Liver transplantation is an accepted therapy for end-stage liver disease. After allografting, a variety of clinical problems may require laboratory involvement for accurate and timely diagnosis and intervention. Critical factors in the choice of a laboratory test menu to support a transplant program include turnaround times that support clinical decisionmaking, real diagnostic value, and real value for money. Particular clinical problems, whose early presentation must be anticipated, include graft ischemia, primary nonfunction, and hepatic artery thrombosis. Acute rejection is common at 5–10 days posttransplantation, the principal target being the biliary tree. Longer-term problems are associated with the therapeutic drug measurement of cyclosporin A and, increasingly, tacrolimus (FK506); the side effects of immunosuppressant therapy also require monitoring. A successful liver transplant program can be adequately supported with a simple battery of automated tests that are cheap, fast, and available at all times.

INDEXING TERMS: liver transplantation • liver function tests • laboratory costs • graft ischemia • rejection • therapeutic drug monitoring

Liver transplantation is now an established therapy for end-stage liver disease [1]. In 1995 in the US alone, 3925 liver transplants were performed. Average 1-year graft survival was 69.1%, and patient survival was 79.2% [2]. Our own unit (Queensland Liver Transplant Service) has transplanted 484 livers into 437 patients between January 1, 1985, and December 31, 1996, with an overall 1-year graft survival of 82%. Over the last 4 years the 1-year graft survival has been 84% and the patient survival 88%.

After the patient is wheeled from the operating theater to the intensive care ward, several important problems may arise, for which the laboratory may be central to the diagnosis and management. The most important of these are listed in Table 1. For convenience these problems are listed at the time at which they most commonly present, although many of them can occur at any time. Some of these problems are considered individually below.

All laboratories are being forced to exercise rigorous cost containment. Thus assessment of the liver transplant recipient requires the choice of tests that provide adequate diagnostic information, at the minimum cost. Whereas many tests have been proposed as being potentially useful in assessing the posttransplant recipient, only tests that can be turned around in a time course that makes them of diagnostic use are of real value in routine clinical practice on the transplant ward. This generally means within 2 h.

Most of the routine tests that are used in assessing the liver transplant recipient are individually nonspecific. However, because of the high prevalence of disease, the use of tests in combination increases their diagnostic efficacy. In our experience, most problems can be satisfactorily assessed with a routine panel of liver function tests (LFTs) generated quickly and cheaply on the laboratory analyzer, which operates 24 h each day. Our routine profile of LFTs is shown in Table 2. In themselves they are useful in that they identify the presence of a problem, but not the problem itself. Abnormal test results can be meaningful only when used with other data, e.g., coagulation results, and when the clinical status of the patient is considered.

Tests of liver function need not only be available from the laboratory. Some liver transplant units leave in place a T-tube draining the bile duct after surgery, whenever...
Technically feasible. With such patients, an excellent general indicator of a successful operation comes independently of the laboratory: the flow of black bile from the draining T-tube.

Immediate Problems

Of the many problems that may occur after liver transplantation, some are a consequence of preexisting disease, others a result of the surgical procedure, and still others a result of the immune response against the grafted organ. Hepatorenal syndrome is probably more common in transplant recipients than is usually appreciated. In one series the reported incidence was 9.8%, and the condition was associated with a lower survival rate [3]. The condition may persist for some time posttransplant and when later combined with the nephrotoxicity of immunosuppressant agents such as cyclosporin A (CsA), there may be substantial impairment of renal function. Hepatopulmonary syndrome is the presence of an increased alveolar–arterial gradient, and evidence of dilatation of intrapulmonary vessels in a patient with liver disease. Whereas the underlying cause of the disease is speculative, the net clinical result is a spectrum of abnormalities of gas exchange and widely varying degrees of hypoxia. In one series, 13.2% of patients fulfilled the criteria for hepato-pulmonary syndrome [4]. Hyperacute rejection is a rare complication of liver transplantation, as is portal vein thrombosis. Infection and sepsis are important complications at any time after liver transplantation, being the sequela of poor physical condition preoperatively, the major surgical procedure, and long-term immunosuppression. This problem is handled in another area of the laboratory and will not be considered further here.

