## Other Considerations

# A Summary of the Status of De Novo Cancer in Transplant Recipients

By Israel Penn and Thomas E. Starzl

IN 1968 an informal registry was started in Denver to record all tumors which occurred in organ homograft recipients, including preexisting malignancies, inadvertently transplanted tumors, and lesions arising de novo after transplantation. Physicians from transplant centers throughout the world have generously contributed data concerning their patients. The present report deals with cases recorded up till May, 1972.

## CLINICAL OBSERVATIONS

Ninety-three patients developed 95 malignancies. There were 91 and two recipients of renal and cardiac homografts, respectively. Data concerning the cases are summarized in Tables 1 and 2.

### *Incidence*

Up to the spring of 1972, 9131 renal and 189 cardiac homografts had been recorded by the ACS–NIH organ transplant registry. Because these figures and those regarding the number of tumors reported are incomplete it is not possible to calculate accurately the incidence of malignancies from these statistics. However, data from the renal transplant program at the University of Colorado Medical Center and the Denver Veterans Administration Hospital do provide accurate figures. Of 366 patients who received their transplants from 6 mo to 9½ yr ago, 18 developed tumors, an incidence of 4.9%. Without making any correction for patients who died very soon after transplantation (before exposure to the hazard under discussion), the risk of developing cancer is thus about 80 times greater than in the general population in the same age range.

### *Type of Tumors*

Of the 95 tumors 59 (62%) were of epithelial origin and 36 (38%) were mesenchymal. The most common lesions were reticulum cell sarcomas (21 cases, 22%), various forms of skin cancer (20 cases, 21%), in situ carcinoma of the cervix (eight cases, 8%), carcinoma of the lip (eight cases, 8%) and a variety of lymphomas (seven cases, 7%). A wide spectrum of other tumors are listed in Table 1 and 2.

Two patients each presented with two varieties of tumor. One had a reticulum cell sarcoma of the brain and Kaposi's sarcoma of the skin. The other had a differentiated adenocarcinoma of the pancreas and a markedly anaplastic carcinoma in the mediastinum which may possibly have been an intramediastinal seminoma.

This paper confirms the findings reported in previous publications[1-3] concerning the remarkable predilection of the lymphomas, and, in particular, the reticulum cell sarcomas to involve the central nervous system. Of 30 patients with various types of lymphoma the brain or spinal cord was involved in 14 instances and in 11 cases

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Table 1. Epithelial Tumors in Organ Homograft Recipients

