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THE ABSENCE OF CHRONIC REJECTION IN PEDIATRIC PRIMARY LIVER TRANSPLANT PATIENTS WHO ARE MAINTAINED ON TACROLIMUS-BASED IMMUNOSUPPRESSION: A LONG-TERM ANALYSIS[1]

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Background. **Although the outcome of liver transplantation has improved significantly during the past two decades, graft loss caused by chronic rejection after liver transplantation still occurs in 2% to 20% of recipients. The overall incidence of chronic rejection is also reported to be low in adult recipients, and risk factors have been identified. Chronic rejection is associated with the inability to maintain baseline immunosuppression. Additionally, the diagnoses of primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, hepatitis B virus, and hepatitis C virus, common indications for liver transplantation in adults, are associated with a higher incidence of chronic rejection. Fortunately, these diagnoses are rarely seen in children. Little is known about chronic rejection in long-term pediatric liver transplant survivors. The purpose of this longitudinal study was to examine the incidence of biopsy-proven chronic rejection in long-term survivors of primary pediatric liver transplantation under tacrolimus-based immunosuppression.**

Methods. **From October 1989 to December 1992, 166 children (boys=95, girls=71; mean age=5.0±2.9 years) received a primary liver transplant. These patients were followed until March 2000 with a mean follow-up of 9±0.8 (range, 7.4–10.4) years. All liver biopsy specimens and explanted grafts were evaluated for evidence of chronic rejection using the International Banff Criteria.**

Results. **The mortality rate during the follow-up period was 15% (n=25). Retransplantation was required in 11% (n=18) of recipients. Actuarial patient and graft survival rates at 10 years were 84.9% and 80.1%, respectively. There were 535 liver biopsy samples available for evaluation, including the 18 explanted allografts. Biopsy specimens of three other functioning allografts showed evidence of chronic rejection. Immunosuppression had been discontinued or drastically reduced in these recipients because of life-threatening infections, noncompliance, or both. On restoring baseline immunosuppression, all three children had normalized liver function and the allografts were maintained; the liver transplant patients who are alive currently have normal liver functions.**

Conclusion. **The findings of this study suggest that chronic rejection does not occur in pediatric liver transplant recipients receiving tacrolimus-based immunosuppression, provided baseline immunosuppression is maintained.**

Chronic rejection is a significant cause of graft failure after liver transplantation, with a reported incidence of 2% to 20% (*1–3*). The prevention and treatment of chronic rejection remains elusive and can lead to graft failure requiring retransplantation. After retransplantation for chronic rejection, a recurrence rate as high as 90% has been reported (*4*). Chronic rejection, occurring under cyclosporine (CsA)-based therapy, was controlled or reversed in up to 70% of cases after the initiation of tacrolimus-based therapy (*5–8*).

Relatively little is known about the incidence of chronic rejection in long-term liver transplant survivors receiving tacrolimus-based immunosuppression. In a recent review of adult liver transplant recipients who were receiving tacrolimus (n=1048), 5252 biopsy specimens were evaluated, with a mean follow-up of 6 years. The incidence of chronic rejection leading to graft loss or death was 1.8%. Biopsy specimens revealed chronic rejection in an additional 1.3%; however, optimizing baseline immunosuppression led to recovery in all patients. Several risk factors for the development of chronic rejection were identified including the presence of viral infections such as hepatitis C virus (HCV) or hepatitis B virus (HBV); autoimmune processes such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis (AI); and the inability to maintain therapeutic baseline immunosuppression because of concurrent life-threatening infections, Epstein-Barr virus (EBV), post-transplant lymphoproliferative disease (PTLD), or noncompliance (*9*). Because HCV, HBV, PBC, PSC, and AI are rare indications for liver transplantation in children, little is known about the relationship between these risk factors and chronic rejection in pediatric liver transplant recipients receiving tacrolimus. A recent study of 326 pediatric liver allografts with a follow-up of 3 to 12 years reported that graft loss, directly related to acute or chronic rejection, was not encountered (*10*). The purpose of this longitudinal study was to examine the incidence of biopsy-proven chronic rejection in primary pediatric liver transplantation under tacrolimus-based immunosuppression.

