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# Contribution of Organ Transplantation to the Biology of Cancer

*Thomas E. Starzl*

The interface between transplantation and oncology has been an incompletely explored one with potential implications ranging from the simple and obvious to the most sophisticated and surprising.

## IMMUNOSUPPRESSION

To succeed with transplantation, it is necessary to drastically alter the immune system of the recipient and to reduce thereby one of the natural defenses against malignant tumors. The principal advances in clinical immunosuppression[1-8] are summarized in Table 1. With each of the relatively small number of regimens, the effectiveness and practicality of therapy have been improved. The introduction of cyclosporine[5] and its combination with steroids[6] about a decade ago were a major event that made practical on a large scale the transplantation of extrarenal organs.

Recently, we have developed and started clinical trials with an even more powerful and considerably less toxic agent called FK 506.[8] FK 506, like cyclosporine, has a relatively specific effect on T-lymphocytes. Both cyclosporine and FK 506 inhibit the synthesis and expression of the cytokine, interleukin 2.[9,10]

The combination of any of the immunosuppressive agents with continuously present antigens can induce "graft acceptance"[11] for reasons not adequately explained. In rodents, this is very easy to accomplish with FK 506,[12] the drug which seems destined to dominate all developments in transplantation in the immediate future.

## IMMUNOSUPPRESSION AND THE TUMOR ENVIRONMENT

More than two decades ago, we speculated[13] that the development of cancer, or acceleration of its growth might be consequences of immunosuppression. There were two principal lines of evidence for this hypothesis.

### *The Accidental Transplantation of Malignant Tumors*

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# Transplantation of Cancer

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TUMOR ENVIRONMENT

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TABLE 1. Immunosuppressive Drug Regimens Used Clinically for Whole Organ Transplantation

| Reference | Agents | Year described and reported | Place | Deficiencies |
|---|---|---|---|---|
| 1 | Azathioprine | 1962 | Boston | Ineffective, dangerous |
| 2 | Azathioprine-steroids | 1963 | Denver | Suboptimal |
| 3 | ALG as adjunct | 1966 | Denver | Suboptimal |
| 4 | Cyclophosphamide substitute for azathioprine | 1970 | Denver | No advantage except for patients with azathioprine toxicity |
| 5 | Cyclosporine | 1978–1979 | Cambridge | Suboptimal |
| 6 | Cyclosporine-steroids with or without other adjuncts* | 1980 | Denver | Nephrotoxicity limits dose: rejection not always controlled |
| 7 | Monoclonal OKT3 | 1981 | Boston | High incidence of infection |
| 8 | FD 506 | 1989 | Pittsburgh | Being evaluated |

* Lymphoid depletion with thoracic duct drainage, anti-lymphocyte globulin (ALG), OKT3, and/or azathioprine.

human to another normally are rejected. About 25 years ago, several patients were given grossly normal kidneys from donors who had died of carcinomas of the lung, hypopharynx, thyroid, breast, or liver (summarized in Ref. 14). Micrometastases were present in these seemingly normal cadaveric organs because the immunosuppressed recipients of the kidneys developed metastases from the donor tumors. In two of the patients, the tumors had become autonomous by the time the diagnosis was made. Although immunosuppression was stopped, these patients died of widespread metastases.[15,16] However, in two other cases,[17,18] carcinomas which had diffusely infiltrated the renal graft and surrounding area or even had spread to both lungs disappeared without a trace after azathioprine and prednisone were stopped; at the same time the kidney grafts were rejected.

Even in recent times, tumors have been accidentally transplanted.[19] In April 1986, a liver, heart, and two kidneys were procured from a 36-year-old female donor who had died from a stroke. Later, stored donor serum was shown to have an astronomical level of chorionic gonadotrophin. Metastatic choriocarcinoma developed in the liver recipient and in both kidney recipients. The heart recipient was spared, at least for the first half year. Tumor was irradicated in one of the kidney recipients after graft nephrectomy and methotrexate therapy. The other two recipients died within a few months of widespread metastases.