All transplanted livers show some degree of injury posttransplant. This may be a result of the period of ischemic storage between the time of harvest and transplant or reperfusion injury [5]. Fig. 1 shows the changes in the routine LFTs in various clinical states after transplantation. Even in uncomplicated cases, on day 1 plasma transaminase activity will be increased at least 4–5 times the upper limit of the reference range. The prothrombin time (PT) settles quickly to near-normal values. The initial bilirubin concentration is dependent upon the nature of the pretransplant liver disease, often with a small rise during the first week as blood products are metabolized. Its concentration may increase posttransplant as a consequence of tissue injury during surgery and blood trans-

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**Table 1. Potential problems postliver transplantation.**

<table>
<thead>
<tr>
<th>Early</th>
<th>Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft ischemia</td>
<td>Rejection—acute and chronic</td>
</tr>
<tr>
<td>Primary nonfunction</td>
<td>Immunosuppressant side effects</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>Biliary stenosis</td>
</tr>
<tr>
<td>Hepatopulmonary syndrome</td>
<td>Disease recurrence</td>
</tr>
<tr>
<td>Hepatic artery thrombosis</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Immunosuppressant toxicity</td>
<td></td>
</tr>
<tr>
<td>Hyperacute rejection</td>
<td></td>
</tr>
<tr>
<td>Early acute rejection</td>
<td></td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td></td>
</tr>
<tr>
<td>Infection and sepsis*</td>
<td></td>
</tr>
</tbody>
</table>

* Can occur at any stage.

---

**Table 2. Liver function tests available at all times.**

<table>
<thead>
<tr>
<th>Function assessed</th>
<th>Analyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic</td>
<td>Albumin</td>
</tr>
<tr>
<td></td>
<td>Ammonia</td>
</tr>
<tr>
<td></td>
<td>PT</td>
</tr>
<tr>
<td>Multicompartmental</td>
<td>Bilirubin (total)</td>
</tr>
<tr>
<td>Biliary</td>
<td>ALP</td>
</tr>
<tr>
<td></td>
<td>GGT</td>
</tr>
<tr>
<td>Hepatocyte integrity</td>
<td>Aspartate transaminase</td>
</tr>
<tr>
<td></td>
<td>Alanine transaminase</td>
</tr>
<tr>
<td>Dynamic real-time test</td>
<td>Monoethylglycine xylidide (this test is performed sparingly)</td>
</tr>
</tbody>
</table>

Fig. 1. Changes in the principal LFTs in the period after liver transplantation.

Concentrations or activities are expressed as multiples of the upper limit of the reference range. Data are shown from three representative patients as examples of uncomplicated clinical course (○—○), severe ischemia (●—●), and mild-moderate rejection with liver biopsy on day 10 (□—□). The important diagnostic points are discussed within the appropriate sections in the text. ALT, alanine transaminase.
fusion. In uncomplicated cases, the biliary markers alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT) usually remain within the reference range.

Two important complications may arise immediately on arrival in intensive care: primary nonfunction and hepatic artery thrombosis. The latter may present weeks after the surgery but is considered here for convenience.

**Graft Ischemia and Primary Nonfunction**

There may be extended periods of ischemic storage between harvest and revascularization. Immediately after the blood supply is reconnected, there will be evidence of hepatocyte injury, with a rise in plasma transaminase activity that is approximately proportional to the degree of injury suffered. The change of storage solution for donor livers from EuroCollins to University of Wisconsin solution dramatically reduced the degree of ischemic injury. Signs of severe injury are poor bile flow, high transaminase activities, and coagulopathy. Fig. 1 shows the changes in LFTs from a case with severe ischemic liver damage. The transaminase activity on day 1 was nearly 80 times the reference range. PT remained elevated to at least twice the normal value for 10 days. The bilirubin concentration rose progressively over the fortnight posttransplant, poor liver function, tissue injury, and blood transfusion all contributing. Cholestasis is common after severe ischemia, and activities of both ALP and GGT increased.

At its worst, ischemic injury becomes primary nonfunction, which is a catastrophic although infrequent complication of liver transplantation. The reported incidence in most series averages ~6% [6]. The cause of primary nonfunction is gross graft ischemia with massive infarction of the liver secondary to various pathologies such as hepatic artery or portal vein thrombosis, preservation injury or hypoperfusion of the donor liver due to prolonged hypotension, or cardiac arrest before or during donor hepatectomy, although it appears that some preexisting pathologies in the donor liver, e.g., steatosis, may contribute. The presentation is usually dramatic and resembles fulminant hepatic failure with worsening coagulopathy refractory to clotting factor infusions, gross increase of transaminases (>50×), hypoglycemia, acidosis, hyperkalemia, hypophosphatemia, and the clinical features of oliguria, hypotension, adult respiratory distress syndrome, and progressive cerebral edema. Some patients with primary nonfunction may have massive ascitic fluid loss, which can confound the diagnosis. Because of the loss in the ascitic fluid the rise in transaminases may be much smaller than usually seen [7]. Clotting factors may be lost in ascitic fluid and if the ascitic fluid loss is due to reasons other than primary nonfunction, a similar prolongation in PT may still result. However, if due to dilutional causes, there is a good response to infusion of fresh frozen plasma.