MATERIALS AND METHODS

Cadaveric liver transplantation was performed in 166 consecutive children (boys=95, girls=71) from October 1989 through December 1992 under tacrolimus-based immunosuppression. Immunosuppressive protocols have been described previously (*11*). Mean age at

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transplantation was 5.9±2.9 years. Patients were followed until March 2000, with a mean follow-up of 9.0±0.8 (range, 7.4–10.4; median, 9.2) years. The indications for liver transplant are listed in Table 1. Biliary atresia was the most common indication, accounting for nearly 50% of cases, followed by metabolic disorders (13.8%).

Liver biopsies were performed only when clinically indicated, and protocol biopsy specimens in patients with normal liver function were not obtained. Biopsy specimens were evaluated for evidence of chronic rejection using the International Banff criteria (*12*) by a pathologist who had no knowledge of the patient's clinical course. Biopsy specimens were graded for bile duct loss, damage, and atrophy and for arteriolar changes and arteriopathy. Sections from the explanted hepatic grafts and autopsy material were also evaluated for chronic rejection.

RESULTS

During the follow-up period, there were 25 deaths (15%), which were a result of sepsis (n=7), central nervous system complications (n=5), intraoperative death (n=4), primary graft nonfunction (n=4), recurrence of primary malignancy (n=2), PTLD (n=2), and postoperative subclavian vein bleeding (n=1) (Table 2). Eighteen children (10.8%) required retransplantation for primary nonfunction (n=8), hepatic artery thrombosis (n=6), recurrent giant cell hepatitis (n=1), and viral hepatitis (n=3) including HCV (n=1), adenovirus (n=1), and EBV (n=1) (Table 2). The 10-year Kaplan-Meier patient and graft survival rates were 84.9% and 80.1%, respectively (Fig. 1). There were 535 liver biopsy specimens available for examination, including 18 samples from explanted grafts (3.2±0.8 per patient).

Explanted Liver Biopsy Specimens

Only one of the 18 explanted liver grafts revealed chronic rejection. This child received a liver transplant for biliary atresia at 17 months of age and had two steroid-responsive episodes of acute cellular rejection. At 1 year after transplantation, he developed PTLD, which was treated by discontinuing immunosuppression. Additionally, the patient was diagnosed with de novo HCV and was treated with interferon alfa. The child developed liver failure 14 months after immunosuppression was discontinued and required retransplantation. The explanted liver revealed a combination of acute cellular rejection, as evidenced by mixed portal infiltrates and bile duct damage (Fig. 2a), and chronic rejection characterized by bile duct loss in more than 50% of the portal tracts and subintimal foam cell accumulation in the large perihilar hepatic artery branches (Figs. 2b,c). Lobular inflammation was also present and suggested concomitant hepatitis (Fig. 2d).

TABLE 1. Indications for liver transplantation

Indications	n	%
Biliary atresia	82	49.3
Congenital metabolic disorder (A1A=8, Wilson's=5, GSD-IV=2, trans carbamylase deficiency=1, cabamylphosphatase synthetase deficiency=1, Crigler Najar=1, oxalosis=1, tyrosinemia=3, histiocytosis=1	23	13.8
Cryptogenic cirrhosis	12	7.2
Postnecrotic cirrhosis (HBV=1, NANB=3, AI=3, CMV=1)	9	5.4
Acute fulminant failure (viral=2, Acetamenophine=1, unknown=7)	10	6
Familial cholestasis	6	3.6
Cystic fibrosis	5	3
Congenital hepatic fibrosis	5	3
Neonatal hepatitis	3	1.8
Secondary biliary cirrhosis	3	1.8
Hepatoblastoma (n=3) and angiosarcoma (n=1)	4	2.4
Budd Chiari	1	0.6
Other (histiocytosis=1, nodular regenerative hyperplasia=1, and unknown=1)	3	1.8
Total	166	

A1A, alpha 1 antitryptsine deficiency; GSD-IV, glycogen storage disease type 4; NANB, nonA nonB hepatitis; ICC, Indian childhood cirrhosis.

