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The Prospect of Organ Transplantation in Cancer Surgery*

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In terms of potential need, the role of organ replacement might be an important possibility with neoplastic diseases confined to the lung or liver and to a lesser extent to the kidney or heart. As a preliminary statement it should be conceded that the role of transplantation in treating malignancies of these various organs is not yet known. However, there already is some evidence that such therapeutic efforts may not be as effective as might be hoped.

A SELF-DEFEATING ASPECT

From a practical standpoint, the greatest appeal of organ replacement in cancer surgery would be that the boundaries of permissible resection could be considerably expanded. For example, liver tumors which could not be completely excised by standard techniques of subtotal hepatectomy might become removable if the whole organ could be extirpated. The same might apply for rhabdomyosarcomas of the heart or for renal or pulmonary tumors in patients who could not spare the functional loss of one kidney or lung. Of course, the extension by this means of the surgical procedure would not necessarily ensure against metastases.

Indeed there is the possibility that the growth of residual tumor could actually be accelerated as a consequence of the immunosuppressive therapy which is necessary for prevention of homograft rejection. There has been increasing acceptance of the concept that the immunologic system provides a surveillance function[11,28] by which mutant neoplastic cells are identified and either eliminated or restricted in their growth potential. The individuality of such cells which allows their recognition as foreign has been thought to be due to tumor specific antigens.[20,22,25,27,28,30,37,43,44]

Should the surveillance hypothesis be valid, it would follow that neoplastic sequellae of one kind or other would constitute a threat in immunosuppressed patients after clinical transplantation procedures. Several observations that have been made in human recipients of whole organ homografts have tended to confirm this expectation.

CLINICAL AND EXPERIMENTAL OBSERVATIONS ON THE ONCOGENIC PROPERTIES OF IMMUNOSUPPRESSION

Immunosuppression and the Transplantibility of Tumors

A few years ago, three different teams used renal homografts that had been obtained from patients whose deaths were caused by carcinoma of the lung[31,51] or of

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TABLE 1. Clinical Features of De Novo Malignancies in Renal Transplant Recipients*

Number	Patient	Transplant Center	Age	Sex	Date of Transplant	Donor	Date Malignancy Diagnosed	Organs Involved	Splenectomy	Thymectomy	Imuran	Prednisone	ALG	Type of Tumor	Outcome
1	P. H.	Denver	42	M	9/30/63	Unrelated	3/1/66	Ear	Yes	No	Yes	Yes	No	Squamous cell carcinoma	Cured, surgical excision
2	T. C.	Denver	14	M	5/29/67	Mother	11/16/67	Brain	Yes	No	Yes	Yes	Yes	Reticulum cell sarcoma	Died 12/4/67
3	S. D.	Denver	23	M	6/15/65	Father	12/6/67	Thyroid Lung Liver Stomach Prostate Pituitary Skin Psoas muscle	Yes	Yes	Yes	Yes	No	Reticulum cell sarcoma	Died 12/6/67
4	E. C.	Denver	20	F	9/15/67	Father	4/11/68	Brain	Yes	No	Yes	Yes	Yes	Possible plasmacytoma	Alive and well 3/15/69
5	W. A.	Minneapolis†	27	M	Sept. '64	Brother	June '65	Liver Brain Bone marrow	Yes	No	Yes	Yes	No	Lymphosarcoma	Died 11/6/65
6	M. M.	Edinburgh, Scotland‡	26	F	1/17/66	Mother	2/1/68	Mediastinal lymph nodes Pleura	No	No	Yes	Yes	Yes	Reticulum cell sarcoma	Died 2/16/68

*The cases have been reported elsewhere.[38, 45, 47] Since our original reports, about 15 more examples of malignant neoplasia have been reported to us from different centers. These have not been included here because the details are not fully known in many of the cases.
†C. R. Hitchcock: Personal communication. The case has been extensively reviewed since it was first reported to us by Dr. Hitchcock. On retrospective evaluation, many of the consulting pathologists believe the actual diagnosis to be undifferentiated carcinoma, rather than lymphosarcoma.
‡M. F. A. Woodruff: Personal communication.

