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# De Novo Malignant Tumors in Organ Transplant Recipients

**I. Penn**, **C. G. Halgrimson**, and **T. E. Starzl**
Department of Surgery, University of Colorado School of Medicine, and Denver Veterans Administration Hospital, Denver, Colo

Following the initial reports of de novo malignancies in transplant recipients in 1968,[1–3] an informal tumor registry for such cases was established in Denver.[4] To date, accounts of malignant neoplasms in 39 renal recipients have been compiled from our own program or else submitted by a number of other groups to this registry (Tables 1 and 2). One patient has developed a carcinoma of the stomach following heart transplantation (Table 1).

## Incidence

It is not possible to give accurate figures based on the world experience of approximately 4000 renal transplantations since the exact number of malignancies and the numbers of patients at risk at various postoperative times are not known. However, there are accurate figures from our own renal transplantation series. In this experience, there have been 11 patients who developed malignant tumors in 236 renal homograft recipients with potential followups of 18 months to almost 8 years. This incidence of 4.7 per cent does not reflect the true frequency of posttransplantation neoplasia since 52 patients died of a variety of other complications before the end of the fourth postoperative month. The 11 neoplasms developed in the remaining 184 patients for a partially corrected incidence of 6.0 per cent. The rate of tumor development in these young patients (3½ to 49 years, average 27 years) compares with the yearly incidence of 58 per 100,000 (0.058%) in the general population in a comparable age range. Even if the four skin tumors are excluded, the corrected incidence of malignant disease (3.8%) in our series is still high.

## Type of Tumor

Twenty-three of the 40 tumors in the world collections were of epithelial origin (Tables 1 and 2). The most common epithelial tumors were carcinoma in situ of the cervix uteri (five cases), squamous cell carcinoma of the lip (five cases), squamous or basal cell skin carcinomas (four cases), and highly anaplastic carcinomas of uncertain origin (two cases). In addition there was one example each of carcinoma of the colon, testis (embryonal cell), ovary (dysgerminoma) and stomach. The origin of a widespread squamous cell carcinoma was never discovered in a final case.

The 17 mesenchymal tumors were a much more homogenous group in that 15 were varieties of lymphoma including 12 examples of reticulum cell sarcoma and one case each of visceral Kaposi's sarcoma, lympholeukosarcoma and a lymphoma of unclassified type. The two other mesenchymal tumors were gastrointestinal leiomyosarcomas.

## Behavior of Tumors

The mesenchymal tumors occurred in a younger average-age group than the epithelial lesions, 29 compared with 38 years. The former tumors occurred at an average of 26 months after transplantation compared with the somewhat longer interval of 33 months with the carcinomas.

A number of epithelial tumors were of low-grade malignancy and could be cured with standard therapy (Table 1). Of the 23 patients in this group 13 are currently alive including 13 of the 14 skin, lip, and uterine cervical carcinomas. In contrast, the epithelial malignancies within the thorax and abdomen tended to be rapidly lethal (Table 1).

Similarly, there was a dismal prognosis with the mesenchymal tumors inasmuch as only one of the 17 patients is still living (Table 2). All 12 of the kidney recipients in the subgroup of patients who developed reticulum cell sarcomas died within a short time, usually as the direct consequence of the tumor. Reticulum cell sarcoma most commonly involves the hematopoietic system and invasion of the brain is uncommon.[5] Among the 12 transplant recipients with this diagnosis, there was invasion of the bone marrow in two cases, the lymph nodes in three, the liver in four and the brain in six. At autopsy, the brain was the *only* site affected in four patients and in a fifth (case 32) cerebral involvement was the sole clinical feature although autopsy permission could not be obtained.

Dr. Rupert Billingham of the Wistar Institute, Philadelphia, has suggested to us an interesting explanation for the predilection of reticulum cell sarcoma for the brain in immunosuppressed patients. The hypothesis accepts the concept that there is a loss of “tumor surveillance” consequent to weakening of the immune system and further holds that the brain would be especially vulnerable to tumor that is ordinarily checked by immune defenses since the brain is a privileged site for the transplantation of tissues.

## Etiology of Tumors

### Preexisting Recipient Neoplasia

A malignant tumor was proved to be present at the time of transplantation in only one of the 40 patients. A small low-grade renal carcinoma of one of the native kidneys was found at the time of transplantation in Case 31. When the recipient died there was a reticulum cell sarcoma of the brain but no trace of metastases from the renal carcinoma.