TABLE 2. Causes of death and retransplantation

	n	%
Causes of death		
Sepsis	7	4.2
CNS complications	5	3.0
Intraoperative	4	2.4
Primary liver failure	4	2.4
PTLD	2	1.2
Primary recurrent malignancy	2	1.2
Subclavian vein injury	1	0.6
Total	25	15.1
Causes of retransplantation		
Primary nonfunction	8	4.8
Hepatic artery thrombosis	6	3.6
Viral hepatitis (Adeno, HCV, EBV)	3	1.8
Recurrent giant cell hepatitis	1	0.6
Total	18	10.8

CNS, central nervous system.

Liver Biopsy Specimens

There was evidence of chronic rejection in the liver biopsy specimens in three pediatric recipients. All three children were maintained on low baseline immunosuppression for life-threatening infections, but one patient was noncompliant with medications. All had previously presented with multiple episodes of acute cellular rejection, and all had improved biochemical profiles after optimization of baseline immunosuppression. Case 1 was a 6-month-old girl who had seven episodes of acute rejection after liver transplantation for biliary atresia and required a course of OKT3. The rejection resolved with no further complications. About 6 years later, the child developed varicella, which was treated by reducing baseline immunosuppression by 50%. Although the varicella infection resolved, she subsequently presented with increased liver function tests. A biopsy specimen obtained 10 months after the immunosuppression reduction revealed centrilobular fibrosis and bile duct loss in more than 50% of the portal triads (Fig. 2, top). After optimizing tacrolimus levels, liver functions have substantially improved (Table 3). Case 2 was a girl with biliary atresia who received a liver transplant at 2 years of age. Over the following 10 years, she had seven episodes of acute rejection, cytomegalovirus (CMV) pneumonia, CMV gastritis, and EBV lymphadenitis; she had documented noncompliance in taking medications. At 11 years after transplantation, she presented with a serum bilirubin of 12 mg/dL. A liver biopsy specimen at that time revealed bile duct loss in more than 50% of the portal triads (Fig. 2, bottom). After optimizing immunosuppression, the serum bilirubin improved to 2.2 mg/dL (Table 3). Case 3 was a boy who received a liver transplant at 6 months of age for

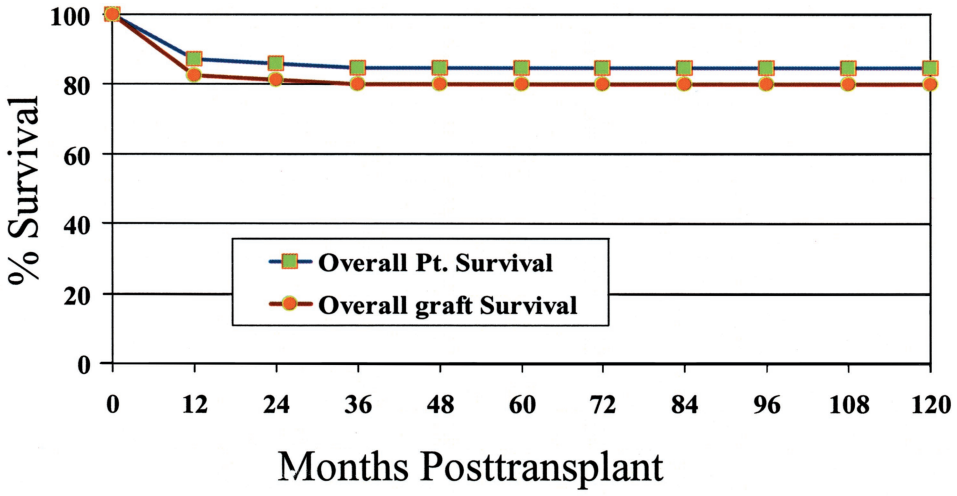

FIGURE 1. Kaplan-Meier patient and graft survival (y-axis); months after liver transplantation (x-axis).

biliary atresia. He had three episodes of steroid-responsive acute cellular rejection after transplantation. At 5 years after transplantation, he developed EBV lymphadenitis, which was treated by discontinuing immunosuppression for 2 months. The patient subsequently presented with increased hepatic enzymes but a normal serum bilirubin. A liver biopsy specimen was obtained and revealed bile duct loss in less than 50% of the portal tracts, consistent with early chronic rejection (Figs. 2c,d). Immunosuppression was reintroduced, and liver function tests have returned to near-normal levels (Table 3).

