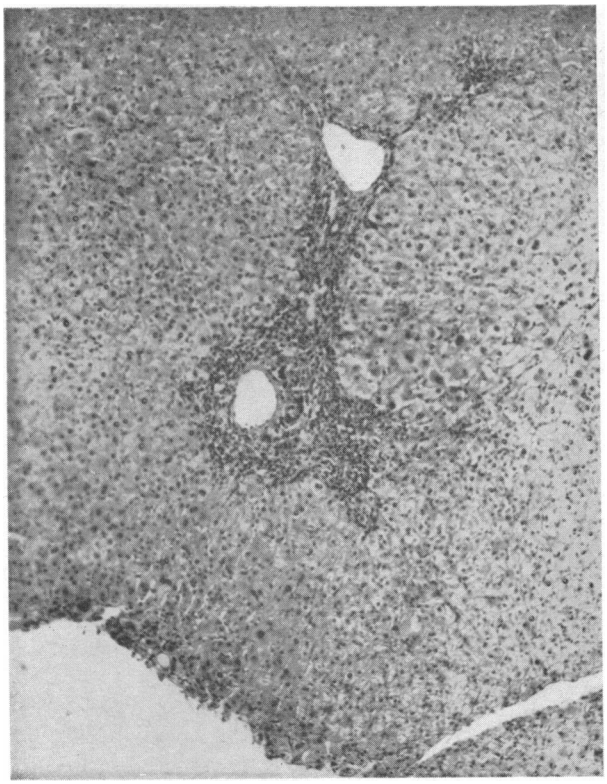

FIG. 1.—Case 2. Conspicuous infiltration of portal tracts. (H. and E. ×65.)

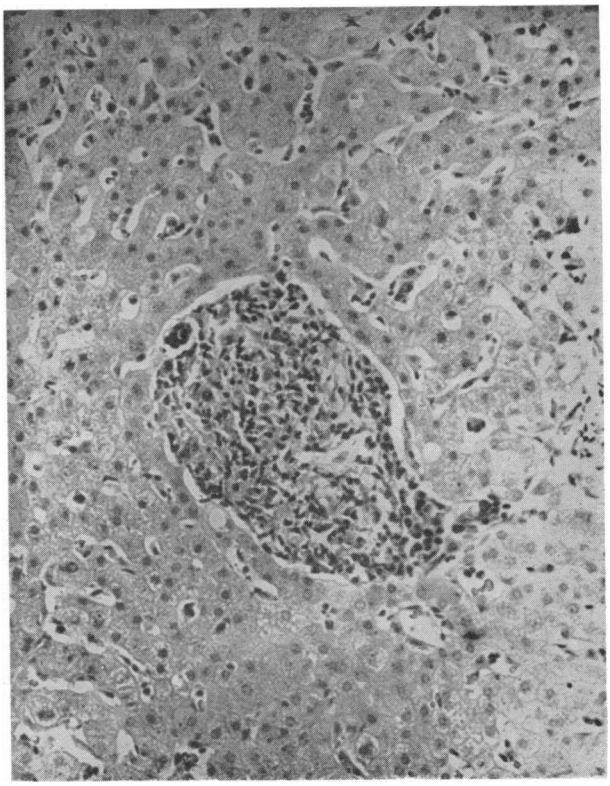

FIG. 2.—Case 9. Pleomorphic portal infiltration and diffuse Küpffer-cell hyperplasia. (H. and E. ×165.)

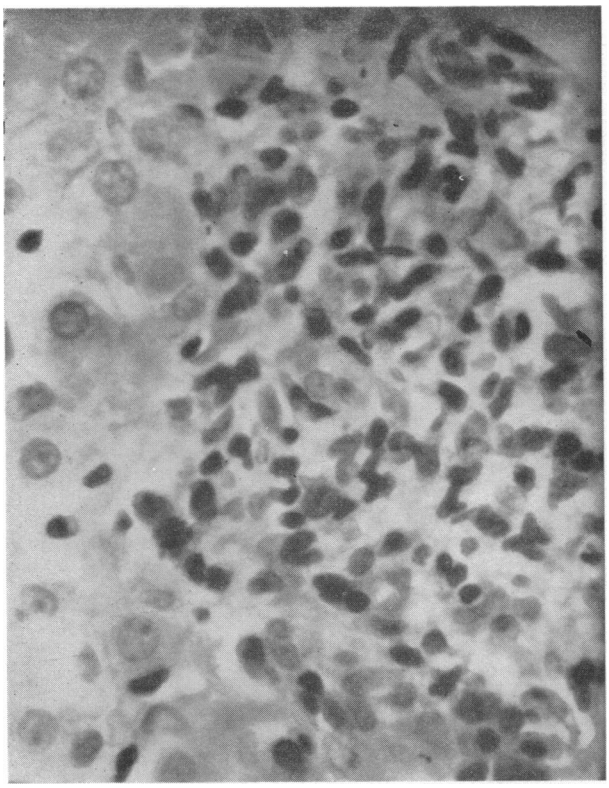

FIG. 3.—Case 4. Edge of area of portal infiltration. (H. and E. ×660.)

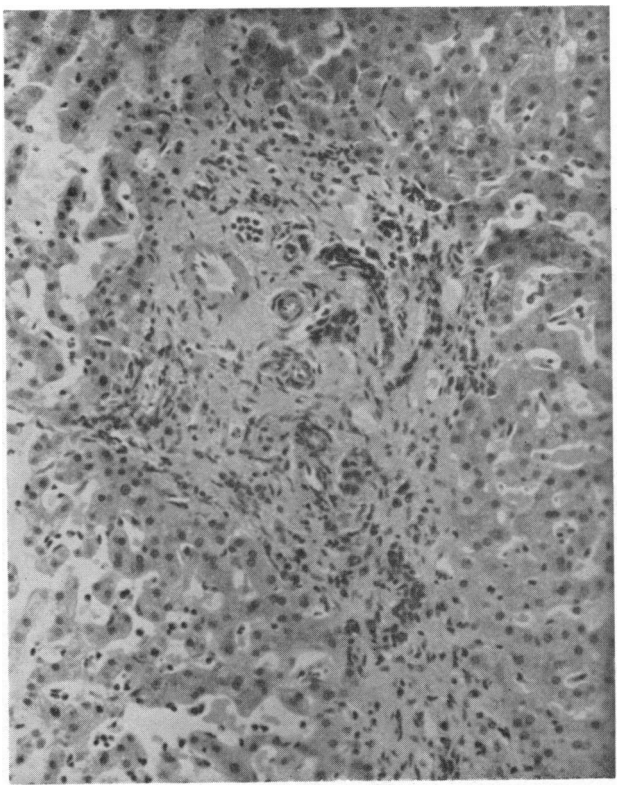

FIG. 4.—Case 5. Fibroblastic activity in a portal tract, with moderate infiltration and adjacent Küpffer-cell activity. (H. and E. ×165.)