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Immunosuppression and Neoplasia

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This entire session is based upon a fairly simple assumption that the state of the host immune system is an important factor in determining whether or not malignant tumors develop and/or with what aggressiveness the tumors grow and spread after their inception. The objective of the presentation is to report to you some observations that quite definitely support an immunologic hypothesis for the etiology of cancer.

Surveillance and Infection

It is axiomatic that some element of host immunologic crippling must be accepted as the price for success after renal transplantation. As a consequence, there is a definitely increased incidence of the kind of infection you see in Fig. 1. Shown is the brain of a heart recipient who died 4 months after operation. The lesion was caused by the fungus, Aspergillus Fumigatus. The sequence of events leading to this death could be envisioned as one in which the recognition of the kidney as "non-self" was deliberately prevented and that the surveillance of a variety of inimical antigens was coincidently and unfortunately lost.

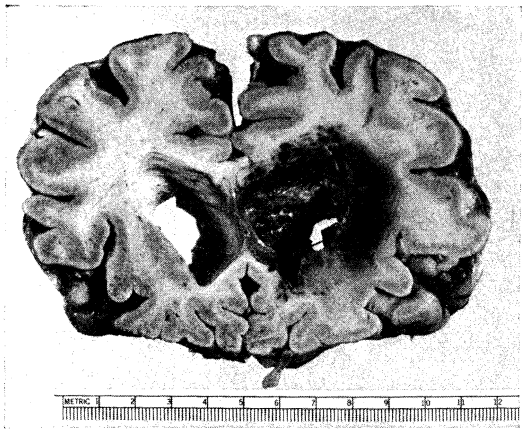

Fig. 1:
Fungus brain abscess in a patient who died more than four months after combined cardiac and renal transplantation.

Surveillance and Malignancy

In the foregoing example, the weakening or loss of surveillance was to fungi or bacteria. It now seems established that the same thing applies with tumors. In 1968 we reported the first examples of this complication from the iatrogenic immunosuppression of renal recipients. At that time an informal tumor registry was established in Denver. Contributions to this registry have been made from virtually every major transplantation center in the world. By last December, neoplasms in 74 renal recipients had been compiled from our own program or else submitted by other groups to this registry. In addtion 1 patient had developed a carcinoma of the stomach following heart transplantation. The incidence of this complication is truly amazing (Table 1).

Table 1:
Malignant Tumors in Renal Homograft Recipients (University of Colorado Series)

Number of patients	352
Number with tumors	16
Incidence	4.5 %
Number of deaths in first 4 months	66
Number of patients at risk	286
Corrected Incidence	5.6 %

It is not possible to give accurate figures based on the world experience 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, as of last December, there were 16 patients who developed malignant tumors in 352 renal homograft recipients with potential followups of 6 months to 9½ years. This incidence of 4.5% 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 fourth postoperative month. The 16 neoplasms developed in the remaining 286 patients for a partially corrected incidence of 5.6% (Table 1). The rate of tumor development in these young patients (3½ to 49 years, average less than 30 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 half dozen skin tumors are excluded, which is sometimes done in compiling such cancer risk statistics, the corrected incidence of malignant disease in our series is still extraordinarily high. Now to turn to the world collection. Forty four of the tumors in the world collection were of epithelial origin (Table 2). The most common

Table 2:
Malignant Tumors in Organ Homograft Recipients (World Experience)

Types of tumors	
I. Epithelial tumors	44
Skin tumors	11
Carcinoma in situ of cervix	8
Carcinoma of lip	8
Lung tumors	4
Hepatoma	2
Miscellaneous carcinomas	11

epithelial tumors were carcinoma *in situ* of the cervix uteri (8 cases); squamous cell carcinoma of the lip (8 cases); and squamous or basal cell skin carcinomas (11 cases). Miscellaneous and generally more serious carcinomas made up the other half.

The 32 mesenchymal tumors were a much more homogenous group in that 28 were varieties of lymphoma including 21 examples of reticulum cell sarcoma or malignant reticulosis. A variety of other sarcomas are listed in Table 3.