Liver Function

The current mean total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphate, and gamma glutamyl transferase levels of the total population (n=141) are within normal ranges at the last follow-up (Table 4).

Immunosuppression

The current immunosuppressive regimens of this population (n=141) are described in Table 4. Monotherapy with tacrolimus is maintained in 69% (n=97) of pediatric liver recipients, with 21% receiving low-dose prednisone (n=30). Dual-drug therapy, with or without prednisone, is required in 18% (n=25) of patients and 4% (n=6) receive triple-drug therapy. Currently, 9% of patients (n=13) are not receiving any immunosuppression (Table 4).

DISCUSSION

The incidence of chronic rejection in liver transplant recipients under CsA-based immunosuppression is reported to be from 2.4% to 16.8% (*1*,*2*,*13*). In the past, azathioprine has reportedly reduced the incidence of chronic rejection (*14*). Results from our center, and multicenter trials, have suggested that chronic rejection can be successfully treated by conversion to tacrolimus-based immunosuppression (*5*–*7*,*15*).We have reported a 1.8% incidence of graft loss or death from chronic rejection from a study of 1048 adult liver transplant recipients with a mean follow-up of 6 years. An additional 1.3% had evidence of chronic rejection on biopsy specimen, but demonstrated significant biochemical improvement and normalized liver function after optimization of baseline immunosuppression. Risk factors for the development of chronic rejection in this population included a primary diagnosis of a viral infection (HCV, HBV), an autoimmune process (PBS, PSC, AI), and the inability to maintain therapeutic baseline immunosuppression because of treatment for a life-threatening infection (PTLD) or as a result of medication noncompliance (*9*). Other known risk factors include multiple episodes of acute rejection and CMV hepatitis (*16*–*19*). Fortunately, the indications for liver transplantation in children are different than in adults (*10*,*20*). In the present pediatric series, less than 4% of patients were diagnosed with PBC, PS, AI, HCV, or HBV.

The absence of chronic rejection under tacrolimus-based immunosuppression has not been studied conclusively. However, this center has reported that in a 3- to -12 year follow-up study, there was no graft loss or mortality directly related to acute or chronic rejection in 326 children treated with tacrolimus-based immunosuppression (*10*). A limitation to the study, however, was that not all liver biopsy specimens were examined for the presence of chronic rejection.

Tacrolimus has been beneficial in pediatric liver transplantation, as evidenced by a decrease in the severity and incidence of acute cellular rejection, a significantly lower rate of steroid-resistant rejection, and decreased graft loss caused by severe rejection (*11*,*21*,*22*). Additionally, hypertension and hyperlipidemia occur at a much lower rate under tacrolimus therapy as compared with CsA. Facial stigmata such as gingival hyperplasia and hirsutism are not associated with tacrolimus (*23*–*25*). Additionally, it is possible to withdraw steroids or maintain a low dose with tacrolimus therapy, consequently improving growth and development for these children (*8*,*24*,*26*).

In this study, we identified only 4 of 166 patients who had histopathologic evidence of chronic rejection. The common risk factor in these patients was the inability to maintain a therapeutic baseline level of immunosuppression with tacrolimus, because of immunosuppression reduction for a life-threatening infection or medication noncompliance. As observed in the adult population, these children responded to an optimization of baseline immunosuppression (*9*). Graft loss from chronic rejection was seen only once in this series and occurred in a child diagnosed with PTLD, who required discontinuation of tacroli-