Conceivably, three other patients could have had preexisting malignancies although this docs not seem likely. Patient 22 developed massive metastases of a testicular carcinoma less than 2 months after transplantation. A small primary tumor of the testis was then found that might have been present at the time of transplantation with widespread dissemination under the influence of immunosuppression. In Cases 24 and 31 there were some neurologic symptoms prior to transplantation that were attributed to hypertensive encephalopathy or other manifestations of uremia. The findings receded after operation but neurologic abnormalities developed 5½ and 5 months later that were ultimately shown to be due to cerebral reticulum cell sarcomas.

### Preexisting Donor Neoplasia

It is also most unlikely that the tumors were transmitted from the 44 donors who provided organs for the 40 recipients. In 27 instances, kidneys were obtained from living volunteers who have remained in good health for periods of as long as seven and one half years. The other 17 homo grafts were obtained from cadavers that, with one exception, were free of malignant disease. In Case 27 the donor had a medulloblastoma whereas the recipient subsequently developed a reticulum cell sarcoma at the gluteal site of an antilymphocyte globulin (ALG) injection among other locations. There was no morphologic relationship between the two tumors and probably no etiologic connection unless they were both caused by an oncogenic virus that was transmitted with the donor kidney. In Case 32 the donor had a carcinoma of the colon resected 5 years previously but was apparently free of tumor at the time of transplantation. The recipient developed a reticulum cell sarcoma.

### Individual Immunosuppressive Agents

It has been proposed[1–4] that the malignancies are an effect of iatrogenic immunosuppression with a consequent loss of the immunologic surveillance mechanism by which tumor mutants are normally detected and destroyed. So far, a unique contribution of anyone of the individual immunosuppressive measures has not been evident. All of the patients (Table 1 and 2) received azathioprine and prednisone, 18 underwent splenectomy, and five had thymectomy. Eight received antilymphocyte serum (ALS) or globulin (ALG) but in one of these patients (Case 26) there was radiologic evidence of an intrathoracic reticulum cell sarcoma before ALS treatment was begun. Before the onset of the diagnosed tumor growth, many of the patients had had difficulties with homograft rejection and in an effort to control this process had received increased doses of immunosuppressive agents, especially steroids.

Acceptance of the surveillance hypothesis as the *indirect* explanation for postransplantation neoplasia does not exclude a variety of specific etiologic factors that could *directly* cause malignant transformation of cells. These could include a toxic effect of the actual immunosuppressive agents, carcinogens (such as tobacco, ultraviolet light or irradiation) in the environment or oncogenic viruses. Concerning the last possibility, it is of interest that infections by the herpes family have been very common in transplantation recipients. Two human strains of this virus, the Epstein–Barr and herpes hominis II, have been found to be commonly associated with although not necessarily responsible for Burkitt's lymphoma and uterine cervical carcinoma respectively.

## Treatment of Tumors

The epithelial malignancies of the skin, lip and uterine cervix were successfully treated by standard surgical techniques without risking the homo grafts by arbitrary reductions in immunosuppression.

The "deep" malignancies could not be effectively treated with this approach and led or contributed to death in eight of nine epithelial and 16 of 17 mesenchymal tumors. The exceptional patient in the epithelial group had an ovarian dysgerminoma with abdominal and intrathoracic spread. The primary tumor and metastases were treated with irradiation. She discontinued at least the steroid part of her immunosuppressive regimen and died 16 months after the appearance of the neoplasm and 50 months after transplantation. At autopsy, residual tumor was not found. The word "cure" used in the title of the article reporting this case[6] would be questionable with such a short followup, even in a non-immunosuppressed patient.

One patient is still alive among those with mesenchymal malignancies. She had a lymphoma of the basal diencephalon that was treated with local irradiation. In addition, her immunosuppression was drastically reduced despite which rejection of the renal homograft did not occur.[2] She is in excellent health 3 years after transplantation and 2½ years after the diagnosis of the tumor.

## Conclusions

A significant incidence of de novo malignancy is part of the price for successful organ transplantation. In our institution 11 malignant neoplasms have been seen in renal recipients followed for 1½ to 8 years for an incidence greater than 5 per cent. Twenty-nine other examples of this complication have been collected from other institutions including a gastric carcinoma in a heart recipient. Twenty-three of the tumors were of epithelial origin and the other 17 were of mesenchymal derivation. "Superficial" carcinomas of the skin, lip and cervix were treated with uniform success by conventional means. "Deep" carcinomas in the body cavities as well as mesenchymal tumors led or contributed to early death in almost all cases. In view of the

virtually hopeless prognosis, drastic reductions or even discontinuance of immunosuppression could be considered in the latter kinds of patients.