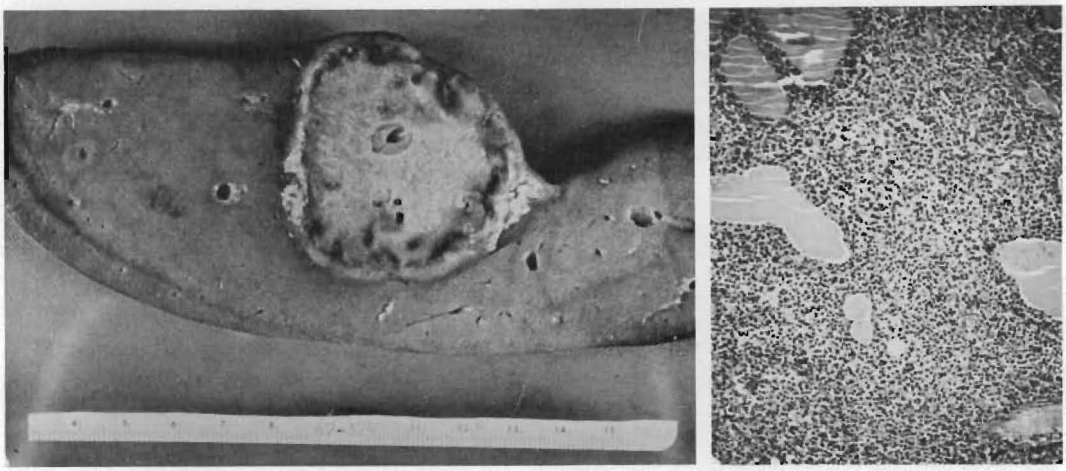


FIG. 1. Reticulum cell sarcoma in a 23-year-old male who died of this complication 2½ years after successful renal homotransplantation. A summary of the clinical and pathologic features are under Case 3, Table 1.
Left—This 5 cm nodule was one of several found in the liver.
Right—Malignant reticulum cells have massively infiltrated the thyroid, separating the follicles widely (× 80).

the pyriform sinus.[33] In each instance, the transplanted kidney was not thought to be involved by tumor at the time of the organ removal. Good homograft function was obtained with the aid of azathioprine and prednisone therapy. Four to 18 months later, neoplastic growth of the same histologic type as that which had been present in the donor was found in the homografts.

In all three cases, the accidentally transplanted tumors had become autonomous by the time the diagnosis was made.[31,33,51] Even though immunosuppression was discontinued, metastases developed in two of the recipients and led to death. The third patient recovered after drug therapy was stopped and radical but probably incomplete excision carried out of the renal homograft and the local neoplastic growth in the transplant wound.[51] It was concluded that the remaining tumor had undergone rejection coincident with recovery from partial immune paralysis.

THE SPONTANEOUS DEVELOPMENT OF NEW TUMORS

Since neoplastic and non-neoplastic tissues are rejected by a common mechanism and are subject to similar rules of histocompatibility,[11,19,21,26,30,36,37,41,42] protection of inadvertently transferred tumor by antirejection therapy in the renal patients was hardly surprising. A much more specific example of the oncogenic effect of immunosuppression has been the development of new malignancies in a number of renal homograft recipients whose kidneys were obtained from healthy donors. This complication was first reported from our institutions[38,45,47] on the basis of four of our own cases and two more from other centers (Table 1). In at least four of the six patients the neoplasia was of cells of mesenchymal origin. Approximately a dozen other published[18,40] or unpublished instances of *de novo* malignancies after renal transplantation have been brought to our attention. About half of these were carcinomas and the rest were lymphomas.