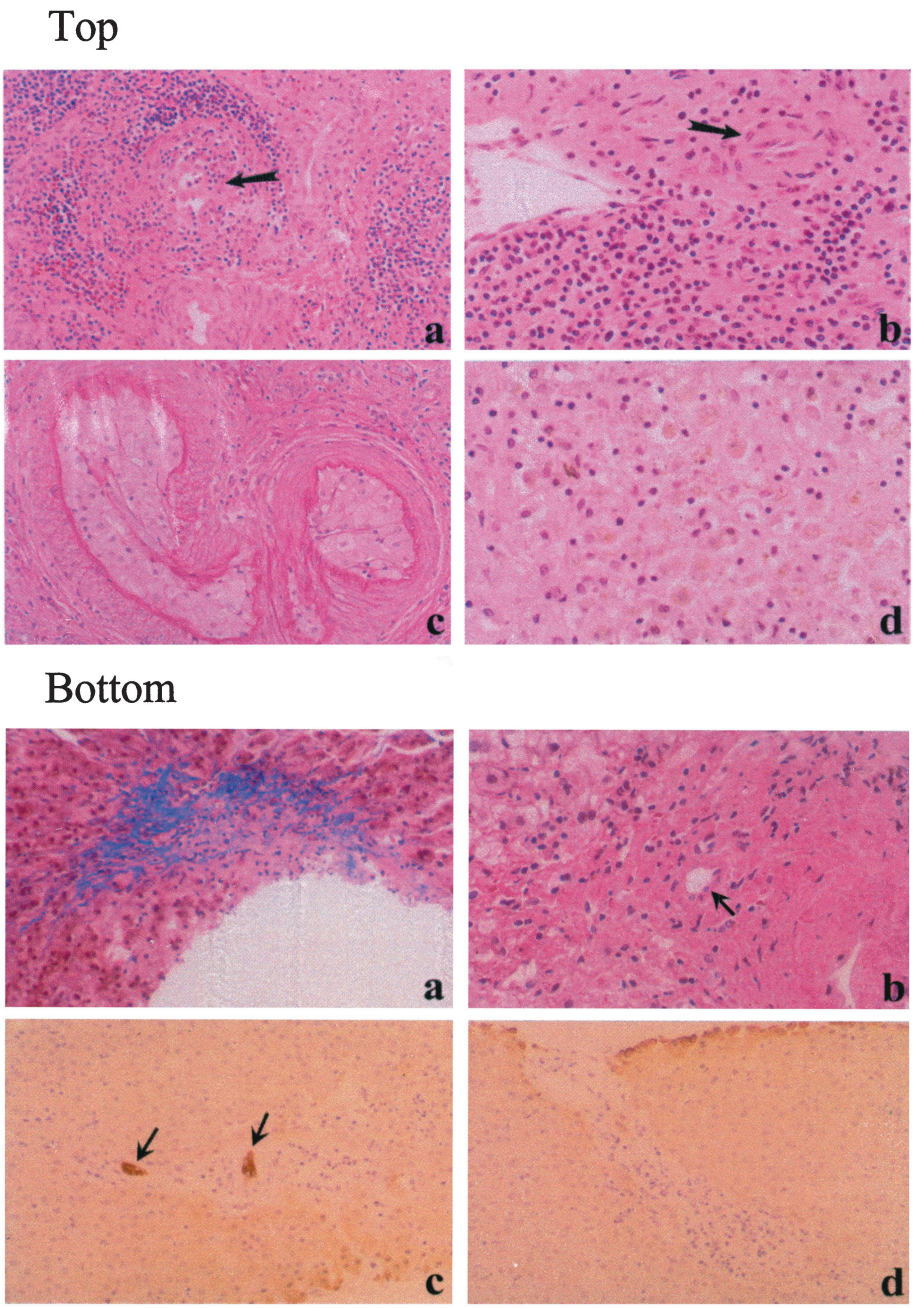

FIGURE 2. (*Top*) Explanted liver with features of acute rejection, chronic rejection, and hepatitis. (a) Portal tract with a mixed inflammatory infiltrate and a damaged bile duct with intraepithelial lymphocytes (*arrow*) (hematoxylin-eosin, ×100). (b) Inflamed portal tract with artery (*arrow*) without accompanying bile duct (hematoxylin-eosin, ×200). (c) Large perihilar hepatic artery with subintimal foam cell accumulation (periodic acid Schiff stain, ×200). (d) Hepatic lobule with sinusoidal lymphocytes and hepatocellular cholestasis (hematoxylin-eosin, ×200). (*Bottom*) Patients (n=3) with a drastic reduction or discontinuation of immunosuppression, showing evidence of chronic rejection. Liver function has recovered after optimization of immunosuppression. (a) Case 1. There is fibrosis of the central vein and obliteration of its lumen (trichrome stain, ×100). (b) Case 2. Loss of bile ducts. There is an artery (*arrow*) without a corresponding bile duct. The portal infiltrate is minimal. (hematoxylin-eosin, ×100). (c) Case 3. Some portal areas show preserved bile ducts (*arrows*) (cytokeratin AE1/AE3; ×100). (d) Case 3. Other portal areas show lack of bile ducts (cytokeratin AE1/AE3, ×100).

