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Liver Transplantation: A 31-Year Perspective Part III

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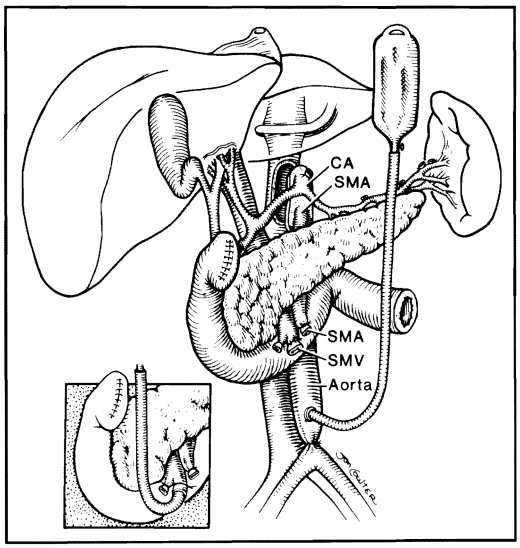
Anthony J. Demetris, M.D.



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LIVER TRANSPLANTATION: A 31-YEAR PERSPECTIVE*† Part III

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FOREWORD

Occasionally in medicine, a single individual makes a contribution of such magnitude and significance that it clearly represents a new direction in the field. Such is the case in this and the two subsequent issues of *Current Problems in Surgery*, which are devoted to transplantation of the liver. Dr. Thomas Starzl and his colleagues, formerly of the University of Colorado and now of the University of Pittsburgh, have, by their many seminal contributions, had a great influence on the entire field of transplantation, but it is transplantation of the liver which has gained these scientists their widest recognition.

The operation began as an idea only 30 years ago and the seemingly painful and slow steps which subsequently led from early clinical trials to the current stage of development are remarkable. Today, the procedure is performed in a number of medical centers around the world, in all age groups of patients, and for a wide variety of indications—a tribute to the remarkable efforts and the persistence of Dr. Starzl and his group.

In the span of the three issues, Dr. Starzl and Dr. Demetris cover all aspects of hepatic transplantation, including the technical points of the replacement operation, the prevention of rejection, and the complications both of the operation and of the postoperative immunosuppressed state. In the closing parts of this treatise, the authors review the newly emerging technique of multiple organ transplantation, auxillary transplantation, and the practical limitations of the procedure, including organ donation and economic factors.

This contribution is authoritative and excellent, and will surely become a classic in the field.

Samuel A. Wells, Jr., M.D.
Editor-in-Chief

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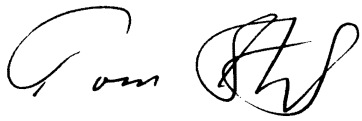

Thomas E. Starzl, M.D., Ph.D., is Professor of Surgery at the University of Pittsburgh, where he has worked since January 1981. Before that he spent 19 years at the University of Colorado, the last 8 years as Chairman of the Department of Surgery. The central theme of almost all of his work has been organ transplantation, with particular reference to the kidney and liver. His research with liver transplantation, in dogs, began in the summer of 1958 and has continued to the present time, providing the 31-year perspective mentioned in the title.

Anthony J. Demetris, M.D., is an Assistant Professor of Pathology at the University of Pittsburgh. His medical school training was at the University of Pittsburgh. He is a native of the Pittsburgh area, coming from Kittanning, Pennsylvania, and obtained his medical school degree from the University of Pittsburgh. His training in pathology was in the University of Pittsburgh program under the chairmanship of Dr. Thomas Gill, a noted transplantation pathologist and experimentalist. Dr. Demetris' pathology residency (1982–1986) coincided with the burgeoning development of the University of Pittsburgh Transplantation Program, and he quickly became a nuclear force in its clinical as well as its experimental programs. The extent of his contributions, many of them new, can be appreciated in the extremely complete pathology sections of this monograph. The monograph itself is the most complete update of liver transplantation pathology since the classical publications (in collaboration with Dr. Starzl) of Professor K. A. Porter of St. Mary's Hospital and Medical School, London.

LIVER TRANSPLANTATION: A 31-YEAR PERSPECTIVE PART III

INFECTIOUS PROBLEMS IN LIVER TRANSPLANTATION

BACTERIAL AND FUNGAL INFECTIONS

Although liver grafts may possess some immunologic advantage, as discussed earlier, the practical reality is that heavy initial immunosuppression and later maintenance therapy are required in the same way as with other organs. The balance between immunosuppression and infectious disease control is more delicate than with cardiac and renal transplantation because the hepatic graft is exposed to the intestinal tract through the biliary tract or by hematogenous contamination from the splanchnic venous bed. The devastating role of consequent graft infection by organisms indigenous to the gastrointestinal (GI) tract was delineated in the early clinical trials[18, 470–472] as well as those in the cyclosporine era.[358, 436, 473–475] Experiments in dogs performed 25 years ago provided an example of what now is called *bacterial translocation* in that the liver graft itself became a porous entry site for bacteria indigenous to the GI tract.[476] A liver damaged by rejection becomes unusually vulnerable to invasion by such microorganisms. Effective immunosuppression has long been recognized to be the only way to maintain intact tissue barriers and to avoid this kind of infection.[18]

There has been recent interest in controlling the bacterial and fungal population of the GI tract with preoperative nonabsorbable oral antibiotics.[252, 477] These antibiotics selectively suppress pathogenic gram-negative organisms and fungi but allow survival of anaerobes. This has been called *selective intestinal decontamination.* A typical antibiotic regimen consists of polymyxin E, gentamycin, and nystatin. The morbidity from infection after liver transplantation has been reduced with this approach, but the mortality has not.[252] In addition to its unproved value, a practical limitation of selective decontamination is the inability to find a cadaveric liver at the optimal time ordained by the antibiotic preparation.

Much about the subtle relationships between host defenses and

invasive bacteria remains to be learned in the liver transplant model. The host macrophage system, of which the liver is an important component,[218] is profoundly altered by transplantation. The possible role of altered graft Kuppfer's cells in contributing to endotoxemia was discussed in an earlier section.

Liver recipients also suffer frequently from virus infections. The recurrence of hepatitis viruses in grafts will be discussed in the next section. Other virus infections occur at some postoperative time in the majority of liver recipients.[478]

CLINICOPATHOLOGIC FEATURES OF ALLOGRAFT VIRAL HEPATITIS

Clinical symptoms, along with the use of core biopsy, are used to establish the diagnosis of allograft hepatitis. In general, the clinical features and histologic appearance of allograft viral hepatitidies are identical to those observed in other immunosuppressed patients. It is helpful, however, to anticipate the relative time of onset of the different viral syndromes, since they tend to occur at characteristic times after liver replacement (Table 10).* The following sections are separated into discussions of those viruses that are classically associated with hepatitis from those that are more opportunistic in nature.

Opportunistic Viruses

The most common viral pathogens in the opportunistic category that cause allograft hepatitis belong to the herpes family: CMV, HSV types 1 and 2, varicella-zoster (VZ) virus, and EBV. Another cause of allograft hepatitis not commonly seen in the general population is adenovirus (ADV). The following are presented in order of frequency.

TABLE 10.

Peak Incidence of Graft Syndromes vs. the Time After Transplant

Viral Syndromes	Time After Transplant
Cytomegalovirus	3–8 wk, often after treatment of rejection
Herpes simplex	Any time after transplant
Epstein-Barr	Most common in first 2 mo. but may occur anytime thereafter
Adenovirus	3–4 wk after transplant.
Hepatitis B	Onset usually after 4–6 wk, and graft remains infected
Hepatitis A	No experience to date
non-A, non-B hepatitis	Usually after 4 wk

*Table 1 appears in Part I; Tables 2–9 appear in Part II.

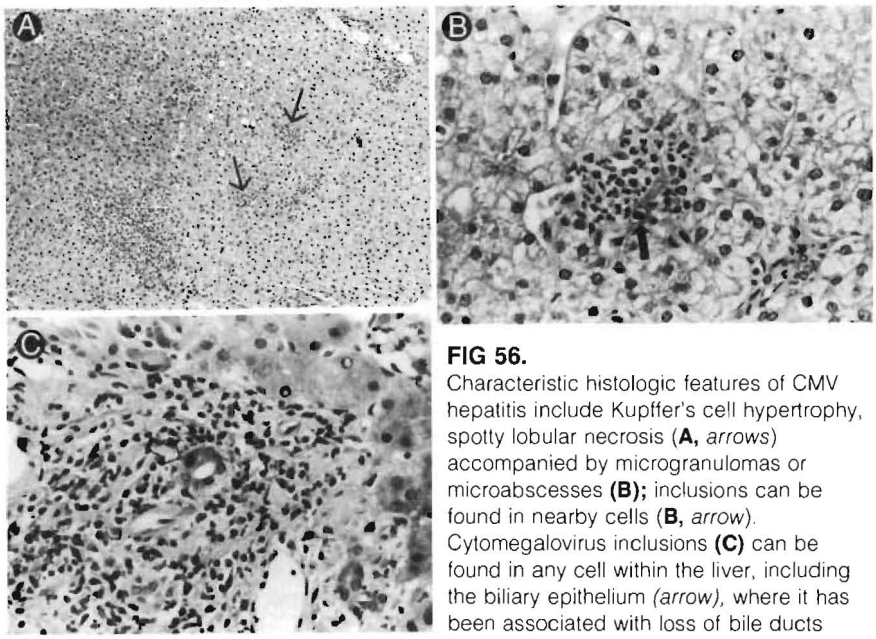

FIG 56.
Characteristic histologic features of CMV hepatitis include Kupffer's cell hypertrophy, spotty lobular necrosis (**A,** *arrows*) accompanied by microgranulomas or microabscesses **(B);** inclusions can be found in nearby cells (**B,** *arrow*). Cytomegalovirus inclusions **(C)** can be found in any cell within the liver, including the biliary epithelium *(arrow),* where it has been associated with loss of bile ducts (see text).

Cytomegaloviral Hepatitis

The most common serious infections are with CMV, which can cause lesions in many organs.[353, 354, 478–480] Cytomegalovirus is the most common cause of postoperative graft hepatitis and is seen most frequently between 3 and 8 weeks after transplant.[353, 354, 478–480] Protection from serious CMV infection has been reported with hyperimmune globulin.[481] Recovery is the rule if immunosuppression is lightened and especially if therapy is given with ganciclovir (Gancyclovir).[479, 482] However, CMV strains resistant to ganciclovir have been reported recently.[483] The onset of CMV is often temporally related to episodes of rejection, where the patient has just received additional immunosuppressive therapy for an acute cellular rejection episode.[353, 354, 478–480]

Clinically, patients usually present with a low-grade fever and mildly elevated liver injury test results. Leukocytopenia, diarrhea, GI ulcers, and respiratory symptoms are not uncommon.[353, 354, 478–480] The diagnosis of liver involvement is confirmed by needle biopsy.[144, 145, 353]

Cytomegaloviral hepatitis is characterized by lobular alterations (Fig 56).*[144, 145, 353] Any cell type of the liver may be infected, and

*Figures 1–42 appear in Part I; Figures 43–55 appear in Part II.

those that are may demonstrate cytomegalic change, intranuclear eosinophilic inclusions surrounded by a halo, and/or small basophilic cytoplasmic inclusions. These foci are often infiltrated with clusters of inflammatory cells, consisting of neutrophils, macrophages (microabscesses and microgranulomata), or both. Other lobular alterations include mild Kupffer's cell hypertrophy. Significant lobular disarray, massive or submassive necrosis, or even severe liver damage from CMV alone is rare. Recognition of any of these changes should prompt a careful search for viral inclusions, the use of immunohistochemical stains for the detection of the CMV antigens, or both.

Tissues containing rapidly dividing cells, such as young granulation tissue, proliferating cholangioles, edges of infarcts, and abscesses or other defects are fertile soil for CMV growth.[144, 145] When such tissue is encountered, a more careful search of CMV is warranted.[144, 145]

Finally, CMV can be associated with a plasmacytoid or blastic infiltrate (or both) similar to that seen in EBV hepatitis (unpublished observations). Cytomegalovirus inclusions are not usually detected in such cases. Differentiation from rejection and lymphoproliferative disease associated with EBV may be difficult and is based on careful microscopic examination and immunohistochemical stains to detect viral antigens. The clinical profile and various hematologic parameters are also helpful.