### *An Increased Incidence of* De Novo *Tumors*

A more subtle demonstration of the liability of depressed immunologic surveillance is the high incidence of *de novo* tumors in patients

under chronic immunosuppression. Earlier observations by Dr. Robert Good and his associates[20] had already identified this risk in patients with natural immune deficiency states. We reported the same ominous development in our immunosuppressed kidney recipients at several meetings in 1968 (summarized in Ref. 14). The unusually high incidence was emphasized of the lymphoreticular tumors (then called recticulum cell sarcomas or histiocytic lymphomas), which are now known to be B-cell lymphomas.[21,22] There was an increase also of epithelial and other malignancies. Dr. Israel Penn, who joined our faculty at the University of Colorado in July, 1968, made these cases[23] the nucleus of an international registry of *de novo* malignancies in transplant recipients[24] which he still maintains. Two decades later, more than 5000 cases have been contributed.[25] The overall profile of the original cameo reports has not been changed in principle by the accrual of these huge numbers.

*An infectious etiology.* Because of a high incidence in organ recipients of the facial and uterine cervical cancers that are associated with infections of the Herpes virus family, we suspected at the outset that *de novo* tumors under immunosuppression might have an infectious etiology.[24] The B-cell lymphomas which have been linked to Epstein-Barr virus provide the best example. The characteristics of such tumors were described by Klein and Portillo in patients with a familial immune deficiency disease,[26] and convincing evidence that they were caused by primary infection or reinfection with Epstein-Barr virus under immunosuppression has been provided from many transplant centers, beginning with the insightful reports of Simmons and his associates.[27] A virus etiology is suspected but not established for other *de novo* tumors under immunosuppression.

*Tumor regression with immune modulation.* A special and reasonably predictable feature of the Epstein-Barr associated B-cell lymphomas is their regression in the majority of cases when immunosuppression is lightened or stopped.[22] We recognized long ago the responsiveness of histiocytic lymphomas to immune modulation,[14,28,29] but uncertainty about the nature and histopathologic classification of these lesions made interpretation of the dramatic clinical events following discontinuance of immunosuppression difficult. The instinctive conclusion of skeptics was that the regression of a mass after stopping or reducing immunosuppression implied that the diagnosis of lymphoma must have been incorrect in the first place. The term "pseudolymphoma" was applied.[28] However, with modern methods of lymphoma classification,[30] including those made possible with gene probe techniques,[31] the conclusion became inescapable that the complete involution of true B-cell neoplasms, including many with monoclonal constituency could be accomplished by allowing the recipient's immune system to recover. This was the first clear example in humans of immune surveillance. The prospects of recovery from these virus-associated malignancies can be improved further by treatment with the anti-viral agent, acyclovir.[32]

We have also seen growth or recession of Kaposi's sarcomas, corresponding perfectly with the institution of discontinuance of cyclosporine-steroid therapy.[33] It is almost certain that the complete disappearance of a malignant dysgerminoma in a kidney transplant recipient was because of restored immune surveillance after discontinuance of immunosuppression.[34] Ironically, the case had been reported originally as a claim that chemotherapy and irradiation were effective in spite of immunosuppression.[35]

*Aids plus immunosuppression.* During the first half of the 1980s, when screening for HIV was not available, an accidental experiment was begun which continues to the present. Twenty-five patients were treated with liver, heart, or kidney transplantation without knowing that they already were HIV carriers, or would be infected perioperatively with transfusions or with the donor organs.[36] Twelve of these patients are still alive 1 1/6 to 7 years later, none with tumor. However, one liver recipient died of an intra-abdominal immunoblastic sarcoma 19 months postoperatively. Another (whose original disease was sclerosing cholangitis) developed a carcinoma of the rectum which was resected 2 years ago with no subsequent recurrence. These patients with their natural immune deficiency plus immunosuppression have had organ rejection as vigorous as normal patients. They have not had the overwhelming incidence of *de novo* tumors that might have been predicted.

