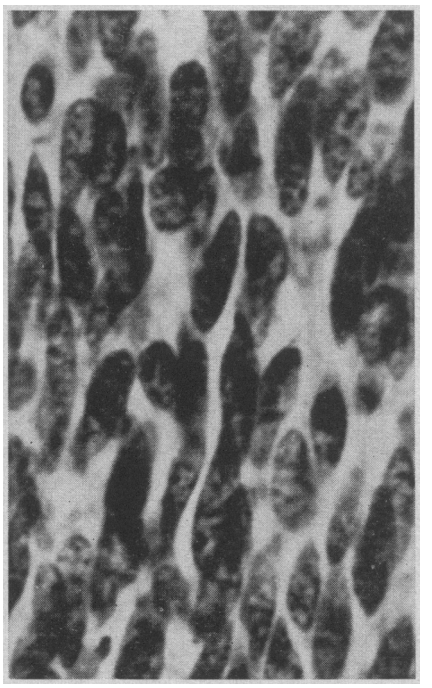
Homotransplantation of a Cadaver Neoplasm and a Renal Homograft

To the Editor:—Success with human renal homografts in identical twins with renal failure and the development of better immunosuppressive techniques have resulted in more widespread application of this experimental mode to the treatment of end-stage kidney disease.[1-3] An increasing number of recipients with kidneys from related and unrelated donors are achieving one-year survival.[1]

The source of donor kidneys has been a major concern because of a logical reluctance to subject healthy, living donors to a procedure with inherent immediate and potential long-range risks. To date, there have been no reports of serious sequelae in a living donor, but their occurrence would seem to be inevitable.

The use of cadaver organs offers an acceptable alternative to living donors and has been attempted in a number of centers.[1] It has become apparent that such usage presents many problems including the medico-legal aspects, organ preservation, investigation of histocompatibility, and best choice of donor. Under the existing circumstances, cadaver kidneys may be exceedingly difficult to obtain if one waits for the "ideal" cadaver donor. The contraindications to the use of cadaver tissues, as suggested by Couch et al,[4] who excluded the use of patients dying of cancer, seem to be very reasonable in the light of our experience with a cadaver homograft in which it appears that malignant neoplasm was transplanted with the kidney.

Report of a Case—A 24-year-old white woman was admitted to the Wilford Hall USAF Hospital on Feb 3, 1964, because of end-stage renal disease, with uremia, anemia, and hypertension. Despite peritoneal dialysis and later intermittent hemodialysis, she failed to do well. A peripheral neuropathy developed with a left foot drop and cardiac failure secondary to hypertension. Because of her deteriorating status she was considered for renal homotransplantation, and a cadaver kidney was sought. The administration of azathioprine (Imuran), 50 mg a day, was begun and 12 days later, on March 31, 1964, the patient received a renal homograft. The donor was a 39-year-old woman who died of a malignancy; her left kidney was removed within 30 minutes of death and placed in the patient's right iliac fossa. Then anastamosis of the renal artery end to end with the hypogastric artery and of the renal vein end to side onto the iliac vein was accomplished. The kidney appeared grossly normal with no apparent tumor. After lymphatic cannulation of a lower extremity, iliac lymph nodes were perfused with thio-tepa 15 mg, and subsequent adenectomy of all visible nodes stained with sky-blue dye was accomplished. Bilateral



1. Microscopic appearance of tumor in recipient's liver (×1,450).

nephrectomy through a retroperitoneal approach was performed at the same time. She received 600 roentgens to the right iliac fossa in divided doses over the first 10 postoperative days. Urine output was 153 ml on the first day, rose to 790 ml by the third day, and was 1,490 ml by the fifth postoperative day; a hemodialysis was necessary following surgery. She was maintained on 50 mg azathioprine daily without interruption and therapy with prednisone, 60 mg daily, was started on the 13th day when it was thought that the first evidence of rejection was present. She gained weight and felt well much of the time, but had persistent edema and mild diastolic hypertension, seemingly related to salt intake and prednisone therapy. Dactinomycin (Cosmegen) was given intermittently to supplement the prednisone in controlling rejection. The patient reached her peak of well-being at approximately 180 days after surgery and remained quite well until the 210th day, when she began to complain of muscle aches, fatigue, and vague epigastric pain not responsive to antacids. Serum alkaline phosphatase value was found to be 23 units (King-Armstrong, normal up to 13 units), and she was admitted for evaluation. On admission, her blood pressure was 120/90 mm Hg, and tenderness was noted in the right upper quadrant of the abdomen with a vague mass in that area. She was somewhat Cushingoid with a full face, slight buffalo hump, and acne-form eruption on her face and thorax. Considerable peripheral and presacral edema was present. Admission blood chemistry studies revealed the following values: blood urea nitrogen, 64 mg/100 ml; creatinine, 2.6 mg/100 ml; serum alkaline phosphatase, 31 units (King-Armstrong); serum glutamic oxaloacetic transaminase, 225 units; bilirubin, 3.5 mg/100 ml, with direct fraction, 1.9 mg/100 ml; thymol turbidity, 1.8 units; zinc flocculation, less than 1 unit; total protein, 5.6 gm/100 ml; and serum albumin, 3.5 gm/100 ml. The hematocrit reading was 43%; hemoglobin level, 14 gm/100 ml; and the 24-hour urine protein, 70 mg. Chest x-ray films were normal. It was believed that the clinical picture was compatible with a cholangiolitic hepatitis, similar to that associated with azathioprine in several other patients.[5] Therefore, the drug was discontinued and cyclophosphamide (Cytoxan), 100 mg a day, was started. A liver biopsy was obtained, and it contained undifferentiated neoplasm; the patient died two days later after a seizure.

