The liver in Hodgkin's disease¹

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SYNOPSIS This is a survey of the incidence, morphology, and significance of hepatic changes in Hodgkin's disease

Hepatomegaly and abnormal results in liver function tests are frequently encountered in patients during the course of Hodgkin's disease. It is tacitly assumed in many cases that these findings are part of the general disease process. We were impressed, however, by the frequent occurrence of hepatic changes unrelated to the presence of Hodgkin's disease, and by the difficulty in distinguishing Hodgkin's disease involving the liver from other liver disease in these patients. The present study analyses 112 necropsied cases of Hodgkin's disease with clinical or laboratory evidence of liver disease during life, or both, and reviews the literature in an attempt to elucidate this difficult problem.

REVIEW OF THE LITERATURE

A brief review of the literature cannot possibly include all the papers on this subject; therefore we apologize for any oversights or omissions.

Thomas Hodgkin (1832), in his original paper, described liver involvement incidentally, and Wilks (1865) noted involvement of the liver with Hodgkin's disease in seven of his 13 cases. In a critical analysis of Hodgkin's original cases, Fox accepted the diagnosis of Hodgkin's disease involving the liver in only two cases (Fox, 1936). In succeeding years, many cases of Hodgkin's disease with pathologically proven liver involvement were recorded by different authors (Barié, 1875; Barron, 1926; Beatty, 1954; Brauneck, 1889; Coronini, 1928; Chevallier and Bernard, 1932; Craver, 1957; Fabian, 1911; Foulon, 1932; Hartfall, 1932; Gall, 1956; Jackson and Parker, 1947; Newman and Pushkin, 1951; Klein, 1955;

Murchison, 1869; Reed, 1902; Rolleston, 1912; Sternberg, 1936; Symmers, 1944; Wilks, 1865). Liver involvement in Hodgkin's disease was discussed in papers by Fabian (1911), Longcope (1903), Ziegler (1911), Chevallier and Bernard (1932), Sternberg (1936), Wallhauser (1933), Jackson and Parker (1947), and others (Ackerman and del Regato, 1954; Baker and Mann, 1939; Burnam, 1926; Goldman, 1940; Hoster, Dratman, Craver, and Rolnick, 1948; Symmers, 1944; Uddströmer, 1934; Terplan and Mittelbach, 1929), and was more specifically dealt with in papers by Coronini (1928) and later by Gruber (1930), Foulon (1932), Abbattucci and Beatty (1953), and Beatty (1954).

Students of the problem describe Hodgkin's disease involving the liver at necropsy in from 10 to 60% of the cases (Table I) (Ackerman and del Regato, 1954; Jackson and Parker, 1947; Sternberg, 1936; Symmers, 1944; Wallhauser, 1933; Ziegler, 1911). Hepatomegaly was observed clinically in from 2.3 to 60% of another series of collected cases (Table I) (Baker and Mann, 1939; Burnam, 1926; Goldman, 1940; Murray, 1908; Uddströmer, 1934). Some authors, basing their opinions on necropsy material primarily, claim that hepatic involvement is a late manifestation of Hodgkin's disease (Diamond, 1958a; Pène, du Paquier, and Pène, 1955), while others maintain that silent liver involvement can be demonstrated early in the course of the disease by liver biopsy (Pène, 1952). There is a similar difference of opinion regarding the onset of hepatomegaly, some describing it as a sign of the terminal stage of Hodgkin's disease (Ackerman and del Regato, 1954), others describing hepatomegaly as a presenting sign ('...forme hépatique et forme hépatosplénomégaly de la maladie de Hodgkin') (Pène, 1952; Pène *et al.*, 1955).

Hodgkin's disease limited to the liver has been reported (Goia, 1935; Symmers, 1944), but most

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TABLE I

INCIDENCE OF HEPATIC ENLARGEMENT AND INVOLVEMENT WITH HODGKIN'S DISEASE IN PATIENTS WITH HODGKIN'S DISEASE AS REPORTED IN THE LITERATURE

Author	No. of Cases	Hepatic Enlargement (%)	Liver Involvement at Necropsy (%)
Ziegler (1911)	220	60.0	
Burnam (1926) ¹	173	2.3	
Longcope and McAlpin (1927)	77	50.0	
Terplan and Mittelbach (1929)	29 ²		10.0
Wallhauser (1933) ¹	1447 (collected from the literature)		50.0
Uddströmer (1934)	548	25.9	
Sternberg (1936)	52 ²		38.0
Baker and Mann (1939)	65	30.0	
Longscope (Baker and Mann, 1939)	117	47.0	
Goldman (1940)	212	30.6	
Symmers (1944)	30 ²		58.0
Jackson and Parker (1947)	63 ² (Hodgkin's granuloma) 19 ² (Hodgkin's sarcoma)		55.0 60.0
Abbatucci and Beatty (1953)	82 ²		53.0
Ackerman and del Regato (1954) ¹			50.0
Leviton <i>et al.</i> (1961)	112 ² 875 ²	79.6 32.5	66.0

¹Review article

²Necropsy series

³Among 875 patients with Hodgkin's disease reviewed

workers believe that it is almost invariably a part of a generalized process (Craver, 1957; Hoster *et al.*, 1949). Involvement of the liver is generally, but not always, cited as occurring in conjunction with involvement of the spleen (Craver, 1957; Wallhauser, 1933; Ziegler, 1911).

Coronini (1928), Gruber (1930), and Foulon (1932) distinguish the following types of hepatic involvement by Hodgkin's disease; (1) capsular, (2) nodular or granulomatous lesions localized to the portal triad, (3) diffuse, and (4) encroachment upon or invasion of blood vessels. Simonds (1926) first noted Hodgkin's lesions invading the portal vein. According to some investigators, Hodgkin's disease primarily invades the liver within the portal spaces (Schmorl, 1922; Sternberg, 1936), while others claim that it extends along the periportal spaces (Fabian, 1911; Ziegler, 1911) or along the major biliary ducts and portal vein (Chevallier and Bernard, 1932; Sternberg, 1936).

In Hodgkin's granuloma one encounters focal circumscribed lesions or yellow streaks along the course of the portal areas (Jackson and Parker, 1947), and when extensive fibrosis is present the lesions may resemble gummas (Jackson and Parker, 1947). The hepatic parenchyma surrounding the large lesions may become atrophic (Sherlock, 1955; Symmers, 1944) or may be completely destroyed.

