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Pathology of Hepatic Transplantation

A Review of 62 Adult Allograft Recipients Immunosuppressed With a Cyclosporine/Steroid Regimen

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The pathologic specimens (n = 118) and hospital course pertinent to each of 62 adult liver allograft recipients were reviewed. Biopsies and retransplanted organs were obtained at the discretion of the surgical team on the basis of the postoperative clinical course (<1 day to >12 years after transplantation), and final interpretation of the pathologic material was based on a correlation of all available data. Most of the specimens (n = 85) were obtained within the first 2 months, and diagnoses in this time period included rejection, biliary obstruction/cholangitis, vascular injury, herpesvirus and cytomegalovirus hepatitis, graft necrosis, and functional cholestasis. Thereafter, rejection and recurrent or primary viral hepatitis were the

major causes of graft dysfunction. Histologically, hepatic rejection is manifested by a cellular mediated injury of hepatocytes and bile ductules and a spectrum of vascular lesions in medium-sized hilar arteries. Morphologic changes of biliary duct obstruction and viral liver disease were at times difficult to differentiate from rejection. Two pretransplant disorders, type B viral hepatitis and the Budd-Chiari syndrome, recurred in grafted organs. Although interpretation of pathologic material may be difficult at times, it frequently is helpful in planning an approach to management of liver allograft recipients. (Am J Pathol 1985, 118:151-161)

RECOGNITION of rejection and other hepatic complications by needle biopsy can play a significant role in the management of liver allograft recipients.¹⁻³ Clinically, the diagnosis of rejection is difficult and is often made by the exclusion of other causes of graft dysfunction. Discrepancies exist, however, in the histologic description of rejection, particularly in reference to the appearance of acute and chronic forms and the extent of involvement of small interlobular bile ductules.^{1-5,9,10} Moreover, description of other hepatic complications⁶⁻¹⁰ and recurrent disease^{8,11} is limited.

The following is a review of hepatic pathology in 62 adult liver allograft recipients maintained on cyclosporine/steroid immunosuppression. The report is based upon a review of all the needle biopsies, failed allografts, and autopsy specimens from these patients. The histologic recognition of rejection and its separation from other hepatic complications and recurrent disease is discussed and correlated with the clinical data.

Materials and Methods

Case Selection

Patients were selected on the basis that at least one posttransplant liver specimen were available for pathologic review. The population consisted of 30 males and 32 females with an average age of 33 years (range, 16-58 years) who underwent transplants from 1972 to 1981 at Denver (4 patients) and from 1981 to the present at the University of Pittsburgh (58 patients).

Accepted for publication August 23, 1984.

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Table 1—Summary of Histologic Findings in Specimens With Rejection

	<2 Months post-Tx* (%)	>2 Months post-Tx* (%)
Total specimens	21 (100)	15 (100)
Portal inflammation	Moderate-severe (100)	Mild-Moderate (100)
Disruption of limiting plate	5 (24)	11 (73)
Bile ductular injury†	9 (43)	12 (80)
Centrilobular necrosis	18 (86)	7 (47)
Centrilobular inflammation‡	19 (90)	7 (47)
Cholestasis	Moderate (100)	Mild-Moderate (73)§

* After transplantation.

† Paranuclear vacuolization, cytoplasmic eosinophilia, nuclear pyknosis, inflammatory-cell infiltration, or loss of bile ductules.

‡ Large lymphocytes in the center of the lobule and/or infiltrating the subendothelial space of terminal hepatic (central) veins.

§ The remaining specimens had minimal or no cholestasis.

Pathologic Material and Review

A total of 118 specimens were reviewed, which included 71 needle biopsies, 26 surgically removed allografts, and 21 autopsies. Surgical specimens ranging from less than 30 minutes to greater than 12 years after transplantation were obtained at the discretion of the surgical team. All slides were routinely stained with hematoxylin and eosin (H&E), reticulin, and trichrome. Special stains were utilized when appropriate and included orcein, rhodamine, iron, elastin, and the immunoperoxidase technique¹² for hepatitis B surface and core antigen and herpes simplex. The slides were reviewed once blindly and a second time with clinical information available.

Clinical Review and Final Diagnosis

Hospital charts were reviewed; and the hospital course pertinent to each specimen, including radiographic, endoscopic, and surgical procedures, along with laboratory data, medications, and clinical impressions, was recorded. A final diagnosis for each specimen was made after a correlative review of both the pathologic and clinical material.

Operative Procedure and Immunosuppression

All operative procedures were orthotopic allograft transplantations with end-to-end vascular anastomosis of all pre- and post-hepatic vessels. The majority of the biliary anastomoses were choledochocholedochostomies or Roux-en-Y choledochojejunostomies, both with donor cholecystectomy.

The immunosuppression protocol in 58 of the 62 patients studied consisted of a loading dose of cyclosporine (17.5 mg/kg/day) given just prior to surgery, fol-

lowed by a maintenance dose of 10 mg/kg/day. This was combined with steroids at an initial dose of 200 mg/day prednisone, which was tapered rapidly to 40 mg/day and then gradually to a maintenance dose of 10–20 mg/day. Suspected rejection was treated with supplemental steroids generally given as a 1-g bolus of Solu-cortef (Upjohn) on alternate days.

