TRANSPLANTATION

Vol. 14, No. 4
Printed in U.S.A.

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Transplantation

ARTICLES

MALIGNANT TUMORS ARISING DE NOVO IN IMMUNOSUPPRESSED ORGAN TRANSPLANT RECIPIENTS[1]

ISRAEL PENN AND THOMAS E. STARZL

Department of Surgery, University of Colorado School of Medicine, and the Veterans Administration Hospital, Denver, Colorado 80220

SUMMARY

De novo malignant tumors have been observed throughout the world in 75 chronic survivors of organ transplantation, including 16 of our own patients. The incidence of tumors was approximately 80 times greater than in the average population in a comparable age range. Chronic uremia may have predisposed to the development of some of the tumors, but this has not yet been proved. It seems clear that the predominant etiology was chronic immunosuppression post-transplantation. Forty-four of the patients had epithelial tumors and in 31 the lesions were of mesenchymal origin. On the average the malignancies appeared 29 months after transplantation. Lymphomas showed an unusual predilection for involvement of the central nervous system. Carcinomas of the skin, lip, and uterine cervix were successfully treated by conventional techniques. On the other hand, carcinomas of the thoracic or abdominal organs and mesenchymal tumors led or contributed to early death in most cases. For this reason drastic reduction or even discontinuance of immunosuppression should be considered in the management of these latter tumors.

In recent years a convincing association between immunosuppression and malignant neoplasms in organ transplant recipients has become evident. In some patients tumors have been accidentally transplanted from donors with cancer (*15, 28, 29*), or there has been growth of residual or metastatic tumor in patients with preexisting malignancy (*15, 28, 29*), or neoplasms have arisen de novo at some time after transplantation. This report will be restricted to the last group of tumors.

After we first described the development of de novo malignancies in renal homograft recipients in 1968 (*18, 25, 27*), an informal tumor registry was established in Denver. Physicians from transplant centers throughout the world have generously contributed data concerning their patients. The present report deals with all cases recorded until December 31, 1971 and involves 75 patients with 76 types of tumors.

INCIDENCE

Up to the fall of 1971, 7,581 renal and 179 cardiac homografts had been reported to the American Cancer Society-National Institutes of Health Organ Transplant Registry (*2*). However, it is well recognized that these figures are incomplete as are the numbers of tumors reported. In order to determine accurately the incidence of de novo malignancies, we have re-

[1] This work was supported by research grants from the Veterans Administration, by Grants RR-00051 and RR-00069 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health, and by Grants AI-10176-01, AI-AM-08898, AM-17772, and HE-09110 from the United States Public Health Service.

