arguments begin to split physicians from patients and from each other.

Recognizing and correcting homophobia may be difficult for many, but insisting on actual data regarding transmission risk should be easier. Here, with respect to the risk of physicians acquiring HIV from patients, the data have been increasingly reassuring. Even orthopedic surgeons, argued by some to be at a theoretically high occupational risk, have been shown to be free of HIV unless they have had nonoccupational transmission-prone behaviors. The *documented* degree of risk, as opposed to the *speculated* risk, is insufficient as the basis for compromises in patient confidentiality or limitations in access to optimal medical or surgical care. Similarly, evidence of any benefit to physicians from routine nonvoluntary testing and reporting of patients for HIV is also lacking.

Now that data show the limited risk of transmitting HIV from patients to professionals, the number of calls for involuntary HIV testing and reporting of patients has decreased. Our current situation with HIV-infected physicians appears at first to be very different. The transmission of HIV to patients in the office of an infected dentist is recognized to have occurred. Instead of physicians being afraid, patients are now afraid. Instead of patients putting physicians at risk because of their socially disapproved behaviors, medical professionals are portrayed as irresponsible and selfish and willing to put their patients in jeopardy to protect their own privacy and careers. If opinion polls are to be believed, 90% of all adult Americans believe that something needs to be done to protect them from their physicians. In a rapid response, especially following the publication of these opinion polls, draconian (Helmsian) bills criminalizing the practice of medicine have passed the US Senate, and even the most moderate positions taken by the Centers for Disease Control, the American Medical Association, and the Senate "leadership" bill would probably eventuate in mandatory physician HIV testing, at least in some states, and an essentially forced termination of practice. How confident are we that when left to local specialty boards, "exposure-prone procedures" will not include essentially all surgery? Recall the Chicago physician with HIV for whom "invasive" procedures included routine oral examination with an instrument no sharper than a tongue depressor.

Is all of this necessary? Will we look back at these measures as appropriate and useful in instilling public confidence in the medical profession? Or will we see it as an overreaction that perpetuates the fractures of the medical communities and abdicates responsibility for the profession and for public health in favor of momentarily popular and political forces? Certainly our past experience with physicians' fears of patients might have taught that data can be reassuring, not just alarming, and that initial reactions in the absence of data might be based more on fear and discrimination.

Given that, what is the strength of the current data on the risk physicians might pose to patients? Five patients were infected in one dentist's office, but not one of the hundreds of other patients of HIV-infected surgeons who have been "recalled" for testing are reported to have acquired HIV. Many physicians, on receiving an HIV-positive report, immediately ask themselves whether they should alter their practice. Some have done so, whereas others—again after careful consideration and consultation with AIDS experts—decide to

outweighs the remote risk of transmission. Some of these conscientious physicians nevertheless live in mortal fear that they will be publicly exposed, humiliated, and ruined.

Most American adults may be afraid, but perhaps they are also wrong. Knowing how little data are now available, we can at least assume that public opinion is not fully informed. We might also believe that it recognizes neither the potential harm in taking the wrong steps at this time nor that other approaches are possible. The media will forget about HIV-infected physicians, as they have forgotten about other health-related issues after an amazingly short period. With more time and data, public opinion will also change rapidly. Most physicians will continue to act in their patients' and their own best interests. Physicians will be voluntarily tested for HIV in confidential settings, and they will use this information to adjust their practices if they think they pose any risk to their patients.

Meanwhile, the medical profession must stop reacting to uninformed political pressure and insist that it can and must deal with this issue itself. As voluntary guidelines are established, physicians can vigorously and quickly collect additional information. They can develop a consensus about the degree of risk that can be tolerated, as is done for other common conditions that might impair a physician's performance and hence patients' safety. In a sense, the difficulties of charting a course on the current debate and the scrutiny physicians are under offer unique opportunities. If the medical profession succeeds in creating an informed public and political opinion and if rational policies result from this, at least some pride in its leadership could be restored. Also, if it is insisted that standards of safe physician behavior be developed beyond those that simply address HIV, the overall quality of medical care can benefit from these efforts.