**Hepatic Artery Thrombosis**

Hepatic artery thrombosis is an important potential complication postoperatively. In established programs, the incidence is characteristically on the order of 5–10% [8]. Although ligation of the hepatic artery as a treatment of liver metastases is usually well tolerated, in the liver transplant patient hepatic artery thrombosis is associated with considerable morbidity and mortality, presumably because the graft is devoid of the normal collateral blood supply delivered through the hepatic ligaments. While thrombosis may occur at any time after transplantation, most cases occur within the first 2 weeks, and the complication is often fatal without retransplantation. Late hepatic artery thrombosis may be asymptomatic, although a more distinct presentation usually occurs. This may be relatively subtle and present as relapsing sepsis following bile duct ischemia, or at the other extreme it may present as fulminant hepatic failure with an abrupt clinical deterioration accompanied by gross prolongation of the PT and massive increase of the transaminases. In the latter circumstance, without prompt retransplantation, the mortality is 100%. Because of the variable clinical presentation, a high index of suspicion is required. Dynamic, real-time tests such as the monoethylglycine xylidide test [9] may be of value in identifying the presence of problems such as the less obvious hepatic artery thrombosis; we emphasize, however, that the tests are not specific and serve simply to indicate that a problem exists.

In our experience we have found it necessary to provide a 24-h stat service for the routine LFT profile and the monoethylglycine xylidide test, and our hematology service offers a coagulation service including PT.

**Intermediate Problems**

**Rejection**

Rejection is an important and interesting complication of allogeneic transplantation and is considered here in some detail. About 50% of patients undergoing liver transplantation will show some signs of acute rejection of their new organ [10], and in earlier series, rejection has been reported to be the cause of death in 7.5% of liver transplants [11]. Acute and chronic rejection together may be the cause for 20% of retransplantations [12]. Rejection is a major cause of mortality, especially morbidity after liver transplantation, and rapid identification of this problem is important. Consideration of the changes seen with acute rejection follows. The biology of chronic rejection is less well-characterized and understood.

Diagnosis of rejection on clinical grounds alone is unreliable, and laboratory data are also required. Liver biopsy is still generally considered to be the best means of objectively identifying developing liver transplant rejection [13]. However, biopsy is a procedure that is time-consuming and not without morbidity, and by itself is not an absolutely reliable index of clinically significant rejection with a substantial number of false positive results.
The search continues for other reliable indices of rejection.

To identify possible useful indices of rejection, some understanding of the rejection process is necessary. Briefly, it is generally agreed that during acute rejection expression of both Class I and Class II antigens, primarily involving the biliary epithelium and vascular endothelium, is greatly increased. The major target for the inflammatory response is thus the biliary tract and to a lesser extent the hepatocytes [10]. Thus indices of Class I and Class II antigen expression, the inflammatory response directed against these foreign antigens or markers associated with the biliary system, might be anticipated to provide the greatest information in the early stages of acute rejection. As the initial target in the rejection process is the biliary tree, it might be anticipated that bile should reflect any pathological changes. An indwelling T-tube provides ready access to bile, and samples can be collected directly from the site of rejection, which theoretically should provide more useful information than in peripheral blood.

**NONSPECIFIC INDICES ASSOCIATED WITH REJECTION**

Because of the nature of the rejection process, it is of particular value to look at specific markers. However, such markers are not readily available in all centers, the assays usually have a longer turnaround time, and costs are usually substantially more than the routine, simple LFTs. Although standard LFTs are nonspecific, how informative they are with regard to liver transplant rejection should be considered.