TABLE 1. Epithelial tumors in organ homograft recipients

Case No.	Transplant center	Age at time of transplant (years)	Sex	Donor	Immunosuppression by					Type of tumor	Time after transplantation (months)	Organs involved	Outcome	Referring physician
					Splenectomy	Thymectomy	Imuran	Prednisone	ALG					
1	Denver	37	F	Unrelated living	Yes	Yes	Yes	Yes	No	Squamous cell carcinoma in situ	50	Cervix of uterus	Alive, no recurrence after hysterectomy	
2	Minneapolis	28	F	Brother	No	No	Yes	Yes	No	Squamous cell carcinoma in situ	30	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	Cervix of uterus	Alive, no recurrence after cryosurgery	K. Pritzker
4	Los Angeles	38	F	Mother	No	No	Yes	Yes	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	No	No	Yes	Yes	No	Squamous cell carcinoma in situ	36	Cervix of uterus	Cone biopsy; patient being observed at regular intervals	H. Lee
6	Denver	26	F	Father	Yes	No	Yes	Yes	No	Squamous cell carcinoma in situ	65	Cervix of uterus	Died of causes unrelated to carcinoma	
7	Denver	17	F	Father	Yes	No	Yes	Yes	Yes	Squamous cell carcinoma in situ	51	Cervix of uterus	Alive, awaiting hysterectomy	
8	Minneapolis	32	F	Sister	Yes	No	Yes	Yes	No	Squamous cell carcinoma in situ	45	Cervix of uterus	Alive, no recurrence after hysterectomy	R. L. Simmons
9	Denver	40	M	Unrelated living	Yes	No	Yes	Yes	No	Superficial squamous cell carcinoma	66	Lower lip	Alive, no recurrence following excision	
10	Denver	39	M	Brother	Yes	Yes	Yes	Yes	No	Superficial squamous cell carcinoma	36	Lower lip	Alive, no recurrence following excision	
11	Louisville	35	M	Brother	No	No	Yes	Yes	No	Squamous cell carcinoma	8	Lower lip	Alive, no recurrence following excision	D. Leb
12	Los Angeles	27	M	Mother	No	No	Yes	Yes	No	Squamous cell carcinoma	25	Lower lip	Alive, no recurrence following excision	R. Goldman
13	Los Angeles	25	F	Brother	No	No	Yes	Yes	No	Squamous cell carcinoma	35	Lower lip	Alive, no recurrence following excision	R. Goldman
14	Salt Lake City	42	M	Cadaver	No	No	Yes	Yes	Yes	Squamous cell carcinoma	32	Lip	Alive, no recurrence following excision	L. Stevens
15	San Francisco	28	M	Cadaver Cadaver	Yes	No	Yes	Yes	No	Infiltrating squamous cell carcinoma	32	Lower left lip	Alive, recurrent lesion in lip removed 6 months after primary excision	F. O. Belzer
16	San Francisco	23	M	Brother	Yes	No	Yes	Yes	No	Infiltrating squamous cell carcinoma	37	Right lower lip	Alive, no recurrence following excision	F. O. Belzer
17	Denver	40	M	Unrelated living	Yes	Yes	Yes	Yes	No	Squamous cell carcinoma	32	Skin of ear	No recurrence after excision, died of other causes	

18	Denver	43	M	Uncle	Yes	No	Yes	Yes	Yes	Basal cell carcinoma	33	Nasolabial fold	Alive, no recurrence following excision	
19	Denver	30	M	Brother	Yes	Yes	Yes	Yes	No	Basal cell carcinoma	75	Nasolabial fold	Alive, no recurrence following excision	
20	Denver	34	M	Sister	Yes	No	Yes	Yes	No	Squamous cell carcinoma	74	Left forearm; right forearm; right arm; scalp	Dead (myocardial infarction)	
21	Stockholm	58	M	Cadaver	No	No	Yes	Yes	No	Multiple squamous cell carcinomas	38	Scalp	Alive	C. Franksson
22	Denver	22	M	Cousin	Yes	No	Yes	Yes	No	Squamous cell carcinoma	78	Left hand	Alive, no recurrence following excision	
23	Denver	30	M	Brother	Yes	No	Yes	Yes	Yes	Superficial squamous cell carcinomas	36	Face (3 areas)	Alive, 4 fresh areas excised from face and neck 4 months after initial lesions	
24[a]	Sydney	44	F	Cadaver	No	No	Yes	Yes	No	Basal cell carcinoma	3	Nose	Alive following radiotherapy	J. F. Mahony
25	Sydney	48	F	Cadaver	No	No	Yes	Yes	No	Multiple squamous cell carcinomas Basal cell carcinoma	29	Forehead; right nasolabial fold; left temple; left preauricular lymph node	Alive following excisions and radiotherapy	J. H. Stewart
26	Denver	21	M	Father	Yes	No	Yes	Yes	No	Squamous cell carcinoma	87	Skin of face	Alive following excision	W. Alexander
27	San Francisco	41	M	Brother	Yes	No	Yes	Yes	No	Squamous cell carcinoma	73	Multiple sites dorsum of left hand	Alive following wide excision	F. O. Belzer
28	San Francisco	46	M	Sister	Yes	No	Yes	Yes	No	Squamous cell carcinoma	76	Floor of mouth; tongue; cervical lymph nodes	Dead	F. O. Belzer
29	Nashville	34	M	Cadaver	No	No	Yes	Yes	No	Squamous cell carcinoma	62	Metastases in lymph nodes of neck; later widespread metastases; primary site of tumor unknown	Dead	C. Zukoski
30	Montreal	13	M	Brother	No	No	Yes	Yes	No	Hepatocellular carcinoma	32	Liver	Dead	K. Pritzker
31	Toronto	8	F	Cadaver	No	No	Yes	Yes	Yes	Well differentiated hepatoma	13	Liver	Dead	A. Millner
32	Minneapolis	27	M	Brother	Yes	No	Yes	Yes	No	Undifferentiated carcinoma	10	Liver; brain; bone marrow	Dead	C. Hitchcock
33	Nashville	47	M	Cadaver	No	No	Yes	Yes	No	Undifferentiated carcinoma	19	Lung; mediastinal lymph nodes; brain; liver	Dead	C. Zukoski
34	Denver	44	F	Sister	Yes	No	Yes	Yes	Yes	Moderately differentiated adenocarcinoma	31	Lung	Dead	
35	San Francisco	46	M	Son; cadaver	Yes	No	Yes	Yes	No	Alveolar cell carcinoma of lung	9	Lungs	Dead	S. Kountz
36	Sydney	43	F	Cadaver	No	No	Yes	Yes	Yes (after development of tumor)	Adenocarcinoma	32	Lungs; mediastinal lymph nodes; liver	Dead	J. F. Mahony
37	Minneapolis	16	F	Cadaver	No	No	Yes	Yes	No	Dysgerminoma	32	Ovary; peritoneum; mediastinal and axillary lymph nodes	Dead	W. Kelly