PAUL A. VOLBERDING, MD
Professor of Medicine
University of California, San Francisco, School of Medicine
Director, AIDS Program
San Francisco General Hospital Medical Center
San Francisco, California

Liver Transplantation—Challenges for the Future

ORTHOTOPIC LIVER transplantation (OLT) is the accepted treatment of a variety of irreversible acute and chronic liver diseases for which no other form of therapy is available.[1-3] Liver transplantation was initiated nearly 30 years ago when the first human OLT was performed by Starzl in 1963; survival for more than a year was not achieved until 1967, however. The one-year survival rate following OLT was approximately 30% before 1980 but increased to 65% in the early 1980s at the University of Pittsburgh (Pennsylvania).[1] These improved results led a consensus development conference of the National Institutes of Health to conclude in June 1983 that liver transplantation was no longer experimental.[4] This conference was instrumental in broadening funding for the procedure by health insurance carriers and government agencies and in stimulating the development of more transplant centers, resulting in the increased availability and performance of liver transplantation.[5] In 1989, a total of 2,162 liver transplantations were done at 69 transplant centers in the United States; in 1990, there were 2,656 liver transplants performed, a 23% increase over the previous year. In 1989,

were performed at 10 centers doing 50 or more per year, and 40% were carried out in the remaining 59 smaller, and often newer, programs. Liver transplant programs are now situated in most major metropolitan areas in the US, and OLT is considered in virtually every patient with irreversible acute and chronic liver disease. As demonstrated by Szpakowski and co-workers elsewhere in this issue of the journal, new liver transplant centers can achieve excellent results—that is, an 85% two-year survival.[6]

Currently more than 80% of private insurance carriers provide liver transplant coverage. Medicare limits coverage for the procedure to federally designated medical centers and restricts the underlying causes of liver diseases that qualify—postnecrotic cirrhosis associated with the presence of hepatitis B surface antigen and primary hepatic malignancy are excluded. Organ transplantation is an optional benefit under the Medicaid program; most states, however, provide coverage for OLT, although about 20% of states limit it to children only. Finally, a substantial number of Americans are uninsured, and insurance does not fully cover the total costs of OLT. Thus, significant gaps remain in coverage for the procedure; the challenge of the 1990s is to close this gap. The current 75% to 80% survival rate three to five years following the operation and the results of quality-of-life studies showing that more than 85% of patients are able to return to work[7] should be an impetus to broaden coverage for the procedure.

Another important challenge, as organ donation rates stabilize and waiting lists continue to grow, is to increase the number of donors. For too many potential liver transplant recipients, particularly children, the wait for a donor liver proves fatal. It is estimated that between 20,000 and 25,000 of the 2.2 million Americans who die each year meet age and medical criteria that would allow organ donation, but the number of organ donors in 1989 to 1990 was only about 6,000.[5] In recent years, several measures have been adopted to increase organ donation: incorporating donor cards onto drivers' licenses, distributing donor cards by hospitals and other groups, and enacting required request laws. More innovative approaches are needed to further promote donation and relieve the increasing shortage of organs.

New operative procedures have been developed in the past few years to alleviate the shortage of size-matched organ donors for children.[8,9] Reduced-size OLT is a procedure in which part of the liver graft is reduced by dissecting appropriate right or left lobe anatomic segments and then implanting in the orthotopic position after total recipient hepatectomy. It is also possible to obtain two grafts from a single donor, known as the "split-liver" procedure.[8] Another approach to the scarcity of infant and child donors is transplantation of a liver graft from a living related donor.[9] The donor undergoes a resection of the left lateral segment of the liver, which is then transplanted into the recipient. Experience with this approach is increasing in the United States at the University of Chicago Hospitals, and the ethical issues are being addressed.

Introduction of the University of Wisconsin (UW) solution is another new development that has revolutionized liver transplantation.[10] In an experience with liver homografts preserved for 4 to 24 hours with UW solution compared with grafts preserved for 3 to 9 hours with conventional Euro-Collins solution, the UW-preserved grafts had a lower rate of primary nonfunction with a reduced need for retransplantation.[10] In addition, the UW solution has improved donor operation logistics, reduced the costs of transplantation, and allowed a semielective approach to liver transplantation. In the 1990s, we may witness the discovery of even better organ-preserving solutions.