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## Table 1

Epithelial Tumors in Organ Homograft Recipients

| | | | | | Immunosuppression | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number** | **Transplant Center** | **Age at Time of Transplant** | **Sex** | **Donor** | **Splenectomy** | **Thymectomy** | **Imuran** | **Prednisone** | **ALG** | **Type of Tumor** | **Time After Transplantation** | **Organs Involved** | **Outcome** | **Referring Physician** |
| 1 | Denver | 37 | F | Unrelated living donor | Yes | Yes | Yes | Yes | No | Squamous cell carcinoma in situ | 50 months | Cervix of uterus | Alive, no recurrence after hysterectomy | |
| 2 | Minneapolis | 28 | F | Brother | No | No | Yes | Yes | No | Squamous cell carcinoma in situ | 30 months | Cervix of uterus | Alive, no recurrence after hysterectomy | R. L. Simmons |
| 3 | Montreal | 38 | F | Cadaver | No | No | Yes | Yes | Yes | Squamous cell carcinoma in situ | 6 months | Cervix of uterus | Alive, no recurrence following cryosurgery | K. Pritzker |
| 4 | Los Angeles | 38 | F | Mother | No | No | Yes | Yes | No | Squamous cell carcinoma in situ | 35 months | Cervix of uterus; anterior wall of vagina | Alive, no recurrence after excision | A. Gordon |
| 5 | Richmond | 33 | F | Sister | No | No | Yes | Yes | No | Squamous cell carcinoma in situ | 36 months | Cervix of uterus | Cone biopsy, patient being observed at regular intervals | H. Lee |
| 6 | Denver | 40 | M | Unrelated living donor | Yes | No | Yes | Yes | No | Superficial squamous cell carcinoma | 66 months | Lower lip | Alive, no recurrence following excision | |
| 7 | Denver | 39 | M | Brother | Yes | Yes | Yes | Yes | No | Superficial squamous cell carcinoma | 36 months | Lower lip | Alive, no recurrence following excision | |
| 8 | Louisville | 35 | M | Brother | No | No | Yes | Yes | No | Squamous cell carcinoma | 8 months | Lower lip | Alive, no recurrence following excision | D. Leb |
| 9 | Los Angeles | 27 | M | Mother | No | No | Yes | Yes | No | Squamous cell carcinoma | 25 months | Lower lip | Alive, no recurrence following excision | R. Goldman |
| 10 | Los Angeles | 25 | F | Brother | No | No | Yes | Yes | No | Squamous cell carcinoma | 35 months | Lower lip | Alive, no recurrence following excision | R. Goldman |
| 11 | Denver | 40 | M | Unrelated living donor | Yes | Yes | Yes | Yes | No | Squamous cell carcinoma | 32 months | Skin of ear | No recurrence after excision, died of other causes | |
| 12 | Denver | 43 | M | Uncle | Yes | No | Yes | Yes | Yes | Basal cell carcinoma | 33 months | Nasolabial fold | Alive, no recurrence following excision | |
| 13 | Denver | 30 | M | Brother | Yes | Yes | Yes | Yes | No | Basal cell carcinoma | 75 months | Nasolabial fold | Alive, no recurrence following excision | |
| 14 | Denver | 34 | M | Sister | Yes | No | Yes | Yes | No | Squamous cell carcinoma | 74 months | Left forearm, right forearm | Alive, no recurrence following excision | |
| 15 | Minneapolis | 27 | M | Brother | Yes | No | Yes | Yes | No | Undifferentiated carcinoma | 10 months | Liver; brain; bone marrow | Dead | C. Hitchcock |
| 16 | Nashville | 47 | M | Cadaver | No | No | Yes | Yes | No | Undifferentiated carcinoma | 19 months | Lung, mediastinal lymph nodes; brain and liver | Dead | C. Zukoski |
| 17 | Denver | 44 | F | Sister | Yes | No | Yes | Yes | Yes | Moderately differentiated adenocarcinoma | 31 months | Lung | Dead | |
| 18 | San Francisco | 46 | M | (a) Son<br>(b) Cadaver | Yes | No | Yes | Yes | No | Alveolar cell carcinoma of lung | 9 months | Lungs | Dead | S. Kountz |
| 19 | Minneapolis | 16 | F | Cadaver | No | No | Yes | Yes | No | Dysgerminoma | 32 months | Ovary; Peritoneum; mediastinal and axillary lymph nodes | Dead | W. Kelly |
| 20 | Ghent, Belgium | 53 | F | Cadaver | No | No | Yes | Yes | No | Adenocarcinoma | 35 months | Sigmoid colon | Dead | F. Derom |
| 21 | Nashville | 34 | M | Cadaver | No | No | Yes | Yes | No | Squamous cell carcinoma | 62 months | Metastases in lymph nodes of neck, later widespread metastases. Primary site of tumor unknown | Dead | C. Zukoski |
| 22 | Louisville | 32 | M | Brother | Yes | No | Yes | Yes | No | Embryonal cell carcinoma | 2 months | Testis; abdominal organs; ureter of transplanted kidney; lung | Dead | D. Leb |
| 23 | Cape Town* | 50 | M | Cadaver | No | No | Yes | Yes | Yes | Anaplastic small cell adenocarcinoma | 17 months | Stomach; liver; mesentery; peritoneum | Dead | S. Bosman |

*Heart transplant recipient.