TABLE 1—*Continued*

Case No.	Transplant center	Age at time of transplant (years)	Sex	Donor	Immunosuppression by					Type of tumor	Time after transplantation (months)	Organs involved	Outcome	Referring physician
					Splenectomy	Thymectomy	Imuran	Prednisone	ALG					
38[a]	Louisville	32	M	Brother	Yes	No	Yes	Yes	No	Embryonal cell carcinoma	2	Testis; abdominal organs; ureter of transplanted kidney; lung	Dead	D. Leb
39	Ghent	53	F	Cadaver	No	No	Yes	Yes	No	Adenocarcinoma	35	Sigmoid colon; liver	Dead	F. Derom
40[a]	Chicago	41	M	Brother	No	No	Yes	Yes	No	Adenocarcinoma	1	Colon	Dead	D. Jonasson
41[b]	Cape Town	52	M	Cadaver	No	No	Yes	Yes	Yes	Anaplastic small cell adenocarcinoma	17	Stomach; liver; mesentery; peritoneum	Dead	S. Bosman
42[c]	Toronto	21	M	Cadaver	No	No	Yes	Yes	Yes	Highly anaplastic transitional cell tumor	6	Kidney; liver; brain; heart; lung	Dead	G. DeVeber
43[a]	Cleveland	45	M	Cadaver	No	No	Yes	Yes	Yes	Adenocarcinoma	1	Thyroid gland	Alive following thyroidectomy	S. Deodhar
44	San Francisco	32	F	Brother Cadaver	Yes	No	Yes	Yes	No	Adenocarcinoma	32	Breast; axillary lymph nodes	Alive following radical mastectomy	F. O. Belzer

[a] Tumors may have been present at time of transplantation.
[b] Heart transplant recipient.
[c] Tumor may have been present in homograft at time of transplantation.

viewed the renal transplantation experience at the University of Colorado Medical Center and the Denver Veterans Administration Hospital. The studies involved patients treated between November 1962 and July 1, 1971, who on December 31, 1971 had potential followups of from 6 months to more than 9 years. Sixteen of 352 patients had developed tumors (Tables 1 and 2), giving a crude incidence of 4.5%. This figure does not reflect the true frequency of post-transplantation neoplasia, since 66 patients died of a variety of other complications before the end of the 4th postoperative month. The 16 tumors occurred in the remaining 286 patients for a partially corrected incidence of 5.6%. This correction, obtained by excluding from the denominator those patients who did not survive a minimum of 4 months after transplantation, may no longer be justified, since tumors have been diagnosed in several centers during this early period as will be described later.