In Hodgkin's sarcoma grayish nodules are seen scattered throughout the liver. These lesions are histologically similar to those in the lymph nodes (Jackson and Parker, 1947). The occurrence of pathological changes unrelated to Hodgkin's disease has been appreciated by others (Abbatucci and Beatty, 1953; Beatty, 1954; Brunner, 1925; Chevallier and Bernard, 1932; Ewing, 1940; Foulon, 1932; Hoster, Zanes, and von Haam, 1949; Loeper and Lebret, 1940; Longcope, 1903; Muller and Boles, 1927; Reed, 1902; Wallhauser, 1933). Specifically noted have been tuberculosis, amyloidosis, focal necrosis, fatty degeneration, fibrosis, cirrhosis, viral hepatitis, congestion, and adhesions. Simultaneous involvement of the liver with Hodgkin's disease and tuberculosis (Loeper and Lebret, 1940; Wallhauser, 1933), fatty degeneration (Longcope, 1903; Muller and Boles, 1927; Reed, 1902) and fibrosis (Longcope, 1903; Reed, 1902; Tschekulajev, 1951) has also been reported.

Routine laboratory liver function tests have usually been of little help in the diagnosis of lymphomatous involvement of the liver (Sherlock, 1955). Bromosulphalein retention and alkaline phosphatase levels may be abnormal (Sherlock, 1955). According to some, however, the serum alkaline phosphatase level is not as helpful in Hodgkin's disease as in detecting involvement of the liver by cancer (Abbatucci and Beatty, 1953; Ariel and Shahon, 1950; Bodansky and Bodansky, 1952; Mendelsohn and Bodansky, 1952; Ross, Iber, and Harvey, 1956). A similar negative opinion has been expressed with regard to the serum glutamic oxalacetic transaminase (SGOT) level which is, however, invaluable in the diagnosis of hepatitis (Wróblewski and LaDue, 1955). Of all the laboratory tests currently in general use, liver biopsy is probably most helpful in establishing the presence of Hodgkin's disease of the liver. But it must be recognized that a negative biopsy does not necessarily exclude the presence of hepatic Hodgkin's disease (Gall, 1956; Lichtman, 1953; Pène, 1952; Pène *et al.*, 1955; Robert, Bréchet, and Ruynat, 1957; Sherlock, 1955).

MATERIAL AND METHODS

The case records of 875 patients who were seen at the Memorial Center for Cancer and Allied Disease between 1947 and 1957 and in whom a tissue diagnosis of Hodgkin's disease was made or confirmed by members of the Department of Pathology were reviewed. Three hundred patients (34.3%) of the above group presented with clinical evidence pointing to liver disease such as hepatomegaly and/or abnormal liver function tests.¹ Of this group with

¹The cases without hepatomegaly were either jaundiced or had an abnormal bromosulphalein test.

clinical signs of liver disease and histological proof of Hodgkin's disease, 112 cases (44%) were necropsied. The present report is concerned with an analysis of the clinical and pathological data of the latter group only. The significance of the data was evaluated by the application of a corrected χ^2 test (Yates) (Hill, 1955) and the degree of significance expressed by the P value.

RESULTS

Of the 112 necropsied cases, 74 (66%) revealed Hodgkin's disease involving the liver and 38 (34%) did not. In the latter group, however, all the livers exhibited some abnormality of major or minor degree.

The weight of the liver varied between 900 and 4,900 g., the medium weight being 2,600 g. There was no significant difference in weight between those livers involved with Hodgkin's disease and those free of Hodgkin's disease.

Of the 74 cases of Hodgkin's disease directly involving the liver, 64 (86.5%) presented with diffuse infiltration, eight (10.8%) presented with nodular lesions, and two (2.7%) exhibited mixed lesions. Both lobes of the liver were involved in most cases. Hodgkin's paraganuloma was not encountered in the liver in any instance. Fifty-six cases were classed histologically as Hodgkin's granuloma of the liver, and of these 46 (82.3%) showed almost exclusive involvement of the portal triads. In two cases the lesions were limited to the liver capsule. All cases with nodular lesions were classified histologically as granuloma, and in no patient was there invasion or involvement of hepatic blood vessels by Hodgkin's granuloma.

Hodgkin's sarcoma was present in 18 of the 74 cases (24.3%) with Hodgkin's disease directly involving the liver. Of this number, 14 presented diffuse, extensive liver infiltration while the remaining four involved primarily the portal triads. In five instances, the hepatic parenchyma adjacent to the specific lesions showed marked necrosis. The sarcomatous lesions were necrotic in three instances and invasion of blood vessels was found in five. Invasion of the main trunk of the portal vein with thrombosis was encountered in one case. In another patient, marked fibrosis of a sarcomatous lesion adjacent to the portal vein resulted in portal vein thrombosis without invasion. The hepatic vein was occluded by a thrombus (Chiari's syndrome) without invasion in a case with marked constriction of the portal vein secondary to fibrosis; the portal vein was free of thrombus and the liver was small (900 g.).

Fifty-nine (79.6%) of the 74 cases of Hodgkin's disease of the liver also presented additional patho-

logical changes (Table II). Biliary tree pathology related to the Hodgkin's disease was found in 24 patients (34%) secondary to granulomatous as well as sarcomatous lesions (Table III). Gall bladder

TABLE II
ABNORMALITIES IN LIVER UNRELATED TO
HODGKIN'S DISEASE

	Group A No. without Hodgkin's Disease in Liver: 38 Cases	Group B No. with Hodgkin's Disease in Liver ¹ : 74 Cases	Total No. with Liver Abnormalities in 112 Cases
Passive congestion ¹	21 (55.2%)	25 (33.3%)	46 (41%)
Fatty metamorphosis	9 (23.6%)	14 (18.9%)	23 (20.5%)
Haemosiderosis	6 (15.8%)	9 (12.2%)	15 (13.4%)
Portal fibrosis	—	4 (5.4%)	4 (3.6%)
Bacterial abscesses	1 (2.6%)	2 (2.7%)	3 (2.7%)
<i>Clostridium welchii</i> —1 case	—	—	—
Multiple pyogenic—1 case	—	—	—
Nocardia abscess	—	1 (1.3%)	1 (0.9%)
Moniliasis of liver capsule	—	1 (1.3%)	1 (0.9%)
Viral hepatitis	1 (2.6%)	1 (1.3%)	2 (1.8%)
Toxic hepatitis	1 (2.6%)	—	1 (0.9%)
Portal cirrhosis	5 (13.1%)	—	5 (4.8%)
Post-necrotic cirrhosis	1 (2.6%)	—	1 (0.9%)
Amyloid	1 (2.6%)	—	1 (0.9%)
Tuberculosis	2 (5.3%)	—	2 (1.8%)
Miscellaneous	13 (34.2%)	6 (8.1%)	19 (16.9%)

¹The incidence in this finding differs between both groups A and B significantly ($p=0.05$).

