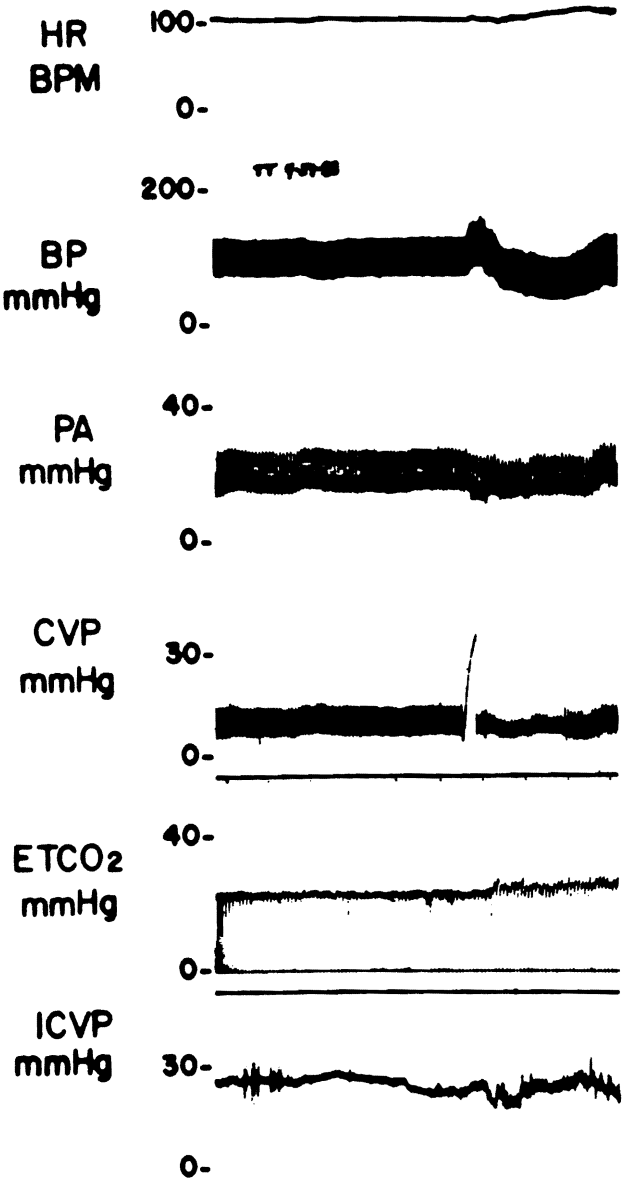

FIGURE 4. The abrupt rise in BP is associated with calcium chloride therapy just before reperfusion of the new liver. Reperfusion is associated with a drop in BP and filling pressures, but no rise in IVCP pressure, suggesting myocardial depression and/or hemorrhage as etiologies, rather than impaired venous return. Time, in minutes, is indicated by the vertical marks on the dark horizontal line at the bottom of the CVP tracing. (HR) heart rate; (BP) blood pressure; (PA) pulmonary artery; (CVP) central venous pressure; ($ETCO_2$) end-tidal carbon dioxide; (ICVP) inferior vena cava pressure.

TABLE 2. Relative magnitude of Clinical Events on Measured Pressures*

	IVCP	CVP	GRAD
Blood loss	↓	↓	↓–
Retraction or VVB occlusion	↑	–↓	↑↑
Myocardial depression	–↑	↑–	–↓

* Width of arrow shaft indicates relative magnitude of event on measured pressure. – indicates no effect; GRAD, IVCP – CUP.

rhage, all common occurrences during OLT. Increases in IVCP suggest the former two problems as a cause, and dictate mechanical (rather than pharmacologic) fluid or blood product therapy. (Table 2). It is intuitive that maximizing VVB pump flows should lead to higher VR, CO and blood pressure as well, while minimizing the gradient to venous return. Finally, it is possible to assess the quality of vena caval anastomosis since normal flow should yield a low gradient.

We conclude that IVCP and the gradient to venous return are simple to measure and that knowledge of acute and chronic trends provides valuable adjunctive hemodynamic information during OLT.