Because the rejection process involves an attack upon the grafted liver, and particularly upon the biliary system, that LFTs should change is to be expected, and many papers have reported attempts to use these comparatively simple measures to identify developing rejection. That results are quickly available is an advantage of these tests. The disadvantage is that they are nonspecific. For example, after severe ischemia, cholestasis is common, and the changes seen may be similar in cholestasis and rejection, thus indicating the importance of considering results only in the context of the clinical history. Fig. 1 shows the changes in LFTs in a case with mild to moderate rejection, confirmed by liver biopsy on day 10, and treated with methylprednisolone. The transaminase activity was initially at 20 times the reference range, indicating a moderate degree of ischemic injury, independent of the rejection episode. The PT fell steadily towards the reference range. The bilirubin concentration rose over the first 8 days and started to fall before the rejection was treated. GGT rose to twice the reference range on day 3–4 and rose progressively until the rejection was treated. ALP did not rise above the reference range until day 9.

That an increase in bilirubin concentration is an early sign of developing rejection is a widely held belief [16, 17]. However, in our experience bilirubin changes are of little help in this context. Fig. 2 shows the changes in bilirubin concentration in nine patients with biopsy-diagnosed steroid-sensitive rejection, over the period before and after treatment with methylprednisolone (1 g intravenously on 3 consecutive days). Whereas almost all cases show a decrease in bilirubin concentration after treatment, the pattern before treatment is very variable, and no confident prediction about developing rejection could be made on the basis of the bilirubin concentration alone. Application of receiver-operating characteristic analysis confirms the poor diagnostic value for bilirubin [18].

Acute rejection is common within the first few days after transplantation, at a time when the tissue damage associated with the major surgery and occasional large blood transfusions intraoperatively make it likely that bilirubin concentration will be increased without any diagnostic importance being attached.

Because the initial attack in a rejection episode is specifically directed against the biliary system, it might be anticipated that biliary markers would be the most informative. ALP is the usual marker used in this capacity [13, 19] although it is not a particularly good marker of rejection. Despite periodic reports of the value of GGT as a marker of rejection [20, 21], this enzyme has been undervalued in this context. We have recently studied the relative utility of GGT and ALP in the diagnosis of
rejection and found GGT to be very much more useful with a diagnostic sensitivity for clinically significant rejection of 91.0% compared with ALP's diagnostic sensitivity of 68.7%. The positive predictive value for GGT was 70.9% and for ALP 67.6% [22]. We believe that GGT estimation is an essential cost-effective component of the posttransplant LFT panel used for patient monitoring.

Because the initial target in rejection is the biliary system, transaminases that reflect hepatocyte damage should not rise until rejection is well established. A rise in transaminase activity should therefore not be used as a principal index of rejection. It has been reported that an early rise in transaminase activity associated with rejection is associated with more severe disease [23], although this assertion is disputed [24].

A variety of other nonspecific markers, e.g., α-glutathione S-transferase (α-GST) [25], have been proposed as useful indices of rejection. For the reasons outlined above, α-GST, an intrahepatocyte enzyme, should rise later in the rejection process than the biliary markers, although it is an excellent index of hepatocyte injury. More-specific markers have been proposed, and the performance of some of these is considered below.

**SPECIFIC PRODUCTS RELATED TO LYMPHOCYTE ACTIVATION**

When a foreign graft is inserted into a recipient, recipient leukocytes respond to the foreign antigens by producing soluble factors that induce both lymphocyte and antigen proliferation. Thus cytokines such as the interleukins (IL) IL-1, IL-2, IL-5, IL-6, tumor necrosis factor (TNF), and γ-interferon (γ-IFN) may be expected to rise in response to an episode of acute rejection. Substances such as β2-microglobulin (β2-M), intercellular adhesion molecule-1 (ICAM-1) and neopterin, which are induced by cytokines, may also be expected to be of potential use. However, secretion of these substances is a reflection of leukocyte activation and is not specific for rejection. Below we present an overview of the extensive literature on potential markers of liver transplant rejection.

Measurement of IL-1, TNF, and γ-IFN has proven disappointing, with increases in all agents seen in rejection, infection, and other complications [26]. Likewise, increases in IL-6 in bile are seen in both rejection and inflammation [27]. Serum concentrations of IL-5, the T cell-derived eosinophil-activating cytokine, may be increased in both rejection and cholangitis, but biliary concentrations appear to have high specificity with relatively low diagnostic sensitivity [28]. Whereas serum concentrations of soluble IL-2 receptor are higher in rejection, substantial overlap occurs with amounts seen in infection [29]. However, biliary IL-2 receptor is reported to have a diagnostic sensitivity of 94% and a specificity of 84% for acute rejection [30].