²Some patients showed more than one abnormality.

TABLE III
PATHOLOGY DUE TO HODGKIN'S DISEASE
IN THE BILIARY SYSTEM

	Group A No. without Hodgkin's Disease in Liver: 38 Cases	Group B No. with Hodgkin's Disease in Liver: 74 Cases	Total No. with Disease in Biliary System in 112 Cases
Common duct infiltration by tumour	1	4	5
Pressure on common duct by tumour	—	10	10
Obstruction of one hepatic duct by tumour due to pressure	2	2	4
Infiltration of intra-hepatic duct by tumour	—	1	1
Infiltration and pressure on common duct and one hepatic duct by tumour	—	1	1
Partial constriction of common duct and cystic duct by surrounding tumour	—	1	1
Tumour infiltrating gall bladder wall	1	4	5
Tumour infiltrating gall bladder and cystic duct	—	1	1
Total	4 (10.5%)	24 (32.4%)	28 (25.0%)

The difference in incidence in biliary tree pathology due to Hodgkin's disease between the two groups is statistically significant ($p=0.05$).

TABLE IV

GALL BLADDER PATHOLOGY UNRELATED
TO HODGKIN'S DISEASE

	Group A	Group B	Total
	No. without Hodgkin's Disease in Liver	No. with Hodgkin's Disease in Liver	
Cholelithiasis	1 ¹	3 ¹	4
Chronic cholecystitis	1	1	2
Choledocholithiasis	1	—	1
Total	3	4	7

¹One patient had chronic cholecystitis and cholelithiasis and at the same time Hodgkin's disease of the gall bladder.

²This patient also had a mucocele of the gall bladder.

pathology unrelated to Hodgkin's disease was found in only four of the 74 cases (5.4%) (Table IV).

Nineteen of the 38 cases in which Hodgkin's disease spared the liver (50%) exhibited at least one pathological lesion in the liver while the remaining 19 had multiple abnormalities (Table II). Hodgkin's disease limited to the biliary tree, without liver involvement, was seen in only four instances (10.5%); this figure was significantly lower than in the group in which the liver itself was also involved.

Associated pathological changes encountered in other organs within the bed of the portal venous system were: (1) Two instances of oesophageal varices in patients with Hodgkin's disease involving the liver parenchyma (detailed report elsewhere, Levitan, Diamond, and Craver, 1959); (2) 30 instances of congestion, infarction, or haemosiderosis of the spleen and one case of amyloidosis of the spleen and pancreas with generalized amyloidosis as well; (3) 15 cases of fibrosis, focal necrosis, or abscesses of the pancreas; (4) four benign gastric ulcers and five duodenal ulcers. The distribution of Hodgkin's lesions in various organs in general is listed in Table V.

TABLE V

ORGANS AFFECTED BY HODGKIN'S DISEASE AT
TIME OF NECROPSY IN 112 CASES¹

Organ	No. of Cases	Organ	No. of Cases
Spleen	76 (67.8%)	Breast	4 (3.6%)
Liver	74 (66%)	Bladder	4 (3.6%)
Lungs	39 (34.8%)	Uterus	4 (3.6%)
Bone marrow	33 (29.5%)	Pericardium	3 (2.7%)
Gastrointestinal tract	26 (23.2%)	Ovaries	3 (2.7%)
Pancreas	26 (23.2%)	Fallopian tubes	2 (1.8%)
Kidney	12 (10.7%)	Ureter	1 (0.9%)
Adrenal	12 (10.7%)	Vagina	1 (0.9%)
Diaphragm	9 (8.0%)	Brain (proper)	1 (0.9%)
Thyroid	6 (5.4%)	Dura	1 (0.9%)
Heart	4 (3.6%)	Pituitary	1 (0.9%)

¹Most patients had several organs involved.

TABLE VI

MECHANISMS CONTRIBUTORY TO DEATH
AS DETERMINED AT NECROPSY

Infection	49 cases (43.7%)
Septicaemia	4
Organisms	
<i>Clostridium welchii</i>	1
<i>Nocardia</i>	1
<i>Actinomyces</i>	1
<i>Salmonella</i>	1
Meningitis	4
Organisms	
<i>Cryptococcus neoformans</i>	2
<i>Pneumococcus</i> Type I	1
<i>Listeria monocytogenes</i>	1
Pulmonary pyogenic abscess	3
Bronchopneumonia	23
Lobar pneumonia	1
Tuberculosis	10
Miliary	2
Tuberculoma of brain	1
Tuberculoma of lung	7
Moniliasis of lung	2
Pulmonary histoplasmosis	1
Acute bacterial endocarditis (organism?)	1
Generalized Hodgkin's disease (with debility, toxæmia)	27 cases (24.0%)
Uraemia	14 cases (12.5%)
Compression of both pelves by tumour	1
Tumour in both kidneys (extensive)	3
Tumour in kidney and papillary necrosis	1
Membranous glomerulonephritis	3
Radiation arteriolitis and acute membranous glomerulonephritis	1
Multiple renal cysts and nephrosclerosis	1
Chronic pyelonephritis and renal infarct	1
Chronic pyelonephritis, membranous	
Glomerulonephritis and multiple calculi	1
Cholemic nephrosis	2
Haemorrhage	12 cases (10.7%)
Cerebral and/or subarachnoid	4
Gastrointestinal	7
Retropitoneal	1
Hepatic coma	3 cases (2.8%)
Hepatitis	2
Hodgkin's disease of the liver	1
Perforation of stomach due to Hodgkin's disease	2 cases (1.8%)
Congestive heart failure	2 cases (1.8%)
Constrictive pericarditis	1
Verrucous endocarditis	1
Brain tumour (ependymoma of fourth ventricle)	1 case (0.9%)
Hodgkin's disease of the brain	1 case (0.9%)
Amyloid	1 case (0.9%)