Results

Histopathology

Rejection

Rejection was the primary process in 36 of the 118 specimens examined. This diagnosis was never made before 6–7 days after transplantation, occurred commonly within the first 2 months, but could be seen any time thereafter. In early (less than 2 months) episodes of rejection (see Table 1), a moderate to severe inflammatory infiltrate expanded the portal tracts (Figure 1a). It consisted of large and plasmacytoid lymphocytes with occasional mitotic figures, macrophages, and small lymphocytes with fewer polymorphonuclear leukocytes and eosinophils. These cells occasionally spilled into the periphery of the lobule and were associated with periportal hepatocyte necrosis (5 of 21 specimens). Inflammatory cells were also seen in and around the central veins (19 of 21 specimens) and to a much lesser degree permeating through the sinusoids and space of Disse. Branches of the portal veins within the portal tracts contained subendothelial inflammatory cells and frequently had a hyperplastic and focally disrupted endothelium (Figure 1b). Fibrin in the portal tracts was frequently deposited in a concentric fashion around the veins. Small bile ductules generally showed hyperplastic changes; however, ductular cell damage as evidenced by inflammatory-cell infiltration, paranuclear vacuolization, nuclear pyknosis, cytoplasmic eosinophilia, mitoses, dysplasia, or luminal disruption was present in 9 of 21 specimens (Figure 1d). Changes in the small arterioles included intimal sclerosis and hyperplasia, thickening, and eosinophilia, evaluation of which was quite subjective. Alterations in the terminal hepatic (central) veins (Figure 1c) were identical to those described for portal veins except for the degree of inflammation, which was generally less. A moderate degree of canalicular and hepatocellular bile stasis was present in Zone 3 and occasionally also in Zone 2 (of Rappaport) in all specimens with rejection (less than 2 months). These changes were accompanied by varying degrees of centrilobular necrosis (18 of 21), reticulin collapse with central-to-central linkage (2 of 21) (Figure 1e), centrilobular inflammation (19 of 21 specimens) similar in nature to that present in portal tracts, and hemorrhage. In more severe examples (2 specimens) the