The rate of tumor development in these generally young patients (3½–53 years old, average age approximately 28 years) compares with an annual incidence of 58/100,000 (0.058%) in the general population in a comparable age range (*7*). The latter statistic excludes carcinomas in situ. In our transplant series 3 of the 16 malignancies were of this kind. Even if these 3 cases are omitted the incidence of malignancy in the 286 patients is 4.5%, still a high figure.

TUMOR TYPES AND ORGANS AFFECTED

Of the 76 tumors reported to date, 44 were of epithelial origin (Table 1). The most common of these were squamous or basal cell skin carcinomas (11 cases), in situ carcinomas of the cervix uteri (8 cases), carcinomas of the lip (8 cases), carcinomas of the lung (3 cases), hepatomas (2 cases), colonic carcinomas (2 cases), and highly anaplastic carcinomas of uncertain origin (2 cases). In addition, there was one example each of carcinoma of the ovary, testis, floor of the mouth, stomach, thyroid, and breast. In a further case the origin of a widespread squamous cell neoplasm was never established. There was also a case of a primary carcinoma involving the transplanted kidney (case 42, Table 1), but there is some question as to whether this was truly a de novo neoplasm or whether a small undetected tumor may have been present in the organ at the time it was harvested from a cadaver donor.

Thirty-two mesenchymal tumors were encountered in 31 patients (Table 2). These neoplasms were a much more homogenous group in that 28 were varieties of lymphoma including 21 examples of reticulum cell sarcoma. One of the latter patients also had a Kaposi's sarcoma. This type of lesion was found in two further patients, while unclassified lymphomas were found in 3, and a lymphosarcoma was found in 1. Of the nonlymphomatous tumors, 2 were leiomyosarcomas, 1 was a synovial sarcoma, and 1 was a rhabdomyosarcoma.

An unusual feature of the lymphomas was the frequency with which the central nervous system was involved (*21, 22*). Of the 27 patients with lymphoma there were 14 with involvement of either the brain or spinal cord including 10 of the patients with reticulum cell sarcoma, 3 with unclassified lymphoma, and 1 patient with lymphosarcoma. Lymphoreticular tumors within the central nervous system are uncommon (0.04 and 1.5% in two large series) (*19, 20*); yet, in 11 instances in the present study, the brain or spinal cord were the only regions so affected. Probable explanations for the high incidence of central nervous system involvement have been discussed elsewhere (*17, 21, 22*).

BEHAVIOR OF TUMORS

The mesenchymal tumors occurred in a slightly younger average age group than the epithelial lesions, 31 years compared with 35 years. The average time of appearance of the tumors after transplantation was 29 months. The mesenchymal neoplasms occurred at an average of 21 months after operation compared with the longer interval of 35 months with the carcinomas.

A number of the epithelial tumors were of low grade malignancy and were treated successfully by conventional techniques (Table 1). Of the 44 patients in this group, 26 are currently alive including most of the patients with carcinomas of the skin, cervix uteri, and lip. The deaths of 3 patients with these latter lesions were unrelated to cancer. In contrast, the epithelial malignancies within the thorax and abdomen were the primary cause of death or contributed significantly to the fatal outcome. The recipients with mesenchymal tumors had a similar gloomy prog-