| Number | Transplant Center | Age at Time of Transplant | Sex | Donor | Immunosuppression | | | | | Type of Tumor | Time After Transplantation (mo) | Organs Involved | Outcome | Referring Physician |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Imuran | Prednisone | ALG | Splenectomy | Other | | | | | |
| 1 | Denver | 37 | F | Unrelated living donor | Yes | Yes | No | Yes | Thym, Acti C LRT | Squamous cell carcinoma in situ | 50 | Cervix of uterus | Alive, no recurrence after hysterectomy | |
| 2 | Minneapolis | 28 | F | Brother | Yes | Yes | No | No | — | Squamous cell carcinoma in situ | 30 | Cervix of uterus | Alive, no recurrence after hysterectomy | R. L. Simmons |
| 3 | Montreal | 38 | F | Cadaver | Yes | Yes | Yes | No | Acti D, LRT | Squamous cell carcinoma in situ | 6 | Cervix of uterus | Alive, no recurrence after cryosurgery | K. Pritzker |
| 4 | Los Angeles | 38 | F | Mother | Yes | Yes | No | No | — | Squamous cell carcinoma in situ | 35 | Cervix of uterus; Anterior wall of vagina | Alive, no recurrence after excision | A. Gordon |
| 5 | Richmond | 33 | F | Sister | Yes | Yes | No | No | LRT | Squamous cell carcinoma in situ | 36 | Cervix of uterus | Alive, patient being observed at regular intervals following cone biopsy | H. Lee |
| 6 | Denver | 26 | F | Father | Yes | Yes | No | Yes | Acti C | Squamous cell carcinoma in situ | 65 | Cervix of uterus | Died of causes unrelated to carcinoma | |
| 7 | Denver | 17 | F | Father | Yes | Yes | Yes | Yes | Acti C | Squamous cell carcinoma in situ | 51 | Cervix of uterus | Alive, no recurrence after hysterectomy | |
| 8 | Minneapolis | 32 | F | Sister | Yes | Yes | No | Yes | — | Squamous cell carcinoma in situ | 45 | Cervix of uterus | Alive, no recurrence after hysterectomy | R. L. Simmons |
| 9* | Mayo Clinic | 31 | F | (1) Cadaver (2) Cadaver | Yes | Yes | No | Yes | — | Endometrial carcinoma | 20 | Uterus; ovaries | Alive, no recurrence following hysterectomy and salpingo-oophorectomy | J. E. Woods |
| 10 | Denver | 40 | M | Unrelated living donor | Yes | Yes | No | Yes | Acti C, LRT | Superficial squamous cell carcinoma | 66 | Lower lip | Alive, no recurrence following excision | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 11 | Denver | 39 | M | Brother | Yes | Yes | No | Yes | Thym, Acti C, LRT | Superficial squamous cell carcinoma | 36 | Lower lip | Alive; recurred 33 mo after excision; no recurrence following second excision | |
| 12 | Louisville | 35 | M | Brother | Yes | Yes | No | No | – | Squamous cell carcinoma | 8 | Lower lip | Alive, no recurrence following excision | D. Leb |
| 13 | Los Angeles | 27 | M | Mother | Yes | Yes | No | No | Metho Acti C | Squamous cell carcinoma | 25 | Lower lip | Alive, no recurrence following excision | R. Goldman |
| 14 | Los Angeles | 25 | F | Brother | Yes | Yes | No | No | LRT | Squamous cell carcinoma | 35 | Lower lip | Alive, no recurrence following excision | R. Goldman |
| 15 | Salt Lake City | 42 | M | Cadaver | Yes | Yes | Yes | No | – | Squamous cell carcinoma | 32 | Lip | Alive, no recurrence following excision | L. Stevens |
| 16 | San Francisco | 28 | M | (1) Cadaver (2) Cadaver | Yes | Yes | No | Yes | Acti | Infiltrating squamous cell carcinoma | 32 | Lower left lip | Alive, recurrent lesion in lip removed 6 mo after primary excision | F. O. Belzer |
| 17 | San Francisco | 23 | M | Brother | Yes | Yes | No | Yes | – | Infiltrating squamous cell carcinoma | 37 | Right lower lip | Alive, no recurrence following excision | F. O. Belzer |
| 18 | Denver | 40 | M | Unrelated living donor | Yes | Yes | No | Yes | Thym, Acti C, LRT | Squamous cell carcinoma | 32 | Skin of ear | No recurrence after excision, died of other causes | |
| 19 | Denver | 43 | M | Uncle | Yes | Yes | Yes | Yes | LRT | Basal cell carcinoma | 33 | Nasolabial fold | Alive, no recurrence following excision | |
| 20 | Denver | 30 | M | Brother | Yes | Yes | No | Yes | Thym, Acti C | Basal cell carcinoma | 75 | Nasolabial fold | Alive, no recurrence following excision | |
| 21 | Denver | 34 | M | Sister | Yes | Yes | No | Yes | Acti C | Squamous cell carcinoma | 74 | Both forearms; right arm; scalp | Dead (Myocardial infarction) | |
| 22 | Stockholm, Sweden | 58 | M | Cadaver | Yes | Yes | No | No | TD F, Acti C | Multiple squamous cell carcinomas | 38 | Scalp (multiple sites) | Alive | C. Franksson |