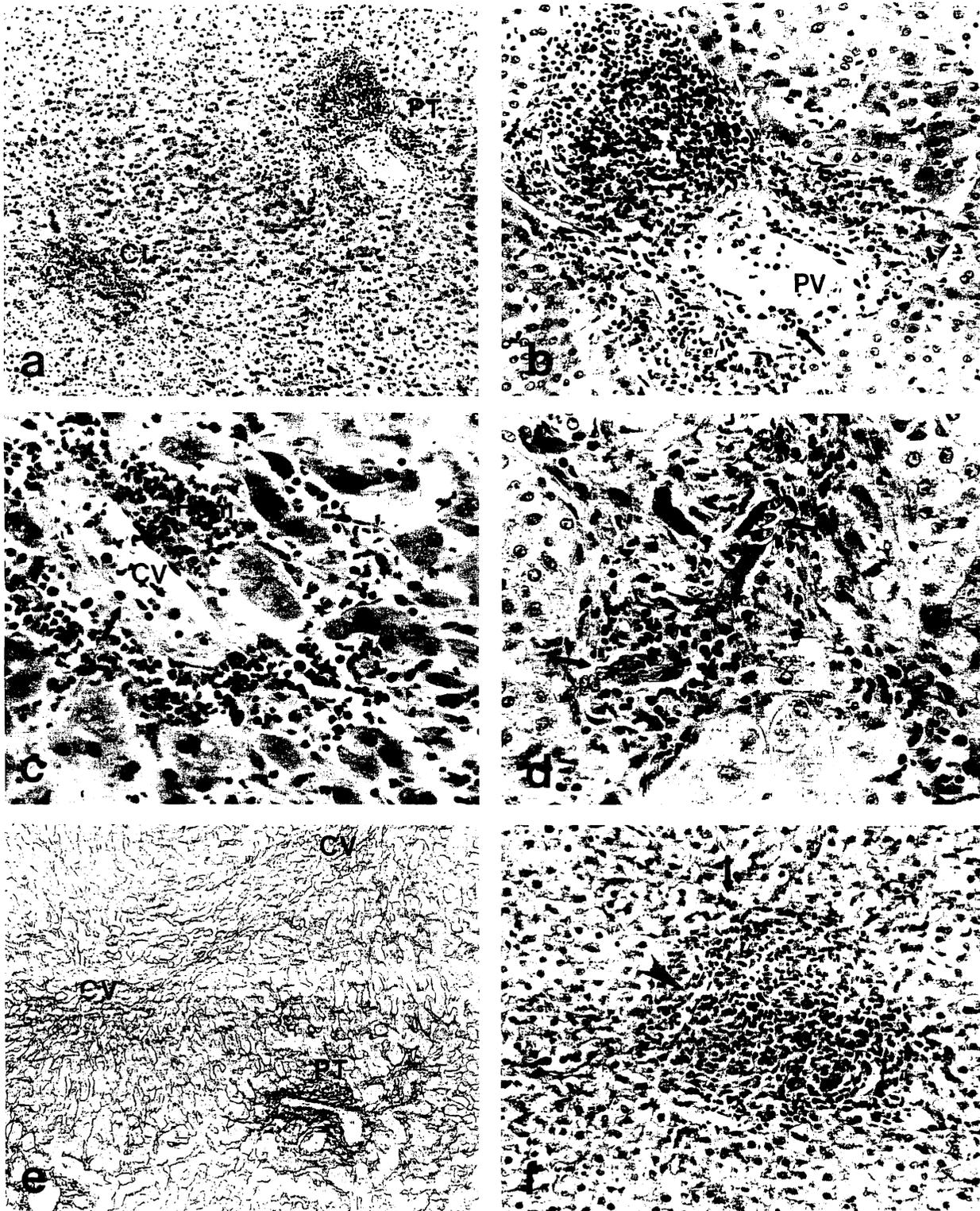


Figure 1 — Rejection. **a** — Retransplant specimen from OLT 310, 58 days after transplantation. Note the prominent inflammatory infiltrate in the portal tract (PT) and centrilobular region (CL). (H&E, $\times 100$) **b** — High-power photograph of the portal tract from **a**. Note the infiltration of the portal vein (PV) by inflammatory (arrow) cells and diffuse portal infiltrate obscuring bile ductules. (H&E, $\times 250$) **c** — High-power photograph of centrilobular region from **a**. Note the subendothelial inflammatory cells (arrow) in the central vein (CV) and hemorrhage (Hem). (H&E, $\times 250$) **d** — Retransplant specimen from OLT 225, 19 days after transplantation. Note the inflammatory-cell infiltration and disruption of the bile ductular lumen and changes indicative of biliary epithelial cell damage (arrows). (H&E, $\times 250$) **e** — Retransplant specimen from OLT 339, 9 days after transplantation. Note the centrilobular reticulin collapse with central-to-central bridging. (Reticulin stain, $\times 100$) **f** — Needle biopsy specimen from OLT 181, 1 year after transplantation showing diffuse portal tract inflammation with spillover into lobule (small arrow) and lack of recognizable bile ductules. The portal vein contains subendothelial inflammatory cells (large arrow). (H&E, $\times 250$)

inflammatory infiltrate increased in intensity and in the relative number of polymorphonuclear leukocytes. In addition, in these 2 cases of severe rejection, bile ductular cell proliferation was more prominent, as well as centrilobular necrosis, hemorrhage, and reticulin collapse. As the rejection episode abated, as a consequence of bolstered immunosuppression, the inflammatory infiltrate subsided, leaving a mild residual thickening of the portal and terminal hepatic (central) veins and a mild to moderate degree of centrilobular cholestasis and portal fibrosis.

Early rejection episodes (within the first 2 months) appeared to have the most intense inflammatory infiltrate, whereas subsequent episodes (greater than 2 months after transplant) were generally less severe but on occasion could also be quite severe. Although similar in composition, the inflammatory infiltrate in cases of rejection greater than 2 months appeared less intense in portal tracts and frequently was absent from the centrilobular areas. Specimens obtained later than 2 months after transplantation (Figure 1f) were also characterized by the presence of more prevalent disruption of the limiting plate (11 of 15 specimens), bile ductular injury (12 of 15), and centrilobular hepatocellular atrophy. Cholestasis and centrilobular necrosis (7 of 15 specimens) were much less prevalent. This histologic appearance was similar to that seen in chronic persistent or active liver disease. In these particular specimens immunoperoxidase studies for hepatitis B-related antigens were performed and found to be negative, which ruled out primary or recurrent B viral infection. Bile ductular damage and venous subendothelial infiltration were prominent in these specimens. Moreover, several of the patients with this change had a prompt biopsy-proven-histopathologic response to bolstered immunosuppression. A summary of these histologic findings is shown in Table 1.

In patients experiencing several episodes of rejection, over a period of time there was a decrease in the number of small interlobular bile ductules (5 patients). Although this finding was focal and nonquantitative, it was commonly associated with a remarkably high serum level of gammaglutamyl transpeptidase (GGTP) in the absence of clinically documented large-duct obstruction.

Arterial Alterations in Rejection

The arterial lesions of rejection (Figure 2a-d) were most recognizable in medium-sized hilar arteries and therefore better appreciated in retransplant and autopsy specimens than in biopsy specimens. Acute arterial lesions were seen within the first 2 months after transplantation and included inflammatory-cell infiltration

(vasculitis) consisting of lymphocytes and macrophages with disruption of the elastic lamina and fibrinoid necrosis.

Chronic arterial lesions were seen usually later than 4 months after transplantation and included deposition of subintimal foam cells, intimal sclerosis, and myointimal hyperplasia. These alterations often led to significant narrowing or complete occlusion of these arteries. A summary of the vascular lesions is presented in Table 2.

Two of the 36 specimens with rejection (11 and 144 months after transplantation) had significant chronic arterial lesions and only a mild to moderate parenchymal inflammatory infiltrate. Usually, however, both arterial and parenchymal lesions were present simultaneously.

One liver removed 12 years after transplantation had significant narrowing of the hepatic arteries secondary to subintimal foam cells and myointimal hyperplasia (Figure 2d). There was only a scant inflammatory infiltrate in the portal tracts. Terminal hepatic (central) and portal veins were mildly thickened, and in addition there was subsinusoidal and moderate portal fibrosis indicative of earlier rejection episodes. Portal-to-portal and portal-to-central linkage by thin fibrous bands associated with an intralobular regenerative nodularity was also present. Many portal tracts were entirely devoid of small bile ductules, and curiously some of these same portal tracts were free of inflammation. Centrilobular hepatocytes were atrophic, which resulted in an apparent widening of the sinusoids. Foam cells similar to those seen in the hilar arteries were present (occasionally in small clusters) within the sinusoids. As indicated above, the changes noted in the small interlobular portal arterioles were rather subjective and consisted of intimal sclerosis and medial thickening with eosinophilia, findings which may not be reliable for the diagnosis of chronic vascular lesions of rejection in the absence of clinical data ruling out other causes for graft injury or failure.