TABLE 2. Mesenchymal tumors in organ homograft recipients

Case No.	Transplant center	Age at time of transplant (years)	Sex	Donor	Immunosuppression by					Type of tumor	Time after transplantation (months)	Organs involved	Outcome	Referring physician
					Splenectomy	Thymectomy	Imuran	Prednisone	ALG					
1	Denver	14	M	Mother	Yes	No	Yes	Yes	Yes	Reticulum cell sarcoma	5½	Brain	Dead	
2	Denver	23	M	Father	Yes	Yes	Yes	Yes	No	Reticulum cell sarcoma	30	Thyroid; liver; lung; stomach; prostate; pituitary; skin; psoas muscle	Dead	
3	Edinburgh	26	F	Mother	No	No	Yes	Yes	Yes	Reticulum cell sarcoma	25	Lymph nodes; pleura; spleen; liver; ovary; adrenal; bone marrow; transplanted kidney	Dead	M. Woodruff
4	Cleveland	32	M	Cadaver	No	No	Yes	Yes	Yes	Reticulum cell sarcoma	22	Buttock; lungs; aortic lymph nodes	Dead	S. D. Deodhar
5	Richmond	38	M	Cadaver	No	No	Yes	Yes	No	Reticulum cell sarcoma	31	Lung; aortic lymph nodes	Dead	J. Pierce
6	Auckland	34	M	Cadaver Cadaver Cadaver	No	No	Yes	Yes	No	Reticulum cell sarcoma	7	Tongue; esophagus; liver	Dead	P. Doak
7	Auckland	46	F	Cadaver	No	No	Yes	Yes	No	Reticulum cell sarcoma	9	Brain	Dead	P. Doak
8	New York	18	M	Uncle	No	No	Yes	Yes	No	Reticulum cell sarcoma	9	Brain	Dead	R. Porro
9	New York	36	M	Cadaver	No	No	Yes	Yes	No	Reticulum cell sarcoma	10	Brain	Dead	F. Veith
10	Richmond	29	M	Brother	Yes	No	Yes	Yes	No	Reticulum cell sarcoma	67	Widespread lymph nodes; liver; vertebrae	Dead	H. Lee
11	Little Rock	21	M	Father	Yes	No	Yes	Yes	No	Reticulum cell sarcoma	24	Brain	Dead	C. Araoz
12	San Francisco	39	F	Sister	Yes	No	Yes	Yes	No	Reticulum cell sarcoma	14	Brain; lungs	Dead	F. O. Belzer
13	Richmond	18	M	Father	Yes	No	Yes	Yes	No	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	No	No	Yes	Yes	No	Reticulum cell sarcoma	13	Lungs; liver; spleen; rectum; transplanted kidney; mesentery; bone marrow	Dead	Y. Muto
15	Chicago	52	M	Cadaver	No	No	Yes	Yes	No	Reticulum cell sarcoma	7½	Brain	Dead	N. Levine
16	New York	28	M	Cadaver	No	No	Yes	Yes	No	Reticulum cell sarcoma	7	Liver	Dead	L. Burrows

16	New York	28	M	Cadaver	No	No	Yes	Yes	No	Reticulum cell sarcoma	7	Liver	Dead	L. Burrows
17	San Francisco	40	F	Cadaver Cadaver	No	No	Yes	Yes	No	Reticulum cell sarcoma	14	Brain	Dead	F. O. Belzer
18	Galveston	45	M	Cadaver	No (Had thoracic duct fistula)	No	Yes	Yes	Yes	Reticulum cell sarcoma	19	S.c. tissues of buttock	Alive[c]	J. C. Fish
19	Zurich	50	F	Cadaver	No (Had thoracic duct fistula)	No	Yes	Yes	Yes	Malignant reticulosis	8	Liver; spleen; lymph nodes; bone marrow; esophagus; tongue; transplanted kidney; adrenal glands	Dead	W. Wegmann
20	Israel	34	F	Cadaver	No	No	Yes	Yes	Yes	Reticulum cell sarcoma Kaposi's sarcoma	9	Brain Skin	Dead[d]	B. Myers
21	Israel	27	M	Cadaver	No	No	Yes	Yes	Yes	Kaposi's sarcoma	8	Skin; mucosa of mouth	Alive[e]	B. Myers
22	New York	35	F	Cadaver	No	No	Yes	Yes	No	Visceral Kaposi's sarcoma	10	Lungs; esophagus; stomach; urinary bladder; mediastinal and abdominal lymph nodes	Dead	J. H. Siegel
23	Denver	20	F	Father	Yes	No	Yes	Yes	Yes	Unclassified lymphoma	7	Brain	Alive following radiotherapy	
24	Los Angeles	23	M	Cadaver	No	No	Yes	Yes	No	Unclassified lymphoma	46	Brain	Dead	R. Goldman
25[a]	Montreal	29	M	Cadaver	No	No	Yes	Yes	Yes	Unclassified lymphoma	2	Spinal cord	Dead	P. Daloze
26	San Francisco	21	M	Brother Cadaver Cadaver Cadaver	Yes	No	Yes	Yes	No	Reticulum cell sarcoma	41	Brain (multifocal); cervical lymph nodes	Dead	F. O. Belzer
27[a]	Edmonton	8	M	Father	No	No	Yes	Yes	No	Lymphosarcoma	3½	Brain; meninges	Dead	W. Lakey
28	Boston	34	M	Cadaver; half-sister	No	No	Yes	Yes	No	Leiomyosarcoma	47	Stomach; perigastric lymph node; peritoneum; bowel; liver; lungs; vertebrae and ribs	Dead	R. E. Wilson
29	Montreal	36	M	Cadaver	No	No	Yes	Yes	No	Leiomyosarcoma	51	Small bowel; liver; pancreas	Dead	L. D. MacLean
30[b]	Chapel Hill	39	M	Cadaver	No	No	Yes	Yes	Yes	Synovial sarcoma	12	Lungs; liver; small bowel; right popliteal fossa	Dead	W. B. Blythe
31	New York	40	F	Cadaver	No	No	Yes	Yes	No	Rhabdomyosarcoma	19	Iliac muscles	Dead	L. Burrows