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Table 1. Epithelial Tumors in Organ Homograft Recipients (Continued)

| Number | Transplant Center | Age at Time of Transplant | Sex | Donor | Immunosuppression | | | | | Type of Tumor | Time After Transplantation (mo) | Organs Involved | Outcome | Referring Physician |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Imuran | Prednisone | ALG | Splenectomy | Other | | | | | |
| 23 | Denver | 22 | M | Cousin | Yes | Yes | No | Yes | LRT | Squamous cell carcinoma | 78 | Left hand (two areas); face | Alive, no recurrence following excision | |
| 24 | Denver | 30 | M | Brother | Yes | Yes | Yes | Yes | – | Superficial squamous cell carcinomas | 36 | Face and neck (multiple sites) | Alive, no recurrence following excision | |
| 25† | Sydney, Australia | 44 | F | Cadaver | Yes | Yes | No | No | – | Basal cell carcinoma | 3 | Nose | Alive, following radiotherapy | J. F. Mahony |
| 26 | Sydney, Australia | 48 | F | Cadaver | Yes | Yes | No | No | – | (1) Multiple squamous cell carcinomas (2) Basal cell carcinoma | 29 | Forehead; right nasolabial fold; left temple; left preauricular lymph node | Alive, following excision and radiotherapy | J. H. Stewart |
| 27 | Denver | 21 | M | Father | Yes | Yes | No | Yes | Acti C, LRT | Squamous cell carcinoma | 87 | Skin of face | Alive, following excision | W. Alexander |
| 28 | San Francisco | 41 | M | Brother | Yes | Yes | No | Yes | – | Squamous cell carcinoma | 73 | Multiple sites dorsum of left hand | Alive, following wide excision | F. O. Belzer |
| 29 | Little bay, Australia | 56 | M | Cadaver | Yes | Yes | No | No | – | Squamous cell carcinoma | 16 | Skin of temple, arm, forehead, hand, and ear | Alive, following multiple wide excisions | B. K. Walder |
| 30 | Little bay, Australia | 30 | F | Cadaver | Yes | Yes | No | No | – | Squamous cell carcinoma | 45 | Multiple tumors of skin of hand | Alive, following multiple wide excisions | B. K. Walder |
| 31 | Little bay, Australia | 38 | F | Cadaver | Yes | Yes | No | No | – | Squamous cell carcinoma | 4 | Skin of hand | Died of unrelated causes at 22 mo | B. K. Walder |
| 32 | Little bay, Australia | 39 | F | Cadaver | Yes | Yes | No | No | – | Squamous cell carcinoma | 24 | Skin and neck and chest | Alive, following wide excisions | B. K. Walder |
| 33 | Little bay, Australia | 56 | M | Cadaver | Yes | Yes | No | No | – | Squamous cell carcinoma | 10 | Skin of nose and shoulder | Died at 18 mo of metastatic carcinoma of the ureter. Tumor had been removed 2 wk prior to transplantation | B. K. Walder |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 34 | Little bay, Australia | 52 | M | Cadaver | Yes | Yes | No | No | – | Squamous cell carcinoma | 12 | Skin of ear | Died of unrelated causes at 23 mo | B. K. Walder |
| 35 | Galveston, Texas | 43 | M | Cadaver | Yes | Yes | No | No | TD F | Squamous cell carcinoma | 2 | Hand | Alive, following wide excision | J. C. Fish |
| 36 | Aarhus, Denmark | 45 | F | Cadaver | Yes | Yes | No | No | – | Squamous cell carcinoma | 2 | Face | Alive, no recurrence following radiotherapy | V. P. Peterson |
| 37 | Denver | 23 | F | Mother | Yes | Yes | Yes | Yes | Cyclo | Malignant melanoma | 4.5 | Groin | Alive, no recurrence following excision | |
| 38 | Montreal | 13 | M | Brother | Yes | Yes | No | No | – | Hepatocellular carcinoma | 32 | Liver | Dead | K. Pritzker |
| 39 | Toronto | 8 | F | Cadaver | Yes | Yes | Yes | No | Acti D, LRT | Well-differentiated hepatoma | 13 | Liver | Dead | A. Millner |
| 40 | Aarhus, Denmark | 51 | M | Sister | Yes | Yes | No | No | – | Carcinoma, possibly of bile duct origin | 29 | Liver; bones; lungs; pleura; peritoneum; retroperitoneal lymph nodes; adrenal | Dead | V. P. Petersen |
| 41 | Denver | 44 | F | Sister | Yes | Yes | Yes | Yes | Acti C, LRT | Moderately differentiated adenocarcinoma | 31 | Lung | Dead | |
| 42 | San Francisco | 46 | M | (1) Son (2) Cadaver | Yes | Yes | No | Yes | Acti C | Alveolar cell carcinoma of the lung | 9 | Lungs | Dead | S. Kountz |
| 43 | Sydney, Australia | 43 | F | Cadaver | Yes | Yes | Yes (after development of tumor) | No | – | Adenocarcinoma | 32 | Lungs, mediastinal lymph nodes; liver | Dead | J. F. Mahony |
| 44 | Ghent, Belgium | 53 | F | Cadaver | Yes | Yes | No | No | Acti C | Adenocarcinoma | 35 | Sigmoid colon; liver | Dead | F. Derom |
| 45† | Chicago | 41 | M | Brother | Yes | Yes | No | No | – | Adenocarcinoma | 1 | Colon | Dead | D. Jonasson |