Factors contributing to death in this series are listed in Table VI. It is of interest to note that five patients (4.5%) died of causes apparently unrelated to Hodgkin's disease, viz., hepatic coma secondary to hepatitis (two cases), congestive heart failure (two cases), and ependymoma of the fourth ventricle (one case). An important role was attributed to infection in 49 cases (43.7%), but was considered the primary cause of death in only 16 (14.3%), the presenting infection being in the form of septicaemia, meningitis, miliary tuberculosis, cerebral tuberculoma, acute endocarditis, lobar pneumonia, or pulmonary abscess. In the remaining patients, infection was considered to be a terminal event. Four patients succumbed to cerebral or subarachnoid haemorrhage, or both, in each case apparently

secondary to severe thrombocytopenia. In contrast, of seven patients in whom gastrointestinal haemorrhage was a major factor contributing to death, only one showed thrombocytopenia, the source of bleeding in the remaining six being attributable to oesophageal varices (one case), Hodgkin's disease of the stomach (two cases), or duodenal ulcer (three cases). Uraemia was a frequent terminal event (14 cases), and membranous glomerulonephritis was encountered in five of these cases. Gastric perforation secondary to Hodgkin's disease was seen in two cases. Generalized Hodgkin's disease, with debility and 'toxaemia' in the absence of any specific additional cause, was considered the cause of death in 26 cases (24%). Only one patient in the present series was considered to have died as a direct consequence of Hodgkin's disease of the liver.

Seventeen cases of other neoplastic growths (15.2%) were encountered in the total necropsy series (Table VII).

TABLE VII
TUMOURS UNRELATED TO HODGKIN'S DISEASE
IN 112 PATIENTS

Carcinomas	4
Adenocarcinoma of rectum	1
Adenocarcinoma of colon	1
Papillary carcinoma of thyroid	1
Epidermoid carcinoma of skin	1
Osteogenic sarcoma	1
Kaposi's sarcoma	1
Brain	4
Meningioma of pons	1
Ependymoma of fourth ventricle	1
Pinealoma	1
Myoblastoma of pituitary	1
Mycosis fungoides	1
Adrenal adenoma	2
Haemangioma of liver	3
Benign ovarian cyst	1
Total	17

The clinical data in the necropsied group are arrayed, for comparison, into Group A comprising cases with Hodgkin's disease not involving the liver, and Group B cases with Hodgkin's disease involving the liver, and the combined total series.

Sex and age distribution is given in Table VIII. The ratio of males to females in the total series is 1.6 : 1. With one exception all the patients were white. The sex distribution in this series is identical with that reported in whites with Hodgkin's disease dying in 1956 for the entire United States (U.S. Dept. of Health, Education and Welfare, 1958). The youngest patient in our series was aged 15, the oldest aged 78. There was no significant difference in sex distribution between patients with Hodgkin's disease involving the liver and those without such involvement. The clinical diagnosis of histological subtype of Hodgkin's disease, based on tissue biopsy during life, is listed in Table IX. There was no significant difference in distribution of histological types of Hodgkin's disease between Groups A and B. The first clinical evidence of liver disease in relation to the time of diagnosis of Hodgkin's disease was well documented in 74 cases (66.1%) of the total series (Table Xa). Over half (56.2%) of these developed clinical evidence of liver disease within 24 months of diagnosis of Hodgkin's disease, while 73.8% developed such evidence within 36 months.

Although liver pathology was often suspected, a clinical diagnosis of a specific type of liver disease was difficult, and a diagnosis of specific liver disease was not overtly expressed in 88 cases (78.5%) of the necropsy group. In the remaining cases, Hodgkin's disease involving the liver was diagnosed in 17 (18.2%), viral hepatitis in five (4.5%), toxic hepatitis in one (0.9%), and passive congestion of

TABLE VIII

AGE¹ AND SEX² DISTRIBUTION

Age	Group A				Group B				Ratio	No. in Total Series of 112 Cases			
	No. without Hodgkin's Disease in Liver				No. with Hodgkin's Disease in Liver				Group A:B				
	Males	Females	M/F Ratio	Total	Males	Females	M/F Ratio	Total		Males	Females	M/F Ratio	Total
15-19	6	0	∞	6	1	2	0.5	3	2.0	7	2	3.5	9
20-29	4	7	0.57	11	6	4	1.5	10	1.1	10	11	0.91	21
30-39	7	7	1.00	14	17	7	2.4	24	0.58	24	14	1.7	38
40-49	1	3	0.33	4	8	5	1.6	13	0.34	9	8	1.1	17
50-59	1	1	1.0	2	10	4	2.5	14	0.14	11	5	2.2	16
60-69	0	1	0.0	1	5	2	2.5	7	0.14	5	3	1.7	8
70-79	0	0	0.0	0	3	0	3.0	3	0.0	3	0	3.0	3
Total	19	19	1.0	38	50	24	2.08	74	0.51	69	43	1.6	112

¹The youngest patient in our series was 15 years old.

²The sex distribution between Group A and Group B is not statistically significant as determined by the χ^2 (corrected) test.

TABLE IX

HISTOLOGICAL DIAGNOSIS AS DETERMINED AT BIOPSY¹

	No. in Total Necropsy Series of 112 Cases	Group A	Group B
		No. without Hodgkin's Disease in Liver in 38 Cases	No. with Hodgkin's Disease in Liver in 74 Cases
Hodgkin's granuloma	104 (93.0%)	36 (34.5*, 94.8% ²)	68 (65.5*, 91.9% ⁴)
Hodgkin's sarcoma	5 (4.4%)	1 (20*, 2.6% ²)	4 (80.0*, 5.4% ⁴)
Hodgkin's paragranuloma	3 (2.6%)	1 (33.3*, 2.6% ²)	2 (66.7*, 2.7% ⁴)

¹The biopsies were performed before the onset of liver abnormalities.²Percentage of 104 cases of Hodgkin's granuloma³Percentage of 38 cases⁴Percentage of 74 cases⁵Percentage of 5 cases of Hodgkin's sarcoma⁶Percentage of 3 cases of Hodgkin's paragranuloma

TABLE Xa

DURATION FROM DIAGNOSIS OF HODGKIN'S DISEASE
TO CLINICAL EVIDENCE OF LIVER
ABNORMALITY IN 74 CASES

Time in Months	No. of Cases
1-6	17 (23.0%)
7-12	8 (10.8%)
13-18	8 (10.8%)
19-24	9 (12.2%)
25-30	6 (8.1%)
31-36	6 (8.1%)
37-42	3 (4.1%)
43-48	4 (5.4%)
49 or more	13 (17.5%)

the liver in one (0.9%). Two of the 17 cases diagnosed during life as having Hodgkin's disease of the liver were not so confirmed at necropsy. (Cholelithiasis, fatty liver, and haemangioma were present in one, and hepatomegaly of undetermined aetiology in the other.) Only two of the five cases diagnosed in life as viral hepatitis gave evidence of viral hepatitis at necropsy, and one of these exhibited Hodgkin's disease in the liver as well. It is possible that the remaining three cases diagnosed as viral hepatitis had healed, without pathological residua, by the time of death.