The development of an occasional neoplasm in any patient group of substantial size would not be particularly alarming. However, the incidence of malignancies in our renal recipient pool far exceeds that which would be expected by chance. Before May, 1967, approximately 170 patients were treated with renal homografts. In about 70 percent of the cases, survival of six months or longer was obtained. It was within this group of less than 120 chronic survivors that the four malignancies were detected, giving

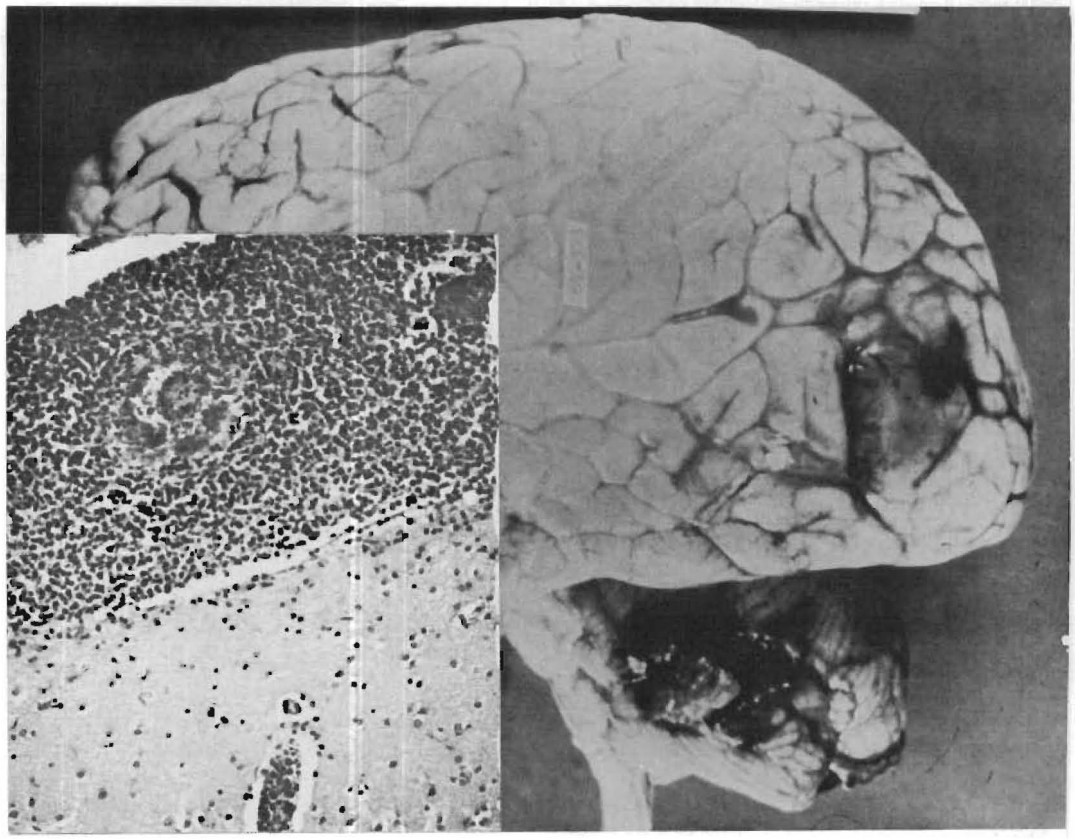


FIG. 2. Case 2 (Table 1), in the Denver series of patients who developed malignancies after renal homotransplantation. Tumor nodules are seen in the left occipital lobe and cerebellum. The flattened gyri reflect increased intracranial pressure caused by the tumor.

Inset—The large, uniform cells with indistinct cytoplasm and round to oval nuclei are characteristic of reticulum cell sarcoma (× 350).

an incidence of between three and four percent in those patients who lived long enough for meaningful observations to be made.

The diagnosis of malignant neoplasia was made postmortem in one of the four patients followed by us. In that case, renal homotransplantation had been carried out more than two and one-half years previously. Death occurred six days after emergency vagotomy and gastrectomy were performed to control massive upper gastrointestinal bleeding. The resected portion of the stomach contained several ulcers in the bases of which were small foci of reticulum cell sarcoma that were strikingly similar histologically to larger deposits found at autopsy in many other organs (Fig. 1).