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Table 1. Epithelial Tumors in Organ Homograft Recipients (Continued)

| Number | Transplant Center | Age at Time of Transplant | Sex | Donor | Immunosuppression | | | | | Type of Tumor | Time After Transplantation (mo) | Organs Involved | Outcome | Referring Physician |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Imuran | Prednisone | ALG | Splenectomy | Other | | | | | |
| 46 | Minneapolis | 16 | F | Cadaver | Yes | Yes | No | No | – | Dysgerminoma | 32 | Ovary; peritoneum; mediastinal and axillary lymph nodes | Dead | W. Kelly |
| 47† | Louisville | 32 | M | Brother | Yes | Yes | No | Yes | – | Embryonal cell carcinoma | 2 | Testis; abdominal organs; ureter of transplanted kidney; lung | Dead | D. Leb |
| 48 | San Francisco | 32 | F | (1) Brother (2))Cadaver | Yes | Yes | No | Yes | Acti D, LRT | Adenocarcinoma | 32 | Breast; axillary lymph nodes | Alive, following radical mastectomy | F. O. Belzer |
| 49 | Montreal | 64 | F | Cadaver | Yes | Yes | Yes | No | Acti, LRT | Poorly differentiated adenocarcinoma (?) arising from breast | 32 | Skeleton; right adrenal gland | Dead | J. G. Beaudoin |
| 50 | San Francisco | 46 | M | Sister | Yes | Yes | No | Yes | LRT | Squamous cell carcinoma | 76 | Floor of mouth; tongue; cervical lymph nodes | Dead | F. O. Belzer |
| 51 | Nashville | 34 | M | Cadaver | Yes | Yes | No | No | LRT | Squamous cell carcinoma | 62 | Metastases in lymph nodes of neck; later widespread metastases. Primary site unknown. | Dead | C. Zukoski |
| 52‡ | Cape Town | 52 | M | Cadaver | Yes | Yes | Yes | No | – | Anaplastic small cell adenocarcinoma | 17 | Stomach; liver; mesentery; peritoneum | Dead | S. Bosman |
| 53‡ | Denver | 48 | M | Cadaver | Yes | Yes | Yes | No | Cyclo | (1) Differentiated adenocarcinoma (2) Markedly anaplastic carcinoma ([?] seminoma) | 26 | (1) Pancreas; liver; peritoneum (2) Mediastinum | Dead | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 54§ | Toronto | 21 | M | Cadaver | Yes | Yes | Yes | No | Acti D, LRT | Highly anaplastic transitional cell tumor | 6 | Kidney; liver; brain; heart; lung | Dead | K. DeVeber |
| 55† | Cleveland | 45 | M | Cadaver | Yes | Yes | Yes | No | – | Adenocarcinoma | 1 | Thyroid gland | Alive following thyroidectomy | S. Deodhar |
| 56 | Minneapolis | 27 | M | Brother | Yes | Yes | No | Yes | – | Undifferentiated carcinoma | 10 | Liver; brain; bone marrow | Dead | C. Hitchcock |
| 57 | Nashville | 47 | M | Cadaver | Yes | Yes | No | No | LRT | Undifferentiated carcinoma | 19 | Lung; mediastinal lymph nodes; brain; liver | Dead | C. Zukoski |
| 58¶ | Paris | 26 | F | (1) Mother (2) Cadaver | Yes | Yes | No | Yes | Thy irr | Carcinoma possibly of suprarenal origin | 86 | (?) Suprarenal; liver | Alive 1 wk after diagnosis of tumor | J. Hamburger |

*Total duration of immunosuppression was 6 mo: 2 mo after first and 4 mo after second transplant. Tumor diagnosed 4 mo after immunosuppression was discontinued.