Table 3:
Malignant Tumors in Organ Homograft Recipients (World Experience)

Types of tumors	
II. Mesenchymal tumors	32*
Reticulum cell sarcoma	21
Lymphoma	4
Kaposi's sarcoma	3
Leiomyosarcoma	2
Rhabdomyosarcoma	1
Synovial sarcoma	1

* Includes a patient with 2 tumors – a reticulum cell sarcoma of the brain and a *Kaposi's* sarcoma of the skin.

Now we would like to say something about the behavior of these neoplasms. In the world collection, the mesenchymal tumors occurred in a younger average age group than the epithelial lesions, 35 versus 31 years. These mesenchymal tumors occurred relatively early, postoperatively, at an average of 21 months after transplantation compared to the somewhat longer interval of 35 months with the carcinomas.

A number of epithelial tumors were of low grade malignancy and could be cured with standard therapy. Of the 44 patients in this group, more than half are currently alive including almost all those with skin, lip, and uterine cervical carcinomas. In contrast, the epithelial malignancies within the thorax and abdomen tended to be rapidly lethal. Both of our patients with tumors in these locations have died and the same is probably nearly completely true in the world experience.

Similarly, there has been a dismal prognosis with the mesenchymal tumors inasmuch as only three of the 32 patients is still living to our certain knowledge (one patient each in Denver, Galveston, and Israel). All 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 in the non-immunosuppressed patient is uncommon. Amongst the 21 trans-

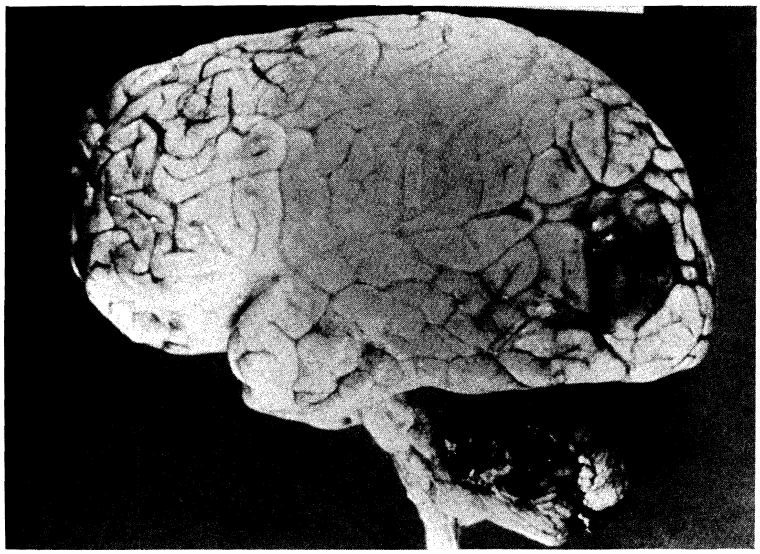

Fig. 2:
Tumor nodules in the left occipital lobe and cerebellum. The flattened gyri reflect increased intracranial pressure caused by reticulum cell sarcoma.

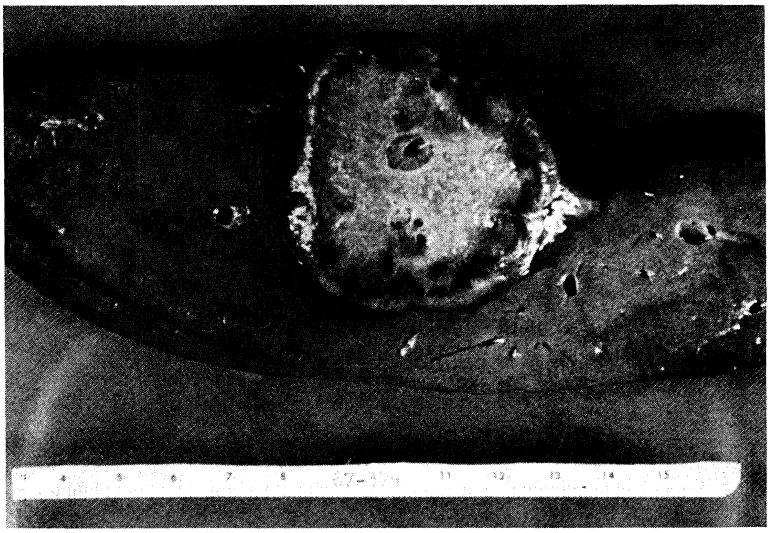

Fig. 3:
Disseminated reticulum cell sarcoma in a renal homograft recipient in our series. This 5 cm nodule was one of several found in the liver. The patient was never treated with ALG.