The overall goals of OLT are to prolong life and improve the quality of life. The selection of appropriate patients to achieve these goals is difficult and inexact, with no uniformly agreed-on national criteria. Even more troublesome is determining the appropriate timing of liver transplantation during the course of advanced chronic liver disease. General indications for liver transplantation in adults are as follows[1-3]: irreversible advanced chronic liver disease, fulminant hepatic failure, unresectable hepatic cancer confined to the liver, and metabolic liver disease. In addition, there should be no contraindications to the procedure and the patient should be able to provide for its costs. The absolute and relative contraindications to OLT have evolved over the past ten years of cumulative experience. The usual absolute contraindications include the following[1-3]: the acquired immunodeficiency syndrome or human immunodeficiency virus positivity, malignancy outside the liver, uncontrollable infection outside the hepatobiliary system, active alcoholism or intravenous drug abuse, and advanced cardiopulmonary disease. Relative contraindications or conditions that complicate and increase the risk of transplantation include advanced age, stage III to IV hepatic coma, advanced chronic renal failure, hypoxemia from intrapulmonary shunts, portal vein thrombosis, previous portosystemic shunt operation, previous biliary tract operation, severe malnutrition, and massive ascites.

Guidelines are needed for referring patients with fulminant or chronic end-stage liver disease for OLT.[11] The optimal timing of the procedure requires a knowledge of prognostic indices and the natural history of each specific liver disease suitable for transplantation. The best application of prognostic survival models to the timing and outcome of OLT in chronic liver disease has been applied to primary biliary cirrhosis, a disease with the most predictable natural history.[12,13] The application of the Mayo Clinic model, which includes five independent prognostic variables (serum levels of bilirubin and albumin, prothrombin time, age, and the presence of peripheral edema), has demonstrated that the procedure improves survival compared with supportive therapy in patients with primary biliary cirrhosis.[12,13] Primary sclerosing cholangitis has a less predictable natural history because of a fluctuating course and the possibility of cholangiocarcinoma developing, but similar independent predictors of prognosis can be identified.[14] Investigators at King's College Hospital in London have proposed specific demographic and laboratory criteria for liver transplantation in patients with fulminant hepatic failure based on a large and longitudinal experience.[15] Separate criteria have been established for patients with fulminant hepatic failure due to acetaminophen overdose and those with failure caused by viral or drug-induced hepatitis. Clinical judgment and assessment of the patient's quality of life, important factors not found in any of the current models, will likely remain critical in deciding the timing of OLT, but they require standardization.

Immunosuppressive drug regimens vary from center to center but generally include corticosteroids, cyclosporine, and azathioprine. Corticosteroids are used initially in high doses, which are progressively reduced to maintenance levels of 10 to 20 mg daily during the initial several months after the operation and then to 5 to 10 mg daily long term. Cyclo-

sporine is administered at a dose to maintain therapeutic trough levels, and its use is often begun postoperatively only after adequate urinary output is established. Several centers use so-called triple therapy with azathioprine, which allows the use of lower doses of all three drugs, thus avoiding toxicity of individual agents. A recent immunosuppressive variation is the use of prophylactic OKT3 for 7 to 12 days following the operation, with the later introduction of cyclosporine. In general, however, OKT3 is reserved for episodes of rejection. In this decade, three new candidate immunosuppressive drugs have been developed: FK 506,[16] rapamycin, and 15-deoxyspergualin. FK 506 appears to be the most promising, both as an agent to reverse rejection unresponsive to conventional drugs and as primary immunosuppressive therapy to achieve better patient survival and fewer episodes of rejection. Multicenter studies are under way in Europe and the United States to determine the efficacy of FK 506 compared with cyclosporine and to better define toxicity. The treatment of rejection episodes following OLT typically includes giving a bolus of corticosteroids, sometimes followed by an oral recycle of high doses with rapid tapering back to a maintenance level, the use of OKT3, and retransplantation. These treatments are usually applied in a stepwise fashion. With refinements in the indications, timing, and technical aspects of the procedure, the scarcity of organs and the precise diagnosis and optimal management of rejection loom as the major challenges of transplantation.