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LIVER TRANSPLANTATION IN PATIENTS WITH LANGERHANS' CELL HISTIOCYTOSIS[1]

Langerhans' cell histiocytosis (LCH)* is an uncommon disease, characterized by an abnormal proliferation of histiocytic cells of the dendritic family. Some patients with systemic LCH have primary liver involvement that may resemble sclerosing cholangitis. Others may develop end-stage liver disease as a result of the chemotherapeutic agents used to control the primary disorder. We have performed liver transplantation in two children and one adult with this disease, the largest single-center experience in the world. A follow-up of these cases may be of special interest for two reasons. First, perturbations in the immune system are common in this disease. Second, light can be shed on whether immunosuppression can influence a disease with a possible autoimmune etiology.

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* Abbreviation: LCH, Langerhans' cell hystiocytosis.

Two children and one adult with a history of LCH underwent orthotopic liver transplantation at the University of Pittsburgh since 1984. As noted, the diagnosis of the disease preceded their end-stage liver disease by 5–15 years. All three had received some form of chemotherapy that succeeded in controlling the active disease. In two of the patients (R.W. and H.C.), the end-stage liver disease was a direct result of the LCH. In the third patient (G.C.), the cirrhosis was the result of the chemotherapy treatment with methotrexate. The LCH seemed to be in complete remission at the time of the transplantation in the two pediatric cases, but appeared to be still active, at least in the liver (by histology) in the adult case.

No tissue from pretransplant pathological studies was available to us at the time of the preoperative evaluation. The patients were referred to us with a diagnosis of LCH that had been previously established in other centers. The first pediatric patient (R.W.), was initially diagnosed with an eosinophilic granuloma of the skull. Subsequently he had skin involvement, with Langerhans' cell infiltration. At the age of 6 years, he also developed diabetes insipidus. The adult patient (H.C.) was diagnosed as having LCH on the basis of an open-lung biopsy. There is no evidence that the immunological markers were searched for. Multiple intrahepatic masses by CT scan were interpreted as LCH. The removed livers were thoroughly examined for the presence of the typical Langerhans cells (below) with hematoxylin-eosin staining as well as staining for the characteristic surface markers.

The hilar areas and peripheral sections of the resected livers were searched for evidence of LCH. Only the adult specimen contained histiocytes that stained positively for the S-100 protein, and all the specimens were negative for clusters of ovoid cells bearing class II T6 surface antigen markers.

All three patients underwent orthotopic liver transplantation according to a technique amply described (*1*). One of the children required two retransplants due to repeated episodes of rejection. All three received the standard immunosuppressive regimen in place at the time at the University of Pittsburgh, based on cyclosporine (Sandimmune) and steroids. Rejection was treated with either a temporary increase of the steroid doses or with the antithymocyte monoclonal antibody preparation OKT3 (Orthoclone). Small doses of azathioprine (Imuran) were added as needed for persistent low-grade rejection.

All three patients did well intraoperatively and survived for at least 1 year. The adult patient died 14 months after his transplant from pulmonary embolism following a traumatic long bone fracture. The two pediatric patients are still alive, 5 and 4¾ years later. There is no evidence of recurrence of LCH in the pediatric patients. In the adult patient, there was no clinical evidence of recurrence of the disorder at the time of his death. Unfortunately, the family denied permission for autopsy, so no tissue was available for analysis. All three patients had repeated episodes of acute cellular rejection. The first child given a transplant by us necessitated two retransplants, both because of uncontrollable rejection. All three patients required treatment with OKT3, two of them more than once.