In the other three patients, the presence of neoplasia was appreciated during life. In one case, the diagnosis of reticulum cell sarcoma was made by craniotomy a few days before the very extensive tumor of the brain (Fig. 2) caused the patient's death almost six and one-half months after renal transplantation. A third patient developed a mass in the basal diencephalon that was biopsied with a stereotaxic instrument and which proved to be a plasmocytoma. The doses of the immunosuppressive agents were drastically reduced and the brain stem was treated with local irradiation. Fortunately the kidney did not reject (Fig. 3) but the tumor apparently underwent involution since she has now been well for more than a year. The fourth patient developed a squamous cell carcinoma of the ear two and one-half

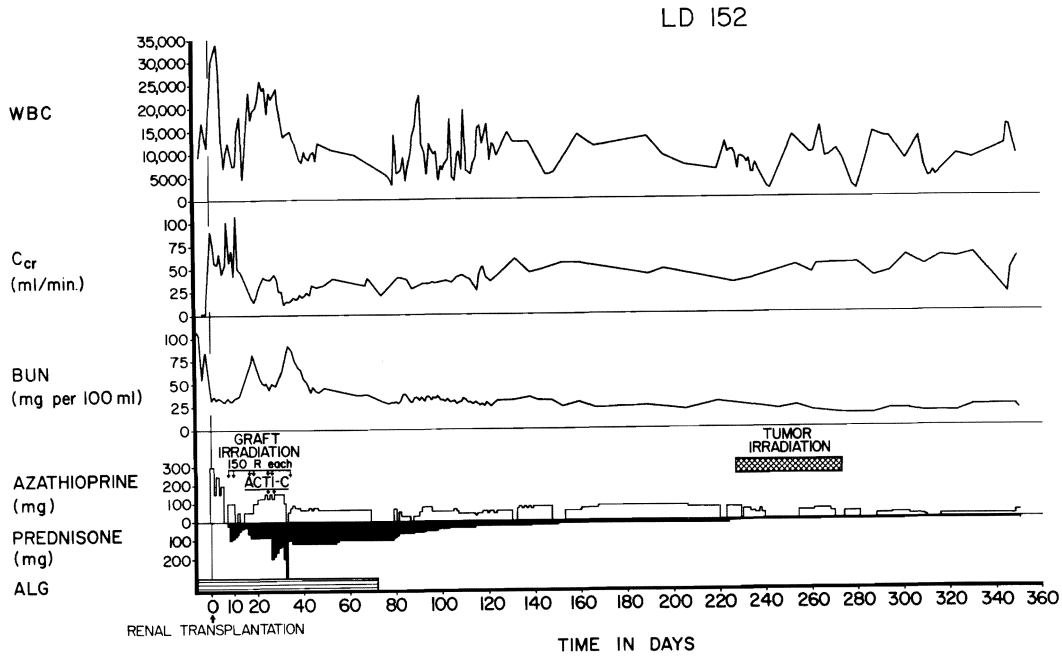


FIG. 3. The course of a patient (Case 4) who developed a plasma-cytoma in the diencephalon more than 7 months after renal homotransplantation from her father. The tumor was irradiated and the doses of both azathioprine and prednisone were drastically reduced. The neurologic deficit was partially reversed and has not progressed in the subsequent year. Renal function has remained good. (By permission of Grune and Stratton, New York, 1969)

years after renal transplantation (Table 1). Radical surgical excision resulted in an apparent cure.

In recipients of renal homografts, there could be many ways in which biologic surveillance might be eroded, beginning with the loss of immunologic reactivity that may accompany the pre-existing uremia.[15,52] In addition, each of the main immunosuppressive agents, azathioprine,[12,13] prednisone,[1,2,8,9,53] and ALG[4,5,6,7,10,16,17,24] has been shown in animals either to: (1) increase a normally low incidence of spontaneous, virus-induced, or chemically-initiated tumors; (2) to facilitate the ease with which malignant cells can be transplanted; or (3) to accelerate metastatic growth. In addition, thymectomy[4,16,23,29,32,35] or splenectomy[3] have a similar but less certain effect.