There are several controversial areas in liver transplantation today. Alcoholic cirrhosis is the leading cause of hepatic morbidity and mortality in the US. The major deterrents to liver transplantation in patients with alcoholism are concerns regarding abstinence after transplantation and the possible presence of medical problems associated with chronic alcoholism, such as pancreatitis, cardiomyopathy, neuromuscular syndromes, or severe malnutrition. In a recent report by Starzl and colleagues, of 41 patients with alcoholic cirrhosis treated with liver transplantation, 73% were alive at one year and 68% between one and three years.[17] These results were no different from those obtained in 625 adult patients who received liver transplants for other reasons. Moreover, of 35 patients who survived longer than six months, only 2 returned to active alcoholism. These preliminary results, which require verification in other centers and longer periods of follow-up, have led to the consensus that patients with end-stage alcoholic liver disease should not be excluded from consideration for liver transplantation. The current policy of many transplant centers is to require some period of alcohol abstinence, typically six months, to mandate involvement in a structured alcohol rehabilitation program and to verify that the patient has a stable and supportive psychosocial structure.

Hepatitis B typically recurs after liver transplantation, and the long-term survival of patients (45% to 50%) is substantially less than for patients receiving transplants for other causes of end-stage liver disease (75% to 80%).[18] Efforts to treat hepatitis B infection perioperatively or postoperatively with hepatitis B immune globulin or interferon alfa have generally failed. Not all centers continue to do OLT in patients with hepatitis B, and newer experimental modalities to prevent or treat recurrent hepatitis B are desperately needed. Although data are preliminary, the hepatitis C status of the donor and recipient appear to have little bearing on the subsequent course following the operation. One large retrospective study found that the loss of antibody to the hepatitis C virus (anti-HCV) was frequent and acquisition of anti-HCV rare following the procedure. The development of hepatitis after transplantation was unrelated to the anti-HCV status.[19] There are no data that suggest a lower survival rate following OLT for postnecrotic cirrhosis due to hepatitis C, but longer follow-up with surveillance using more sensitive serologic assays is needed.

Although transplantation for hepatocellular malignancy has a long-term survival that is inferior to all other indications for liver transplantation, selected patients may obtain meaningful palliation and even long-term survival. Survival is distinctly better in those patients receiving transplants for hepatocellular carcinoma compared with that for cholangiocarcinoma.[20] Certain tumor types have a favorable prognosis—hemangioendothelioma, fibrolamellar hepatocellular carcinoma, and incidental hepatocellular carcinoma—and remain excellent indications for liver transplantation. In the 1990s, it is desirable that all patients with hepatocellular carcinoma be placed on experimental adjuvant therapy protocols to accumulate data regarding the possible benefits of such therapy. Orthotopic liver transplantation for cholangiocarcinoma or for primary diseases metastatic to the liver should be considered investigational.

As demonstrated in the report of Szpakowski and associates, transplantation can be carried out with excellent results in a new liver transplant center at a private medical center.[6] The two critical factors that determine the success of a new program are the training and experience of the transplant surgeons and a full institutional commitment. These good results may have been influenced in part by selection factors—a third of the patients were children, and only one patient underwent OLT for primary hepatic malignancy. On the other hand, seven patients had hepatitis B; six were reinfected, and three died. It should be pointed out to skeptics that all 11 patients with alcoholic cirrhosis survived, and only 1 returned to drinking. Finally, the immunosuppressive regimen using prophylactic antilymphocyte globulin, cyclosporine, and low-dose corticosteroids was associated with a low rate of fungal and viral infections and likely contributed to the excellent outcome of these first 100 liver transplant operations.