†Tumors may have been present at time of transplantation.

‡Heart transplant recipient.

§Tumor may have been present in homograft at time of transplantation.

¶No immunosuppression for almost 29 mo after failure of first transplant except for a brief period 11 mo before diagnosis of the tumor for treatment of a short-lived second transplant.

LRT, local radiation to transplant; Acti C, actinomycin C; Acti D, actinomycin D; Acti, actinomycin; Metho, methotrexate; TD F, thoracic duct fistula; Thym, thymectomy; Thy Irr, thymic irradiation; Cyclo, cyclophosphamide; TBI, total-body irradiation; MP, 6-mercaptopurine.

Table 2. Mesenchymal Tumors in Organ Homograft Recipients

| Number | Transplant Center | Age at Time of Transplant | Sex | Donor | Immunosuppression | | | | | Type of Tumor | Time After Transplantation (mo) | Organs Involved | Outcome | Referring Physician |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Imuran | Prednisone | ALG | Splenectomy | Other | | | | | |
| 1 | Denver | 14 | M | Mother | Yes | Yes | Yes | Yes | LRT | Reticulum cell sarcoma | 5.5 | Brain | Dead | |
| 2 | Denver | 23 | M | Father | Yes | Yes | No | Yes | Acti C, Thym, LRT | Reticulum cell sarcoma | 30 | Thyroid; liver; lung; stomach; pituitary; skin; psoas muscle | Dead | |
| 3 | Edinburgh, Scotland | 26 | F | Mother | Yes | Yes | Yes (after development of tumor) | No | LRT | Reticulum cell sarcoma | 25 | Lymph nodes; pleura; spleen; liver; ovary; adrenal; bone marrow; and transplanted kidney | Dead | M. Woodruff |
| 4 | Cleveland | 32 | M | Cadaver | Yes | Yes | Yes | No | Acti C LRT | Reticulum cell sarcoma | 22 | Buttock; lungs; aortic lymph nodes | Dead | S. D. Deodhar |
| 5 | Richmond | 38 | M | Cadaver | Yes | Yes | No | No | LRT Acti C | Reticulum cell sarcoma | 31 | Lung; aortic lymph nodes | Dead | J. Pierce |
| 6 | Auckland, New Zealand | 34 | M | (1) Cadaver (2) Cadaver (3) Cadaver | Yes | Yes | No | No | Acti C | Reticulum cell sarcoma | 7 | Tongue; esophagus; liver | Dead | P. Doak |
| 7 | Auckland, New Zealand | 46 | F | Cadaver | Yes | Yes | No | No | – | Reticulum cell sarcoma | 9 | Brain | Dead | P. Doak |
| 8 | New York (Cornell) | 18 | M | Uncle | Yes | Yes | No | No | – | Reticulum cell sarcoma | 9 | Brain | Dead | R. Porro |
| 9 | New York (Montefiore) | 36 | M | Cadaver | Yes | Yes | No | No | – | Reticulum cell sarcoma | 10 | Brain | Dead | F. Veith |
| 10 | Richmond | 29 | M | Brother | Yes | Yes | No | Yes | LRT | Reticulum cell sarcoma | 67 | Widespread lymph nodes; liver; vertebrae | Dead | H. Lee |
| 11 | Little Rock, Arkansas | 21 | M | Father | Yes | Yes | No | Yes | – | Reticulum cell sarcoma | 24 | Brain | Dead | C. Araoz |
| 12 | San Francisco | 39 | F | Sister | Yes | Yes | No | Yes | Acti D LRT | Reticulum cell sarcoma | 14 | Brain; lungs | Dead | F. O. Belzer |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | Richmond | 18 | M | Father | Yes | Yes | No | Yes | Acti C, LRT | Reticulum cell sarcoma | 73 | Widespread lymph nodes; liver; pancreas; bone marrow; meninges; bladder; testes; transplanted kidney; accessory spleen; sciatic nerve; lung | Dead | H. M. Lee |
| 14 | Oklahoma City | 19 | F | Cadaver | Yes | Yes | No | No | – | Reticulum cell sarcoma | 13 | Lungs; liver; spleen; rectum; transplanted kidney; mesentery; bone marrow | Dead | Y. Muto |
| 15 | Chicago | 52 | M | Cadaver | Yes | Yes | No | No | LRT | Reticulum cell sarcoma | 7.5 | Brain | Dead | N. Levine |
| 16 | New York (Mt. Sinai) | 28 | M | Cadaver | Yes | Yes | No | No | – | Reticulum cell sarcoma | 7 | Liver | Dead | L. Burrows |
| 17 | San Francisco | 40 | F | (1) Cadaver (2) Cadaver | Yes | Yes | No | No | Acti D, LRT | Reticulum cell sarcoma | 14 | Brain | Dead | F .O. Belzer |
| 18 | Galveston | 45 | M | Cadaver | Yes | Yes | Yes | No | TD F | Reticulum cell sarcoma | 19 | Subcutaneous tissues of buttock | Alive* | J. C. Fish |
| 19 | San Francisco | 21 | M | (1) Brother (2) Cadaver (3) Cadaver (4) Cadaver | Yes | Yes | No | Yes | Acti D, LRT | Reticulum cell sarcoma | 41 | Brain (multifocal); cervical lymph nodes | Dead | F. O. Belzer |
| 20 | Zurich | 50 | F | Cadaver | Yes | Yes | Yes | No | TD F | Malignant Reticulosis | 8 | Liver; spleen; lymph nodes; bone marrow; esophagus; tongue; transplanted kidney; adrenal glands | Dead | W. Wegmann |
| 21 | Israel | 34 | F | Cadaver | Yes | Yes | Yes | No | Acti, LRT | (1) Reticulum cell sarcoma (2) Kaposi's sarcoma | 9 | (1) Brain (2) Skin | Dead† | B. Myers |
| 22 | Israel | 27 | M | Cadaver | Yes | Yes | Yes | No | – | Kaposi's sarcoma | 8 | Skin; mucosa of mouth | Alive‡ | B. Myers |