## SURVEILLANCE REVISITED VIA LIVER REGENERATION

The concept of immunotherapy is based upon two inherent premises in the surveillance hypothesis. The first is that the tumor cell is sufficiently different from normal cells, perhaps by virtue of tumor specific antigens, to be recognized as alien. The second premise is that a malignant tumor cell will be a more sensitive prey to immunologic attack than the healthy cell. The simplistic hypothesis of immune surveillance[37] along with its therapeutic implications was the subject of a complete issue in 1971 (Vol. 7, p. 3–178) of a journal then called *Transplantation Reviews* and later renamed *Immunological Reviews*. In a subsequent issue only 5 years later (1976; 28:3–98) were described inconsistencies of the surveillance hypothesis,[38] failure of the hypothesis to explain why tumors never developed in the T-cell deficient nude mice,[39] and reasons why it should be abandoned. Discussion of the reverse stampede away from the surveillance hypothesis is beyond the scope of my assignment today. However, I have brought up the subject in order to ask if some recent work on liver regeneration might permit a new and different look at immune surveillance. Liver regeneration is an example of intense cell renewal rivaling or surpassing that seen in the most rapidly growing malignant tumors. Yet, the process is under perfect biologic control and entirely self-limiting. Why?

We have studied liver regeneration in rats submitted to 40 and 70 per cent partial hepatic resection, with or without immunosuppression with the two most potent immunosuppressive drugs available, namely cyclosporine[40,41] and the even more powerful new agent named FK 506.[41] Both drugs augment regeneration.[40,41] The mechanism of this effect is obscure. Although the two drugs have completely different molecular structure, they have in common the specific depression of the T-cell response.[9,10] We have asked if a natural function of the immune system, and particularly its T-cell component might be to "brake" (modulate) hepatocyte replication, but only when this replication is occurring at an increased rate. Thus, cyclosporine and FK 506 markedly augment mitoses if it is already higher than normal in regenerating livers, in livers damaged by Eck fistulas and in livers stimulated with thyroxin.[42,43] This is a phenomenon of the intact animal. Neither drug has any effect on resting or stimulated (with epidermal growth factor) hepatocytes in culture. The mitotic rate is not increased, meaning that the stimulation of cell renewal is not a direct effect on the liver cells.[42]

In any discussion of regeneration, a central question is why the regenerating liver knows how to stop its regrowth at the proper size and time. Endogeneously produced chemical inhibitory factors or hormones often are candidate control substances.[44,45] Perhaps, insufficient attention has been paid to immune modulation as the explanation. Research on immunosuppression for transplantation, combined with investigations of hepatic regeneration, could lead to a better understanding of the relation between growth control and immune function. There could be major implications in oncology and revision of the meaning of surveillance.

## TRANSPLANTATION TO INCREASE SURGICAL MARGINS

### *Total Hepatectomy and Liver Transplantation*

In the early trials of orthotopic liver transplantation, the ideal indication for liver replacement was thought to be a malignant tumor which could be removed completely by total hepatectomy, but not by conventional subtotal hepatic resection. Unfortunately, the majority of recipients who survived liver transplantation died later of metastatic disease.[13,46,47] Nevertheless, some patients did live for a long time, and, in fact, practically all of those recipients who had small incidental malignancies in livers removed for other reasons (*e.g.*, biliary atresia) were rendered tumor free.[46] The longest survivor after liver transplantation in the world (now 20 years) had a 2-cm hepatoma in her cirrhotic liver, and 4 mg% of $\alpha$-fetoprotein in her preoperative serum. Thus, the size and stage of development of the malignancy was important in the tumor prognosis.