[a] Tumors may have been present at time of transplantation.
[b] Tumor first diagnosed 9 months after immunosuppressive therapy had been discontinued.
[c] Alive 3 months following radical local excision and radiotherapy and reduction of immunosuppressive therapy.
[d] Tumors had disappeared following resection or irradiation of the lesions and withdrawal of ALG and Imuran therapy; no tumors at autopsy.
[e] No recurrence after irradiation of lesions and withdrawal of ALG and Imuran therapy.

nosis in that only 3 of the 31 patients are currently alive.

BORDERLINE LESIONS

An interesting feature of the present report is that in 6 of the 75 cases, the lesions were diagnosed in less than 4 months after transplantation (Tables 1 and 2). These included one case each of carcinoma of the skin, testis, colon, and thyroid gland, a lymphosarcoma of the brain, and a lymphoma of the spinal cord. One reasonable explanation could be that at least some of these tumors or even some of those with a later appearance were already present at the time of transplantation, but were small and undetected, and grew rapidly under the influence of the immunosuppressive therapy. This raises the question whether chronic renal failure per se may predispose the patient to malignant disease (*15*) by virtue of the well known depression in uremia of immune responses (*6, 10, 13, 32*).

Observations reported to the National Dialysis Registry (*5*) are neither for nor against this hypothesis. Among 4,600 patients on chronic dialysis programs, 1% were reported to have died from malignancies. However, these statistics were incomplete, as the cause of death in 7% of the patients was not known; besides, the patients' ages were not stated so it is not possible to compare cancer death rates in this group with those in the general population. Furthermore, the Dialysis Registry does not provide figures giving the incidence of tumors among living dialysis patients.

Among our own 352 renal recipients, there have been 3 patients who were proved to have malignant growths prior to transplantation. The lesions were of the bladder, the thyroid, and the skin. The thyroid carcinoma was an incidental finding at autopsy following sudden death 2 days after transplantation, but the bladder and skin cancers required surgical management both before and after transplantation. These latter tumors are now under control with post-transplantation followups of 1 and 2½ years.

A similar case to our thyroid carcinoma was in a patient of Dr. R. Simmons (personal communication) who underwent a parathyroidectomy 2 weeks after renal transplantation and was found to have an unsuspected papillary carcinoma of the thyroid gland. A patient on chronic hemodialysis at our medical center (A. Alfrey, personal communication) was also found to have a carcinoma of the thyroid gland during parathyroidectomy. Other malignancies encountered in patients with chronic uremia include a carcinoma of the parathyroid gland discovered during thymectomy performed 2 months before renal transplantation (S. Nakamoto, personal communication), a rhabdomyosarcoma of the shoulder in a patient on hemodialysis who was awaiting a cadaver kidney transplant (P. Ivanovitch, personal communication), and a carcinoma of the ureter in a patient with chronic renal failure caused by analgesic nephropathy (M. Robertson, personal communication).