Viral Liver Disease

There were 2 cases of recurrent type B viral hepatitis, with one leading to cirrhosis. The histologic appearance of viral hepatitis in this setting (Figure 3a) was not dissimilar to that seen in nonallograft livers and was characterized by a greater degree of lobular disarray, hepatocyte ballooning, and individual hepatocyte necrosis throughout the lobule when compared with those in which rejection was the primary process. In addition, the inflammatory infiltrate in these cases of recurrent viral disease appeared to extend a greater distance from portal tracts into the lobule and to surround individual or clusters of hepatocytes (i.e., piecemeal

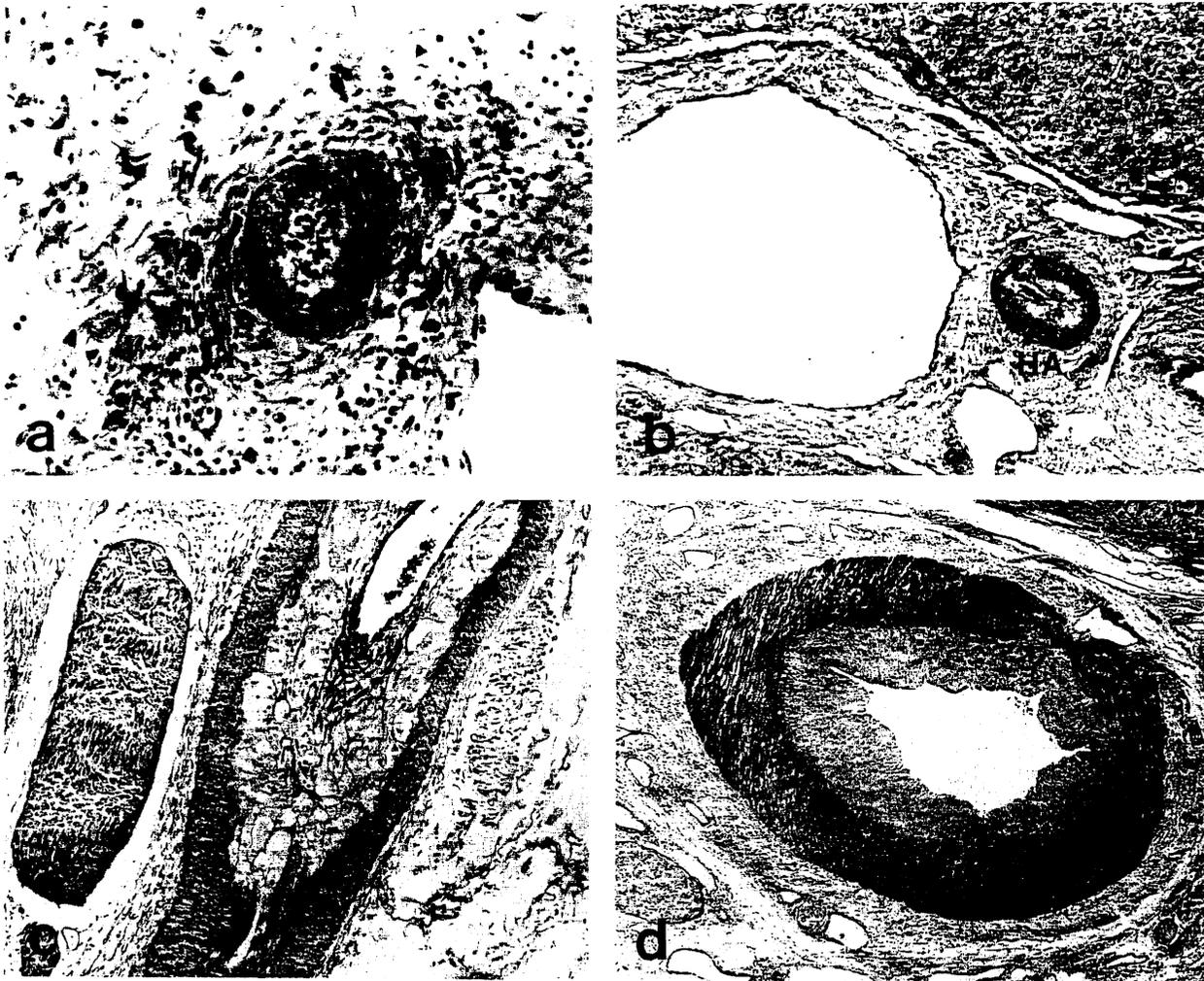


Figure 2—Vascular alterations of rejection. **a**—Retransplant specimen from OLT 31, 58 days after transplantation showing fibrinoid necrosis of medium-sized hilar artery. (H&E, $\times 250$) **b**—Retransplant specimen from OLT 212, 8 months after transplantation, showing a thickened branch of hepatic artery (HA) with deposition of foam cells in media. (H&E, $\times 100$) **c**—Same specimen as in **b** showing subintimal foam cells narrowing a hilar artery. (H&E, $\times 100$) **d**—Retransplant specimen from OLT 56, 12 years after transplantation, showing myointimal hyperplasia of the hilar artery.

necrosis) and contained fewer large lymphocytes. Conversely, inflammatory cell infiltration and disruption of the venous subendothelium and bile ductular destruction was much less conspicuous. All diagnoses of recurrent viral disease were confirmed by the immunoperoxidase technique for core (HBcAg) and/or surface (HGsAg) antigens.