EMMET B. KEEFFE, MD
Professor of Medicine
Division of Gastroenterology
Oregon Health Sciences University
Portland, Oregon

REFERENCES

1. Starzl TE, Demetris AJ, Van Thiel D: Liver transplantation (parts 1 and 2). N Engl J Med 1989; 321:1014-1022; 1092-1099

2. Dindzans VJ, Schade RR, Gavaler JS, Tarter RE, Van Thiel DH: Liver transplantation: A primer for practicing gastroenterologists, parts I and II. Dig Dis Sci 1989; 34:2-8; 161-166

3. Maddrey WC (Ed): Transplantation of the Liver. New York, NY, Elsevier, 1988

4. National Institutes of Health Consensus Development Conference Statement: Liver transplantation. JAMA 1983; 250:2961-2964

5. US Department of Health and Human Services, Public Health Service, Health Resources and Services Administration, Bureau of Health Resources Development, Division of Organ Tranplantation: Annual report on the US Scientific Registry for Organ Transplantation and the Organ Procurement and Transplantation Network, 1988 and 1989

6. Szpakowski JL, Cox K, Nakazato P, Concepcion W, Levin B, Esquivel CO: Liver transplantation—Experience with 100 cases. West J Med 1991 Nov; 155:494-499

7. Tarter RE, Erb S, Biller PA, Switala J, Van Thiel DH: The quality of life following liver transplantation: A preliminary report. Gastroenterol Clin North Am 1988; 17:207-217

8. Broelsch CE, Emond JC, Thistlethwaite JR, et al: Liver transplantation with reduced-size donor organs. Transplantation 1988; 45:519-523

cessful liver transplantation from a living donor to her son. N Engl J Med 1990; 322:1505-1507

10. Todo S, Nery J, Yanaga K, Podesta L, Gordon RD, Starzl TE: Extended preservation of human liver grafts with UW solution. JAMA 1989; 261:711-714

11. Donovan JP, Zetterman RK, Burnett DA, Sorrell MF: Preoperative evaluation, preparation, and timing of orthotopic liver transplantation in the adult. Semin Liv Dis 1989; 9:168-175

12. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A: Prognosis in primary biliary cirrhosis: Model for decision making. Hepatology 1989; 10:1-7

13. Markus BH, Dickson ER, Grambsch PM: Efficacy of liver transplantation in patients with primary biliary cirrhosis. N Engl J Med 1989; 320:1709-1713

14. Wiesner RH, Grambsch PM, Dickson ER, et al: Primary sclerosing cholangitis: Natural history, prognostic factors, and survival analysis. Hepatology 1989; 10:430-436

15. O'Grady JG, Alexander GJM, Hayllar KM, Williams R: Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97:439-445

16. Macleod AM, Thomson AW: FK 506: An immunosuppressant for the 1990s? Lancet 1991; 337:25-27

17. Starzl TE, Van Thiel D, Tzakis AG, et al: Orthotopic liver transplantation for alcoholic cirrhosis. JAMA 1988; 260:2542-2544

18. Demetris AJ, Todo S, Van Thiel DH, et al: Evaluation of hepatitis B virus liver disease after hepatic replacement: Practical and theoretical considerations. Am J Pathol 1990; 137:667-676

19. Read AE, Donegan E, Lake J, et al: Hepatitis C in patients undergoing liver transplantation. Ann Intern Med 1991; 114:282-284

20. O'Grady JG, Polson RJ, Rolles K, et al: Liver transplantation for malignant disease: Results in 93 consecutive patients. Ann Surg 1988; 207:373-379

Molecular Genetics in the Cancer Clinic

THE INCORPORATION OF modern molecular approaches into research on clinical problems is now extensive. Indeed, one can hardly read a medical journal these days without at least a general understanding of the various techniques in molecular biology. This is arguably as true for investigations of the neoplastic diseases as it is anywhere, perhaps reflecting a relatively early appreciation that malignant neoplasms are, in essence, genetic disorders. Many results of "basic" research on the molecular mechanisms of oncogenesis are rapidly approaching the point of clinical application in the diagnosis and management of human cancer. This work is thus of more than passing concern to physicians who care for patients in their practice with cancer. The literature in this discipline is vast and often minutely focused, however, and so is not always readily accessible to interested clinicians. In this issue of the journal, Koeffler and colleagues have distilled from this mass of information a usefully concise and current summary of the genetic lesions that have been identified in human tumors.[1] They also touch on many of the ideas that these findings have prompted regarding molecular mechanisms in the pathogenesis of cancer. Several of the models that the authors discuss are particularly useful in their generality. I wish to illustrate this point by reviewing some important related findings published too recently for inclusion in their article.