**Table 2**

Mesenchymal Tumors in Organ Homograft Recipients

| | | | | | Immunosuppression | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number** | **Transplant Center** | **Age at Time of Transplant** | **Sex** | **Donor** | **Splenectomy** | **Thyrectomy** | **Imuran** | **Prednisone** | **ALG** | **Type of Tumor** | **Time After Transplantation** | **Organs Involved** | **Outcome** | **Referring Physician** |
| 24 | Denver | 14 | M | Mother | Yes | No | Yes | Yes | Yes | Reticulum cell sarcoma | 5½ months | Brain | Dead | |
| 25 | Denver | 23 | M | Father | Yes | Yes | Yes | Yes | No | Reticulum cell sarcoma | 30 months | Thyroid; liver; lung; stomach; prostate; pituitary; skin; psoas muscle | Dead | |
| 26 | Edinburgh, Scotland | 26 | F | Mother | No | No | Yes | Yes | Yes | Reticulum cell sarcoma | 25 months | Lymph nodes; pleura; spleen; liver; ovary; adrenal; bone marrow; and transplanted kidney | Dead | M. Woodruff |
| 27 | Cleveland | 32 | M | Cadaver | No | No | Yes | Yes | Yes | Reticulum cell sarcoma | 22 months | Buttock; lungs; aortic lymph nodes | Dead | S. D. Deodhar |
| 28 | Richmond | 35 | M | Cadaver | No | No | Yes | Yes | No | Reticulum cell sarcoma | 31 months | Lung | Dead | J. Pierce |
| 29 | Aukland, New Zealand | 34 | M | (a) Cadaver<br>(b) Cadaver<br>(c) Cadaver | No | No | Yes | Yes | No | Reticulum cell sarcoma | 7 months | Tongue, esophagus; liver | Dead | P. Doak |
| 30 | Auckland, New Zealand | 46 | F | Cadaver | No | No | Yes | Yes | No | Reticulum cell sarcoma | 9 months | Brain | Dead | P. Doak |
| 31 | New York | 18 | M | Uncle | No | No | Yes | Yes | No | Reticulum cell sarcoma | 9 months | Brain | Dead | R. Porro |
| 32 | New York | 36 | M | Cadaver | No | No | Yes | Yes | No | Reticulum cell sarcoma | 10 months | Brain | Dead | F. Veith |
| 33 | Richmond | 29 | M | Brother | Yes | No | Yes | Yes | No | Reticulum cell sarcoma | 67 months | Lymph nodes; liver; vertebrae | Dead | H. Lee |
| 34 | Little Rock, Arkansas | 21 | M | Father | Yes | No | Yes | Yes | No | Reticulum cell sarcoma | 24 months | Brain | Dead | C. Araoz |
| 35 | San Francisco | 39 | F | Sister | Yes | No | Yes | Yes | No | Reticulum cell sarcoma | 14 months | Brain; lungs | Dead | F. O. Belzer |
| 36 | Richmond | 17 | M | Father | Yes | No | Yes | Yes | No | Lympholeukosarcoma | 75 months | Lymph nodes; liver; pancreas; bone marrow; meninges; bladder; testes; transplanted kidney, accessory spleen, sciatic nerve | Dead | H. M. Lee |
| 37 | Denver | 20 | F | Father | Yes | No | Yes | Yes | Yes | Unclassified lymphoma | 7 months | Brain | Alive, following radiotherapy | |
| 38 | New York | 35 | F | Cadaver | No | No | Yes | Yes | No | Visceral Kaposi’s sarcoma | 10 months | Lungs; esophagus; stomach; urinary bladder; mediastinal and abdominal lymph nodes | Dead | J. H. Siegel |
| 39 | Boston | 34 | M | (a) Cadaver<br>(b) Half-sister | No | No | Yes | Yes | No | Leiomyosarcoma | 47 months | Stomach, abdominal lymph nodes; peritoneum; bowel; liver; lungs; pleura and ribs | Dead | R. E. Wilson |
| 40 | Montreal | 36 | M | Cadaver | No | No | Yes | Yes | No | Leiomyosarcoma | 51 months | Small bowel; liver; pancreas | Dead | L. D. Maclean |