Serum concentrations of β2-M rise in response to any substantial inflammation [26] and are not specific for rejection. However, if the ratio of bile:serum β2-M is used, then a very high specificity for rejection has been reported with little overlap between rejection and infection, and a diagnostic sensitivity of 96% and specificity of 87% [31].

ICAM-1 is an adhesion molecule induced by cytokines that is found on the surface of several different cells and appears important in the rejection process. Serum concentrations rise in response to a variety of inflammatory processes, but it is reported that ICAM-1 in bile increases only in response to developing rejection [32]. Neopterin is released by stimulated leukocytes under the control of γ-IFN. Serum concentrations rise in response to various inflammatory stimuli [33], but in bile a rise in neopterin concentration is reported to be specific for rejection [34]. Our own experience with cytokines and neopterin in bile, however, is that substantial intraindividual variation exists and that concentrations may be increased in conditions other than rejection.

Based upon our practical experience and from our reading of the literature, Table 3 compares the relative diagnostic efficacy of some of these proposed markers.

**Longer-Term Monitoring of the Liver Transplant Patient**

**THERAPEUTIC DRUG MONITORING**

On a longer-term basis, the problems that the laboratory sees are primarily related to immunosuppressant therapy. The majority of liver transplant units have, at least until recently, used a combination of azathioprine, steroids, and CsA [35], although there is the progressive introduction of the newer immunosuppressants, particularly tacrolimus (FK506).

Measurement of blood azathioprine and prednisolone concentrations is performed infrequently. Occasionally, area under the curve measurement of prednisolone may be useful in determining dosage [36]. Azathioprine’s major toxic effects are upon the bone marrow. The most important side effects of treatment with prednisolone include glucose intolerance and diabetes mellitus [37], hyperlipidemia [38], and bone loss [39].

The mainline drug for immunosuppression in liver transplantation is CsA, with tacrolimus being used increasingly either as first-line immunosuppression or as rescue therapy in rejection. Both drugs act primarily by blocking synthesis of cytokines, including IL-2 and TNF [40]. CsA in particular is poorly absorbed, although the new formulation of CsA, known as Neoral (Novartus), has much greater bioavailability. Both CsA and tacrolimus are toxic in high concentrations, and low blood concentrations are associated with rejection [41, 42]. Thus the first requirement from the laboratory is drug measurement. Because of the extreme lipophilicity and temperature-dependent partitioning into erythrocytes of these drugs, whole blood is required for analysis, and the best clinical correlation is found when trough concentrations are used [43]. Target blood concentrations fall with time posttransplant. CsA may be assayed by either HPLC or immunoassay. Because of the potential problem of metabolites cross-reacting in immunoassays, some laboratories...
drug for which therapeutic drug monitoring is not helpful. This claim requires further analysis when more clinical experience with the drug accumulates [55].

Rapamycin (Sirolimus) is structurally related to tacrolimus, although its mechanism of action differs. Few data are available regarding its human toxicity, but animal studies demonstrate much less renal toxicity than either CsA or tacrolimus [56].

OKT3 is used by many units, either as induction therapy or, as with our own unit, for treatment of steroid-resistant rejection. Because OKT3 (a monoclonal antibody) is the product of a murine-derived line, use of OKT3 may result in the formation of anti-mouse antibodies. These have the potential to interfere in vivo with possible future treatment with OKT3 or in vitro with other assays using murine antibodies, i.e., heterophilic antibody interference. Companies producing diagnostic kits add blocking agents to overcome this potential interference, but if antibodies are present in very high concentration, they may overwhelm the added blockers. Identification of heterophilic antibody interference in routine laboratory assays has the potential to be used as a quick, cheap screen for substantial OKT3 antibody presence [58].

**DISEASE RECURRENCE**

Disease recurrence is a major problem in the liver transplant recipient. Hepatitis B [59], hepatitis C [60], and malignancy [61] are especially prone to recur, to the extent that many units have changed their indications for accepting patients onto a liver transplant waiting list [62]. Debate continues about whether conditions such as primary biliary cirrhosis recur [63]. The changes seen with laboratory tests will vary depending upon the original condition. The changes seen with hepatitis and malignancy may initially be confused with sepsis and rejection or cholestasis, and usually liver biopsy is required to resolve the etiology of the changes.

**MALIGNANCY**

The incidence of malignancy of both solid organs and hematological tissues is higher among transplant patients than in the general population [64], and it is well recognized that organ transplant recipients are at greatly increased risk of developing Epstein–Barr virus-associated lymphoproliferative disorders [65], which may regress if immunosuppression is reduced [66]. Monitoring the development of such lesions is primarily clinical, but hematological indices will change and there may also be alterations of LFTs.