Recently, CMV has been implicated in the pathogenesis of the vanishing bile duct syndrome (VBDS).[460] Compatibility between the donor and recipient at the DR MHC locus, along with mismatching at the class I locus and CMV infection have been identified as interdependant risk factors for the development of bile duct loss.[459, 460] The Cambridge group has suggested that MHC-restricted antigen presentation of viral antigens or mismatched class I MHC antigens by DR-compatible bile duct cells is responsible for this observation.[460]

Herpes Simplex and Varicella-Zoster Hepatitis

Both subtypes of HSV (1 and 2) and the VZ virus have been identified as causes of liver allograft hepatitis. Signs of graft infestation have been seen as early as 3 days after transplant and may occur any time thereafter.[144, 354, 484] The clinical presentation with the HSVs includes fever, fatigue, and body pain combined with serologic evidence of hepatic injury.[144, 145, 354] Cutaneous manifestations may or may not be present. With the VZ virus, allograft involvement may be detected several days prior to the eruption of cutaneous vesicles typical of this disorder. Untreated, any of these viruses may rapidly

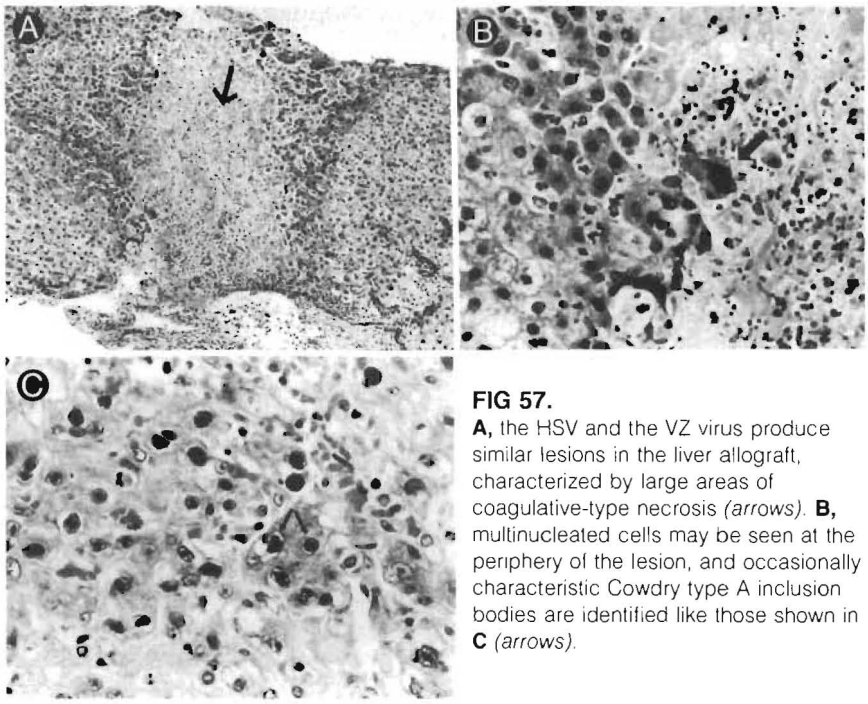

FIG 57.
A, the HSV and the VZ virus produce similar lesions in the liver allograft, characterized by large areas of coagulative-type necrosis *(arrows).* **B,** multinucleated cells may be seen at the periphery of the lesion, and occasionally characteristic Cowdry type A inclusion bodies are identified like those shown in **C** *(arrows).*

lead to massive hepatic necrosis. Therefore, early recognition on needle biopsy is particularly crucial since effective medical therapy (acyclovir) is available.

Microscopically, all three viruses produce similar graft pathology (Fig 57).[144, 145, 484] They are characterized by circumscribed areas of coagulative necrosis, showing no respect for the lobular architecture. Ghosts of hepatocytes intermixed with neutrophils and nuclear debris are seen in the center of the lesions. More viable hepatocytes are seen at the periphery, some of which may contain ground glass nuclei or characteristic inclusion bodies. Multinucleated cells are also occasionally present. Immunoperoxidase stains for various viral antigens confirm the diagnosis when the pathologist is unsure on the basis of the hematoxylin-eosin stains alone.

Epstein-Barr Virus

Consequences of primary infection or reactivation of the EBV after transplantation run the gamut from an infectious mononucleosis syndrome as seen in the general population[485] to severe life-threatening lymphoproliferative disease similar to patients with the X-linked lymphoproliferative disorder[486] or acquired immunodefi-

ciency syndrome (AIDS).[487] Lymphoproliferative tumors (B-cell lymphomas) have been seen with all kinds of transplantations but most frequently in liver recipients[355, 488–491] and especially in infants and children, in whom the risk over the first 2 years after transplantation may be as high as 10%.[355, 492] The liver graft itself is frequently involved. The most effective treatment measure for any of the EBV syndromes is discontinuance or reduction of immunosuppression,[488] to which antiviral therapy with acyclovir should be added.[493] Regression of the symptoms, laboratory abnormalities, and lymphomas usually, although not invariably, follows reduction of immunosuppression whether or not acyclovir is given.[488, 490, 491] This effect may be achieved even though the hepatic graft is not rejected. The regression of these lymphomas, some of which are monoclonal, when the recipient immunologic responsiveness is allowed to recover is thought to be an example of immunologic surveillance in humans.[488]

Clinical signs and symptoms of recipients with EBV syndromes at the more benign end of the spectrum are similar to those seen with infectious mononucleosis, although atypical presentation in the form of fever, rashes, and joint and jaw pain are not uncommon. Liver enzyme levels are usually only modestly elevated, but occasionally significant damage and even submassive or massive necrosis may be seen. Those recipients who develop tumors present clinically with constitutional symptoms similar to those just described in addition to those related to organ system involvement with tumor.[488–491] Atypical lymphocytosis in the peripheral blood smear is invariably present in all patients. The diagnosis of allograft involvement is confirmed by needle biopsy evaluation of the graft.

Like the variety of clinical disorders, involvement of the liver by EBV-associated disorders also runs the histopathologic gamut from typical monohepatitis as seen in the general population to submassive or massive hepatic necrosis[145] or involvement by tumor, comprised of malignant lymphoid cells similar to those seen in immunoblastic lymphomas (Fig 58). Cases resembling lymphomatous involvement of the liver may be difficult to differentiate from acute cellular rejection[145] since subendothelial infiltration of the portal veins along with focal bile duct damage may be present. Usually these are not as severe or as widespread as those seen with rejection. The key to the diagnosis is the monomorphic and atypical appearance of infiltrative cells in the EBV-related disorders. Immunohistochemical staining to detect EBV viral antigens can be performed but requires frozen tissue. Immunophenotypic analysis of the infiltrative cells in EBV-related disorders usually demonstrates a great number of non–T cells, whereas in acute cellular rejection, the T cells predominate.

Biopsy of enlarged lymph nodes (most common) or other organs

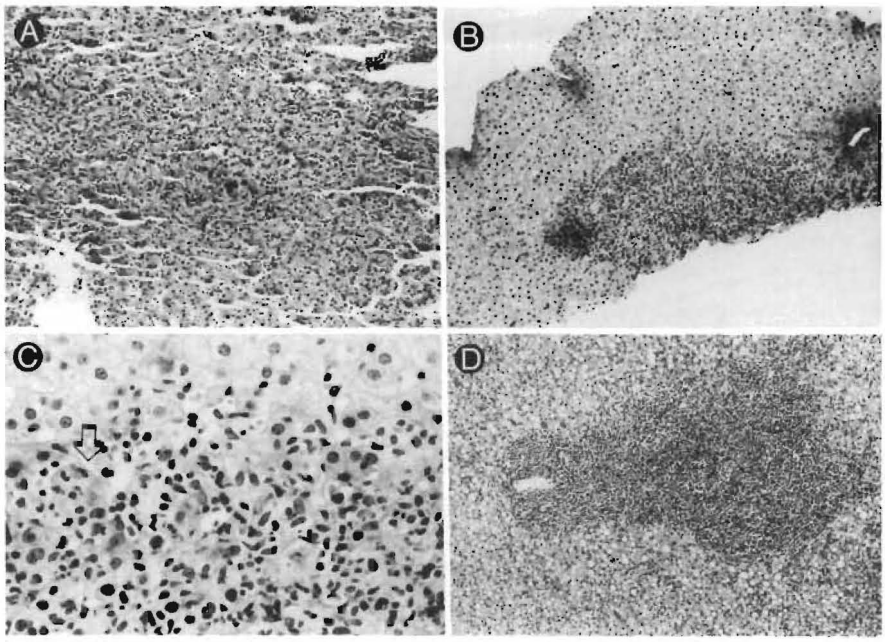

FIG 58.
The EBV causes a spectrum of pathologic lesions in the liver, ranging from mild lobular hepatitis with sinusoidal lymphocytosis **(A)** to granulomatoid collections **(B)** of immunoblastic lymphocytes, which can be associated with hepatocyte necrosis (**C,** *arrow*). Epstein-Barr virus–driven lymphoproliferative lesions in the liver **(D)** are characterized by a monomorphic infiltrate that overruns the normal architectural landmarks. (From Demetris AJ, Jaffe R, Starzl TE: *Pathol Annu* 1987; 22:347–386. Used by permission.)

infiltrated by tumor is also used to establish the diagnosis of an EBV-related disorder. In the nodes, the changes vary from those seen with infectious mononucleosis[494] to a histology indistinguishable from immunoblastic lymphoma.[489] Immunohistochemical and light-chain immunoglobulin gene rearrangement analysis are used to establish the clonality of the tumors, if present.[488–491]

Adenoviral Hepatitis

Allograft hepatitis due to the ADV has been restricted to primarily the pediatric population, although more recently an unequivocal case in an adult has been identified.[356, 357] Adenovirus usually occurs within a very narrow time frame, namely, 20 to 30 days after transplant, and the patients present with fever and elevated liver injury test results.[357] To date, almost all of the cases of ADV in the transplant population have been caused by viral subtype 5.[357] However, other viral subtypes (2, 11, and 16) have been associated with hepatitis in the general population and could be expected to infect

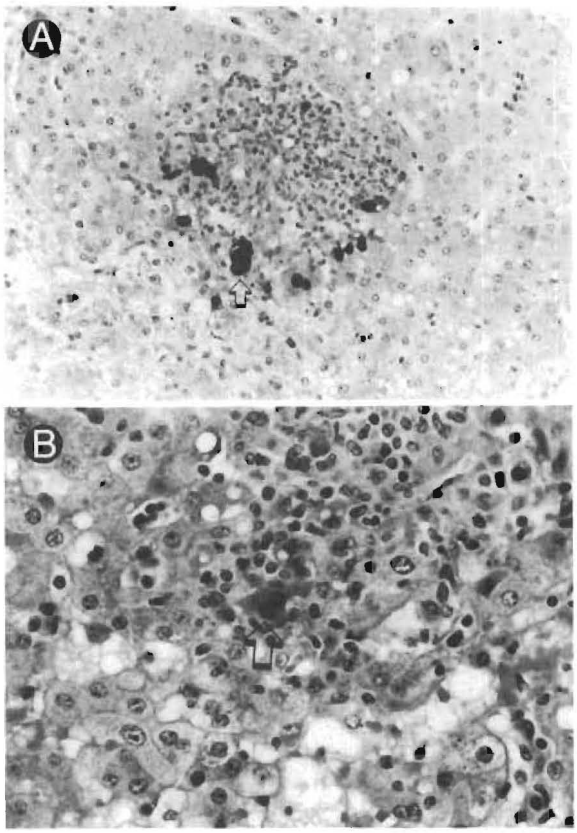

FIG 59.
A, the ADV causes typical granulomas in the liver. Immunoperoxidase stains can be helpful if one cannot identify the inclusion bodies *(arrows).* **B,** at the periphery of the granulomas, infected cells with intranuclear inclusions appear smudgy. (From Demetris AJ, Kakizoe S, Oguma S: Pathology of liver transplantation, in Williams JW [ed]: *Hepatic Transplantation.* Philadelphia, WB Saunders Co [in press]. Used by permission.)

allografts.[495] The diagnosis is made on needle biopsy sampling of the organ,[357] after which immunosuppression should be temporarily stopped.

Histologically, granulomatoid collections of histiocytic cells are randomly located throughout the parenchymal (Fig 59). Hepatocyte necrosis may be detected but usually is less severe than that seen with HSV. Characteristic "smudgy" intranuclear inclusions can be identified in hematoxylin-eosin-stained sections, but experience is required to be confident of the diagnosis without the use of special stains. In infected cells, the chromatin is crowded toward the nuclear membrane, which imparts a muffin-shaped appearance to the nucleus. Immunohistochemical stains are confirmatory.

HEPATITIS VIRUSES

HEPATITIS B VIRUS

Viral hepatitis type B in the posttransplant period is restricted largely to those patients who carried the virus prior to transplantation, although a few patients have acquired an infection, presumably as a result of blood transfusion. Provision of a new liver usually, but not always, lowers the titer of the virus, as measured by the surface antigen,[496, 497] but return of the carrier state is almost universal.[498–502] In spite of this generalization, some chronic carriers have apparently cleared the virus after transplantation[499–503] with passive immunoprophylaxis. In our experience, those chronic carriers who have cleared the virus have been E antibody positive and E antigen negative, although this serologic profile is no guarantee that infection will not recur. Among those recipients who become reinfected, a small percentage will develop a carrier state and experience long-term survival with minimal liver dysfunction. Recapitulation of the original chronic aggressive hepatitis jeopardized the recovery of many of the recipients.[496–499, 501] Delta agent coinfection is an additional confounding factor and recurs along with the B virus.[497, 500, 501] Reinfection of the allograft after transplantation for acute fulminant hepatitis B is less certain, with several patients experiencing long-term survival with viral immunity.[497, 498] The survival with acute disease and fulminant hepatic failure has been acceptable, although less favorable with chronic disease (Fig 60).

In those who develop HBV disease after liver replacement, the on-

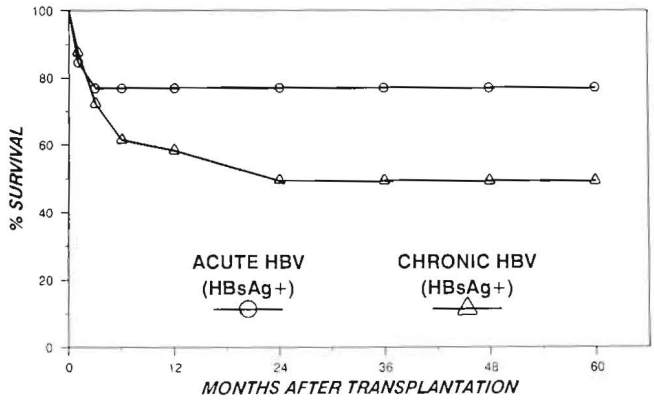

FIG 60.
Patient survival (life table method) after liver transplantation with cyclosporine-prednisone for 65 adults with chronic B virus hepatitis compared with 13 adults with acute B virus hepatitis.

set of symptoms usually occurs 6 to 8 weeks after transplantation. The presentation varies from asymptomatic elevations of liver injury test results to nausea, vomiting, jaundice, and hepatic failure. The clinical syndrome, therefore, is not significantly different from viral hepatitis as seen in other immunosuppressed hosts. Serologic evaluation and needle biopsy of the graft confirm the diagnosis.