The high incidence of tumor recurrence after liver transplantation has prompted speculation,[13,14] that immunosuppression itself might fa-

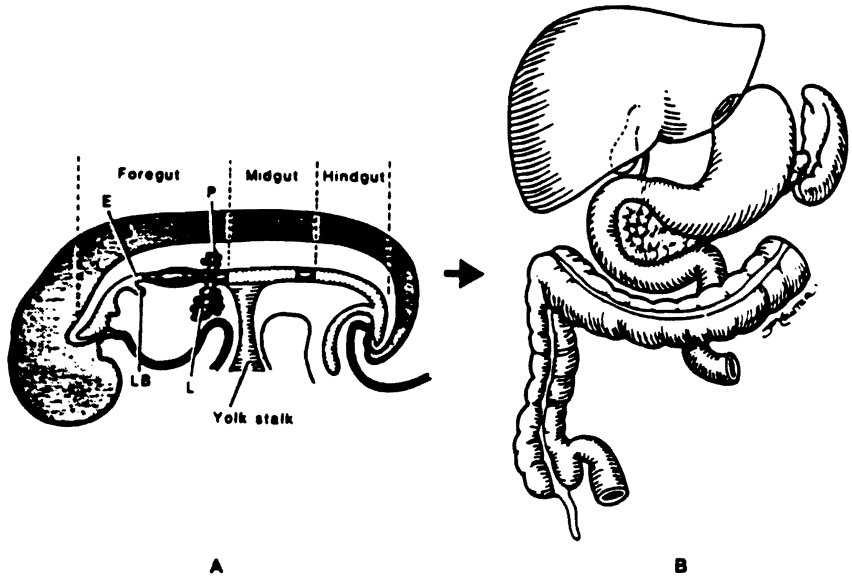
vor the growth of micrometastases which are outside of the liver or expelled from it during the transplantation. This might be a special problem with bulky tumors. In addition to size, the histopathology of the tumor also influenced prognosis. Patients with the so-called fibrolamellar variant of hepatocellular carcinoma have done well after liver transplantation, even when the lesions were enormous.[48] In contrast, patients with large conventional hepatocellular carcinomas almost always have developed recurrence.[46] In spite of initially optimistic expectations, very small duct cell carcinomas in the hilum of the liver (Klatskin tumors) have had a dismal prognosis (reviewed in Ref. 47). In between these extremes are other tumor types such as hemangioendothelial sarcomas.[49] Even patients with massive liver metastases have had an overall 2 year survival of 50 per cent, the best results being with neuroendocrine tumors (in particular, carcinoids) and sarcomas.[50]

Thus, the concept of using liver transplantation to extend resectability limits has not been completely abandoned. In the major liver transplantation centers around the world, the incidence of recipients with hepatic tumors ranges from 4 to 40 per cent,[47] the low figure being ours. Tumor recurrence in all reported series is responsible for a steady decline in survival beginning at 4 to 6 months.[47] Adjuvant chemotherapy, usually including adriamycin, is being used increasingly in addition to liver replacement, but there is no proof as yet that the outcome will be favorably influenced thereby.

## UPPER ABDOMINAL EXENTERATION

It is possible that even the total hepatectomy made possible by transplantation is a fundamentally inadequate resection. Beyond the context of transplantation, an understanding of the embryonal origin of the liver, pancreas, and duodenum can help in understanding why tumor operations on these organs are so ineffectual. In the development of the fetus, the liver and pancreas begin as ventral and dorsal diverticula from that portion of the foregut that later becomes the duodenum (Fig. 1A). The anatomic relationships of these organs becomes more complex during their differentiation and rotation, but their intimacy including the sharing of the terminal hepatic and pancreatic duct drainage into the duodenum is not lost (Fig. 1B). Thus, it is not surprising that malignant tumors developing at or near the original duodenal outpouchings are notoriously refractory to treatment by resection even if these are localized to a portion of a single organ. Tumors that originate in one of the three organs (liver, pancreas, or duodenum) and metastasize to the others or to the transverse mesocolon or colon have been considered to be categorically non-resectable.