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Table 2. Mesenchymal Tumors in Organ Homograft Recipients (Continued)

| Number | Transplant Center | Age at Time of Transplant | Sex | Donor | Immunosuppression: Imuran | Prednisone | ALG | Splenectomy | Other | Type of Tumor | Time After Transplantation (mo) | Organs Involved | Outcome | Referring Physician |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | New York (Albert Einstein) | 35 | F | Cadaver | Yes | Yes | No | No | Acti C, LRT | Visceral Kaposi's sarcoma | 10 | Lungs; esophagus; stomach; urinary bladder; mediastinal and abdominal lymph nodes | Dead | J. H. Siegel |
| 24 | Denver | 20 | F | Father | Yes | Yes | Yes | Yes | Acti C, LRT | Unclassified lymphoma | 7 | Brain | Alive, following radiotherapy | |
| 25 | Los Angeles | 23 | M | Cadaver | Yes | Yes | No | No | – | Unclassified lymphoma | 46 | Brain | Dead | R. Goldman |
| 26§ | Montreal | 29 | M | Cadaver | Yes | Yes | Yes | No | – | Unclassified lymphoma | 2 | Spinal cord | Dead | P. Daloze |
| 27§ | Edmonton, Canada | 8 | M | Father | Yes | Yes | No | No | – | Lymphosarcoma | 3.5 | Brain; meninges | Dead | W. Lakey |
| 28 | Mayo Clinic | 41 | M | Cadaver | Yes | Yes | No | No | – | Plasma cell lymphoma | 6.5 | Terminal ileum | Dead | J. E. Woods |
| 29 | Leyden, Holland | 47 | M | Brother | Yes | Yes | No | No | Acti C | Lymphoreticular malignancy | 2.5 | Liver; spleen; transplanted kidney; thoracic and abdominal lymph nodes | Dead | M. W. Kalff |
| 30 | Denver | 38 | M | Brother | Yes | Yes | Yes | Yes | – | Lymphoma | 45 | Liver | Dead | |
| 31 | Paris | 40 | M | Sister | No | Yes | No | Yes | Thy Irr 6 MP TBI | Acute monocytic leukemia | 48 | Bone marrow | Died almost 4 yr after diagnosis of malignancy despite bone marrow graft | J. Hamburger |
| 32 | Boston | 34 | M | (1) Cadaver (2) Half-sister | Yes | Yes | No | No | Acti D Azasetine TD Fist | Leiomyosarcoma | 47 | Stomach; perigastric lymph node; peritoneum; bowel; liver; lungs vertebrae and ribs | Dead | R. E. Wilson |
| 33 | Montreal | 36 | M | Cadaver | Yes | Yes | No | No | Acti-C LRT | Leiomyosarcoma | 51 | Small bowel; liver; pancreas | Dead | L. D. MacLean |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 34¶ | Chapel Hill | 39 | M | Cadaver | Yes | Yes | Yes | No | – | Synovial sarcoma | 12 | Lungs; liver; small bowel; right popliteal fossa | Dead | W. B. Blythe |
| 35 | New York (Mt. Sinai) | 40 | F | Cadaver | Yes | Yes | No | No | – | Rhabdomyo-sarcoma | 19 | Iliac muscles | Dead | L. Burrows |