mus for 6 months. This patient was also treated with interferon alfa for HCV infection. HCV has been identified as a risk factor for chronic rejection in the adult population (*9*), and interferon alfa is known to up-regulate donor human leukocyte antigen (*27*) and induces irreversible acute rejection in up to 30% of kidney transplant recipients (*28*). This type of acute rejection was not observed in liver transplant recipients who were maintained on immunosuppression (*29*). Additionally, Dousset et al. (*30*) have reported vanishing bile ducts with the use of interferon alfa under relatively low doses of CsA. In this pediatric case, interferon alfa was given without immunosuppres-

TABLE 3. Children who recovered allograft function

Number	Age at transplantation (yr)	Gender	Diagnosis	Clinical course	Interval from transplantation	Liver Bx[a]	Bili	AST	ALT	$ALKPO_4$	GGTP
1	0.5	F	BA	Seven episodes of acute rejections treated with steroids and OKT3, 5 years post LTx chicken pox; tacro. reduced by 50% for 10 months	6 year	>50% (4/4) centri lobular fibrosis	3.3	64	86	334	125
							48	33	79	78	
				Current LFT 25 months post Liver Bx*	1.1		11.5	137	266		333
2	1.9	M	BA	Persistent non-compliance, 7 episodes of acute rejection, CMV pneumonia, CMV gastritis/EBV lymphadenitis/ tacrolimus d/c 11 months	12 year	>50% (2/3) bile duct loss remaining damaged					
					Current 10 months post Liver Bx*		2.2	52	102	465	103
3	0.5	M	BA	3 ACR, EBV lymphadenitis, tacro d/c 2 months	5 year	<50% (9/13) bile duct loss	0.4	225	114	905	710
					Current 18 months post Liver Bx*		0.3	16	35	266	64

[a] Bx, biopsy; LFT, liver function test; d/c, discontinued; Bili, total bilirubin mg/dL; AST, aspartate aminotransferase (μ/L); ALT, alanine aminotransferase (μ/L); $ALKPO_4$, alkaline phosphatase (μ/L); GGTP, gamma glutamyl transferase (μ/L); ACR, acute cellular rejection; Tacro, tacrolimus.

TABLE 4. Current liver function and immunosuppression

Current liver function, all children (n=141)	
Total bilirubin, mg/dL	0.7±0.5
AST, μ/L	39.3±32.8
ALT, μ/L	39±26
GGTP, μ/L	58±79
Current immunosuppression[a] (n=141; mean±SD)	
Tacrolimus dose, mg/day	3.5±3.1
Prednisone (n=30), mg/day	6.0±4.3
Azathioprine (n=4), mg/day	40±28
Mycophenolate mofetil (n=5), mg/day	400±417

[a] Tacrolimus level, 6±5 ng/mL.

[b] 13 (9%) off immunosuppression, 97 (70%) on tacrolimus alone, 25 (18%) on dual-drug therapy, and 6 (4%) on triple-drug therapy.

sion and the explanted liver allograft had the features of acute and chronic rejection and of hepatitis.

The impact of EBV and the direct effect of this virus in the development of chronic rejection have not been documented, although several reports of graft loss after PTLD have been reported. We speculate that EBV is a risk factor for chronic rejection because treatment for EBV usually involves a significant reduction in baseline immunosuppression. Further studies to determine the role of EBV in the development of chronic rejection are necessary.

These observations lead us to conclude that chronic rejection has been relegated to a minor problem in pediatric liver transplantation under tacrolimus-based immunosuppression. Although, in the present study, protocol liver biopsies were not performed, it is conceivable that some children with normal biochemical profiles may have early changes suggestive of chronic rejection. Future studies with protocol liver biopsies may provide this information.

CONCLUSION

This thorough examination (mean follow-up=9 years) of 166 primary pediatric liver transplant recipients under tacrolimus-based immunosuppression has not revealed any evidence of chronic rejection when baseline immunosuppression was maintained.

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