Chromosomal Translocations in Oncogenesis

The finding of a given chromosomal translocation (at the cytogenetic level) in multiple independent specimens of the same tumor type is strong circumstantial evidence for participation of the associated genes in the origin or progression phase of tumorigenesis. Molecular analysis of such recurrent translocations is a venerable, and still fruitful, approach to the isolation of novel genes involved in oncogenesis. This has been particularly true for the lymphoid neoplasms, where one partner in the translocation is frequently an immunoglobulin or T-cell receptor *(TCR)* gene. These can serve as a toehold from which it is possible to "walk" across a cloned translocation break point to the candidate proto-oncogene.

Translocations with up-regulation. As noted by Koeffler and associates, juxtaposition of the c-*myc* locus with the immunoglobulin heavy chain *(IGH)* gene (as in Burkitt's lymphoma) may be regarded as the prototype of situations in which proto-oncogenes suffer deregulation as a consequence of translocation.[1] In instances such as these, the cognate oncoprotein gene products are inappropriately expressed, but they are not physically altered. Several recently described cases of this pathogenic mechanism have made for interesting additions to the list of cellular functions that are apparently oncogenic when corrupted in this context. For example, *BCL2*—a gene "activated" by translocation to the *IGH* locus in most follicular malignant lymphomas—encodes a mitochondrial protein somehow involved in governing B-lymphocyte lifespan[2,3]; overexpression of *BCL2* protein in association with the translocation seems to block programmed cell death in this lineage. This leads in turn to a pathologically expanded B-cell population by decreased attrition rather than increased proliferation.[2,3]

The *BCL1* gene, yet another gene sometimes juxtaposed with the *IGH* locus in lymphoid malignant diseases, codes for a member of the cyclin protein family.[4] Several of the cyclins are known to be intimately connected with the regulation of cell-cycle progression in eukaryotes. The *BCL1* locus is also amplified (without known translocation) in a number of nonlymphoid tumor types.[4] The exact role of *BCL1* deregulation in tumorigenesis is by no means clear at present. It is an intuitively appealing notion, however, that cyclin function could sustain derangement in neoplastic cells, leading to the loss of a normal control of proliferation.

A recurrent translocation of T-cell acute leukemia situates a *TCR* locus adjacent to a so-called homeobox *(HOX)* protein gene.[5] The many *HOX* family proteins appear to figure prominently in regulating cell type-specific differentiation during development. Here, too, nothing is certain regarding detailed pathogenic mechanisms of tumorigenesis supported by the translocation. It is interesting to suggest, though, that this is a case where the abrogation of normal differentiation (perhaps an interfering effect of the inappropriately expressed *HOX* protein), rather than a loss of proliferation control per se, is the root cause of neoplasia.[3,6]

Translocation with protein alteration. Chromosomal translocation can also lead to the synthesis of a functionally abnormal and pathogenic fusion protein; the *BCR/ABL* products in acute lymphocytic and chronic myelogenous leukemias[7] are discussed by Koeffler and co-workers as models for this mechanism of neoplastic change.[1] As another example, the breakpoint of the t(15;17) translocation of acute promyelocytic leukemia occurs in the retinoic acid-receptor-α locus *(RAR)*.[3,8] This is intriguing because retinoic acid and its analogues are known to be potent inducers of differentiation in primitive myeloid cells.[3,8] The translocation event leads to the formation of a protein in which aminoterminal sequences of *RAR* are replaced with those of a previously undescribed gene designated *MYL*.[8] While the *MYL/RAR* fusion protein, like the parent *RAR* protein, can mediate the regulation of gene expression by retinoic acid, its function in this respect is clearly abnormal.[8] It is possible that the *MYL/RAR* fusion protein acts in an inhibitory way in promyelocytic leukemia cells by outcompeting normal *RAR* molecules. The latter would otherwise affect progress along the myeloid differentiation pathway.[3,8] It has recently been found that administering all-*trans*-retinoic acid induces complete re-