Pathologic identification of acute hepatitis B as a cause of dysfunction rests on the recognition of preferential lobular alterations in the absence of significant inflammatory cell damage to bile ducts, arteries, and venular endothelia.[497] However, the pathologic appearance of HBV in the allograft is as varied as the complete spectrum of acute and chronic viral hepatitis as seen in the general population (Fig 61).[145] Simply stated, viral hepatitis in the liver allograft looks like viral hepatitis in other livers except for a relative paucity of inflammation in some cases, even with severe clinical manifestations and pathologic changes.

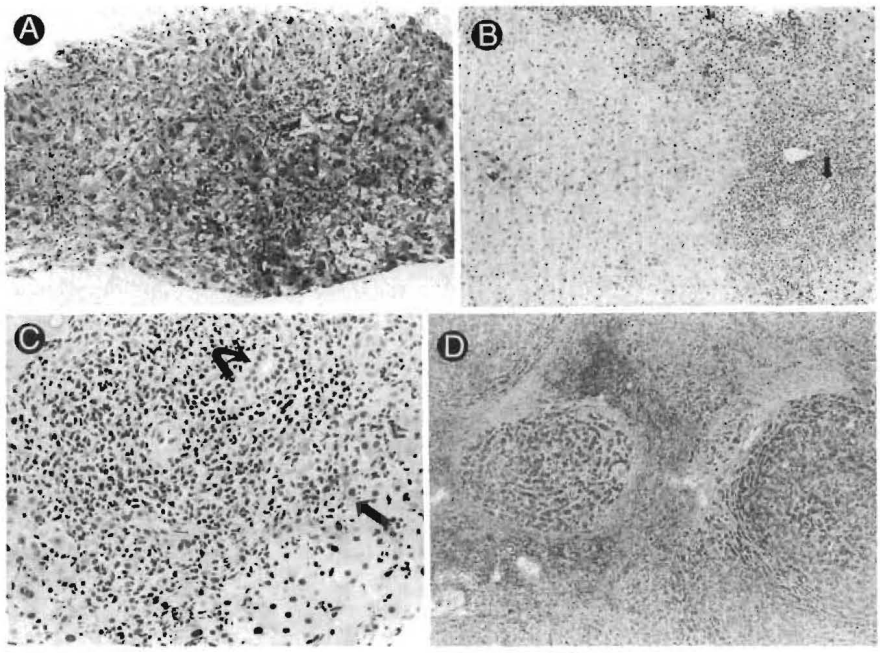

FIG 61.
Hepatitis B virus infection of the allograft causes pathologic lesions similar to those seen in the general population and in other immunosuppressed hosts. In **A** there is an acute hepatitis with lobular disarray, hepatocyte ballooning, and necrosis. **B,** in chronic active B viral hepatitis in the allograft, a portal infiltrate with active piecemeal necrosis (*arrow* indicates intact bile duct) (**C,** *straight arrow*) and preservation of the bile ducts *(curved arrow)* are the identifying features. **D,** the eventual outcome of many cases with chronic active hepatitis after transplantation is graft failure or cirrhosis, which may occur with surprising rapidity (see text).

The natural history of hepatitis B infection of the allograft liver is becoming clearer. In our series of 59 patients who received allografts because of HBV disease, pathologic follow-up was available in 39 of 46 recipients who survived for more than 60 days. Thirty-four of these 39 patients had histologic evidence of recurrent hepatitis B infection, disease, or both.

A very typical sequence of pathologic changes was observed in these specimens. The first evidence of recurrent hepatitis B infection was the detection of hepatitis B core antigen in the cytoplasm of hepatocytes several weeks after transplantation. Little pathologic change was detected at this time. Several weeks thereafter, mild lobular disarray, hepatocyte swelling, and mild spotty acidophilic necrosis with regenerative change coincided clinically with the onset of elevated liver injury test results and signaled the development of disease activity. Most of the specimens at this time had the appearance of a mild acute hepatitis as seen in the general population except for a relative paucity of lobular portal inflammation.

Follow-up of these patients over several weeks to greater than 5 years revealed several clinicopathologic "syndromes." Six of the patients experienced a syndrome of unresolved lobular hepatitis, and five settled into a clinicopathologic profile resembling chronic carriers with little disease activity. Eighteen others developed chronic active hepatitis, and four of these became cirrhotic, 1.5 to 5 years after transplant. A fifth patient rapidly became cirrhotic 147 days after liver replacement without any evidence of intervening chronic active hepatitis after transplantation. Follow-up of the few patients who have apparently cleared the virus with no serologic or histologic evidence of recurrent B viral infection of the liver revealed nonspecific changes in three, non-B chronic active hepatitis in one and acute cellular rejection, which responded to bolstered immunosuppressive therapy, in the remaining patient.

It is not always easy for the pathologist to distinguish between rejection and hepatitis as a cause of malfunction. The most useful feature overall used to differentiate these two causes of malfunction is the focus of lymphocytic damage. The bulk of the injury associated with acute HBV is directed at hepatocytes and is recognized as lobular alterations. Acute rejection, on the other hand, is directed at structures within the portal tracts. In chronic hepatitis, portal inflammation is present, and lobular alterations may be minimal. In these cases, one has to determine if piecemeal necrosis or bile duct destruction is the more prominent feature. It must be stressed that an overall assessment of the entire biopsy specimen with careful examination of each portal tract must be performed. Individual cases may be quite difficult since both bile duct damage and significant piecemeal necrosis may be present. It has been our policy that if a significant amount of duct damage is detected, regardless of the

presence of piecemeal necrosis, a diagnosis of rejection made. A therapeutic or diagnostic clinical trial of immunosuppressive therapy is then initiated. This approach seems prudent, considering the fact that reductions of immunosuppression during hepatitis B infection may result in fulminant liver failure.

NON-A, NON-B HEPATITIS

Although precise identification of at least one of two viruses responsible for non-A, non-B hepatitis has just recently been achieved (hepatitis C),[504] it is undoubtedly a cause of allograft hepatitis.[144, 145, 505] Episodes in patients with cryptogenic cirrhosis, in those with unrelated disorders, and in patients who were thought to have the disease prior to transplantation have been identified. It may therefore be recurrent or develop de novo. The onset of symptoms and laboratory abnormalities usually appear after 6 weeks. The clinical presentation is as variable as that seen in the general population: mild asymptomatic elevation of liver injury test results to massive hepatic necrosis. Bone marrow aplasia, which also can complicate milder attacks of non-A, non-B hepatitis not requiring liver transplantation,[506, 507] has been observed in children a few days or weeks after liver replacement.[508, 509] Four of the nine patients with marrow aplasia survived, usually with slow recovery of the hematopoietic system.[508, 509] At present, the diagnosis is based largely on biochemical evidence of liver injury combined with the histopathologic profile, although supporting serologic data may soon become available.

The histopathologic appearance of presumed non-A-, non-B hepatitis may be as varied as that described for hepatitis B earlier. Needle biopsy specimens from patients thought to be infected during the acute stages show mild Kupffer's cell hypertrophy, spotty acidophilic necrosis of hepatocytes, and a relative paucity of inflammation. However, lobular disarray, mixed inflammatory cell infiltration, hepatocyte ballooning, and necrosis, which may be bridging, have also been seen. The disease may also recur in a more fulminant fashion, as was experienced with two patients in Pittsburgh, where the clinical profile and histologic appearance of the failed graft was remarkably similar to the native organ. Later, features of chronic persistent or active viral hepatitis are not uncommon (Fig 62).

Pathologically, in acute disease the diagnosis is based largely on the lobular insult and is usually not difficult to differentiate from rejection. In chronic disease where the histologic appearance is that of chronic persistence or active hepatitis, it may be hard to differentiate from an indolent rejection reaction. It has been our policy that if there is evidence of significant duct damage, rejection is considered present.[145]

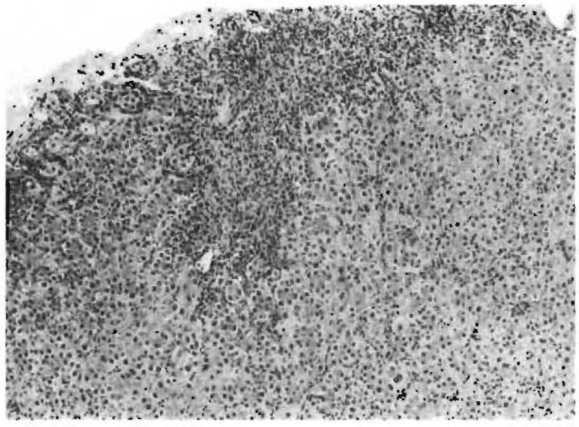

FIG 62.
The histologic appearance of presumed non-A, non-B viral hepatitis in the allograft is similar to the type B virus. In this case a chronic active hepatitic lesion is seen. (From Demetris AJ, Kakizol S, Oguma S: Pathology of liver transplantation, in William JW [ed]: *Hepatic Transplantation*. Philadelphia, WB Saunders Co [in press]. Used by permission.)

HEPATITIS A VIRUS

Although fulminant hepatitis A virus has been an indication for liver replacement, it has not as yet been identified as the cause of allograft dysfunction. Based on these observations, we expect that it may appear quite similar clinically and histologically to that seen in nongrafted livers.

THE PATHOLOGIST'S VIEW OF BILIARY TRACT COMPLICATIONS

Anastomotic breakdown, necrosis, strictures, ascending infection, and obstruction can affect the allograft biliary tree.[84–90, 93] Although these complications are not uncommon in isolation, they often reflect arterial pathology since the biliary tree is dependent solely on the hepatic artery for its blood supply.[146] Most often the diagnosis of biliary complications is made on the basis of clinical symptoms and the results of radiologic procedures such as ultrasonography and cholangiography (see previously).[84–90] In addition, during the early postoperative period, most patients have a percutaneous T tube in place that permits ready access to the biliary tree for radiologic procedures and assessment of bile flow.

Needle biopsies are less useful than radiologic evaluations for the diagnosis of large biliary tract disorders because of the relative nonspecificity and insensitivity of early histologic findings.[144, 145] However, when access to the biliary tree is restricted, (late posttransplant period), biopsies may be more valuable as a screening tool. Biliary

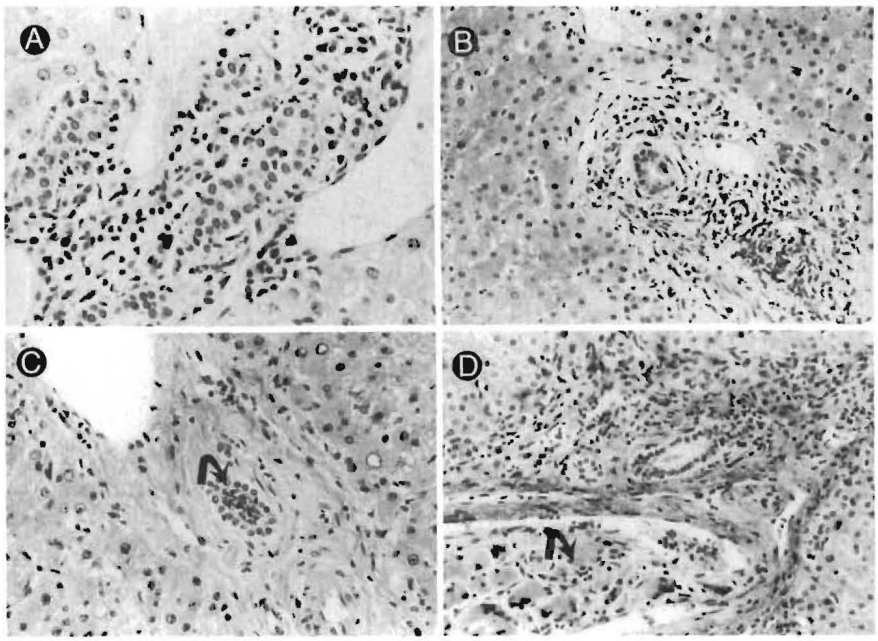

FIG 63.
The histologic manifestation of biliary tract complications in the allograft are similar to those in nonallografted livers. The most important of these features is the neutrophilic predominance of the portal infiltrate in the absence of reactive biliary epithelial cell changes, as shown in this case of acute cholangitis **(A).** When the biliary tree is obstructed, periductal edema accompanies the acute portal inflammation, and cholestasis is present in the lobules **(B).** Fistulas between the biliary tree and the vasculature are recognized by the presence of RBCs in bile ducts (**C,** *arrow*) or bile concretions in blood vessels (**D,** *arrow*). (From Demetris AJ, Kakizol S, Oguma S: Pathology of liver transplantation, in William JW [ed]: *Hepatic Transplantation.* Philadelphia, WB Saunders Co [in press]. Used by permission.)

tract complications that have been recognized histologically include duct stricturing, obstruction, acute cholangitis, and biliary-vascular fistulas.[144, 145] The histologic features of these complications are identical to those seen in the nonallograft liver (Fig 63), which include a predominantly neutrophilic portal infiltrate, periductal edema, intraepithelial and intraductal neutrophils, mild ductular and cholangiolar proliferation, centrilobular hepatocanalicular cholestasis, and small clusters of neutrophils scattered throughout the lobules. Although acute cellular rejection is included in the pathologic differential, biliary tract disorders most commonly are associated with a neutrophilic and eosinophilic portal infiltrate, whereas rejection shows a predominance of mononuclear cells in the portal tracts.