An additional factor was suggested in our reports[38,45,47] to explain the disproportionate number of mesenchymal tumors in the patients.

The possibility was raised that the chronic stimulation of the host reticuloendothelial system by antigens of the homograft was responsible for the nature of the malignancies. The role of antigenic stimulation in increasing the incidence of experimental lymphomas has been well established.[14,34,39,49]

THE EFFECT ON METASTASES

It was mentioned above that azathioprine,[13] prednisone,[1,2,9,53] ALG[24] and splenectomy[3] all can increase the rapidity of metastases of experimental tumors under the appropriate circumstances. There is no real reason to doubt that the same thing would pertain clinically. The very explosive behavior of recurrent disease in some of our liver transplant recipients was compatible with this concept.

We have had four recipients of orthotopic liver homografts who lived through the immediate effects of this operation and who then became available for long term observation.[46,48] In all four, hepatic cell carcinoma (hepatoma) was the indication for the

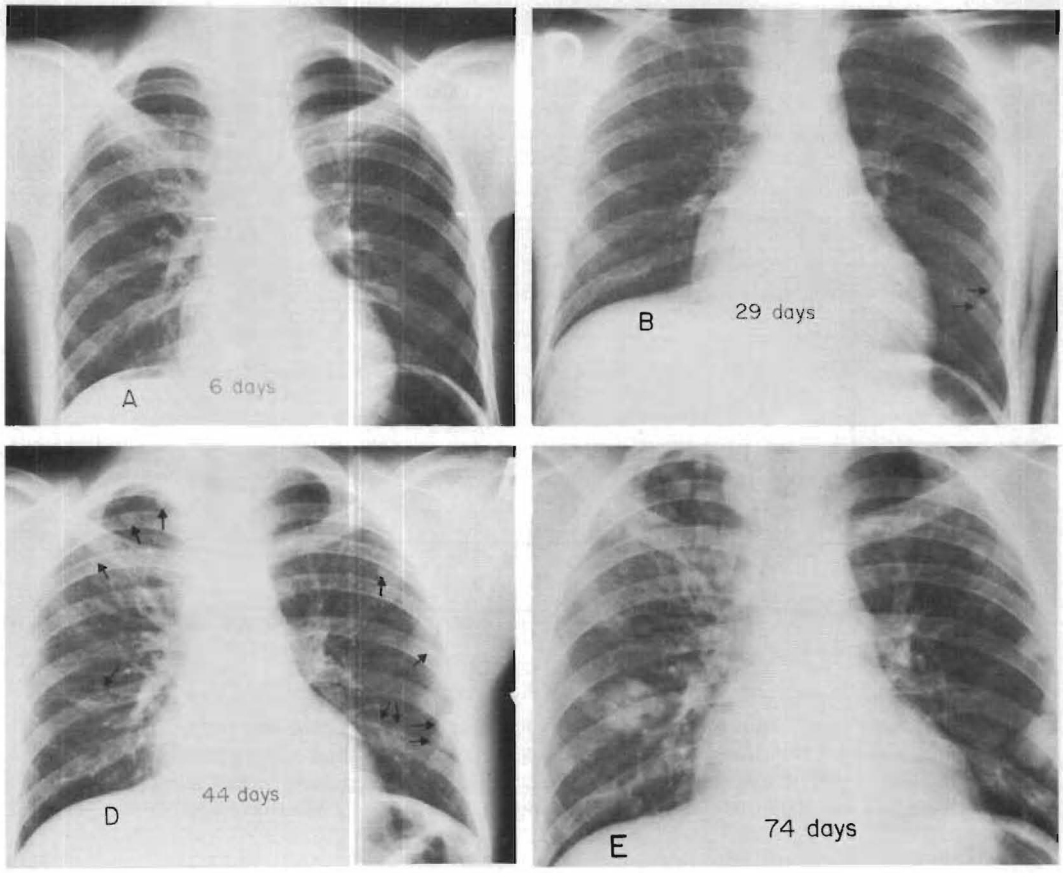


TABLE 2. The Fate of Four Patients Who Received Liver Replacement for the Indication of Hepatoma and Who Lived Long Enough after Operation to Permit Observations About the Behavior of the Malignancy*