During the last 1½ years, we have examined the premise that radical excision of most of the foregut could allow complete removal of certain hepatic duct cell, duodenal, gastric, and pancreatic malignancies that




FIGS. 1A and 1B. Delineation in embryonal life of that region of the gastrointestinal tract (dark shaded) that was resected in the organ cluster operation (A). E, esophagus; LB, lung bud; L, liver; P, pancreas. The adult organs deriving from the shaded primitive analage (B). (By permission of Starzl TE, Ann Surg 1989; 210:374–386.)

had already spread to the liver as well as extirpation of primary liver tumors whose spread was downward. Thirty-three patients with these seemingly untreatable malignancies underwent removal of the liver, stomach, spleen, duodenum, proximal jejunum, terminal ileum, and ascending and transverse colon (Fig. 1B).

*Replacement with organ clusters.* In the first 15 patients,[51,52] the void in the upper abdomen was filled with cadaveric organ cluster grafts that included the liver, pancreas, duodenum, and variable amounts of proximal jejunum (Fig. 2). The primary tumors were duct cell carcinomas ($n$ = 7), carcinoids ($n$ = 3), cholangiocarcinomas ($n$ = 2), sarcomas ($n$ = 2), and one hepatoma. Their locations are summarized in Table 2. The lesions usually involved multiple organs (Table 2) and were untreatable by any conventional criteria. The operations were performed between July 1988 and March 1989, and for the survivors there are potential follow-ups of 7½ months to almost 1½ years (Table 3). Four of the 15 recipients died within the first 4 months, all of technical or mechanical complications. Of the 11 who survived for definitive observation, 2 developed recurrences which caused death, and a third one who is clinically well has had stable nodules in the lungs for a number of months. Four patients with sarcomas and carcinoid tumors have had no recurrences (Table 3). Other survivors had duct cell cancers ($n$ = 3), a cholangiocarcinoma ($n$ = 1), and a hepatoma ($n$ = 1). Duct cell cancers have given the worst results (Table 4) with the prognosis directly linked to the presence or

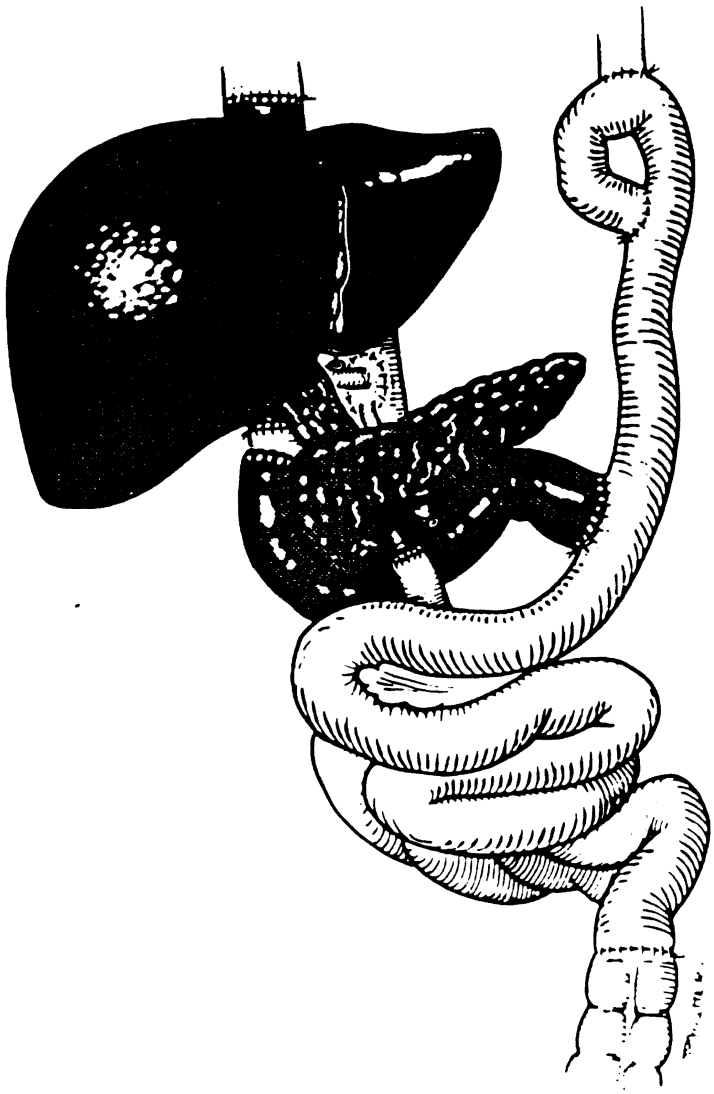


FIG. 2. Completed superior mesenteric vein reconstruction and usual gastrointestinal reconstruction. (By permission of Starzl TE, Ann Surg 1989; 210:374–386.)