Recognition of biliary-vascular fistulas may be first noticed by the

pathologist on needle biopsies and requires alertness to the abnormal presence of RBCs in bile duct lumens or, conversely, bile concretions in blood vessels (see Fig 63). Radiologic localization of the abnormal communication, followed by corrective surgery or retransplantation, is the usual course of events.

SEPSIS

Infection of the blood, especially with gram-negative organisms, can cause allograft dysfunction, which is usually manifested as jaundice. Histologic alterations are also observed in the graft as a result of sepsis (endotoxemia) and are identical to those seen in nonallograft livers.[510] These changes include cholangiolar proliferation with bile plugging, acute cholangiolitis usually without cholangitis, and hepatocanalicular cholestasis. Kupffer's cells are often hypertrophied, and small clusters of neutrophils can be observed in the lobules.[144, 145]

DIFFERENTIAL DIAGNOSIS OF DRUG AND TOXIC INJURY

Drug and toxic injury to the allograft liver are difficult to identify with certainty. The patients receive many potential hepatotoxic drugs and are subjected to other therapeutic maneuvers that may damage the liver. Therefore, if one strictly adheres to criteria for organ specific toxicity, it is extremely difficult to incriminate any agent. Regardless of these difficulties, erythromycin, prolonged peripheral alimentation, high-dose steroids, and azathoprine have been strongly suspected as causes of allograft malfunction.[144, 145] One might expect the allograft liver to behave similar to nongrafted livers in regard to drug toxicities, unless an MHC-restricted immunologic reaction is involved.

INFLUENCE OF HISTOCOMPATIBILITY

Histocompatibility leukocyte antigen (HLA) or MHC compatibility has been shown to either improve patient survival or reduce the onset or incidence acute rejection in kidney[511] and heart allografts.[512] Data collected by Markus and associates concerning the role of HLA matching in liver transplantation were less clear cut.[513] No patient survival advantage was observed for HLA compatibility. By contrast, a statistically significant penalty in terms of survival was detected when either the A, B, or DR locus was matched. Although rejection as a cause of graft failure was more common when DR mismatching was present, other causes of patient death or graft failure were even more common when either class I or II loci were matched. Primary

nonfunctioning of the new liver was particularly common in DR-matched grafts. However, the diagnosis "primary nonfunction" is somewhat of a wastebasket category, which often includes preservation injury, antibody-mediated rejection, vascular thrombosis, surgical misadventures, and cardiovascular instability in the donor or recipient. Markus and associates suggested that MHC compatibility may provide the ideal setup for recurrent disease since some of the immunopathologic mechanisms important in the native diseases are thought to be MHC restricted.[513] Alternatively, they suggested that the alloresponse itself may be MHC restricted. Donaldson and colleagues proposed a similar hypothesis.[459] They found that DR-matched but A and/or B locus–mismatched grafts were more prone to develop the vanishing bile duct syndrome (chronic rejection). They suggested that induction of DR antigens on bile duct cells enabled these cells to act as antigen-presenting cells, presenting the mismatched class I antigens in an MHC-restricted fashion to recipient effector cells.

There are many possible explanations for the somewhat peculiar observations made with respect to HLA matching and liver allograft outcome. Like other allografts, livers seem to experience a lower incidence of rejection when the DR locus is matched. Paradoxically, there does not appear to be a patient or graft survival advantage for DR or class I matching. This may be due to graft loss or patient death from causes other than rejection (e.g., technical mishaps and infection). A higher incidence of recurrent native disease in HLA-matched patients may be a possibility, since cellular "immune" mechanisms are thought to play a prominent role in native hepatic disease. This contrasts to most cardiac and renal diseases for which transplantation is performed, where cellular immunity is not strongly implicated. This argument is appealing because the immune damage purportedly mediated by T lymphocytes in liver diseases such as hepatitis B is thought to be MHC restricted. However, the pathogenic mechanisms responsible for many native liver diseases have yet to be elucidated. Furthermore, recurrent disease must be proved after liver grafting, which is not an easy task. Rather than to continue speculation, reanalysis of the data after collection of a much larger patient population seems wise.

CANDIDACY, ORIGINAL DISEASE, AND OUTCOME

In spite of the diversity of etiologies, manifestations, and variability of technical problems with different diseases, the survival curves have not been greatly influenced by the original diagnosis with the exceptions of fulminant hepatic failure, chronic active hepatitis due to B virus, and liver malignancies (Fig 64).[498, 499, 514–517] These obser-

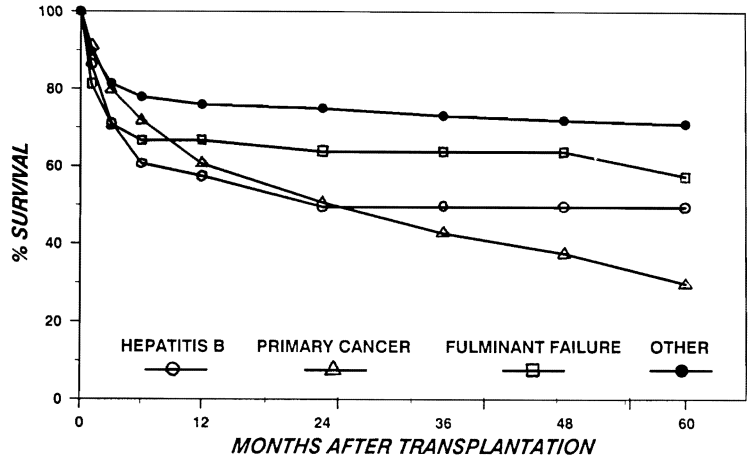

FIG 64.
Comparison of patient survival rates (life table method) after liver transplantation in adults receiving cyclosporine-prednisone for HBsAG-positive postnecrotic cirrhosis (66 cases), primary hepatobiliary cancer (89 cases), fulminant hepatic failure (48 cases), and other nonmalignant indications for liver transplantation (827 cases).

vations, which have been extensively documented, are analogous to those in renal transplantation where the original kidney disease has been said to have little influence on the outcome.

However, the foregoing summary is oversimplified, which could degrade the value of information summarized in the following pages that covers not only the influence of disease on outcome but also many other factors, including the severity of the disease at the time of the liver replacement, issues of organ supply, and the role of socioeconomic factors. Thus, the serious student of hepatology, liver surgery, and liver transplantation is urged to read this section and not skip to the next one.

The medical issues of transplant candidacy are relatively clear. If a patient has end-stage nonmalignant liver disease that does not recur in the hepatic graft, there is little debate about the logic in principle of transplantation (Table 11). Transplantation is more debatable if recurrence of a nonneoplastic disease is a predictable problem. The most controversial indication for liver transplantation is for the treatment of hepatic malignancies. However, none of these broad applications can be arbitrarily excluded from future trials because there is such heterogeneity in each of these three categories.

In adults, the diseases most commonly represented have been postnecrotic cirrhosis, primary biliary cirrhosis, alcoholic cirrhosis,

TABLE 11.

Indications for Liver Transplantation in 438 Pediatric and 1,031 Adult Patients

	Pediatric	Adult	Total	%
Acute hepatic failure	23	48	71	4.8
Postnecrotic cirrhosis	44	361	405	27.6
Alcoholic cirrhosis		113	113	7.7
Biliary atresias	236	5	241	16.4
Congenital hepatic fibrosis	6	4	10	0.7
Cystic fibrosis	3	4	7	0.5
Inborn errors of metabolism	75	52	127	8.6
Familial cholestasic syndrome	16		16	1.1
Neonatal (giant cell) hepatitis	7		7	0.5
Primary biliary cirrhosis		210	210	14.3
Secondary biliary cirrhosis	9	13	22	1.5
Primary sclerosing cholangitis	4	99	103	7.03
Budd-Chiari syndrome	2	21	23	1.6
Benign tumors	4	9	13	0.9
Primary liver cancer	8	59	67	4.6
Bile duct cancer		18	18	1.2
Metastatic cancer		12	12	0.8
Liver trauma	1	2	3	0.2
Secondary sclerosing cholangitis		1	1	0.1
Total	438	1,031	1,469	100.0

sclerosing cholangitis, inborn errors of metabolism, and a heterogenous group of hepatic malignancies (see Table 11). The 5-year life survival curves of the principal benign adult diseases are shown in Figure 65. There has been little variability of survival with these benign diagnoses in contrast to the poorer results in the neoplastic group (see Fig 64).

More than one half of the pediatric recipients have had biliary atresia, with inborn metabolic errors a distant second.[514, 516–526] Survival in the biliary atresia patients is inferior to the other categories (Fig 66). The principal mortality has been perioperative and has been related to technical difficulties caused by earlier Kasai operations.

The experience reflected in these life survival curves will influence future case selection. However, other factors could be singly or cumulatively even more important for prognosis than the original diganosis. Judgment about what constitutes candidacy has been in a state of flux since the first clinical attempts in 1963, and the time is not yet ripe to freeze guidelines.

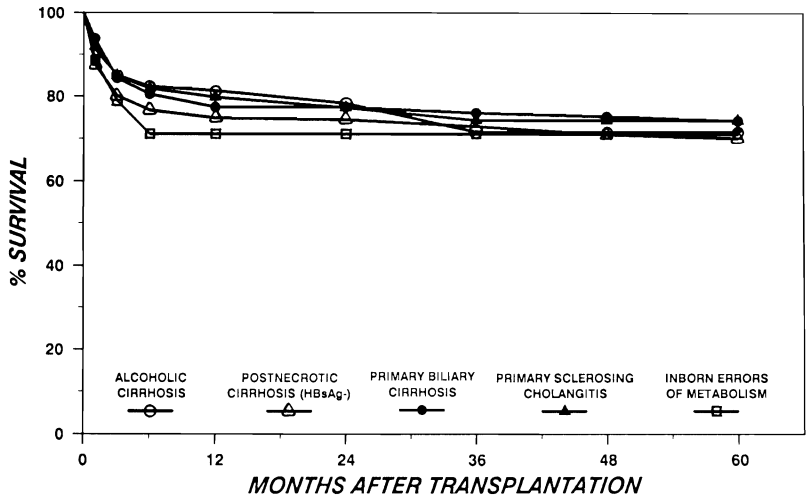

FIG 65.
Patient survival rates (life table method) after liver transplantation using cyclosporine-steroids for the major indications in adults (18 years of age or older at the time they received their first transplant). Included are 296 cases of postnecrotic cirrhosis (excluding HBsAG-positive patients), 210 cases of primary biliary cirrhosis, 113 cases of alcoholic cirrhosis, 99 cases of primary sclerosing cholangitis, and 52 cases of inborn errors of metabolism.

MALIGNANT LIVER DISEASE

In the original efforts at clinical liver transplantation,[18] all of the patients whose reason for transplantation was primary hepatic malignancy and who survived the perioperative period died within 13 months of recurrent tumor. Smaller incidental malignancies behaved differently. The longest survivor in the world today received her new liver at the University of Colorado on January 22, 1970 for biliary atresia. The excised liver contained a 3-cm hepatoma. That little girl, 3 years old at the time of operation, will complete her 20th postoperative year in a few months. She is married to a United States Marine and lives in Okinawa. The same observations with incidental malignancies have been made many times since.[186, 527]

In spite of numerous disappointments, liver transplantation as a means to extend resectability limits for hepatic neoplasms is still being probed by many transplantation teams, often in combination with adjuvant chemotherapy or other experimental treatment protocols.[528–530] The percentage of tumor cases in large programs ranges from 4% to 34%.[514, 518, 519, 531–534] It has been about 5% at the Colorado-Pittsburgh program (see Table 11).

Although strenuous efforts are made beforehand to *rule out* metastases, a high rate of recurrence of all kinds of hepatic malig-

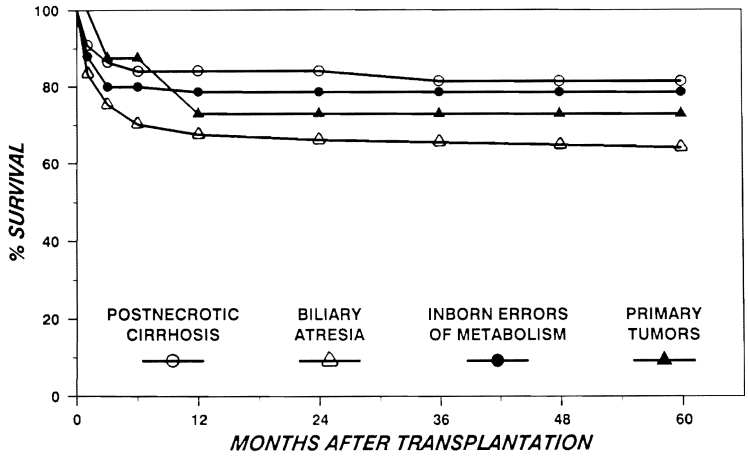

FIG 66.