There was one case of herpes simplex Type I hepatitis characterized by well-demarcated areas of confluent necrosis which was not confined to the limits of the lobular architecture. These areas contained nuclear Cowdry type A inclusions, multinucleated giant cells and an inflammatory cell infiltrate with abundant polymorphonuclear leukocytes.

Four cases of cytomegalovirus (CMV) hepatitis were seen, and two patterns of hepatic involvement were noted. In the first, small collections (microabscesses or microgranuloma) of inflammatory cells (predominantly polymorphonuclear leukocytes or a mixed infiltrate) were present randomly throughout the lobule, some of which surrounded hepatocytes containing nuclear and/or cytoplasmic inclusions typical of CMV (Figure 3b). The portal areas of these same livers were relatively free of inflammatory cells, therefore providing little evidence for the presence of coexistent rejection. The second pattern of CMV involvement was much more extensive, with numerous inclusion-bearing cells, which were noted predominantly in the portal vein en-

Table 2—Summary of Vascular Alterations in Rejection*

	Time after transplant (weeks)									
	1-4		4-8		8-26		26-52		>52	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total number retransplanted livers with rejection	6	100	6	100	3	100	1	100	2	100
Subintimal foam cells	4	67†	4	67†	3	100	1	100	2	100
Fibrinoid necrosis	1	17	2	33	1	33	0	0	0	0
Vasculitis	1	17	2	33	1	33	0	0	0	0
Myointimal hyperplasia	0	0	0	0	0	0	0	0	1	50‡

* Based on retransplant specimens with rejection (n = 18) as the primary process.

† Accumulations were much less than those found in later specimens.

‡ From OLT 56 12 years after transplantation.

dothelium, small bile ductules, and periportal hepatocytes. Although inclusion-bearing cells were distributed randomly throughout the lobule and were often surrounded by inflammatory cells as described above, there also was a prominent lymphocytic infiltrate in the portal tracts and centrilobular regions identical to that seen in rejection (Figure 3c). This latter pattern followed the former in two cases, 3 and 4 days after a decrease of immunosuppressive therapy.

Graft Necrosis

Massive subtotal or total graft necrosis was present in 5 specimens (4 autopsies, 1 surgical retransplant). In only one instance could this finding be attributed to postmortem autolysis. In two of the four others vascular compromise appeared to be the responsible factor. Changes of severe rejection were present in remaining viable liver in the two other cases. Blood and liver cultures from these later two patients were positive for gram-negative organisms. A similar relationship between graft rejection, graft necrosis, and gram-negative infection was reported by Starzl¹³ in the pre-CyA era and has been termed "septic hepatic gangrene."

Functional Cholestasis

There were 8 specimens in which the only histologic finding was moderate to severe centrilobular hepatocellular and canalicular cholestasis. The portal tracts of these livers were relatively free of an inflammatory infiltrate, which suggests cell-mediated injury as an unlikely cause of graft dysfunction. Clinically, all of these patients had a significant elevations of serum bilirubin (30–40% indirect fraction), coagulopathy, and no evidence of large duct obstruction. Medication regimens in these patients were not significantly different from the others, and response to bolstered immunosuppression was disappointing.

Biliary Obstruction, Cholangitis, and Vascular Injury

Hepatic pathology secondary to biliary obstruction,^{14–16} cholangitis,^{17,18} and hepatic vascular injury^{19,20}

occurred most commonly in the first 1–2 months and were histologically identical to that reported to occur in nonallografts. Septic cholangitis, however, was more frequent in those patients with biliary tract infection prior to transplantation.

Nonspecific Changes

Mild histologic alterations were present in many of the tissue specimens examined to which no specific etiology could be ascribed. These changes included mild portal tract edema, lymphatic and portal vein dilation, Kupffer-cell activation, two-cell-thick hepatic plates, and mild centrilobular cholestasis.

Clinical Pathologic Correlative Review

Causes of graft dysfunction were often difficult to determine from clinical parameters alone, and the diagnosis of rejection was often made by exclusion. Likewise, interpretation based on biopsy histology alone, although somewhat more reliable, was also limited. However, when all available information was considered, etiologic factors could be identified in a large majority of cases. During the early postoperative period (the first 2–3 months) most causes of graft dysfunction were attributable to biliary tract obstruction, cholangitis, vascular insults, and rejection (see Table 3). Pathologically, in this time period biliary tract disorders were at times difficult to differentiate from rejection; therefore for substantiation of the diagnosis, results of studies of biliary tract patency (cholangiography, abdominal ultrasonography, etc.) and bile cultures (when available) were examined.