**Costs**

An analysis of the costs and charges for liver transplantation in the US has recently been published [67], and it is interesting to compare them with those in Australia. The overall charge for liver transplantation in the US was about US $141 000. In Australia the charge to foreign nationals is about US $120 000, although the actual cost is

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**Table 3. Relative diagnostic performance of some proposed markers of acute rejection.**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Convenience, cost, and availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood specimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>GGT</td>
<td>++</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>ALP</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Alanine transaminase/aspartate transaminase</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>α-GST</td>
<td>±</td>
<td>±</td>
<td>–</td>
</tr>
<tr>
<td>TNF</td>
<td>++</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>γ-INF</td>
<td>++</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>IL-1</td>
<td>++</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>IL-2</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>IL-5</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>IL-6</td>
<td>++</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>IL-2R</td>
<td>++</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>++</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>β2-M</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Neopterin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bile specimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β2-M</td>
<td>++</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Neopterin</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>IL-2R</td>
<td>++</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>IL-6</td>
<td>++</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>++</td>
<td>+</td>
<td>±</td>
</tr>
</tbody>
</table>

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still use HPLC for analysis, despite the increase in time and operator expertise that is required. Tacrolimus is more potent than CsA, thus blood concentrations are lower. Assay is principally by ELISA, although liquid chromatography-mass spectrometry-mass spectrometry analysis has been used [44]. Special preparation is required for these assays; by negotiation with our transplant unit these assays are not available on a stat basis, but CsA is assayed every day of the week.

Therapeutic drug monitoring is not only therapeutic drug measurement. All immunosuppressant drugs have important side effects that require laboratory support for assessment. CsA is nephrotoxic, particularly at higher concentrations [45]. With multiple immunosuppressant drugs being used simultaneously, it is sometimes difficult to identify which drug is causing which effect. However, CsA by itself certainly worsens glucose tolerance [46], causes hyperlipidemia [47] and hypomagnesemia [48], and increases bone turnover [49]. Hepatic and pancreatic toxicity [50] have both been reported. Tacrolimus has a similar toxicity profile, causes more hepatotoxicity [51], and is more diabetogenic [52], but causes less hyperlipidemia [53].

Mycophenolate mofetil has been developed essentially as an azathioprine substitute. Early trials suggest that it is more efficacious than azathioprine [54] and that it has a relatively low toxicity. Currently it is being promoted as a
substantially less and covers retransplantation if required (S. Lynch, personal communication). The charge for laboratory testing in the US in the first year posttransplant averaged $23,512 or $27,612 for inpatient testing only, depending upon whether the patient was on tacrolimus (FK506) or CsA. Because of the diversity of geographical locations that patients transplanted in Brisbane come from and return to, we were not able to readily determine all the laboratory tests performed over the full year. However, the first 3 months posttransplant (the highest activity period for laboratory investigation) were associated with laboratory work that could be charged at an average of about US $3350 per person, both inpatient and outpatient laboratory testing. We acknowledge that in this sample of 10 consecutive transplants, there were no serious problems requiring extended intensive investigation. Nevertheless, it would appear that laboratory charges are substantially cheaper in Australia, despite the provision of a 24-h service.

In conclusion, the laboratory is an essential component of the liver transplant program. Its role is to provide high-quality, cost-effective, and time-effective results. Staff need to be aware of potential confounding factors, such as heterophile antibodies, that may be outside the experience of even experienced clinical staff. Inexperienced junior medical staff may be rotated into the Transplant Unit. Although they are responsible for the day-to-day care of patients, they are not familiar with the special problems of this area. The laboratory must ensure that clinical staff are aware of these particular concerns. In defining a potential test menu, it should be clear which tests are essential and which are merely interesting. Clinical staff are dealing with acute problems and unless results are available within a time frame that enables them to be used in “real time” to aid in clinical decisionmaking, they will not use the information. Better use can be made of some of the older routine tests, which are substantially cheaper and faster to produce.

Many people have contributed to the thoughts in this paper. In particular we thank our colleagues in the Queensland Liver Transplant Service (Steve Lynch, Russell Strong, Charles Steadman, and Glenda Balderson) and Alan Henderson from the Intensive Care Unit at Princess Alexandra Hospital.

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