Patient survival rates (life table method) after liver transplantation using cyclosporine-steroids for the major indications in children (<18 years of age when they received their first transplant). Included are 235 cases of biliary atresia, 75 cases of inborn errors of metabolism, 44 cases of postnecrotic cirrhosis, and 8 cases of primary hepatobiliary cancer.

nancies continues to be seen after total hepatectomy and transplantation.* Metastases have had a tendency to home to the new liver.[18, 531] Death from tumor recurrence has been reported as early as 3 months, but the principal mortality has been between 6 and 36 months (Fig 67). Small incidental malignancies that develop in cirrhotic livers usually do not recur, but extensive cancers recur in the majority of cases.[527, 531, 534, 535] The results also are influenced by the tumor cell type (Fig 68), presence of hilar lymph node metastases, and presence or absence of underlying liver disease.[67, 499, 527, 531, 536]

Fibrolamellar hepatoma, a slowly growing relatively uncommon hepatocellular carcinoma with distinctive histopathologic features,[537, 538] is a "favorable" malignancy, and long survival has been accomplished even of patients with huge tumors that have invaded the diaphragm.[67, 527, 531, 534, 539] Most authors have reported poor results with duct cell carcinomas, including the small Klatskin tumors that are located high in the hepatic hilum,[527, 530–532, 534] but a recent German experience has been more optimistic.[536] Recurrence has been exceptionally common in patients with conventional hepatocellular carcinomas.[527] Epithelioid hemangioendotheliomas[540] occupy an intermediary position in that survival for at least 2 years has been achieved in more than one half of reported patients.[531, 541]

Whether to continue treating primary hepatic malignancies is con-

*References 18, 499, 514, 527, 531, 534–536.

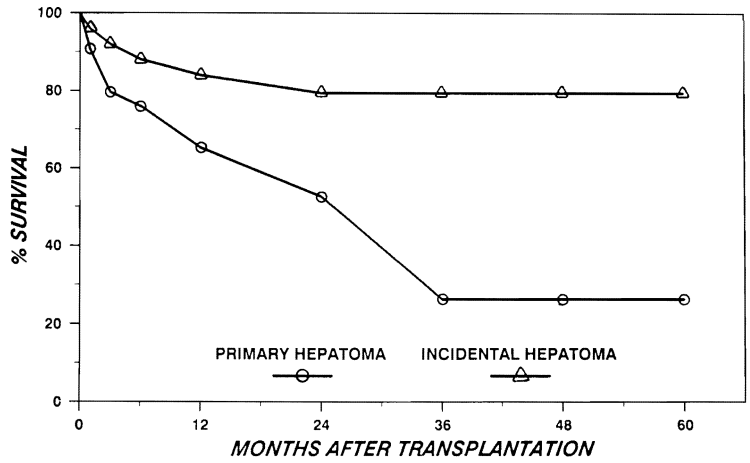

FIG 67.
Patient survival rates for (life table method) after liver transplantation for primary hepatocellular cancer compared with liver transplantation for nonmalignant diseases but with an incidental hepatocellular carcinoma discovered on subsequent pathologic examination of the removed native liver.

troversial. It is difficult to resist continuing these efforts for the treatment of hepatic malignancies in carefully screened recipients, not only because there is a chance of success but because there is so much potential information to be acquired about the biologic behavior of these tumors and the influence on them of immunomodulation and chemotherapy. Even a few patients with metastatic liver disease have benefited from liver transplantation,[514, 529, 530, 535, 542, 543] particularly when the primaries were neuroendocrine in origin.[514, 535, 536] In one remarkable case, a patient with multifocal liver metastases from a carcinoma of the breast was successfully treated with chemotherapy, autotransplantation of the bone marrow, and liver transplantation.[529] Ultimately, she developed recurrences; further efforts at applying this concept have failed.[530]

BENIGN DISEASE: THE POTENTIAL CANDIDACY POOL

The criteria for case selection were blurred until 1980 because of a mortality within the first postoperative year that exceeded 60% (Fig 69). It was impossible to tell for certain how much case selection was influencing results. When this was changed with the advent of cyclosporine (see Fig 69), some issues of candidacy became clearer.

In addition, with the better expectations and more general avail-

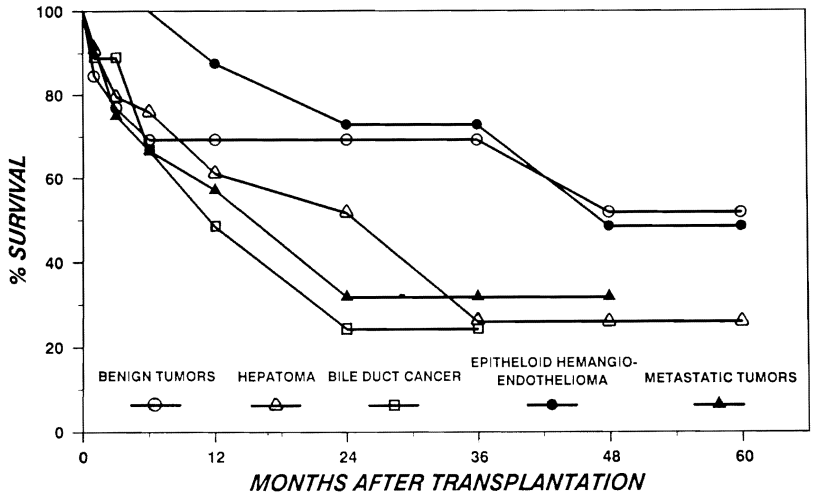

FIG 68.

Patient survival (life table method) after liver transplantation for benign and malignant tumors that could not be treated by subtotal resection. Included are 13 patients with benign tumors, 54 with hepatocellular carcinoma, 18 with bile cancers, 8 with epithelioid hemangioendotheliomas, and 12 with secondary tumors originating outside the liver.

ability of liver transplantation, the conceptual appeal of liver transplantation was so great that this procedure became the court of last appeal for an astonishing number of patients with lethal hepatic disease. Estimates of yearly need for liver transplantation have varied from as low as 15 per million population[67] to as high as 200 per million in an unpublished Canadian projection (Dr. Cal Stiller, personal communication, University of Western Ontario, London, Ontario). Based on these figures, and without a cap imposed by organ supply, between 4,000 and 50,000 liver transplantations per year could be needed in the United States. Since there are no practical means of artificial organ support analagous to renal dialysis, the waiting list of recipients does not grow from year to year.

The variability of inclusion and exclusion factors of candidacy account for the wide-ranging estimates of need. Some of the earlier low estimates were based on the assumption that patients with tumors would be excluded, that the upper age limit would be 50 years, that patients with Laënnec's cirrhosis or other "sin factors" would be eliminated from candidacy, and that the list of applications would not be as extensive as has proved to be the case. Furthermore, a number of factors or diagnoses that precluded or strongly discouraged transplantation 5 or 10 years ago are no longer absolute contraindications, and some are no longer even questionable.

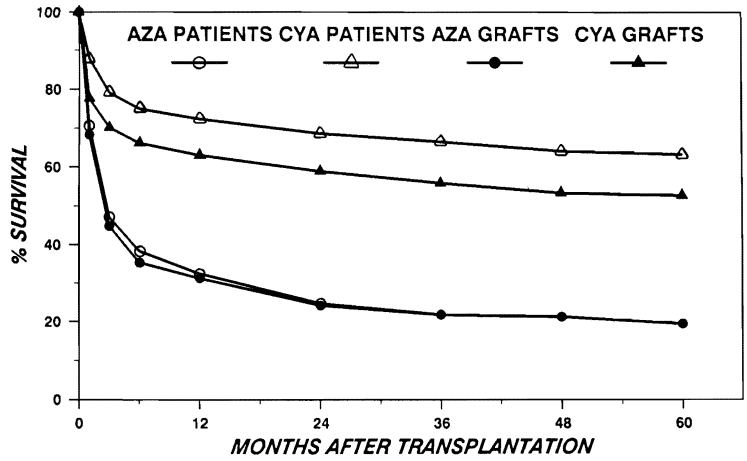

FIG 69.

Patient and primary graft survival rates (life table method) after liver transplantation. One hundred seventy recipients were treated with azathioprine *(AZA)* and steroids between March 1963 and February 1980 compared with 1,469 recipients treated with cyclosporine *(CYA)* and steroids between March 1980 and December 1988. Follow-up is complete through 31 July 1989.

Laënnec's Cirrhosis

A prime example is alcoholic cirrhosis. If there is a history of alcoholism, it is necessary on behalf of the patient to obtain consultation with those who understand this disease. The objective is to ensure abstinence after transplantation by arranging in advance for holistic care. In properly selected cases, Laënnec's cirrhosis may be a good indication (see Fig 65).[544] Recidivism with alcohol use has been less than 10%.

Older Age

An absolute upper age limit has been eliminated by demonstrating that recipients older than 50 years have a similar 5-year survival as younger adults.[545]

Young Age or Small Size

The transplantation of very small infants, even in the newborn period of life, has become common, but the results are not as good as with larger children.[546, 547]

Portal Vein Thrombosis

Although this was formerly a contraindication to transplantation,[548, 549] the newly developed vein graft techniques (see Fig 27) routinely allow liver replacement in recipients who have throm-

bosed portal, splanchnic, or superior mesenteric veins.[549, 550] The vein grafts are jumped from the superior mesenteric vein below the transverse mesocolon, brought anterior to the pancreas, and used for a portal anastomosis in the hepatic hilum.

Multiple Previous Operations

Previous upper abdominal operations can complicate transplantation enormously, particularly in patients with small cirrhotic livers that have extensive scarring of their inflow and outflow vessels with obliteration of potential planes of dissection. The routine measurement of liver size with imaging techniques helps to identify such problem cases in advance.[551] The portal vein is always studied for patency using ultrasound and dynamic computed tomography (CT) scanning techniques. In uncertain cases, magnetic resonance imaging is used. Splenectomy or any kind of shunting can alter the portal vein, and the majority of complications from transplant portal vein reconstruction have been in patients with such earlier operations.[130] The mesocaval and the distal splenorenal (Warren) shunts have been the least harmful of these procedures since they do not involve dissection of the portal hilum. When transplantation is performed, it is necessary to close the shunt to have optimal vascularization of the graft.

The usual indication for a shunt operation is variceal hemorrhage, and the objective is to reduce portal hypertension. Should shunting operations ever be recommended as treatment for variceal hemorrhage, knowing that these procedures can jeopardize the ultimate step of liver transplantation? Probably uncommonly, since endoscopic sclerosis of varices is an effective alternative.[552] In some patients with child's class A (good risk) cirrhosis, a distal splenorenal anastomosis might be the preferred way to relieve portal hypertension. We are using this approach in a small number of highly selected patients. However, it is important to emphasize that the liver transplantation itself decompresses portal hypertension through the capillary bed of the normal new liver. In patients who had variceal bleeding and who were too sick to be considered for any operation other than transplantation, the 5-year survival after liver replacement was far superior to that reported in series of generally better-risk patients treated with shunting operation.[553] The obvious limitations of the shunt approach to variceal bleeding has greatly reduced the frequency of portal diversion procedures in Western countries.

Other operations in the upper abdomen that were designed to palliate complications of liver disease can create even more serious problems. Examples are procedures that disconnect venous collaterals going to lower esophageal varices and radical duct reconstructions such as those used to treat sclerosing cholangitis or biliary atresia (Kasai operation).

As an alternative to these open operations, there has been greater use of interventional radiologic or endoscopic procedures, such as sclerosis of esophageal varices, and transhepatic duct stenting or dilatation. However, problem patients with previous shunts, duct reconstructions, or other operations in the hepatic hilum should not be denied transplantation for this reason. Although the transplant operations are made more formidable, the results in experienced hands can be almost as good as with a virgin operative field.[74, 554–558]

Chronic B Virus Carrier State

It was already mentioned that there is a very high rate of recurrent chronic active hepatitis in these patients, for which there is no effective prevention. Because of this, some programs exclude B virus carriers from candidacy. However, the fact that many such patients have achieved benefit from transplantation makes it difficult to make the carrier state an absolute contraindication.

Most efforts to treat HBsAb carriers with hyperimmune globulin (HBIgG) or interferon alpha have failed.[497, 498, 501, 503] The volume of commercial HBIgG that has been required to treat these patients has been so large as to be impractical.[503] However, a human monoclonal antibody directed against hepatitis B viruses has been produced (Sandoz Corporation, East Hanover, New Jersey) by fusing peripheral blood lymphocytes from an immune adult human male to a mouse × human myeloma cell line.[559] The resulting human monoclonal HBIgG is 50,000 times more potent than commercially available HBIgG prepared from the blood of immune donors. Seven patients were treated with this monoclonal HBIgG beginning preoperatively or at the anhepatic phase of liver transplantation.[54] The first recipient had reduction of surface antigen titer from very high to barely detectable levels. In the second patient, the surface antigen level was undetectable for 5 months, after which it reappeared in low titer at the same time as core antigen was identified in the hepatocytes of a biopsy specimen that otherwise was normal. The half-life of this human monoclonal IgG was long enough to allow maintenance of an antibody excess with injections 2 to 4 weeks apart.[54] Five patients have been treated with larger doses, and all are free of antigenemia after 2 to 7 months. It remains to be seen if the recurrent disease pattern is appreciably altered by this kind of therapy.

Recipients who possess antibodies directed against the HBV surface antigen have been free of hepatitis B virus following transplantation. However, it has been recently recorded that patients with the human immunodeficiency virus (HIV) can regress from an apparently immune state, as defined by anti–B virus antibodies, to an infectious carrier state, apparently by reactivation of residual virus as their immune system fails.[560] Theoretically, the same thing could oc-

cur in a liver transplant recipient maintained on standard posttransplant immunosuppression therapy.

Non-A, Non-B Hepatitis

Recurrence of non-A, non-B hepatitis[144, 505] has not been common. The low incidence of recurrence may merely reflect the difficulty of establishing the diagnosis.