Number	Metastases First Detected Days Postop	Location First Metastases	Treatment Metastases	Metastases to Homograft	Organs Ultimately Involved	Cause and Time of Death
1	90	Lungs	Vincristin sulphate, surgical excision of intraabdominal tumors	Yes (autopsy)	Brain, lungs, liver and other abdominal organs	Carcinomatosis 400 days
2	Free of tumor	—	—	—	—	Alive 1 year
3	60	Lungs	—	Yes (open biopsy)	Lungs, liver, skeleton; (?) brain	Alive 11 months
4	29	Lungs	—	Yes (liver scan)	Lungs, liver; (?) other abdominal organs	Alive 5 months

*The followups are to March 15, 1969.

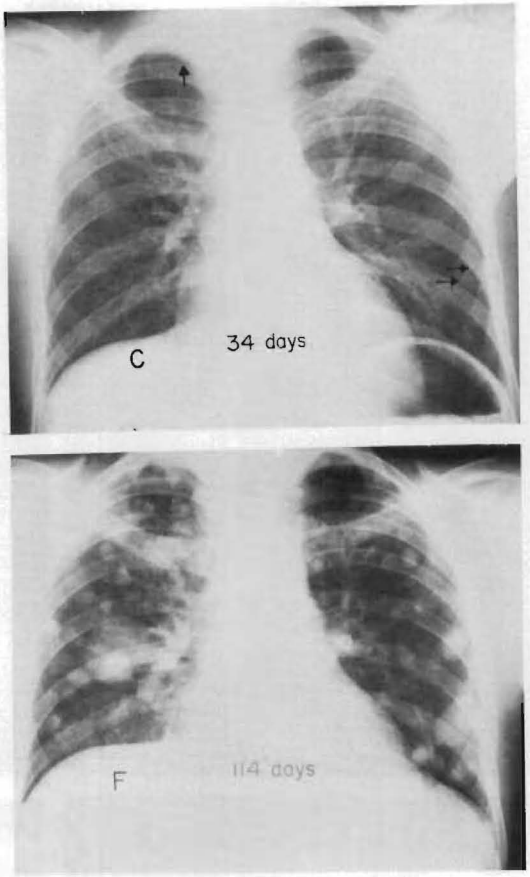


FIG. 4. Extremely rapid development of pulmonary metastases in a 15-year-old boy. The indication for orthotopic liver transplantation was hepatoma.

A—The chest is clear 6 days after operation.

B—Twenty-nine days postoperative. Two metastases are visible in the left lower lung field (arrows).

C—Five days later the tumor deposits previously seen have grown in size (horizontal arrows) and a third focus can now be identified in the right upper lobe (vertical arrow).

D—Forty-four days postoperative. Only 10 days have elapsed since the last examination. Metastatic growths are scattered throughout the lungs (arrows).

E—Seventy-four days postoperative.