Liver disease was suspected clinically, before any form of therapy for Hodgkin's disease, in 25 cases (22.3%). All other patients in whom liver disease was suspected had received radiotherapy, chemotherapy, or steroids, alone or in combination, before the advent of signs suggestive of liver disease. Seventy-five patients (67.8%) received blood transfusions before the onset of liver disease. Six patients (5.4%) were known alcoholics, and five of these had portal cirrhosis at necropsy. Clinical symptoms and signs, and laboratory findings in both Groups A and B are listed in Tables X, XI, and XII. The degree of

TABLE X

SYMPTOMS AND SIGNS AT TIME OF
ONSET OF LIVER DISEASE

	Total Necropsy Group of 112 Cases ¹	Group A	Group B
		No. without Hodgkin's Disease in Liver in 38 Cases ²	No. with Hodgkin's Disease in Liver in 74 Cases ³
Fever	94 (84.0%)	32 (84.1%)	62 (84.0%)
Anaemia	89 (79.5%)	24 (60.5%)	65 (88.0%)
Hepatomegaly	89 (79.5%)	29 (76.4%)	70 (94.6%)
Splenomegaly	63 (56.2%)	21 (55.2%)	42 (56.8%)
Jaundice	57 (50.9%)	15 (39.5%)	42 (56.8%)
Pruritus	45 (40.0%)	11 (28.9%)	34 (46.0%)
Bleeding manifestations	42 (37.6%)	19 (50.0%)	23 (32.1%)
Peripheral oedema	35 (31.3%)	8 (21.1%)	27 (36.5%)
Ascites	34 (30.4%)	11 (28.9%)	23 (31.1%)
Abdominal pain	16 (14.3%)	7 (18.4%)	9 (12.2%)
Light stools	12 (10.7%)	2 (5.3%)	10 (13.5%)
RUQ pressure	11 (9.8%)	4 (10.5%)	7 (9.4%)
Indigestion	11 (9.8%)	5 (13.2%)	6 (8.1%)
Dark urine	11 (9.8%)	2 (5.3%)	9 (12.2%)
Melaena	10 (8.9%)	3 (7.7%)	9 (9.4%)
Abnormal sugar tolerance	8 (7.2%)	2 (5.3%)	6 (8.1%)
Haematemesis	6 (5.3%)	2 (5.3%)	4 (5.4%)
Foetor hepaticus	2 (1.8%)	1 (2.6%)	1 (1.3%)
Spider naevi	1 (0.9%)	1 (2.6%)	—

¹Percentage represents the incidence of signs or symptoms in the whole necropsy group. Many patients had multiple symptoms.²Percentage represents the incidence of signs or symptoms in the 38 cases which had liver pathology other than Hodgkin's disease. Two patients in this group had extrahepatic obstructive jaundice.³Percentage in this column represents incidence of signs or symptoms in the 74 cases with Hodgkin's disease involving the liver.The difference of incidence of symptoms between Groups A and B were determined by the χ^2 test. The differences, however, were not statistically significant.

TABLE XI

PERIPHERAL BLOOD

	No. in Total Necropsy Group of 112 Cases	Group A	Group B
		No. without Hodgkin's Disease in Liver in 38 Cases	No. with Hodgkin's Disease in Liver in 74 Cases
Anaemia ¹	88 (79.5%)	24 (63.1%)	65 (88.0%)
Leucocytosis ²	39 (34.8%)	14 (36.8%)	25 (33.8%)
Leucopenia ³	15 (13.4%)	2 (5.3%)	13 (17.6%)
Thrombocytosis ⁴	11 (9.8%)	3 (7.9%)	8 (10.8%)
Thrombocytopenia ⁵	26 (23.2%)	10 (26.3%)	16 (21.6%)

¹Anaemia, less than 11 g. % haemoglobin²Leucocytosis, over 10,000 white blood cells per mm.³³Leucopenia, less than 4,000 white blood cells per mm.³⁴Thrombocytosis, more than 400,000 platelets per mm.³⁵Thrombocytopenia, less than 90,000 platelets per mm.³

clinical hepatomegaly or splenomegaly, or both, and the sex distribution of cases with clinical splenomegaly are listed in Tables XIII, XIV, and XV.

There was no statistically significant difference between Groups A and B with respect to incidence of symptoms and signs, abnormal results in liver function tests, and the presence or degree of clinical

TABLE XII
LIVER FUNCTION TESTS

Test	Group A		Group B		Total No. Cases Tested	Percentage Abnormal
	No. of Cases Tested	Percentage Abnormal	No. of Cases Tested	Percentage Abnormal		
Bromsulphalein retention	10	100.0	23	100.0	33	100.0
Prothrombin time	8	100.0	23	91.4	31	93.5
Alkaline phosphatase	26	65.4	53	85.0	79	78.5
Total protein	31	83.9	49	85.6	80	85.0
Serum albumin	29	91.0	48	79.0	70	82.9
Serum globulin	22	27.3	48	18.7	70	22.4
Total serum bilirubin	21	52.4	62	56.4	83	55.4
Cephalin flocculation	27	63.0	61	54.1	88	56.8
Thymol turbidity	24	41.7	50	26.0	74	31.1
Total cholesterol	13	30.8	24	25.0 ¹	37	27.0
Serum glutamic oxaloacetic transaminase (SGOT)	4	100.0	20	40.0	24	50.0

Abnormal Values

Bromsulphalein test, retention of 8% or more of injected dye after 45 minutes

Prothrombin time, 16 seconds or more

Alkaline phosphatase, 5 Bodansky units or more

Total protein, below 6.0 g./100 ml.

Serum albumin, below 4.0 g./100 ml.

Serum globulin, below 1.0 g./100 ml. or above 3.0 g./100 ml.

Total serum bilirubin, more than 1.5 mg./100 ml.

Cephalin flocculation, 3+ or more after 48 hours

Thymol turbidity, more than 5.0 units

¹In two cases the values were below 100 mg./100 ml. and in two above 300 mg./100 ml. In the latter two cases, obstructive jaundice was present. The differences in incidence of abnormal tests between Groups A and B were not statistically significant.