Other Recurrent Diseases

The only other unequivocal example of disease recurrence has been with the Budd-Chiari syndrome.[498, 499, 561, 562] This can be prevented with anticoagulation.[561, 563] An initial report of recurrence of primary biliary cirrhosis[564] in three patients has recently been followed by an update on these patients and evaluation of 12 more primary biliary cirrhosis patients who have survived for more than 1 year. A surprising percentage[565] of these long-term survivors showed clinical and histologic evidence of recurrent disease. Other groups have not been able to confirm these observations in larger series,[447, 566–568] although the antimitochondrial antibodies usually do not disappear after transplantation or else they reappear after disappearing transiently.[566, 568] The reason for this discrepancy is not readily apparent, but it appears that cyclosporine may alter disease progression and histology of primary biliary cirrhosis affecting either a native liver or allograft.[565] Therefore, recurrences will probably not be severe or frequent enough to vitiate the value of transplantation.

A syndrome resembling sclerosing cholangitis in a liver homograft has been reported,[569] but the same diagnosis has been made after transplantation in patients who had non–biliary tract disease.[144] There has been one report of recurrent autoimmune hepatitis.[570]

Human Immunodeficiency Virus Carrier State

Whether patients with antibodies to HIV should be excluded from candidacy is an unresolved issue. When screening tests for this disease became generally available in the spring of 1985, examples of HIV infections in kidney recipients were almost immediately reported.[571, 572]

During late 1985, a massive study of the stored sera of 1,043 kidney, heart, or liver recipients treated between 1981 and 1986 was begun at the University of Pittsburgh.[573] Eighteen (1.7%) were found to be asymptomatic carriers. The liver recipients were most commonly affected. In about one third of the liver recipients, the HIV antibodies were demonstrated in their sera, which had been collected and stored before the transplantation. Seroconversion after liver transplantation occurred in the remaining patients, for a total incidence

of 2.6%. The liver allograft itself was a source of infection in a minority of cases,[573, 574] and most infections were attributed to blood component therapy. Seroconversion still occurs at Pittsburgh,[573] as well as other institutions, despite the institution of screening enzyme immunoassays in March 1985.[575, 576]

Almost certainly the presence of HIV antibodies would have precluded candidacy if the diagnosis in the foregoing cases had been made in advance. As it turned out, these unfortunate victims of HIV as well as 7 additional patients became available for long-term study under immunosuppression.[577] Eleven of these 25 recipients were infected before transplantation, although this was not known until later in 8. The other 14 were infected perioperatively. Ten of the 25 recipients were infants or children. The organs transplanted were the liver (n = 15) and the heart or kidney (n = 5 each). After a mean follow-up of 2.75 years (range 0.7–6.6 years), 13 recipients are alive. Survival is 7 out of 15, 2 out of 5, and 4 out of 5 of the liver, heart, and kidney recipients, respectively. The best results were in the pediatric group (70% survival), in which only 1 of 10 patients died of AIDS. In contrast, AIDS caused the death of 5 of 15 adult recipients and was the leading cause of death. Transplantation plus immunosuppression appeared to shorten the AIDS-free time in HIV-positive patients compared with nontransplant hemophiliac and transfusion control groups. Accidental accrual of HIV-positive transplant recipients has slowed markedly since the systematic screening of donors, recipients, and blood products was begun in 1985. However, patients known to be HIV positive are still being treated.

It is clear that many patients can have prolonged benefit from liver transplantation in spite of having positive HIV test results. How to use this information for decision making varies from center to center. The most commonly accepted policy in the United States is to screen all recipients but not to exclude transplantation solely because of a positive HIV test result. If transplantation is undertaken, the health care personnel must be protected from infection. It is a miracle that none of the surgeons who operated on our patients in the early 1980s without knowing the risk has (to our knowledge) been infected. Screening of potential donors for HIV is obligatory at all centers, and a 50-minute test for this purpose has been described.[578] The use of tests that identify the HIV antigens in addition to the antibodies[579] may make donor screening more foolproof than it presently is.

TIMING OF TRANSPLANTATION

In the early days of liver transplantation, this therapeutic step seemed so drastic that it was used as a last resort. What was then defensible conservatism has become regressive today if the patient is

allowed to deteriorate to the point of requiring life support systems before thinking of the transplant option. The rapidity of this deterioration is highly variable.

FULMINANT HEPATIC FAILURE

The diagnosis of fulminant hepatic failure (FHF) can be made when there is sudden massive necrosis of a liver that previously has functioned normally.[580–582] The term FHF has not been used for acute exacerbation of previously unrecognized chronic disease or for acute Wilson's disease. It was rarely treated with liver transplantation before 1982.[67] The results with transplantation has not been good enough to justify this drastic step for a disease syndrome from which recovery might occur in 5% to 20% of cases.[580–582] Since then, FHF has been accepted as an emergency indication for transplantation in almost every liver transplant program worldwide. In several large series,[583–591] the predominant diagnoses have been non-A, non-B hepatitis, B virus hepatitis, and toxic hepatitis from a variety of agents. Mushroom poisoning has been a much publicized toxic etiology.[592] In our hands, the original diagnosis has strongly influenced the outcome (Fig 70). The best results have been with B virus hepatitis.

A decision to proceed with liver replacement often must be made in a few hours. The systematic collation of multiple parameters can help distinguish patients who have a good chance of recovery from those who will die without transplantation.[593, 594] The etiology of the FHF may be an important prognostic determinant.[594] Premonitors of imminent death include relentless progression over a 7- to 14-day period, grade 3 or 4 encephalopathy, severe coagulopathy, rapid shrinkage of the liver as documented with imaging techniques, metabolic acidosis, cardiovascular instability, and sepsis.[585, 586] By the time there is grade 4 encephalopathy and ventilator dependence, it usually is too late.

If transplantation is performed before these grave findings, some livers with reversible lesions may be replaced unnecessarily. A liver biopsy after correction of the coagulopathy may provide decisive information. If clotting cannot be corrected well enough to permit a closed needle biopsy, the patient can be explored with a new liver in hand with the option of aborting the operation if the open biopsy looks favorable histopathologically. In spite of the pitfalls associated with liver replacement for FHF, current posttransplant survival rates of 55% to 75%[583–591] compare favorably with the most optimistic projections of 20% for medical management alone. The results make it certain that these efforts will continue. The perioperative mortality frequently has been due to brain stem herniation during or just after transplantation, sometimes in spite of continuous monitoring of in-

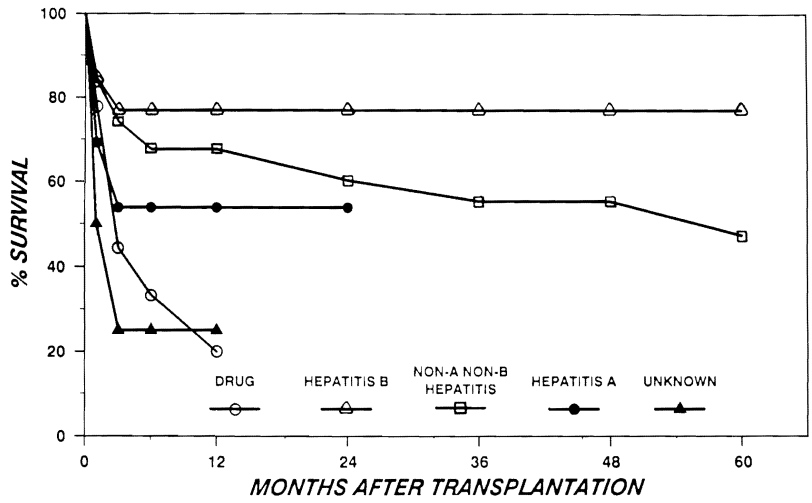

FIG 70.

Patient survival (life table method) after liver transplantation in adults and children for fulminant hepatic failure. Included are 9 cases of drug-related liver failure, 13 cases of acute B virus hepatitis, 31 cases of acute non-A, non-B hepatitis, 13 cases of acute hepatitis A, and 4 cases of fulminant hepatic failure of unknown etiology.

tracranial pressure. Early referral to liver transplant centers, extremely aggressive evaluation plus medical treatment, and an early decision for surgical exploration with immediate transplantation as an option will be necessary to improve results.

It will be unfortunate if the availability of transplantation causes the therapeutic pendulum to swing too far toward liver replacement. In the hepatology unit at King's College, London, the admission of patients with FHF to an intensive care unit, the continuous monitoring of intracranial pressure, and attention to multiple details has resulted in greatly improved survival (more than 50%) of patients whose survival expectation in the past would have been less than 20%.[594] They emphasize the value of IV mannitol treatment as a means of brain shrinkage and hypoventilation on respirator control to encourage cerebrovascular vasodilitation by keeping the P_{CO_2} elevated.[594]

Similarly, Levy Sinclair and associates of Toronto have reported the astonishing recovery of patients (10 or 17) with FHF.[595] Some of their patients had liver biopsies in which it was difficult to find a single living hepatocyte. They ascribed their success to prostaglandin E, namely, Prostin, a synthetic prostaglandin that can be given intravenously or orally. In their opinion, an important, and possibly

the principal, value of Prostin was to preserve the integrity of the hepatic microvasculature and thus to ensure a viable scaffold on which regeneration could proceed.

END-STAGE CHRONIC DISEASE

Ideally, a candidate for liver replacement should have an unequivocal need for transplantation but still be well enough to participate in the complex process of recovery. A decision to go forward requires input from the primary physician, who may see gradually evolving and often appalling social and vocational invalidism that may not be evident at first examination. The disability may be reflected in the loss of intellectual capacity with encephalopathic dementia, frequent hospitalizations for other complications of liver failure, inability to function in a domestic environment, and arrest of growth and development in infants and children. These issues of quality of life loom large in most patients long before the truly terminal events of chronic hepatic failure. Formulas for candidacy based on liver function tests have not been helpful because the abnormalities in these tests are so variable from disease to disease or even within the same disease. Patients with cholestatic disorders (e.g., biliary atresia and primary biliary cirrhosis) usually become deeply jaundiced with good preservation of hepatic synthetic functions for a long time,[520, 525, 557] whereas patients with hepatocellular disease may not be jaundiced in spite of the most profound depressions in albumin and prothrombin synthesis.[548]

The liability of procrastinating too long before making a decision for transplantation has yet to be defined. In one study in which 12% of candidates died "while waiting," most of the lost patients had arrived at the transplant hospital on ventilators and had GI bleeding, coagulopathies, the hepatorenal syndrome, aspiration pneumonitis, subacute bacterial peritonitis, or other end-stage complications.[596] In another center, the mortality in patients considered too well to be placed on the active waiting list was greater than for those admitted to candidacy.[597] When the mistake of underestimating disease severity with the supervention of a catastrophic complication is made, resuscitation is sometimes successful. However, the outlook after subsequent transplantation is demonstrably degraded,[598, 599] notwithstanding observations in a small group of pediatric liver recipients that disease severity did not seem to influence posttransplantation prognosis.[600]

The most precise studies of disease staging vs. posttransplantation outcome have been in adult patients with primary biliary cirrhosis.[601, 602] In the most recent of these investigations,[601] disease severity was defined with a formula in which age, serum bilirubin level, serum albumin level, prothrombin time, and edema severity accu-

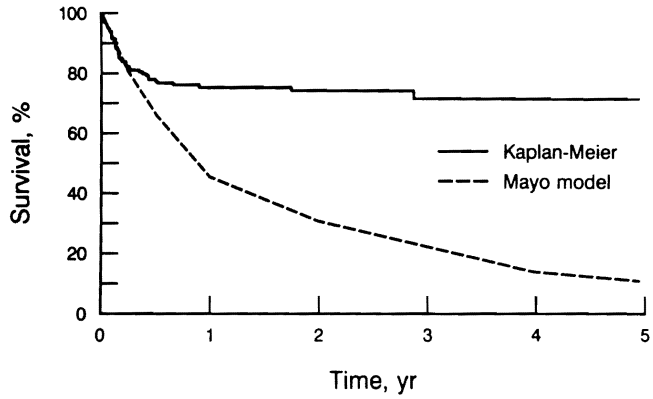

FIG 71.
Comparison of the projected survival in patients with primary biliary cirrhosis when treated with transplantation (Kaplan-Meier) vs. the expected outcome with all alternative forms of treatment (Mayo model). (From Markus BH, Dickson ER, Grambsch PM, et al: *N Engl J Med* 1989; 320:1709–1713. Used by permission.)

rately predicted life expectancy without transplantation.[603] The overall survival in transplant recipients was greatly improved relative to these predictions (Fig 71). However, the patients who were still in reasonable condition had a low perioperative mortality and a 2-year survival of 80%; those with the most serious deterioration had a high perioperative mortality and a 2-year survival of only 55% (Fig 72).[601] The consensus in most centers is that transplantation should be considered at an earlier time before the stage of catastrophic complications is reached.[604]

Recently, an increasing number of patients with normal liver function and nonmalignant hepatic masses have had orthotopic transplantation for polycystic disease,[217,219] cystic hygroma,[605] and adenomatosis. The size of those lesions and the consequent disability and life-threatening complications of the mass lesions were the indications for operation. The largest of the excised livers weighed 16.5 kg.[605]

THE QUESTION OF RETRANSPLANTATION

Before the advent of cyclosporine, retransplantation was a rare event. Consequently, the graft and patient survival were almost synonymous (see Fig 69). Almost immediately after the introduction of cyclosporine, attempts at retransplantation began to be made and with enough success to warrant further such efforts.[67] Now the patient survival curves began to be 10% to 15% above the graft survival

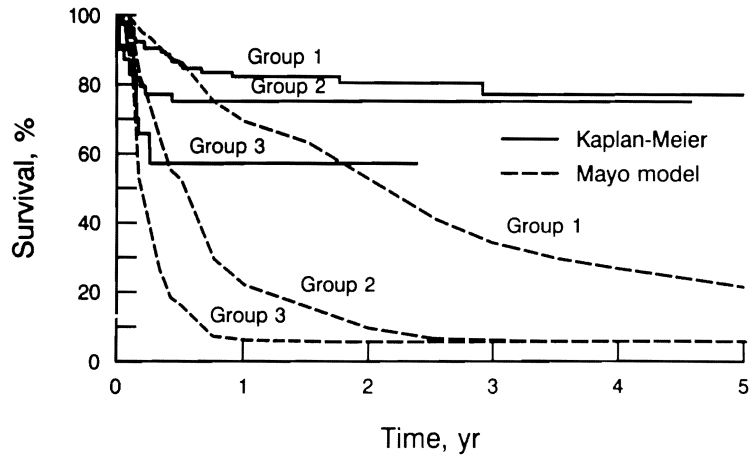

FIG 72.
The influence of disease severity on the projected survival vs. the survival achieved with transplantation. Group 1 patients were in the best condition and group 3 patients in the worst. The prognosis without transplantation was worse in all stratifications, but so were the results after transplantation. This study quantified the penalty of undue procrastination before referral and treatment of patients with this disease. (From Markus BH, Dickson ER, Grambsch PM, et al: *N Engl J Med* 1989; 320:1709–1713. Used by permission.)

curves (see Fig 69). In the United States at the present time, approximately one fifth of all liver grafts are used for retransplantation. The need for retransplantation is often extremely urgent, and many patients have a clinical syndrome comparable with or worse than fulminant hepatic failure.