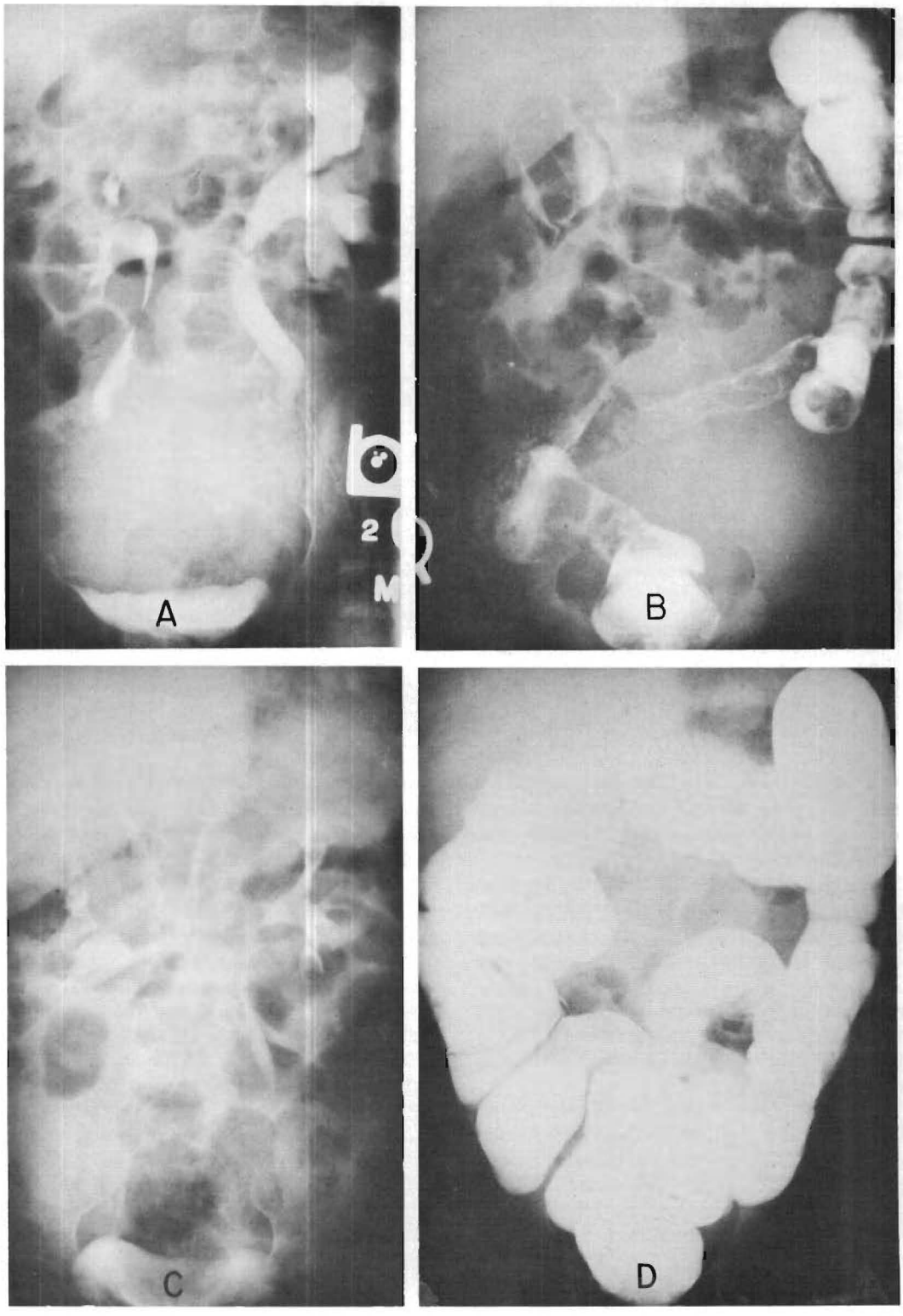
F—Four months postoperative. Transient dyspnea was first noticed several weeks later.

liver replacement. One of the patients is still alive and free of evident metastases after 13 months. Recurrent neoplasm soon became manifest in the other three.

The general features of the cases are summarized in Table 2. In the three patients who developed carcinomatosis, the diagnosis of recurrent malignancy was first made from 29 days to 13 weeks postoperatively on the basis of new abnormalities in the chest x-rays. After the first lesions became visible, these and other deposits enlarged with great rapidity (Fig. 4).