TABLE XIII

DEGREE OF CLINICAL HEPATOMEGALY

Cm. below Right Costal Margin	No. in Total Necropsy Group of 112 Cases	Group A	Group B
		No. without Hodgkin's Disease in Liver in 38 Cases	No. with Hodgkin's Disease in Liver in 74 Cases
1-1.99	14 (12.5%)	7 (18.4%)	7 (9.4%)
2-2.99	13 (11.6%)	5 (13.1%)	8 (10.8%)
3-3.99	12 (10.7%)	4 (10.5%)	8 (10.8%)
4-4.99	17 (15.2%)	1 (2.6%)	16 (21.6%)
5-5.99	4 (3.6%)	1 (2.6%)	3 (4.1%)
6-6.99	5 (4.5%)	1 (2.6%)	4 (5.4%)
7 or more but above pelvic rim	12 (10.7%)	8 (21.1%)	4 (5.4%)
Below pelvic rim	10 (8.9%)	None	10 (13.5%)
No clinical hepatomegaly	23 (20.4%)	9 (23.7%)	14 (18.9%)
Degree of hepato- megaly not stated	2 (1.8%)	2 (5.2%)	None

TABLE XIV

DEGREE OF SPLENOMEGALY

Cm. below Right Costal Margin	No. in Total Necropsy Group of 112 Cases	Group A	Group B
		No. without Hodgkin's Disease in Liver in 38 Cases	No. with Hodgkin's Disease in Liver in 74 Cases
Tip palpable only	10 (8.9%)	5 (13.2%)	5 (6.8%)
1-1.99	8 (7.1%)	None	8 (10.8%)
2-2.99	7 (6.2%)	2 (5.3%)	5 (6.8%)
3-3.99	10 (8.9%)	4 (10.5%)	6 (8.1%)
4-4.99	10 (8.9%)	3 (7.9%)	7 (9.5%)
5-5.99	5 (4.5%)	None	5 (6.8%)
6-6.99	3 (2.7%)	None	3 (4.0%)
7-7.99	3 (2.7%)	None	3 (4.0%)
8 or more	4 (3.6%)	3 (7.9%)	1 (1.4%)
Below pelvic rim	3 (2.7%)	None	3 (4.0%)
No clinical splenomegaly	49 (43.8%)	21 (55.2%)	28 (37.8%)

hepatomegaly or splenomegaly. Splenomegaly was found more commonly in males than females in this series ($P=0.01$). Clinical hepatomegaly was absent in 23 cases (20.4%) and splenomegaly was absent in 49 cases (43.8%), while 15 cases (13.4%) had neither enlarged spleen nor liver and five cases (4.5%) presented with a palpable spleen but not a palpable liver. There was no good correlation between the size of the liver or spleen estimated by palpation and the size found at necropsy. In no instance were nodules felt clinically in the liver. Scout films of the abdomen were helpful in assessing

TABLE XV

RELATION OF CLINICAL SPLENOMEGALY AND SEX

Total Necropsy Series	Males	Females	Ratio Males/Females
Number of cases without splenomegaly	24 (49.0%)	25 (51.0%)	0.96
Number of cases with splenomegaly	45 (71.5%)	18 (28.6%)	2.5
Total	69 (61.5%)	43 (38.4%)	1.6

The difference in sex distribution between the cases with splenomegaly and the cases without splenomegaly is significant ($P=0.01$).

the size of the liver and spleen. Radiological enlargement of the liver was noted in eight cases (7.1%) in which it was not detected clinically. In like manner, radiological enlargement of the spleen was found in six cases (5.4%) without clinically palpable splenomegaly.

Liver biopsy was performed in three cases (2.8%). The biopsy findings are compared with the final anatomical diagnosis of the liver involvement at necropsy in Table XVI. No mortality or morbidity resulted from the procedure.

TABLE XVI

COMPARISON BETWEEN LIVER PATHOLOGY AS SEEN ON
LIVER BIOPSY SPECIMENS AND AT NECROPSY

<i>Findings on Liver Biopsy</i>	<i>Findings at Necropsy</i>
Miliary necrotizing hepatic granulomatous lesions ? Tuberculosis	Hodgkin's granuloma of the liver
Pericholangiolitic inflammation	Cholangitic obstruction of hepatic duct by Hodgkin's disease
Fibrosis	Hodgkin's granuloma with marked fibrosis

The five-year survival from onset of the diagnosis of Hodgkin's disease in the total series (112 cases) was 19.6% and the 10-year survival was 4.5%. No difference was noted between Groups A and B.

DISCUSSION

This retrospective analysis of necropsy material and correlation with clinical data is the only method currently available to assemble complete and detailed information on liver involvement in Hodgkin's disease. Nevertheless, keeping in mind the limitations imposed by the statistical bias of a retrospective study, and the fact that pathological findings at death may not reflect the dynamic changes occurring earlier in the course of the disease, we may acquire an appreciation of the problems encountered in making a precise diagnosis of liver disease, and the nature of the hepatic lesions involved, in patients with Hodgkin's disease.

The several types of Hodgkin's lesions of the liver encountered in this series confirm descriptions by other observers in all important respects (Coronini, 1928; Foulon, 1932; Gruber, 1930; Jackson and Parker, 1947; Simonds, 1926). Diffuse involvement of both lobes of the liver was most common, but the left lobe appeared more extensively involved in cases with associated Hodgkin's disease of the gastrointestinal tract. Nodular lesions were uncommon and, in this series, were seen only with granuloma. Although Hodgkin's sarcoma was found in only 4.4% of the diagnostic biopsy material, it

was found in the liver in 24.3% of the 74 cases of hepatic Hodgkin's disease and in 21.5% of the entire necropsy series, illustrating the fact that Hodgkin's granuloma may change to sarcoma during the course of the process. This conversion took place in 19 instances. No significant difference was found between Hodgkin's sarcoma and Hodgkin's granuloma in the frequency of liver involvement.

The involvement of the liver, when present, was much more extensive in the case of Hodgkin's sarcoma than in granuloma and was characterized by massive invasion, blood vessel invasion, and marked atrophy or necrosis in the normal tissue adjacent to the lesions. In the case of Hodgkin's granuloma, on the other hand, diffuse fibrosis of a degree so marked as to obscure the underlying process was encountered.