absence of lymph node metastases. The experience so far supports further cautious trials with this drastic cancer operation.

*With transplantation of the liver alone.* It is not clear whether the complete cluster replacement graft is necessary. We have performed the upper abdominal exenteration with transplantation of the liver only.[53] The penalty for the limited organ replacement is diabetes mellitus and exocrine pancreatic insufficiency. Eighteen such operations have been carried out, but with follow-ups that are too short to permit definitive

TABLE 2. Primary Tumor Location in Organ Cluster Series*

| | |
|---|---|
| Bile ducts | 7 |
| Liver | 3 |
| Pancreas | 1 |
| Stomach | 1 |
| Duodenum | 3 |

* Number of organs involved: four, 2; three, 4; two, 5; and one, 4.

conclusions. Although the simpler procedure imposes diabetes mellitus and exocrine pancreatic insufficiency, it eliminates the technical complications associated with whole pancreas grafts. One potential strategy for the future is to perform this modified operation, but to then carry out free transplantation into the portal vein of the islets prepared from the pancreas of the liver donor. Islet cell transplantation has never been successfully done in humans, but the remarkable potency of FK 506[8] mentioned, earlier is an incentive for such a trial which is planned for later this year.

## SUMMARY

Patients under immunosuppression variably have lost their immune tumor surveillance. This has been demonstrated by accidentally transplanting malignant tumors to these patients, and by an increased risk of *de novo* tumors of which some have a viral etiology (Epstein-Barr virus) and well-mapped oncogenes. When immunosuppression is lightened or stopped in patients with B-cell lymphomas, with Kaposi's sarcomas and possibly other tumor types, the neoplasms may go away. The immune system may be involved as well in growth control of normal cells. FK 506 and cyclosporine, two drugs which are T-cell specific immunosuppressants, greatly augment the liver regeneration that follows

TABLE 3. Survival by Diagnosis: 15 Cluster Recipients*

| | *n* | Time in months |
|---|---|---|
| Duct cell CA | 3/7 | 8, 11, 12 |
| Sarcoma | 2/2 | 14, 16 |
| Carcinoid | 2/3 | 8, 13 |
| Cholangio CA | 1/2 | 9 |
| Hepatoma | 1/1 | 9 |

* Dates: July 22, 1988 to March 24, 1989; ages: 27–49 years; and sex: 9 males, 6 females.

TABLE 4. Duct Cell Cancer ($n$ = 7)

| | |
|---|---|
| Survival (8–12 months) | 3/7 |
| Negative nodes | 3/4 |
| Positive nodes | 0/3 |

partial hepatectomy and they modulate liver growth in other situations including Eck fistula.

In spite of the handicaps of immunosuppression, liver transplantation has been used to treat patients with primary liver tumors and even metastatic hepatic malignancies. A newer procedure of upper abdominal exenteration has been used recently to remove upper abdominal malignancies which were previously beyond surgical therapy because of their involvement of multiple organs including the liver, pancreas, duodenum, or other structures. Although recurrences have been common, many patients have been rendered tumor free by these seemingly radical operations which are apt to play a slowly increasing role in the therapeutic armamentarium of the future.

## ACKNOWLEDGMENT

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# Discussion

**Margaret L. Kripke:** Dr. Starzl, in the regeneration of normal liver, as far as I am aware, there is no known difference in the regeneration of normal liver in, say, nude mice than in normal mice. So, if this were really a T-cell immunological phenomena, you would expect to see differences in regeneration of those cases. Would you comment?