Langerhans' cell histiocytosis, previously known as histiocytosis X^2, is a term that covers a range of disorders characterized by abnormal proliferation of Langerhans' histiocytic cells (*3*). Terms such as histiocytosis merely describe histological findings, and do not clarify the confusion that still reigns in defining the etiology and pathogenesis of these disorders (*3*). The classic Letterer-Siwe (*4, 5*) and Hand-Schuller-Christian (*6, 7*) diseases and the eosinophilic granuloma of the bone were integrated into a single entity by the landmark research of Lichtenstein in 1953 (*8*). The etiology of the disorder is still unclear, although immunologic (and possibly autoimmunologic) mechanisms obviously play a role. Several hypotheses have been advanced regarding the pathogenesis of LCH (*3*). The characteristic Langerhans' cells are dendritic cells usually found in the skin where they act as antigen-presenting cells (*9*) in a different way from monocytes and macrophages (*10*). These cells contain the S-100 protein (*11*), a calmodulin-like substance and have characteristic surface antigen markers. The Ia antigen is coded for by the HLA-DR locus (*12*). Its expression is not influenced by microbial or lymphokine stimulation, as in macrophages (*13*). The T6 surface antigen may also be present on the surface membrane of the Langerhans' cell; its significance remains unclear (*11*). Intracytoplasmatic organelles called "Birbeck granules" are characteristic of these cells but their significance is unclear (*14*). The majority of patients are of pediatric age, although LCH has been described in adults.

It is not known what causes the histiocytes to proliferate abnormally and infiltrate a variety of organs and sites. The protean nature of the disorder is evidenced by the variability of infiltration sites. When the involvement is in one place (bony or nonbony), the term eosinophilic granuloma may be used. Multifocal involvement produces the eponymous syndromes (Hand-Schuller-Christian or Letterer-Siwe disease).

The infiltrates of histiocytes may produce "punched-out" lesions of the skull, vertebrae, and other bones (*15, 16*). Hypothalamic involvement occurs with diabetes insipidus in 25–50% of the patients (*17*). Extensive invasion of lymph nodes, spleen, and liver is relatively common (*18–20*). Bone marrow involvement, especially with thrombocytopenia (*21*) is particularly ominous. The hepatic involvement can range from mild cholestasis to progressively more severe pictures of histiocytic infiltration and bile duct involvement—and, ultimately, sclerosing cholangitis (*22, 23*). In fact, the last can eventually lead to severe fibrosis and liver failure (*24, 25*). Primary sclerosing cholangitis has been described as associated with LCH in adults (*26*) and in up to 15% of the pediatric cases (*27*). The severity and prognosis of the disease is determined by the age of onset, extent of organ infiltration, number of involved sites, and rapidity of the progression of lesions. Staging of the disorder has been used for prognostic and therapeutic purposes (*3*).

Although not classified as a malignancy (*28*), LCH has many elements in common with malignant lymphomas, especially the abnormal cellular proliferation and the immunologic changes (*11, 29–32*), especially thymic (*33, 34*) and immunoglobulin (*35*) abnormalities. A suppressor T cell deficiency seems to be characteristic of the disease (*36, 37*).

LCH is a relatively infrequent disease that usually has a relatively benign course, particularly if appropriately treated. Local radiation therapy, steroids, chemotherapeutic agents—and, more recently, immunotherapy have been the treatment modalities most widely used (*38–41*). However, chemotherapy administered for diffuse histiocytic lesions, especially methotrexate, may result in irreversible toxic liver damage (*11*).

The relative decrease in the number of T suppressor cells in LCH may, in part, explain the severity and/or frequency of rejection that we observed in our patients. Unfortunately, the T4/T8 ratio is not routinely measured in our transplant population, either pre- or postoperatively, so this can be construed as mere speculation. Also, it is not clear whether successful

treatment of the syndrome results into a restoration of the immunological parameters (including the T4/T8 ratio) to normal, although there is some preliminary evidence that this may occur with immunotherapy. Whether LCH itself or the therapy previously administered to treat it (in particular, immunotherapy) predisposes to rejection more severe than normally expected can only be answered by better monitoring in the few cases that exist.

On the other hand, there has been no recurrence of the disease in our two living patients after up to 5 years of follow-up. As immunosuppressive drugs, including cyclosporine are a part of the usual armamentarium in the treatment of LCH, it is possible that the posttransplant immunosuppression may prevent recurrence. Although the number of patients is very small and the follow up relatively brief, the absence of recurrence is encouraging and leads us to believe that liver transplantation may be indicated for end-stage liver disease associated with LCH.

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