The differential diagnosis of specimens obtained in later (>2 months) instances of graft dysfunction both clinically and pathologically included recurrent or primary viral liver disease, recurrent original disease, and rejection. Differentiation was particularly difficult when the biopsy showed a chronic active or persistent liver disease histology. In addition to biliary tract studies (above), an arteriogram showing diffuse narrowing of

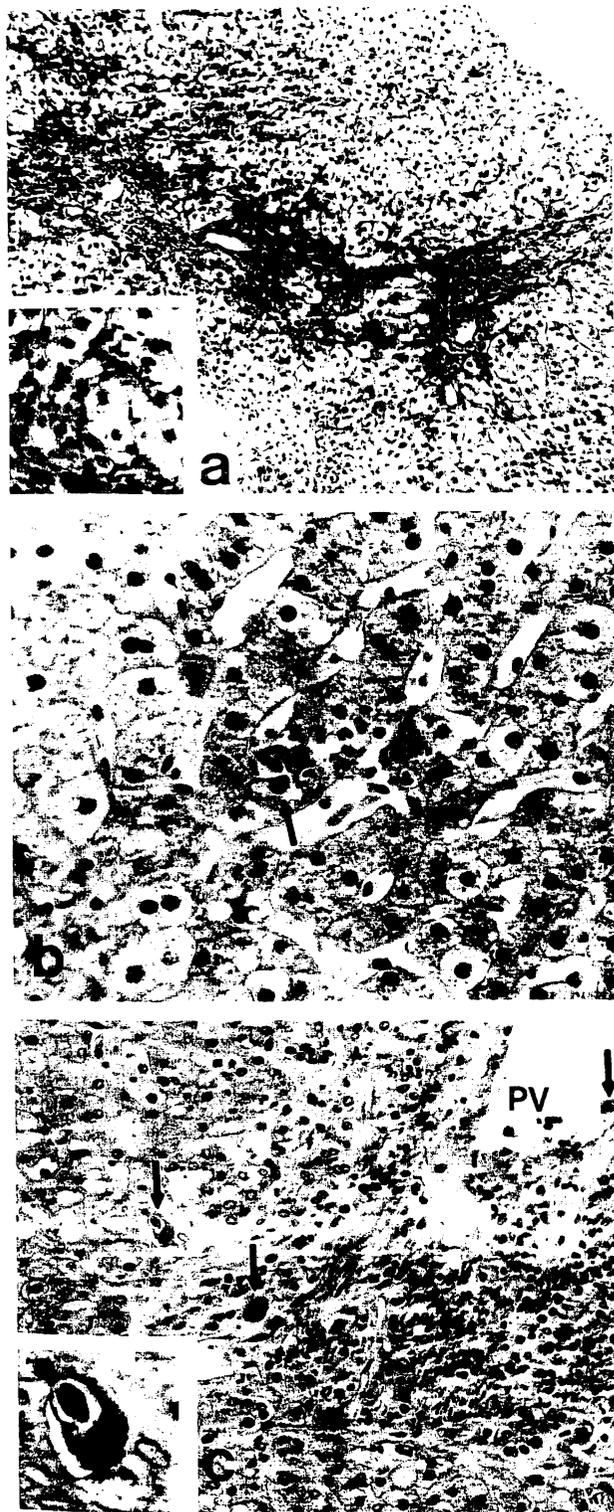


Figure 3—Viral hepatitis. a—Needle biopsy specimen from OLT 195, 10 months after transplantation, with recurrent hepatitis B. Note the ballooning of hepatocytes, lobular "disarray," and extension of infiltrate into the lobule. (H&E, $\times 100$; inset, $\times 250$) b—Needle biopsy specimen from OLT 336, 27 days after transplantation, with CMV hepatitis. Note the few necrotic hepatocytes with inclusions (arrow) surrounded by polymorphonuclear leukocytes. The portal tracts were free of an inflammatory infiltrate. (H&E, $\times 250$) c—

the hepatic arterial tree, negative hepatitis serologic tests negative immunoperoxidase tissue staining (viral antigens), significant elevations of GGTP in the absence of large-duct obstruction, careful histologic examination (see histopathology), and prompt response to bolstered immunosuppression were helpful but not absolute distinguishing features of rejection in such cases.

Cause of Graft Failure

Only livers removed at retransplantation were considered as failed grafts. Autopsy specimens were excluded from this analysis because of frequent complicating clinical circumstances surrounding the patient's demise which made determination of graft viability difficult. The causes of graft failure as a function of time after transplantation are shown in Table 4. Most graft failures (20 of 26 specimens) occurred early within the first 2 months following transplantation, and those which were due to technical complications (8 of 26 specimens) occurred within the first 4 weeks. Thereafter, rejection accounted for 11 of the 12 graft failures necessitating retransplantation.

Incidence of Rejection

No precise statement as to the incidence of rejection can be made from this study because pathologic material available for evaluation came from only 62 of the 95 adult patients undergoing transplantation at Pittsburgh, and suspected rejection was treated without liver biopsy in many cases. Nevertheless, in the Pittsburgh experience, in 35 patients sampled, rejection was present to at least some degree in one specimen. Therefore, the lowest estimate for incidence of rejection, if one assumes that rejection did *not* occur in those patients without specimens available for examination, is 35/95, or 37%; the actual incidence is probably much greater.