The success rate with retransplantation is only about one half of that if a primary graft succeeds (Fig 73). The chances of 5-year survival with a "take" of the first graft is about 75% (see Fig 73), almost twice as good as the expectation if two or more grafts are needed. This low success rate with retransplantation has caused ethicists to question the probity of continuing these efforts. Yet, the salvage of so many patients whose first grafts have failed seems more than adequate justification for what has been done.

If the option of retransplantation was foreclosed, it would have a chilling effect on donor acceptance since the philosophy of one chance only would discourage the transplantation of grafts with more than minimal preservation times and would greatly tighten the requirements for donor consideration. No liver transplant surgeon of whom we are aware would countenance the concept of patient abandonment implicit in a policy that precludes or even discourages retransplantation in a patient who is potentially salvageable.

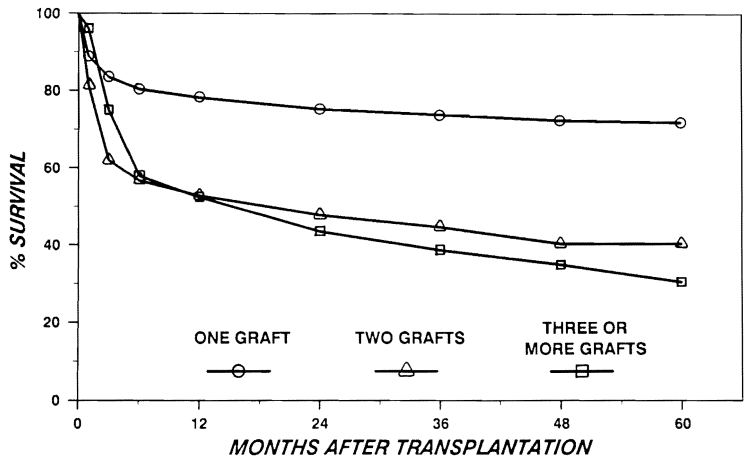

FIG 73.
Survival of patients who required only one graft (1,125 cases) is significantly better ($p < 0.001$) than for patients requiring two transplants (268 cases) or three or more transplants (76 patients).

INBORN ERRORS OF METABOLISM: A PANDORA'S BOX

Patients with liver-based inborn errors of metabolism can be treated by providing a phenotypically normal liver.[237, 464, 606–639] It was recognized long ago and confirmed repeatedly since that the α-globulins, haptoglobin,[237, 464] and group-specific component,[464] as well as other products of hepatic synthesis,[640–645] permanently retain the original metabolic specificity of the donor after transplantation. These observations made it virtually certain that liver transplantation would become a decisive way to treat the inborn errors of metabolism that resulted partly or completely from deficiencies of specific liver enzymes or from abnormal products of hepatic synthesis. This expectation has been fulfilled in many patients for whom follow-ups of as long as 18 years after transplantation are available (Table 12). With other disorders in which the pathogenesis was not well understood, the transplantation itself became a powerful research tool by showing the extent of correction and by elucidating the mechanisms by which correction was accomplished (see Table 12). In one patient, the opposite of a therapeutic correction was achieved in that a coagulation defect present in the donor was conferred on the recipient.[646]

In the majority of these recipients, the inborn error had itself been responsible for damage to the liver, and a conventional indication of liver failure or the development of malignant tumors prompted the

TABLE 12.

Inborn Errors Treated With Liver Transplantation

Disease	Explanation of Disease	Correction of Metabolic Defect	Longest Survival	Associated Liver Disease	Reference
α_1-Antitrypsin deficiency	Structural abnormality of the protease inhibitor synthesized in liver	Yes	13 yr*	Cirrhosis	606–609
Wilson's disease	Abnormal biliary copper excretion, decreased copper binding to ceruloplasmin, and copper accumulation in tissues; autosomal recessive gene mapped to chromosome 13	Yes	16.5 yr*	Cirrhosis	606,610–616
Tyrosinemia	Fumaroylacetoacetate hydrolase deficiency	Nearly complete	7.5 yr*	Cirrhosis, hepatoma	617–619
Type I glycogen storage disease	Glucose-6-phosphatase deficiency	Yes	7 yr*	Glycogen storage, fibrosis, tumors	620
Type IV glycogen storage disease	Amylo-1: 4,1:6-transglucosidase (branching enzyme) defect	Incomplete†	4.5 yr*	Cirrhosis	606,612
Cystic fibrosis	Unknown; pancellular disease, liver often affected	Not known	4.5 yr*	Cirrhosis	621,622
Niemann-Pick disease	Sphingomyelinase deficiency, sphingomyelin storage	Not known	2 yr (died)	None	623
Sea-blue histiocyte syndrome	Unknown, neurovisceral lipochrome storage	No	7 yr*	Cirrhosis	624

Erythropoietic protoporphyria	Hepatic ferrochelatase deficiency, ?overproductive of protoporphyrin by erythropoietic tissues	Incomplete	1.5 yr	Cirrhosis	625,626
Crigler-Najjar syndrome	Glucuronyl transferase deficiency	Yes	4 yr	None	627,628
Type 1 hyperoxaluria	Peroxisomal alanine: glyoxylate aminotransferase deficiency	Yes	8 mo.	None	629
Urea cycle enzyme deficiency	Ornithine carbamoyltransferase deficiency	Yes	8 mo.*	None	630
C protein deficiency	Defective C protein synthesis	Yes	2.25 yr*	None	631
Familial hypercholesterolemia	Low-density lipoprotein receptor deficiency, low-density lipoprotein overproduction	Incomplete	6 yr*	None	632–635
Hemophilia A	Factor VIII deficiency	Yes	4 yr*	Cirrhosis, a complication of blood component therapy	636–638
Hemophilia B	Factor IX deficiency	Yes	6 mo.	Cirrhosis, a complication of blood component therapy	639

*Patients in University of Colorado–University of Pittsburgh series. Follow-up to January 1989.
†Amylopectin deposits found in heart biopsy 4 yr after transplantation.

liver replacement. In these cases, the correction of the metabolic error was incidental. However, an increasing number of transplantations have been carried out solely for the purpose of correcting the inborn error, and in many of these latter patients (see Table 12), the excised liver has been anatomically normal.

Many inborn errors not correctable by liver transplantation can be effectively treated with allogeneic bone marrow engraftment.[647] Determining which kind of transplantation will be effective is crucial whenever somatic metabolic engineering is considered. The guidelines for decision making have become increasingly clear.[54, 647]

TRANSPLANTATION OF MULTIPLE ORGANS

The increasing boldness with which hepatic transplantation has been applied is evident from the many reports of transplantation of the liver plus kidney[217, 219, 648–651] and less frequently used combinations of the liver plus pancreas,[281] liver plus heart,[632–635, 652] and liver plus heart and lung.[653] In these cases, the liver transplantation and transplantation of the other organ have been done in discontinuity so that two standard procedures were performed in the same individual.

A different concept has been the inclusion of the liver in visceral organ clusters. The most complex operation of this kind has been of

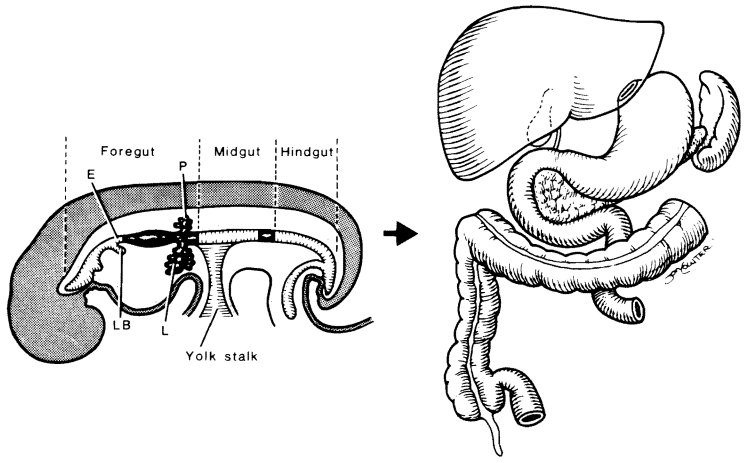

FIG 74.
Left, delineation in embryonal life of that region of the GI tract *(dark shaded)* that was resected in the organ cluster operation (*E* = esophagus; *LB* = lung bud; *L* = liver; *P* = pancreas). **Right,** the adult organs deriving from the shaded primitive analogue. (From Starzl TE, Todo S, Tzakis A: *Ann Surg* 1989; 210:374–386. Used by permission.)

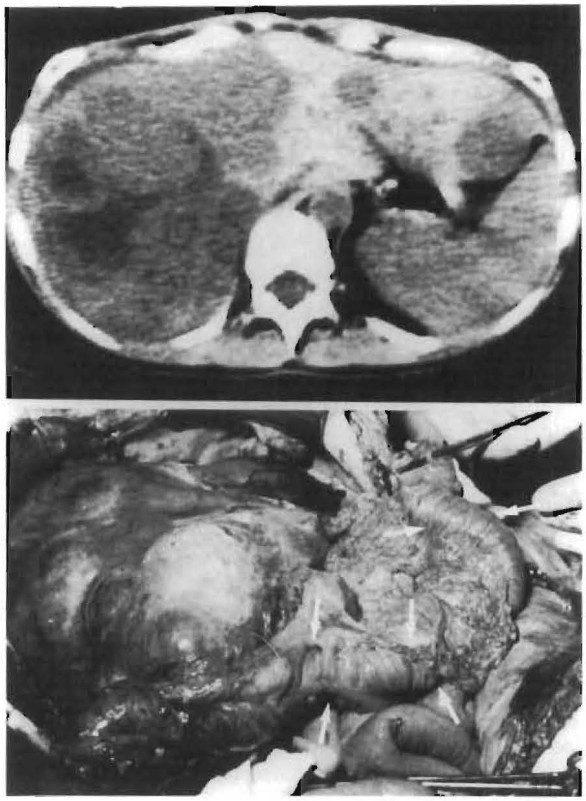

FIG 75.
The CT scan *(top)* of patient whose upper abdomen was filled with spindle cell sarcoma at the time of operation. The tumor-laden liver is the structure to the left of the operating room photograph *(bottom)*. Most of the right half of the diaphragm was removed with the specimen. The transverse colon is marked with *white arrows*. The margins were free of tumor, and none of the 38 lymph nodes studied had metastases. (From Starzl TE, Todo S, Tzakis A: *Ann Surg* 1989; 210:374–386. Used by permission.)

the liver and pancreas plus the entire GI tract in two children with the short-gut syndrome and secondary liver failure that developed during parenteral hyperalimentation.[654, 655] One of these grafts (Fig 74) provided function of all of the organs for more than 6 months before the recipient died of complications of lymphoproliferative tumors in the liver.[654] With an organ mass of this size, the possibility of carrier lymphoid tissue causing GVH disease was feared. In the longest surviving patient, donor pretreatment with OKT3 may have reduced this threat,[654] as has been demonstrated to occur with antilymphocyte serum in rats.[656]

A less drastic version of multivisceral transplantation is the use of an organ cluster in which the pancreas, duodenum, and part of the

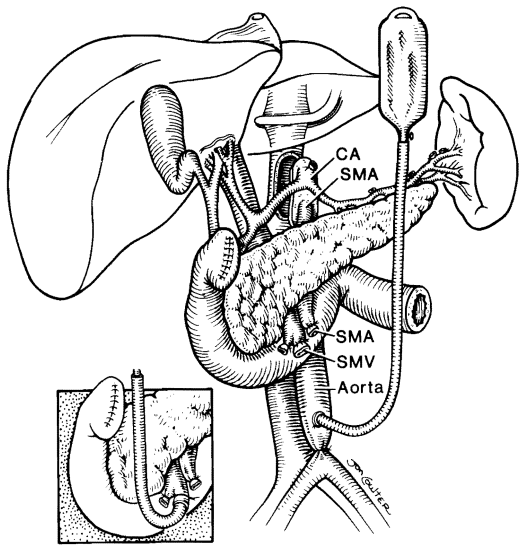

FIG 76.
Removal of organ cluster graft from donor. The specimen is initially cooled with an aortic infusion of UW solution after crossclamping the proximal abdominal aorta. Once the specimen has been removed with a Carrel patch containing the origin of the celiac axis *(CA)* and superior mesenteric artery *(SMA)*, the liver is secondarily perfused on the back table with UW solution *(insert)* through the superior mesenteric vein *(SMV)*. (From Starzl TE, Todo S, Tzakis A: *Ann Surg* 1989; 210:374–386. Used by permission.)

proximal jejunum have been included with the liver.[54, 657] These clusters have been used to replace upper abdominal organs that were removed (see Fig 74) in treating sarcomas and carcinoid tumors of the pancreas or duodenum with liver metastases (Fig 75), bile duct carcinomas with liver metastases, and a hepatoma that had invaded the duodenum and colon.[657] The organs removed from the recipient in continuity have included the liver, stomach, pancreas, spleen, duodenum, proximal jejunum, and ascending plus transverse colon (see Fig 74). The organs transplanted are shown in Figure 76. The completed recipient operation is shown in Figure 77.