The frequent occurrence of other liver pathology, particularly passive congestion, fatty metamorphosis, and haemosiderosis, in all cases of Hodgkin's disease with or without direct involvement of the liver by the primary process, is a striking and important finding. Passive congestion occurred less frequently in livers directly involved with Hodgkin's disease ($P=0.05$), suggesting that it was unrelated to intra-hepatic invasion by Hodgkin's disease. No significant difference was found between the several other categories of hepatic abnormality in relation to the presence or absence of direct involvement by Hodgkin's disease. There is no evidence, therefore, to permit any conclusions regarding local factors predisposing the liver to involvement with Hodgkin's disease.

Passive congestion of the liver, which appeared to be a terminal event in a few instances secondary to congestive heart failure or portal hypertension, was not explicable in most instances by such mechanisms.

The presence of fatty metamorphosis of the liver in an unusually high incidence (20.5%) suggests the operation of nutritional, metabolic or toxic factors, or all three, as well as anoxia (Popper and Schaffner, 1957). All four of these mechanisms are readily demonstrated or deduced to be present in patients with advanced Hodgkin's disease. The presence of pathological changes in the pancreas in 36.6% of the cases (Hodgkin's disease 23.2%, other diseases 13.4%) may have contributed to the development of fatty liver as well (Woldman, Fishman, and Segal, 1959).

All patients with haemosiderosis of the liver (13.4%) presented with anaemia, with or without haemolysis, and had received numerous blood transfusions during life. They probably represented, therefore, secondary haemosiderosis.

In the present series, hepatic involvement with Hodgkin's disease appeared to be part of the generalized process, as has been previously maintained (Craver, 1957; Hoster *et al.*, 1948), and in no instance was Hodgkin's disease limited to the liver alone, as reported in a few cases (Goia, 1935; Symmers, 1944). Extrahepatic biliary pathology due to Hodgkin's disease was more frequent in cases with associated liver involvement ($P=0.05$), suggesting that the portal areas provide a preferred channel for direct dissemination of the process.

The spleen was involved by Hodgkin's disease in 78.4% of the cases with hepatic Hodgkin's disease. Other pathological changes were encountered in the spleen in 18.9%, and normal spleens were observed in only 2.7% of patients with liver involvement. This series confirms the conclusion that '...seldom can the liver be involved and the spleen not' (Ziegler, 1911).

Occlusion of the portal or hepatic vein by associated thrombosis, direct tumour compression or blood vessel invasion (7.2% of this series) must be considered in the differential diagnosis of the onset of ascites, jaundice, or liver enlargement in patients with hepatic involvement with Hodgkin's disease.

The incidence of liver involvement by Hodgkin's disease is somewhat higher (80%) in the necropsy series than reported by others (Table I), an expected finding in view of the method of selection of the material.

The sex distribution of patients with Hodgkin's disease of the liver did not differ significantly from the cases without liver involvement or from the expected sex distribution in Hodgkin's disease at large (Diamond, 1958c; Gall and Mallory, 1942; U.S. Department of Health, Education and Welfare, 1958; Wallhauser, 1933). This is in contrast to the report of Abbattucci and Beatty (1953) that males more frequently exhibited hepatic involvement than could be anticipated on the sex distribution of Hodgkin's disease in general. A critical analysis of the data on which their conclusion was based (31 males and 13 females with liver involvement and 29 males and 19 females without liver involvement in a total series of 82 cases) by the corrected χ^2 test (Yates) (Hill, 1955) reveals no significant difference from the sex distribution of a number of series of cases of generalized Hodgkin's disease (Diamond, 1958b; Gall, 1956; U.S. Dept. of Health, Education and Welfare, 1958; Wallhauser, 1933). There is no basis, therefore, for assuming a hormonal influence on the frequency of hepatic involvement with Hodgkin's disease.

Massive hepatomegaly, with the liver edge below the pelvic brim, was seen in 8.9% of the necropsy

series, an exception to the statement that marked hepatomegaly is uncommon or rare in Hodgkin's disease (Chevallier and Bernard, 1932; Ziegler, 1911). In all cases with massive hepatic enlargement, Hodgkin's disease was found in the liver at necropsy. Sixty-eight per cent of our series exhibited lesser degrees of hepatomegaly, however, and within this group only 52% had Hodgkin's disease involving the liver directly. However, in those cases without clinical evidence of hepatomegaly (20.4% of the necropsy series), Hodgkin's disease was found in 60.8%. It would appear, therefore, that with the exception of massive hepatomegaly, there is no good correlation between hepatic enlargement and the presence of Hodgkin's disease in the liver. This may be due, in part, to the lack of correlation between clinical hepatomegaly in life and hepatic weight at necropsy, an observation made with respect to other disease as well and considered to be due to differences in blood content of the organ in life and after death (Schiff, 1957).

Although it is stated that massive hepatomegaly in Hodgkin's disease is almost always associated with massive splenomegaly (Chevallier and Bernard, 1932; Craver, 1957), no good correlation was noted in the present series between the degree of hepatomegaly and the presence or degree of associated splenomegaly. Indeed, splenomegaly was absent in 30.4% of the cases with hepatomegaly in this series. As with the liver, there was no good correlation between the clinical estimate of splenomegaly and the size of the spleen at necropsy, or between the size of the spleen and the presence of Hodgkin's disease within the spleen.

Splenomegaly was encountered more frequently in males than females both in the necropsy series ($P=0.01$) and in a larger series of 300 cases of Hodgkin's disease with clinical evidence of liver disease. Such an observation has not been previously recorded but its significance is obscure.

It is clear from this series that hepatomegaly can occur early in the course of Hodgkin's disease and is not limited to the terminal stages as claimed by some (Ackerman and del Regato, 1954). A comparison of the duration of life from the time of diagnosis of Hodgkin's disease with, and without, hepatomegaly reveals no significant difference. The five- and 10-year survival in our series did not differ statistically from a series of 713 cases reported by Diamond (1958b) from the Memorial Center, in which survival was calculated from the first hospital visit rather than from the time of diagnosis of Hodgkin's disease. Although the interval from the first hospital visit to death is not identical with the interval from diagnosis to death, the difference was small generally and could not significantly influence

the five- and 10-year survival time. Survival in Diamond's series was 19.5% at five years and 7.2% at 10 years in comparison with 19.6% and 4.5% respectively in this series.

It is noteworthy that, despite the fact that all the patients in our series had liver abnormalities, only three patients (2.8%) died in hepatic coma, two as the result of intercurrent viral hepatitis and only one directly attributable to Hodgkin's disease of the liver.