*Alive, 3 mo following radical local excision and radiotherapy and reduction of immunosuppressive therapy.
†Tumors had disappeared following resection or irradiation of the lesions and withdrawal of ALG and Imuran therapy. No tumors at autopsy.
‡No recurrence after irradiation of lesions and withdrawal of ALG and Imuran therapy.
§Tumors may have been present at time of transplantation.
¶Tumor first diagnosed 9 mo after immunosuppressive therapy had been discontinued.
See Table 1 for key to abbreviations used.

these were the only organs affected by the tumor.

*Age of Patients*

More tumors in patients over the age of 40 yr have recently been reported to the Denver registry. Nevertheless, the affected population is basically a young one with an average age of 35 yr (range 8–64 yr). The epithelial tumors appeared at an average age of 36.5 yr and mesenchymal lesions at 32 yr. More patients with epithelial tumors (40%) were over the age of 40 yr than in the case of the mesenchymal lesions (17%).

*Time of Appearance of Tumors*

The average time of appearance of the tumors after transplantation was 30 mo, with the epithelial lesions manifesting at 33 mo and the mesenchymal malignancies at 22 mo. Lymphomas involving the central nervous system appeared even earlier at an average of 14 mo after transplantation.

In a previous report[4] we drew attention to a group of lesions that were diagnosed in less than 4 mo after transplantation. In the present series, 11 of 93 cases (12%) fell into this category, eight with epithelial lesions and three with mesenchymal tumors (Tables 1 and 2). A reasonable explanation could be that at least some of these cases or even some of those with a later appearance were already present at the time of transplantation. The hypothesis could hold that they were small and could not be detected but grew rapidly under the influence of the immunosuppressive therapy. In turn, it could be proposed that such preexisting tumors were present in increased numbers pretransplantation in consequence of prior chronic renal failure and by virtue of the well-recognized depression of immune responses that occur in uremia. Evidence consistent with but not proving this latter hypothesis is cited in a recent publication.[4] In any event, the most important factor in posttransplantation neoplasia is clearly not preexisting uremia but rather the imposition of posttransplantation immunosuppression.

*Immunosuppressive Measures*

Tables 1 and 2 summarize immunosuppressive measures. All 93 patients received prednisone or some form of corticosteroid therapy. Ninety-two received azathioprine and one was given the related compound 6-mercaptopurine. Only 25 of the recipients were treated with ALG, and in two instances treatment with this agent was started after the appearance of the tumors. Thiry-five patients underwent splenectomy, five thymectomy, two thymic irradiation, five thoracic duct fistula construction, and one total-body irradiation.