If uremia predisposed to malignancy by loss of immunological surveillance, it would not be surprising if carcinomas were found in the diseased native kidneys that are often excised before or at the time of transplantation. In our own case material, there have been no such examples. However, 12 cases of renal neoplasia have now been collected in patients with chronic renal failure. The features of these interesting cases are listed in Table 3.

ETIOLOGY OF TUMORS

Apart from the possibility of preexisting neoplasia in the recipients, it is necessary to consider whether tumors were inadvertently transplanted from the donors. The 75 recipients received their transplants from 85 donors, 41 living volunteers, and 44 cadavers. None of the living donors has manifested evidence of malignant disease during followup periods as long as 9 years. Two cadaver donors (cases 4 and 28, Table 2) had medulloblastomas, whereas the recipients subsequently developed a gluteal reticulum cell sarcoma and a gastric leiomyosarcoma, respectively. The tumors in donor and recipient were morphologically distinct and there was probably no etiological connection unless they were both caused by an oncogenic virus that was transmitted with the donor kidney. A further cadaver donor (case 9, Table 2) had 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.

In experimental animals (*15, 26, 28*), each of the main immunosuppressive agents, azathioprine, prednisone, and antilymphocyte globulin (ALG), has been shown either to: (1) increase

TABLE 3. Renal neoplasms in patients with chronic uremia

Case No.	Transplant or dialysis center	Age (years)	Sex	Underlying renal disease	Type of tumor	Mode of presentation	Relationship to transplantation	Referring physician
1	Minneapolis	45	F	Chronic glomerulonephritis	Hypernephroma of right kidney	Mass in upper pole of right kidney	Not transplanted; on hemodialysis	R. Simmons
2	San Francisco	29	M	Chronic glomerulonephritis	Renal cell carcinoma of left kidney invading capsule and perinephric fat	Incidental finding at bilateral nephrectomy	Twenty months before transplantation	F. Belzer
3	Cleveland	Not stated	Not stated	Not stated	Renal cell carcinoma involving a solitary kidney	Incidental finding at nephrectomy	Four weeks before transplantation	S. Nakamoto
4	Edinburgh	Not stated	Not stated	Not stated	Hypernephroma of one of the kidneys	Incidental finding at bilateral nephrectomy for persistent hypertension	After transplantation	M. Woodruff
5[a]	New York (Cornell)	18	M	End stage renal disease	Low grade papillary renal carcinoma of right kidney	Incidental finding when kidneys removed	At the time of transplantation	R. Porro
6[a]	Boston	34	M	Chronic glomerulonephritis	(1) Well differentiated renal cell carcinoma of left kidney; (2) two adenomas of right kidney[b]	Incidental finding when kidneys removed	At the time of a second transplantation 3 months after insertion of a first homograft which never functioned	R. E. Wilson
7	Ann Arbor	43	M	End stage renal disease	Renal cell carcinoma of right kidney	Incidental finding when kidneys removed	At the time of transplantation	J. Turcotte
8	London	44	M	Hyperparathyroidism with nephrocalcinosis	Renal carcinoma of both kidneys	Incidental finding when kidneys removed	Ten months before transplantation	J. Salaman
9	Los Angeles	35	M	Malignant hypertension	Hypernephroma of a kidney	Massive retroperitoneal hemorrhage from the affected kidney	Fifteen months before transplantation	T. Berne
10	Dallas	21	M	Chronic glomerulonephritis	Renal cell carcinoma in one of his kidneys	Gross hematuria at age 18 years approximately 15 months after immunosuppressive treatment with Imuran and prednisone was started; workup showed mass lesion in one kidney	Not transplanted; on chronic hemodialysis for approximately 3 years	P. Peters
11	Minneapolis	48	F	Chronic pyelonephritis	Adenoma of left kidney[b]	Incidental finding at bilateral nephrectomy	Awaiting transplantation	R. Simmons
12	Tucson	43	M	Chronic glomerulonephritis	Adenoma of left kidney[b]	Incidental finding at bilateral nephrectomy	Several weeks before transplantation	C. Zukoski

[a] These patients are cases 8 and 28 in Table 2.