Liver disease becomes suspect in the patient with Hodgkin's disease by the usual clinical (or radiological) criteria of liver enlargement, jaundice, ascites, peripheral oedema, or abnormal liver function tests. Among the liver function tests, the most useful, in order of frequency of abnormal findings, were bromosulphalein (BSP) retention, prothrombin time, total protein, serum albumin, alkaline phosphatase, cephalin flocculation, serum bilirubin, and thymol turbidity. However, since the incidence of specific abnormalities and clinical signs did not differ significantly in those patients with Hodgkin's disease of the liver from those with other forms of liver disease, these tests fail to distinguish the two groups, findings in agreement with those of other authors (Abbattucci and Beatty, 1953; Sherlock, 1955). Only those patients with massive hepatomegaly (below the pelvic brim) had uniform involvement with Hodgkin's disease, suggesting that this degree of hepatic enlargement is of clinical value in evaluating the state of the liver.

Liver biopsy was performed too infrequently (2.8%) in the present series to permit evaluation of its importance. Haemorrhagic tendencies, a not uncommon manifestation of advanced Hodgkin's disease, particularly after various forms of therapy, prohibited the use of liver biopsy in many instances.

The difficulty in establishing a correct and precise clinical diagnosis of liver pathology in Hodgkin's disease is clearly due to the multiplicity of type of lesions that may be encountered at the same time within the liver and the biliary tree in any one case. The correct diagnosis, however, is not simply of academic interest, particularly in those instances in which choledocholithiasis, hepatitis, cirrhosis, or bacterial infections were present. Radiotherapy or chemotherapy, in such instances, may further complicate the problem. On the other hand, it is equally poor care to withhold specific therapy in the patient who is jaundiced because of tumorous lymph nodes obstructing the extrahepatic bile ducts, where radiotherapy may offer palliation of the very disturbing pruritus (Levitan *et al.*, 1961). Furthermore, any evaluation of the efficacy of a method of therapy for Hodgkin's disease of the liver is obviously impossible without a correct diagnosis at the onset

of therapy. Therefore, every effort should be made to establish, in detail, the cause of liver disease before the institution of therapy in the patient with Hodgkin's disease. A high index of suspicion of the possibility of unrelated liver disease in the patient with established diagnosis of Hodgkin's disease, combined with full utilization of liver function tests, liver biopsy (when feasible), intravenous cholangiography, and/or lienoportography (when feasible) may contribute to a more accurate ante-mortem diagnosis. Evaluation of new diagnostic tests, such as serum iron and serum B₁₂ determinations, and enzyme assays (Grossowicz, Hochman, Aronovitch, Izak, and Rachmilewitz, 1957), and radio-tracer scanning of the liver (Friedell, MacIntyre, and Rejali, 1957) may uncover important clues leading to improved diagnosis. Serial liver function tests or serial liver biopsies may contribute greatly to our understanding of the relationship between Hodgkin's disease and intercurrent liver disease as a dynamic process.

SUMMARY

Three hundred (34.3%) of 875 patients with histologically proven Hodgkin's disease had clinical evidence of associated liver disease. One hundred and twelve cases of the 300 (37%) were subject to necropsy and critical clinical and pathological study. In the necropsy series, 66% had direct involvement of the liver with Hodgkin's disease, and 34% exhibited other pathology in the liver.

Seventy-nine per cent of the patients with Hodgkin's disease of the liver also had other pathological changes in this organ, and 32.4% had biliary tract disease as well.

Diffuse involvement of the liver by Hodgkin's disease was the most common type of intrahepatic distribution (86.5%), whereas discrete nodular lesions were found in only 10.8% and the combined diffuse and nodular type was encountered in only 2.7%.

Hodgkin's granuloma was most frequently localized to the portal triads and was not seen invading the blood vessels.

Hodgkin's sarcoma tended to involve the liver in a more diffuse and extensive manner and frequently invaded the blood vessels.

The larger bile ducts were invaded or compressed by Hodgkin's granuloma or sarcoma in 21.8% of the cases with liver involvement.

In patients free of Hodgkin's disease in the liver itself but with histological evidence of Hodgkin's disease elsewhere, pathological changes of some kind were found in all livers. Some combination of

chronic passive congestion, fatty metamorphosis, or haemosiderosis was encountered in 50% of such cases; biliary tree pathology due to Hodgkin's disease in 10.5%; and unrelated biliary tree pathology in 6.2%. Statistical analysis of the incidence of hepatic changes indicated no significant correlation of these findings with the presence or absence of direct involvement of the liver by Hodgkin's disease.

Despite the almost uniform finding of liver pathology in patients with Hodgkin's disease in this series, only 2.8% of the patients died as a consequence of clinical liver failure, one attributable to Hodgkin's disease directly and two to intercurrent hepatitis.

The five- and 10-year survival rate in this series, selected on the basis of clinical evidence of hepatic disease, did not differ significantly from the survival rate of Hodgkin's disease in general as encountered at Memorial Hospital. The presence or absence of hepatomegaly, the degree of hepatomegaly, splenomegaly, and sex did not significantly influence survival.

At the present time, on the basis of clinical findings and currently available liver function tests, it is impossible to distinguish reliably between liver disease due to Hodgkin's disease itself and that due to associated hepatic changes. Perhaps the only reliable sign of direct involvement of the liver in the Hodgkin's process is the enlargement of the liver below the pelvic brim.

Statistical analysis of the sex distribution of involvement with Hodgkin's disease failed to confirm a previous report of predilection of males to hepatic Hodgkin's disease. By similar statistical criteria, however, splenic involvement with Hodgkin's disease was more frequent, in our series, than the anticipated incidence. The significance of this observation is obscure.

Clinical hepatomegaly was encountered in 79.5% of the necropsied series of patients with Hodgkin's disease selected on the basis of evidence of liver disease, and it was seen relatively early, in some instances, in the course of the Hodgkin's process.

It is concluded that hepatic involvement by Hodgkin's disease is but one manifestation of a generalized disease process, that it carries no prognostic significance for survival, that it may occur early or late, and that it is frequently associated with one or more abnormalities of liver structure which may be unrelated to Hodgkin's disease. With the single exception of massive hepatomegaly, no clinical sign establishes the presence of the Hodgkin's process within the liver itself, and liver biopsy, the only currently available test capable of the definitive diagnosis of hepatic Hodgkin's disease, is often interdicted by complicating factors.

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