plant recipients with this diagnosis, there was invasion of the brain in ten and in seven cases the brain was the only organ involved. The brain was also involved in other kinds of lymphomas. Fig. 2 shows the gross appearance of reticulum cell sarcoma in one of our kidney patients who died almost 5½ months after transplantation. The liver has been the second most commonly involved organ in these patients with reticulum cell sarcoma. The patient whose liver is shown in Fig. 3 died of sarcomatosis almost 3 years post-transplantation.

Etiology

We would like now to turn to some specific questions of the etiology of the de novo malignancies in these immunosuppressed recipients, conceding at the outset that the tumors did not predate transplantation and that they were not systematically transplanted along

with the organs from donors suffering from cancer. Were these neoplasias caused by ALG as has sometimes unfortunately been stated?

The facts are summarized in Table 4. So far, a unique contribution of any one of the individual immunosuppressive measures has not been evident. All 75 patients in which the information about treatment is available received azathioprine and prednisone, 30 underwent splenectomy, and 5 had thymectomy. Twentyone received antilymphocyte serum (ALS) or globulin (ALG) but in 2 of these patients there was evidence of the tumor 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.

Table 4:
Malignant Tumors in Organ Homograft Recipients

Immunosuppressive Measures	
Azathioprine	75 cases
Prednisone	75 cases
Antilymphocyte globulin	21 cases*
Splenectomy	30 cases
Thymectomy	5 cases
Thoracic duct fistula	2 cases

* 2 patients received ALG after the appearance of the tumor.

Instead of indicting any one of the individual immunosuppressive agents, the data we have collected indicates simply that malignant disease is a general complication of immunosuppressive treatment. Furthermore, its frequency, in our judgment, is apt to reflect the effectiveness with which treatment has been delivered. A summary statement would then be 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.

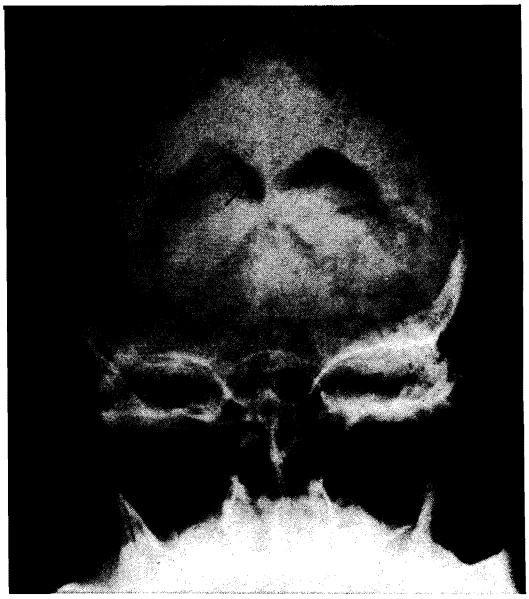

Fig. 4:
Pneumoencephalogram in a 20-year-old woman who had been treated with renal homotransplantation a few months previously. Progressive hemiparesis had developed postoperatively. A mass was found, protruding into the right lateral ventricle. This was biopsied with stereotaxic apparatus and found to be a lymphoma.

Acceptance of the surveillance hypothesis as the *indirect* explantation for post-transplantation neoplasia does not exclude a variety of specific etiologic factors which 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

Before closing, it might be worthwhile to say something about the treatment of these malignancies in transplant patients. The epithelial malignancies of the skin, lip, and uterine cervix were successfully treated by standard surgical techniques without risking the homografts by arbitrary reductions in immunosuppression.

The "deep" malignancies have not been effectively treated with this approach and led or contributed to death with carcinomas of the thoracic and abdominal organs and with mesenchymal tumors. In these latter cases, it may be advisable to lighten or conceivably even stop treatment. The patient shown in Fig. 4 is an example. She had a lymphoma of the basal diencephalon which was treated with local irradiation. In addition, her immunosuppression was drastically reduced despite of which rejection of the renal homograft did not occur. She is in excellent health 5 years after transplantation and $4^1/_2$ years after the diagnosis of the tumor.

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