Of 15 such patients, 9 are alive after 6 to 14 months, 8 without evidence of recurrent tumor. The ninth survivor may have stable pulmonary metastases. The majority of the survivors have been rehabilitated. This experience has illustrated how major components of the GI tract can be transplanted and has demonstrated how the use of organ clusters can allow extirpative procedures of a magnitude not previously imaginable.

The major limitations of the cluster operation have been the diffi-

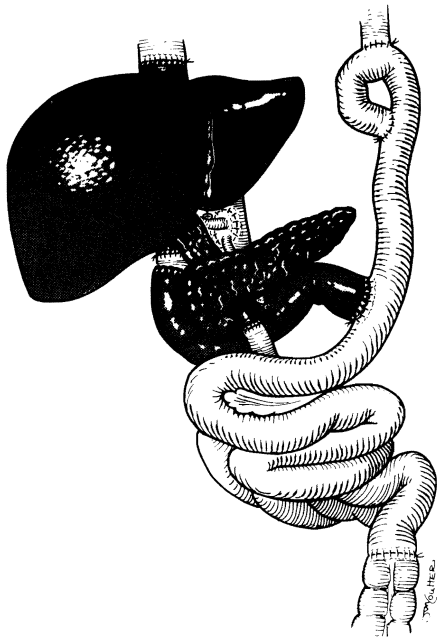

FIG 77.
Completed reconstruction in the recipient. (From Starzl TE, Todo S, Tzakis A: *Ann Surg* 1989; 210:374–386. Used by permission.)

culty of finding appropriate organ donors, the difficulty of the operation, and the complexity of postoperative care. Considering the fact that of the organs being replaced, only the liver is indispensable, an alternative was developed in which the same resection was performed but only the liver was transplanted (Fig 78). Fifteen such patients have been so treated, but the follow-ups are too short to merit comment. This variation of the original cluster procedure has been developed as a more pragmatic operation but at the expense of rendering the patient apancreatic. Malabsorption has been a serious clinical problem thus far, and thus it may influence cyclosporine doses. The day-to-day treatment of diabetes mellitus has not been difficult. If management of the iatrogenic diabetes mellitus proves difficult, pancreas transplantation at a more favorable moment remains an option.

QUALITY OF LIFE

Even in the early days of liver transplantation, the physical and emotional decay caused by chronic liver disease could be stopped

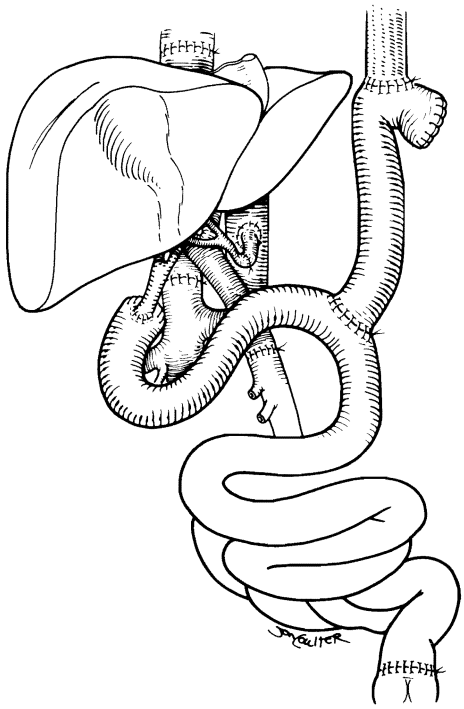

FIG 78.
This is an alternative to the reconstruction after an upper abdominal exenteration in which only the liver is replaced. This operation leaves the patient diabetic, but of 15 patients treated in this way, 13 are alive with follow-ups of several weeks to as long as 6 months. (From Tzakis A, Todo S, Starzl TE: *Transplant Proc* February 1990 [in press]. Used by permission.)

and reversed in many of the recipients who survived chronically. The most powerful determinants of their quality of life were the liver function profile at the 1-year convalescent mark and the quantity of steroids needed to maintain this function.[658] The adverse steroid factor in the quality of posttransplant life has been reduced since the introduction of cyclosporine. Several studies have shown the remarkable restoration of physical and emotional well-being that can be expected in infants and children,[658–660] including resumption of growth or even catch-up growth.[661]

Similarly, a recent group of adult liver transplant recipients studied objectively before and again 2 years after operation demonstrated broad improvement in social interaction, home management, alertness, the utilization of recreation and leisure time, and overall psychosocial functioning.[662] A number of other findings were ob-

tained from these investigations. First, the severity of stress experienced by the patient and the spouse after transplantation correlated significantly with the ease of recovery. More than 90% of the recipients who had a single transplantation state that they have no problems or only minor health problems 2 years after transplantation. More than 85% have returned to work and state that they are able to perform their jobs well. In contrast, the smaller number who required more than one transplant had a much poorer outcome, with only 43% being able to work because of one or more disabilities.

The follow-up of patients treated in the cyclosporine era dates back to only 1980. However, a bellwether group of survivors remains from an original series of 170 patients treated from 1963 to 1979.[67, 663] Twenty-eight of these recipients are still living after 10 to 19 years. These represented exactly one half of the survivors at 1 year. Only two patients who were alive at 5 years died subsequently. One of the late deaths was caused by chronic rejection 12.5 years after retransplantation. The other death was from a lymphoma after 13.5 years. Rehabilitation has been complete in the long survivors.[663]

THE OPTION OF AUXILIARY TRANSPLANTATION

With the auxiliary operation, as originally described in unmodified dogs,[1] the extra liver was placed in the right paravertebral gutter, rearterialized from convenient adjacent vessels, and provided with a portal venous inflow with systemic blood from the recipient iliac vein or lower vena cava. The graft outflow was drained into the recipient inferior vena cava. It was observed that auxiliary grafts were much more severely damaged than were orthotopically placed livers, primarily because of rapid hepatocyte atrophy.[664] These adverse effects could be prevented by diverting splanchnic venous flow through the auxiliary liver and away from the recipient's own liver,[665] suggesting that the splanchnic venous blood contained specific liver-supporting factors. The most important of these so-called portal hepatrophic substances was proved to be insulin.[325, 666]

The condition of providing a splanchnic venous inflow to the graft has been met in almost all of the subsequent clinical trials, which by 1978 numbered more than 50 (Fig 79).[667] Auxiliary liver transplantation with unquestionable prolongation of life was first achieved at the New York Memorial Hospital on December 13, 1972.[668] The recipient, who had biliary atresia, still is alive with a follow-up of more than 16 years.[669] In 1980, Houssin and associates in Paris reported a 29-month survival of an adult who was given an extra liver.[670] This patient was HBsAg-positive and died 8 years following transplantation from a hepatocellular carcinoma in his host liver (H. Bismuth, personal communication, January 1989).

With the increased success of orthotopic liver transplantation, in-

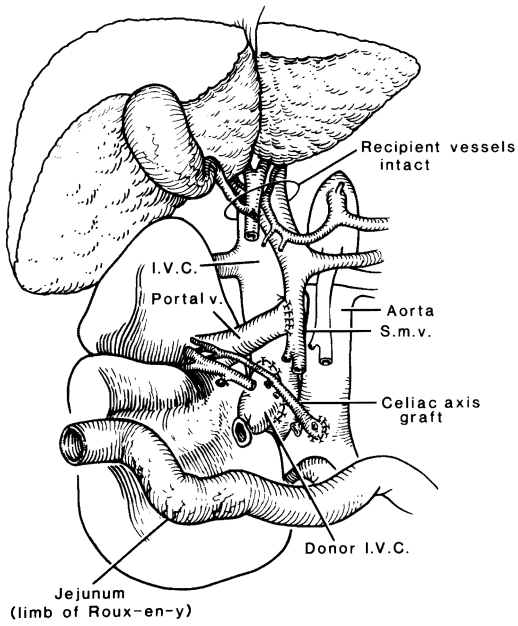

FIG 79.
This is the kind of auxiliary liver transplantation that has permitted several long-term successes. Note that the graft receives a portal flow from the splanchnic venous system *(S.M.V.)* and is drained into the inferior vena cava *(I.V.C.)*. The principles of this operation were originally worked out by Marchioro and colleagues.[18] (From Starzl TE [with the assistance of Putnam CW]: *Experience in Hepatic Transplantation.* Philadelphia, WB Saunders Co, 1969. Used by permission.)

terest in auxiliary transplantation waned. Very few further efforts were reported in the last decade.[671] The resulting pessimism has been lightened by a recent report of the transplantation of whole livers or liver fragments to the right paravertebral gutter of six adult recipients using essentially the same operation as that tried in earlier times.[672] At the time of reporting with follow-ups of 5 to 23 months, all six recipients were alive. Cautious further trials undoubtedly will be forthcoming.

PRACTICAL LIMITATIONS

ORGAN SUPPLY

Organ supply increasingly will influence candidacy criteria. However, discussions about rationing transplant services for this reason are premature since the balance between the need and supply of liv-

ers has not been determined. In the United States, the yearly rate of liver transplantations has reached approximately 1,600,[673] averaging 147 per month between July and December 1988 (Dr. William Vaughn, United Network of Organ Sharing, personal communication, 1989). The annual European total is approaching this figure.[674]

Policies about organ donation will have to be reexamined if substantial further growth is to occur. Probably, many potential liver donors are being rejected for inappropriate reasons. The arbitrary upper age limit for liver donors observed by most programs[675] cannot be justified since the liver is the only organ that does not undergo senescence.[676] Atherosclerosis of its arterial supply usually is not found beyond the origin of the celiac axis.[676] A limited experience with livers from donors older than 50 years has been encouraging.[677]

Other potential donors of all ages often are excluded because of poor blood gases, a need for inotropic or vasopressor drugs, minor abnormalities of liver function test results, or the existence of other diseases such as diabetes mellitus.[675] The results with such donors both in the United States[161, 162] and Europe[163] have been as good as with so-called perfect donors. The use of better preservation techniques[51–53] that allow safe storage of liver grafts for 1 day instead of the previous 6 or 8 hours should reduce organ wastage, since with this extra time, countrywide and worldwide networks of organ sharing can be set up.

ECONOMIC FACTORS

The ability to pay for liver transplantation has had a profound influence on candidacy. Ironically, the feasibility first and then the practicality of liver transplantation were established without considering how to finance this revolutionary form of therapy. In 1983, a planning commission for the state of Massachusetts estimated the average cost of liver transplantation in the first year would be $238,000,[678] although the actual costs were only one third this high in a large program already in existence.[114] It is clear that astronomical bills can be generated if patients are too disabled by the time of transplantation, if the first liver graft does not function well, and if serious complications develop, including the need for retransplantation.[114]

Because of their fear of runaway expenses, many health insurance carriers and government agencies have avoided financial responsibility to their constituents by classifying liver transplantation as "experimental"[679] in spite of the Consensus Development Conference conclusion to the contrary. The response to cost-conscious funding agencies is that liver transplantation can eliminate repeated and expensive hospitalization of patients who are slowly dying with chronic hepatic disease.[680–682] Such considerations were part of a

bitter controversy in Australia[683, 684] about the establishment of what eventually proved to be two outstanding programs.[685, 686]

So far, liver transplantation in the United States has been paid for by a heterogenous system of private health care insurance programs, government agencies, and public or private fund-raising activities. One highly visible consequence has been the recurrent spectacle of a family or patient pleading on television or through other media for economic support or for an organ. All the while, statistics that show gross underparticipation in this new kind of health care by blacks and presumably other disadvantaged groups have been accruing.[687] Development of a system that allows all citizens equal and reasonable access to this kind of treatment without the extraordinary expenses of past programs such as the federally financed End Stage Renal Disease program may require new and creative administrative approaches.

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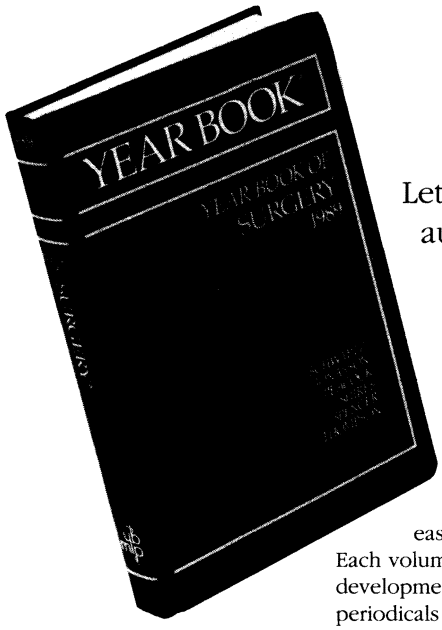

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