Recurrence of Primary Disease and Relationship to Rejection

The possibility of recurrent disease following transplantation is an important consideration in evaluating patients for the procedure. As mentioned, this study is limited to patients with pathology specimens, and

Retransplant specimen from OLT 334, 48 days after transplantation after immunosuppressive therapy had been decreased secondary to CMV hepatitis similarly to that in b. Note the numerous CMV inclusions (arrows) and infiltrate of the portal tracts involving portal vein (PV). The terminal hepatic (central) veins showed similar changes identical to those seen in rejection. (H&E, $\times 100$; inset, $\times 450$)

Table 3—Specimen Diagnosis as a Function of Time After Transplantation

Specimen diagnosis	Time after transplantation (weeks)								Total
	<1	1-2	2-4	4-8	8-12	12-26	26-52	>52	
Rejection	1	5	6	8	3	5	4	4	36
CMV/rejection	0	0	0	3	0	0	0	0	3
Obstruction/Cholangitis	4	6	7	4	2	0	0	0	23
Vascular insult	3	1	5	1	3	0	0	1	14
Viral hepatitis (B)	0	0	0	0	0	3	2	1	6
Herpes/CMV hepatitis	0	0	2	2	0	0	0	0	4
Necrosis	0	0	2	2	0	1	0	0	5
Functional cholestasis	2	4	2	0	0	0	0	0	8
Nonspecific changes	9	5	0	1	0	2	1	1	19
Total	19	21	24	21	8	11	7	7	118

the follow-up period is relatively short. Therefore, no definitive conclusions can be drawn. The number of recurrences confirmed pathologically in patients with specific pretransplant disease is shown in Table 5. Only viral hepatitis B (2 cases at 4 and 10 months) both HBsAg and HBeAg positive at the time of transplantation and the Budd-Chiari syndrome (1 case at 15 months after transplantation) were noted to recur.

No instances of recurrent primary biliary cirrhosis (PBC) were documented either clinically or histologically. The average period of follow-up in this unique group of patients was 10 months, the maximum being 18 months. Recurrence of PBC following orthotopic liver transplantation has been previously reported¹¹ in three patients whose features presented after 3 years. Although the histologic appearance of rejection has been compared with that of PBC,^{4,5} no granulomas, lymphoid follicles, or increased deposition of copper-associated proteins was seen in the cases of rejection observed in our patients whose original disease was PBC. Several of these patients had histologic evidence of bile ductular injury, but the histopathologic features were thought to be more representative of rejection than of recurrent PBC.

Likewise, no definite conclusions on the relationship of rejection to pretransplant disease could be made (see Table 5). However, from the data available, it appears that no group (common pretransplant disease) is more likely to experience rejection than another.

Discussion

Rejection in the transplanted liver was not recognized histologically before 6-7 days. It is frequently seen within the first 2 months and is a common early cause of graft failure. Although this is markedly different from that reported earlier by Fennell,^{6,10} many factors have evolved in hepatic transplantation¹³ since that earlier report. These earlier reports^{6,10} were based largely on autopsy studies in which the majority of patients

reported suffered from infections and technical complications. Since then, surgical techniques have improved, decreasing the frequency of technical complications; and cyclosporine has replaced more conventional immunosuppressants, lowering the incidence of infective complications.¹³ Frequently autopsy specimens also have other complicating lesions and may not show rejection which was present days previously and treated with supplemental steroids.

In early episodes (within the first two months) of rejection, the histologic appearance is very similar to that reported in excellent studies by Porter⁹ and may result in residual portal and central venous thickening. Later episodes of rejection may be severe and can occur at any time but are generally associated with a somewhat milder portal and/or lobular inflammatory infiltrate. Disruption of the limiting plate and bile ductular cell injury is more prevalent in these latter specimens. Repeated or ongoing rejection may lead to a decrease of interlobular bile ducts and portal fibrosis but rarely cirrhosis (one case).

Early episodes of rejection may be confused with biliary obstruction and/or cholangitis,²¹⁻²³ while those episodes occurring later are difficult to distinguish from

Table 4—Cause of Graft Failure (Retransplantation) as a Function of Time After Transplantation

Diagnosis	Time after transplantation (weeks)					Total
	1-4	4-8	8-26	26-52	>52	
Rejection	6	4	3*	1†	2†	16
CMV/rejection	0	2	0	0	0	2
Obstruction/cholangitis	5	0	0	0	0	5
Vascular insult	3	0	0	0	0	3
Total	14	6	3	1	2	26

* Two-thirds of these patients had histologic changes identical to those described below.†

† These cases represent those failures attributed to chronic vascular lesions and a paucity of interlobular bile ducts with a mild to moderate portal inflammatory infiltrate.

Table 5 — Pretransplant Disease: Recurrence and Relationship to Rejection

Pretransplantation diagnosis	Number of cases	Number experiencing rejection	Recurrence of primary disease*	Maximum follow-up (months)
Primary biliary cirrhosis	12	10	0†	18
Sclerosing cholangitis	12	6	0‡	12
Nonalcoholic cirrhosis	10	8	0	72
Alpha-1-antitrypsin deficiency	5	2	0	4
Hepatitis B	4	2	2	15
Budd-Chiari syndrome	3	1	1	15
Hepatocellular carcinoma	3	2	0	6
Cholangiolar carcinoma	3	0	0	2
Caroli's disease	3	1	0	144
Hepatic necrosis (toxin)§	2	1	—	—
Congenital biliary hypoplasia	1	0	0	2
Secondary biliary cirrhosis	1	1	0	8
Tyrosinemia/hepatoma	1	0	0	7
Hemangiosarcoma	1	0	0	1
Wilson's disease	1	1	0	2
Total	62	35	3	

* Histologically documented.

† See text.

‡ Four patients with preoperative biliary sepsis developed septic cholangitis postoperatively.

