Transplantation and Cancer

The editor interviews Joseph G. Fortner, M.D., Chief, Gastric and Mixed Tumor Service, Department of Surgery, Memorial Hospital for Cancer and Allied Diseases, New York, New York; Chief, Transplantation Service, Department of Surgery, Memorial Hospital for Cancer and Allied Diseases; and Chief, Division of Surgical Research, Sloan-Kettering Institute for Cancer Research, New York.

Dr. Holleb
In 1959, Drs. Israel Penn, Thomas Starzl and their associates reported that five renal allograft recipients from the collective transplantation programs of Denver, Minneapolis and Edinburgh developed malignant lymphomas. This brought to the forefront the controversial question: Is there an increased incidence of de novo cancer in patients following transplantation and immunosupression?

Dr. Fortner
In the more than 4,000 kidney transplants done to date, the incidence of de novo cancer in the recipients is definitely higher than one would expect in the general population. In a survey of kidney allograft recipients throughout the world, Dr. Penn and his associates reported 39 cancers, including tumors of epithelial origin, reticulum cell sarcoma, lymphoma of unclassified type, lympholeukosarcoma, Kaposi's sarcoma and gastrointestinal leiomyosarcoma. Four of these 39 patients almost certainly had symptoms suggestive of cancer prior to transplantation. Also, the latency period—33 months for epithelial tumors and 26 months for mesenchymal tumors—is surprisingly short in this series. These factors, combined with the naturally high incidence of some of the tumors make the true frequency of relevant cancer development difficult to assess. Even so, the incidence of cancer is still high.

Dr. Holleb
How do you explain this increased incidence of de novo cancer?

Dr. Fortner
Researchers are now agreed that the high incidence of cancer is not due to antilymphocyte serum. Although a
variety of experimental models have purported to show that ALS increases the growth of viral or chemically induced tumors, it is unlikely that tumor behavior in these highly artificial systems is equivalent to the development of spontaneous tumors in man. Some investigators believe that immunotherapeutic agents such as prednisone and asathioprine are responsible. However, I have another explanation: a kidney transplant is generally performed on a patient with end-stage glomerulonephritis, an autoimmune disease. It's well documented that such a patient normally has a higher incidence of neoplasia, particularly lymphoma, than does the general population.

Dr. Daniel Miller reported the development of malignant lymphomas in 14 patients with immune diseases ranging from diffuse connective tissue disease, such as rheumatoid arthritis and systemic lupus erythematos, to the nephrotic syndrome and ataxiatelangiectasia. This may also be explained by the concept of a susceptible genotype or other underlying abnormality.

Dr. Holleb
Is there experimental evidence to support the theory that the development of cancer in the post-transplant period may be an unrelated and inevitable event in the lives of these patients?

Dr. Fortner
Yes, there are some animal models which illustrate the association of immune disease with neoplasia. As a matter of fact, the concept first occurred to me when I visited Sir Macfarlane Burnet in Australia a few years ago. He was then experimenting with the NZB/BL strain of mice, virtually all of which develop autoimmune complications such as glomerulonephritis and Coombs positive hemolytic anemia. If they live long enough, one third to one half of these mice die of leukemia or lymphoma.

Dr. Holleb
Does your theory pertain only to patients who have had kidney transplants?

Dr. Fortner
Our largest experience has been with kidney transplants. The first successful orthotopic liver transplant was done as recently as 1967 by Dr. Starzl and only about 110 have been performed to date. Therefore, our experience with liver transplantation is not really sufficient. However, according to the available data, Dr. Roy Calne in Cambridge, England, and I agree that there is little, if any, evidence for stimulation of cancer growth following liver transplantation. Since the longest surviving lung transplant patient lived only nine months, and the only successful intestinal transplant patient (we performed the operation here at Memorial Hospital) lived only 76 days, there isn't enough information to draw conclusions about these patients, either.

Dr. Holleb
Will occult cancer cells in a donor grow in a recipient who does not have cancer?

Dr. Fortner
Yes, of course, these cancer cells will grow. There are at least five cases of cancer developing in recipients of renal allografts from donors who died of cancer. Therefore, a patient with known cancer is not a suitable donor except, perhaps, if he has primary brain or skin cancer which rarely metastasize. We, therefore, encourage a high index of suspicion in all donor candidates and a thorough work-up prior to transplantation to rule out the presence of cancer.

Dr. Holleb
I imagine that if cancer were inadvertently transplanted into a recipient, the critics would blame any future development of cancer in the recipient on immunosuppression.

Dr. Fortner
Yes, indeed. Fortuitous events can really lead one astray. Dr. Harry Grabstald of Memorial Hospital recently per-
formed a bilateral total nephrectomy on a patient with bilateral kidney cancer. We both agreed to keep the patient on hemodialysis for nine months before doing a renal transplantation. At six months the patient became more difficult to control and we decided to hasten the transplant. Before we could do the transplant, this otherwise apparently normal man died of a sudden, massive brain hemorrhage. At autopsy, his kidney cancer was found to have metastasized to the brain. This was the only site of metastases. If we’d done the transplant, even a few weeks before, immunosuppression would surely have been blamed.

Dr. Holleb
Following transplantation and immunosuppression, will occult cancer cells be stimulated to grow in a recipient who has had an apparently curative operation for cancer?

Dr. Fortner
The evidence is far from complete. In the Memorial Hospital series of liver transplants for patients with hepatoma or bile duct cancer, we see no growth stimulation of cancer. Dr. Roy Calne has one patient who is alive almost three years after hepatectomy for hepatoma and liver transplantation. Dr. John Najarian and others have reported patients who are alive and well five or more years after renal transplantation when a bilateral nephrectomy had been done for kidney cancer.

Dr. Holleb
Do you then see organ transplantation as a realistic method of therapy for patients with cancer?

Dr. Fortner
Yes, I do. Patients with bilateral kidney cancer can now be safely treated with a bilateral nephrectomy and kidney allograft; there is a one-year success rate of slightly over 90 percent. Patients with primary or biliary tract cancer and even some with cancer which has selectively metastasized to the liver may also benefit from liver transplantation during the next several years. Those patients with cancer involving the intestine or main blood supply to the intestine could also be greatly helped by bowel transplantation. And, with continued progress in lung and heart transplantation, the patient with lung cancer may also have a chance for cure that is currently unavailable. However, since liver, intestinal and lung transplants still present some very complex technical problems, it appears that such transplantation programs will be limited to a few institutions, for at least the foreseeable future. However, there is cause for optimism. Many problems now associated with immunosuppression are being resolved as we gain more experience with modern immunosuppression and as more specific agents are devised.

Dr. Holleb
Thank you very much, Dr. Fortner; this has been most enlightening.