The first chronic survivor after orthotopic hepatic homotransplantation was a 19-month-old child. Three months after operation and a few days after pulmonary metastases were diagnosed, she was found to have a mass in the right upper quadrant between the transverse colon and the liver. Because of its proximity to the cholecystoduodenostomy, the recurrence was excised; it weighed 28 grams. Other intra-abdominal masses soon appeared. The largest of these was in the left lower abdomen and pelvis and eventually caused obstruction of the sigmoid colon and both ureters (Figs. 5-A and 5-B). More than seven months after transplantation, 164 grams of the bulky pelvic tumor were removed piecemeal along with the uterus and one ovary. Small metastatic nodules were present throughout the rest of the abdomen. Temporary palliation was obtained (Figs. 5-C and 5-D). Eventually, a huge metastasis became evident in the same approximate subhepatic location as the first one that had been resected. It appeared to compress the cholecystoduodenostomy and it may have been partly responsible for the jaundice that developed during the last few weeks of life.

Eventually, the child developed Jacksonian seizures, lapsed into coma, and died 400 days after the homotransplantation. At autopsy, large deposits of tumor were found within


A
B
C
D

the calvarium, thorax, and abdominal cavity. It was of special interest that the liver homograft was the site of two moderately large neoplastic nodules (Fig. 6). In this case, the arterial blood supply of the transplanted organ had thrombosed probably a long time before death.[46,48] Consequently, the spread of the tumor was most likely via the portal vein.

The behavior of the metastases in the other 2 patients was similar (Table 2), but the rate of tumor growth was even more rapid. Both of these recipients are alive 5 and 11½ months post-transplantation. However, they are dying of widespread recurrences in the lungs and elsewhere. In both cases, it is known that the homograft is undergoing malignant invasion. A liver biopsy of one of the patients during the tenth postoperative month contained carcinoma. The liver scans of the other shows striking hepatomegaly as well as multiple filling defects.

In the field of kidney transplantation an observation by Williams et al[50] may be relevant to the question of metastatic acceleration. They performed renal homotransplantation in a child 6 months after excision of a Wilm's tumor. Sixteen months after transplantation, at a time when a cure of this kind of neoplasm would usually have been assured under normal conditions, metastases became apparent leading to death within a few weeks.

FIG. 6. The hepatic homograft removed at autopsy more than 13 months after orthotopic liver transplantation in a 19-month-old liver recipient whose indication for operation was hepatoma. The case is the same as that shown in Figure 5. Note the 2 large metastatic nodules in the superior portion of the right lobe of the homografted liver. (By permission of Surg. Gynec. Obstet. **128**:327, 1969).

GENERAL CONCLUSIONS

The clinical trials of organ transplantation as part of the surgical treatment of malignancy have not been large in number. Even in some of these patients who developed metastases, there is no question but that life was prolonged and at least temporarily made more pleasant by the control of the primary neoplastic process. If only for this reason, it would seem premature to abandon the hope of using transplantation procedures in highly selected and otherwise untreatable victims of local cancer. In addition, the feasibility of achieving a more lasting benefit has already been demonstrated in at least one patient, a 16-year-old girl who has no detectable recur-

FIG. 5. Palliation in a child who developed recurrences a few months after orthotopic liver transplantation for hepatoma. A 28 gram metastasis in the right upper quadrant was excised 99 days post-transplantation. Four months later, exploration was again necessary in order to relieve obstruction of the sigmoid colon and ureters.

A—Intravenous pyelogram obtained 219 days after transplantation.

B—Barium enema performed the same day. The rectum is deflected to the right; the sigmoid colon is displaced upward and posteriorly.

C—Shortly after the above examinations, the tumor mass weighing 164 grams was removed from the pelvis. An IVP performed 2 weeks later demonstrated relief of the bilateral ureteral destruction.

D—Barium enema examination 241 days post-transplantation. The colon and rectum appear normal without displacement.

rence more than a year after liver replacement for hepatoma.

If it is elected to attempt transplantation in treating malignancies of various organs, it will be of great importance in future cases to be even more careful than in the past in screening prospective candidates. The experience acquired so far suggests that if the neoplasm is not completely removed, a rapidly progressive downhill course from carcinomatosis can be expected. If total extirpation is not achieved, it is highly likely that the immune suppression can contribute to the rapidity of growth of the secondary deposits.

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