*Possibility of Transmission of Tumor from Donor*

There were 105 donors of whom 58 were cadavers, 44 living-related volunteers, and three living-unrelated donors. All the live donors were free of malignant disease and have remained so. Two cadaver donors had medulloblastomas but their recipients developed presumably unrelated tumors, a reticulum cell sarcoma of the buttock, and a leiomyosarcoma of the stomach, respectively. Another cadaver donor had had a carcinoma of the colon resected 5 yr previously but there was no evidence of residual tumor at the time of transplantation. The recipient developed a reticulum cell sarcoma.

*Known Preexisting Malignancies in the Recipient*

Three of the patients who developed de novo malignancies posttransplantation had either known tumors before or at the time of operation. Two were found to have incidental renal carcinomas when their diseased native kidneys were removed. One of these patients subsequently

developed a reticulum cell sarcoma of the brain, and the other had the gastric leiomyosarcoma mentioned above. Neither had any evidence of the original renal neoplasm at autopsy. A third recipient, who developed a new skin cancer after transplantation, died 18 mo later of metastases of a transitional cell carcinoma of the ureter which had been resected 2 wk before transplantation.

*Prognosis of Patients with De Novo Malignancies*

Thirty-seven of the 93 patients are currently alive. Patients with mesenchymal tumors had the worst prognosis and only three of 35 are alive. The outcome of recipients with epithelial malignancies was better: 34 of 58 are still living. Most of these had low grade malignancies involving the skin, cervix uteri, or lip, whereas those with carcinomas of the thoracic or abdominal organs had a poor outlook.

## DISCUSSION

The chronic use of immunosuppressive agents has been associated with an increased incidence of both mesenchymal and epithelial malignancies. Surprisingly, almost all these tumors have been solid. Some patients have manifested transient leukemoid reactions but only one case of frank leukemia has been recorded to date. Even in this case the immunosuppressive drugs may not have been responsible as the patient was subjected to total-body irradiation, which is well recognized as a cause of leukemia.

The present study again emphasizes that a number of malignancies, usually associated with the older age groups, are being encountered in transplant recipients at a younger age. This particularly applies to several of the more commonly encountered tumors in this series such as skin cancers and neoplasms of the lip, which are ordinarily uncommon under age 40 yr. Reticulum cell sarcomas, which naturally tend to occur somewhat earlier in life, are found at an even younger average age under the influence of immunosuppression.

The true incidence of neoplasia in transplant patients can only be found in very carefully studied series such as our own. For registry collections, however, probably many of the low grade tumors are being missed or dismissed as unimportant, and only the more serious lesions reported. The fact that 19 of 95 cases recorded in the registry are from our own center reflects our keen awareness of the frequency of this problem as well as the large number of long-term followups that we have accumulated. In our center, any suspicious lesion of the skin, lip, or uterine cervix is biopsied and studied microscopically.

A diagnostic problem with the skin cancers is that warts are extremely common in transplant recipients and frequently involve the same exposed areas as do skin cancers. Consequently, the tumors are likely to be misdiagnosed as common warts. By performing numerous and repeated biopsies of suspicious lesions we have found that the skin cancers are often multiple and that extensive areas of skin may be the seat of either frank malignancy or, of intraepithelial cancer (Bowen's disease). Similarly, biopsies of areas of persistent ulceration of the lip have uncovered carcinomas which are often superficial and do not present the classical features of an indurated base and a rolled everted edge.

Dysplasia of the epithelium of the cervix uteri is not uncommon in normal women and it probably occurs with increased frequency under immunosuppression. Consequently, it is not surprising that 8% of the patients in the collected series of de novo tumors carried the diagnosis of in situ carcinomas of the cervix uteri. The incidence is probably even higher as many cases are not diagnosed unless routine cervical smears are done on all female

organ transplant recipients before operation and at regular intervals thereafter.

Neoplasms of the skin, lip, and uterine cervix can be successfully treated using standard surgical or radiotherapeutic techniques without any alteration in immunosuppressive therapy. However, in view of the virtually hopeless prognosis with the more malignant tumors it may be advisable to reduce drastically or even discontinue the immunosuppressive therapy in these cases. The three surviving patients with mesenchymal tumors were all treated in this manner and two other patients with high grade malignancies who were similarly treated and who died of other causes some months after cessation of immunosuppression were found at autopsy to be free of the previously widespread neoplasms.

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