§ Secondary to 2-nitropropane exposure.⁴²

viral liver disease without knowledge of the clinical data. However, infiltration and disruption of the portal and central venous endothelium, prominent bile ductular cell injury, immunoperoxidase studies, and various clinical parameters are helpful distinguishing features of rejection in such cases.

The arterial lesions of rejection may be an important factor in graft failure and are similar to those described in heart and kidney grafts.^{24,25} These lesions are most evident in medium-sized arteries, which are *not* well represented in biopsies. Previous studies^{2,9,10} based on human material have equated the vascular lesions with the presence of subendothelial foam cells, which was the most common finding in this study in such cases. However, as illustrated above, a spectrum of arterial changes may be seen similar to those reported by Porter⁹ in experimental animals. Moreover, because the evaluation of the arterioles is subjective in needle biopsy specimens, such biopsies, may not be a particularly good method for the evaluation of these vascular lesions.

Separation of hepatic rejection into acute and chronic forms may be by convention and somewhat artificial, because any of the lesions attributed to rejection may occur at any time after transplantation. Nevertheless, the more acute lesions are usually seen within the first 2 months, although, as mentioned they may be seen anytime thereafter. The chronic arterial lesions and loss of small interlobular bile ductules associated with a mild to moderate portal infiltrate appears to be a gradual and more indolent or chronic process, somewhat resistant to maintenance immunosuppressive therapy. In many specimens, however, both were present simultaneously.

The lowest estimate for the incidence of hepatic rejection after transplantation was determined to be 37%. Although the actual incidence is probably significantly higher, these findings are appreciably different from those reported by Fennel and Roddy⁶ and Roddy et al.¹⁰

As shown in this study, hepatitis B may occur in transplanted livers either as acute or chronic disease. Although no marker(s) for non-A, non-B (NANB) hepatitis exists, some of the cases in the present study and other reports¹ with "chronic active liver disease" following transplantation may be attributable to this agent(s), rather than rejection. Although a prompt clinical response to supplemental steroids may be indicative of rejection in such cases, we cannot be certain that NANB hepatitis may not do likewise. Herpes simplex and CMV hepatitis can also be a cause of graft dysfunction. The histologic appearance of herpes simplex and the less severe form of CMV hepatitis is similar to that reported in non-liver-allograft patients.²⁶⁻²⁸ However, the deterioration of graft function with a transition from the less to more severe CMV hepatitis after a *decrease* in immunosuppressive therapy is an interesting initial observation. Whether the deterioration is due to 1) CMV alone because of delayed effects of immunosuppression and/or 2) enhanced viral replication^{29,30} secondary to a simultaneous acute rejection episode is uncertain. However, both clinically and histologically, coexistent rejection appears to have been a significant factor in these two cases. The suggestion of a relationship between an exacerbation of CMV infection and allograft rejection episodes has been raised for other organ recipients.³¹

Pathologically documented recurrent primary disorders observed in this study included type B viral hep-

atitis and the Budd–Chiari syndrome. No cases of recurrent primary biliary cirrhosis were seen on the basis of our clinicopathologic analysis. It should be noted, however, that the length of our follow-up is much less than that reported by Neuberger.¹¹

One study based on needle biopsies¹ showed that bile ductular injury was not a component of rejection, as opposed to other earlier studies.^{3–5} Small bile ductular injury was observed in our specimens and, although not prominent in early episodes, was more prevalent in later specimens (see Table 1). The process is focal, however, and is therefore better appreciated in transplant and autopsy specimens than it is in needle biopsies. This fact may account for some of the reported discrepancies. Differences in surgical technique, treatment protocol, and immunosuppressive agents may also be important factors. Although ductular damage appears to be a part of the rejection process, and its recognition may be helpful in differentiating it from other complications, ductular injury should not be the sole criteria used to establish the diagnosis of rejection. Other disorders affecting the graft may also injure interlobular bile ducts^{11,23,32,33} and need to be considered as well.

In this regard, the histologic appearance of rejection in the liver, particularly later than 2 months after transplantation, has been compared with idiopathic autoimmune chronic active hepatitis,^{1,34} primary biliary cirrhosis,^{4,5,35} and chronic graft-versus-host-disease (GVHD).^{4,5,36} It is not surprising that many of the features described for chronic GVHD³⁶ are identical to those seen in rejection. We also noted, as reported in GVHD,³⁷ that bile ductular cell injury, although present in earlier specimens (less than 2 months), is more prevalent in later specimens (greater than 2 months). The cellular injury mediated by T-lymphocytes in GVHD appears to be selective for ductal epithelium,³⁸ which may be related to expression of Ia antigens on target cells that normally do not express the antigen.³⁹ A similar phenomenon may occur in hepatic rejection⁴⁰ and may be also related to the preferential expression of Class I and II HLA antigens on endothelial, reticuloendothelial, and bile ductule cells.⁴¹

Although much has yet to be learned concerning the identification and pathogenesis of the histologic lesions that occur in these patients, the liver biopsy frequently is of significant value in forming treatment plans. However, in some cases, the histopathologic findings can only provide a differential diagnosis, which may only be fully resolvable with the availability of complete clinical data. When no definitive conclusions can be drawn based on histologic study alone, communication between the clinician and the pathologist, preferably with

a select interest in liver pathology, is necessary for provision of optimal care to the transplant patient.

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Acknowledgments

The recognition of the histopathologic changes associated with hepatic rejection was guided by the fundamental detailed observations of K. A. Porter^{7,9} in animals and humans.