[b] There is considerable disagreement among pathologists concerning the difference between a large renal adenoma and a small renal carcinoma. A lesion less than 2 cm in diameter is often regarded as an adenoma and a larger lesion is often regarded as a carcinoma.

the incidence of spontaneous, virus-induced, or chemically initiated tumors; (2) facilitate the ease with which malignant cells can be transplanted; or (3) accelerate metastatic growth. Thymectomy or splenectomy may also cause increased oncogenic susceptibility in experimental animals (*15, 26, 28*).

In man there has so far been no evidence that any one of the individual immunosuppressive measures has made a unique contribution to the development of post-transplantation neoplasia. All the patients (Tables 1 and 2) received azathioprine and prednisone, 30 underwent splenectomy, 5 had thymectomy, and 2 had thoracic duct fistulas. It is of interest that 22 of 44 patients with epithelial tumors (50%) underwent splenectomy, whereas 8 of 31 (26%) with mesenchymal tumors were subjected to this procedure. Only 21 of the 75 patients were treated with ALG and 2 of these recipients received this therapy after the appearance of the tumor. In view of these findings it is difficult to understand the origin of the widespread misconception that the incidence of tumors in the post-transplantation period has increased since the introduction of ALG therapy.

The disproportionately high incidence of lymphomas may, in part, be an artefact in that there may be a tendency to report to the registry only the more florid and lethal malignancies and to dismiss many skin tumors or in situ carcinomas of the cervix as relatively unimportant. However, the disproportionate numbers of lymphomas may be real and may reflect the effects upon the host of the transplanted organ with its foreign histocompatibility antigens. Prolonged antigenic stimulation of the host reticuloendothelial system has been shown to cause a high incidence of lymphomas (*1, 12, 23, 24, 31*).

While this may be the cause of at least some of the lymphomas, the most likely explanation for the wide spectrum of tumors observed in the present series is that chronic immunosuppression causes loss of the immunological surveillance mechanism by which tumor mutants are normally detected and destroyed (*3, 4, 30*). This does not exclude other possible etiological factors such as a direct oncogenic effect of the immunosuppressive agents, potentiation of the effects of environmental carcinogens such as tobacco, ultraviolet light, or irradiation, or activation of oncogenic viruses. Concerning the last possibility, infection by viruses of the Herpes family have been very common in transplant recipients. Two human strains belonging to this group, the Epstein-Barr and *Herpes hominis* II viruses, 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 or radiotherapeutic techniques without risking the homografts by arbitrary reductions in immunosuppression. This approach has proved inadequate for dealing with most carcinomas involving the thoracic and abdominal organs and with most mesenchymal tumors. In view of the virtually hopeless prognosis it may be advisable to reduce drastically or even discontinue the immunosuppressive therapy. Three patients (cases 18, 21, and 23, Table 2) with mesenchymal tumors are currently alive following this form of treatment. One of the patients (case 23) is in excellent health more than 4½ years after transplantation and 4 years after the tumor was diagnosed. Two other patients (case 20, Table 2; case 37, Table 1), in whom immunosuppression was drastically reduced, died of septicemia and rejection, respectively, but at autopsy it was found that the previously widespread tumors had completely regressed.

If drastic reduction in immunosuppression fails to control the neoplasm, then some form of immunotherapy can be attempted (*9, 11, 14*).

FUTURE PROSPECTS

The development of de novo malignant tumors in chronically immunosuppressed organ transplant recipients has added a new dimension to our understanding of the nature of cancer by emphasizing the role played by immune mechanisms in the control of neoplasia. Fortunately, the incidence of tumors is sufficiently low as not to contraindicate transplantation as a form of therapy. Much remains to be learned about the nature of the tumors. Electron microscope and culture studies are currently in progress to determine the role played by oncogenic viruses. Other investigations are aimed at determining whether patients with particular HL-A specificities may be more prone to the development of cancer as has been found in some forms of lym-

phoma (*8*) or whether certain HL-A mismatches between donor and recipient might lead to malignant change.

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Received 22 May 1972.
Accepted 1 June 1972.