**Thomas E. Starzl:** This is an important point. There are reports of normal hepatic regeneration in nude mice. You can rest assured that we have our own colony of nude mice and are doing our own experiments to confirm or deny these reports. There are other studies that can and are being done, including regeneration studies with monoclonal anti-$CD_4$ antibody treatment. Also, in a larger animal model, the dog, we have a proficient way of depleting T-cells with thoracic duct fistula, after which we can study regeneration with a split liver model that has been used to assess other growth control factors such as insulin and a hepatic stimulatory substance that can be found in regenerating livers.

**David Skinner:** On that same line, your data show that the brake on regeneration is the total mass. It stops as the mass gets larger.

**Starzl:** It stops, but those experiments were done for somewhat different reasons. The treatment schedule was to pretreat for 3 days and to give the final dose of immunosuppression on the day of liver resection. Thus, active drug therapy had been stopped at the time regeneration was occurring and receded. When we first discovered this augmentation of regeneration with cyclosporine in 1985 and 1986, the experiments were done with the hypothesis that regeneration would be reduced. We were concerned about whether transplanted livers under immunosuppression would be able to accommodate themselves to the appropriate size, and also we feared that if we had to give Adriamycin to liver recipients being treated for cancer, there would be a double indemnity if both agents (cyclosporine and adriamycin) retarded regeneration (as adriamycin was known to do). What will happen to regeneration with continuous therapy or whether the liver mass will be changed with chronic therapy will have to be learned with further experimentation. We are looking into the matter with the canine split liver model which I mentioned a moment ago. After Eck fistula (portacaval shunt), the liver quickly atrophies and has disruption of its hepatocyte ultrastructure. Both cyclosporine and FK 506 prevent this and stimulate reparative changes, not limited to increased replication. They also preserve the integrity of the organelles in the same way as insulin does. Since both cyclosporine and FK 506 are given orally and reach the liver in high first-pass concentration, we believe that these agents might be capable of promoting healing in the event of liver injury, and with a variety of acute or chronic liver diseases. There could be many therapeutic implications having nothing to do with oncology.

**Sir James Gowans:** In the animals given cyclosporin, where you observed the recent regeneration of the liver, did you look up the cell turnover and other tissues like the gut and the skin, bone marrow, for example, to see how those adjust?

In addition, you hinted you might get an added bonus under cyclosporine and the healing itself might be elsewhere.

**Starzl:** Well, we do not have the complete answer to that, Jim, but we have done experiments with 50 per cent small bowel resection, and unilateral nephrectomy. The regeneration of the residual bowel and contralateral kidney (respectively) was not increased more than in the controls. So for the moment, we are stuck with the idea that this effect is liver specific.

**John D. Minna:** That is not hypertrophy. That is not cell division?

**Starzl:** These were DNA synthesis end points.

**Minna:** On the marrow?

**Starzl:** We did nothing other than those two organs (bowel and kidney).

**Minna:** How about healing?

**Starzl:** Well, we do not have any precise measurements, but wound healing under cyclosporine and FK 506 is grossly normal.

**Minna:** It is not always perfect.

**Joseph Fortner:** What is the effect on regeneration of the cirrhotic liver?

**Starzl:** We do not have an answer for that question, but what we do have, Joe, is the observation that we just published in Lancet about the effect of FK 506 on chronically rejecting livers. These livers look cirrhotic in that there is lobular collapse and fibrosis. The pathology is so advanced that we never have been able to alter the course. What has happened with FK 506 therapy is that the autoimmunity (here being rejection) has been stopped, followed by healing and repair beyond what you would expect just by discontinuing the insult. That is one of the reasons why we are so fascinated by the so-called hepatotrophic effect that can be so precisely studied in the dog and rat. These drugs might, as you are implying, find application in the treatment of chronic liver diseases, not even necessarily with an autoimmune etiology. If they had a reparative effect on the cirrhotic liver, for example caused by alcoholism, it could become a therapeutic issue. That is, in essence, where we are aiming.