At autopsy, the homograft was present in the right iliac fossa in an extraperitoneal position, where it was surrounded by dense fibrous tissue. The anastamoses of the vessels and ureter were intact. The kidney, which weighed 162 gm, was light tan, soft, and easily fragmented. There were 10 tumor nodules in the cortex, varying from 0.2 to 1.6 cm in diameter. Focal fibrosis was present in the kidney, but almost no cellular infiltrate. Glomeruli in regions not involved with scar were well-preserved. The liver weighed 3,600 gm and contained many nodules of tumor which varied in diameter from 0.1 to 3.5 cm. No primary site of tumor was found after thorough examination of the cranial, thoracic, and abdominal cavities. The pharynx and larynx were not abnormal. The microscopic appearance was that of a poorly differentiated tumor composed of spindle-shaped cells which were slightly pleomorphic

and tended to be arranged in a fasciculated pattern (Fig 1). The appearance of the tumor was indistinguishable from that in the donor (vide infra). A microscopic focus of tumor was present in a lymph node in the renal pelvis and lymph channels about the renal vessels. No tumor was present in the other lymph nodes or in lymphatic channels in other organs; in fact, very few nodes were found.

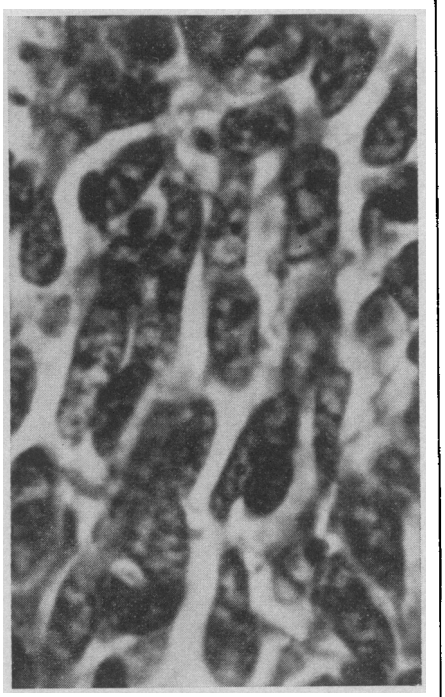
Report on Donor.—The donor was a 39-year-old white woman first admitted to Wilford Hall USAF Hospital on March 5, 1962, because of pain in her throat of six-months' duration. The patient had smoked one package of cigarettes a day for many years, and her father had died at the age of 49 years with carcinoma of the larynx. A large fungating mass involved the left pyriform sinus and arytenoid region and, histologically, it was a well-differentiated squamous-cell carcinoma. Arterial perfusion with methotrexate resulted in a decrease to approximately one half of the size before therapy. On March 26, 1962, a partial laryngectomy and a radical neck dissection on the left were performed. The histologic appearance of the metastatic tumor present in lymph nodes in the middle and upper thirds of the specimen from the neck dissection was similar to that observed in the original biopsy. The tumor consisted of large cells arranged in sheets with abundant eosinophilic cytoplasm, large nuclei, and prominent nucleoli. Intercellular bridges and an abundant amount of keratin were present.

In July 1962 a nodule appeared in the subcutaneous tissue in the region of the previous radical neck dissection. The histologic appearance of the tumor in the nodule resembled that of the previous resection but was less well-differentiated. The cells in this specimen were large with hyperchromatic nuclei and prominent nuceoli but tended to be arranged in less well-defined sheets without a "pavement-like" pattern or intercellular bridges. Only an occasional dyskeratotic cell was present.

Between July 25, 1962, and Sept 5, 1962, 29 treatments of fexternal radiation therapy (5,000 r skin dose; 250 kv) were administered. Except for some transient laryngeal edema and the necessity for small feedings, the patient did well until June 1963 when symptoms of indigestion developed. In January 1964 the liver was palpable 3 cm below the right costal margin, and tenderness in the left costal vertebral angle of the back was present. She was admitted for the last time on Feb 25, 1964, with intestinal obstruction, which was relieved conservatively. Biopsies of the upper portion of the esophagus and liver were interpreted as undifferentiated carcinoma. Difficulty with swallowing increased; she had an ingravescent course and died on March 31, 1964.

At autopsy the larynx was small, but no tumor was found either grossly or on microscopic examination. Light gray tumor surrounded the trachea, and partially occluded the lumen of the esophagus, but the mucosa of the esophagus was intact. The weight of the liver was 7,000 gm and was replaced almost entirely by nodules of light gray firm tumor, some of which were necrotic. Tumor was present in lymph nodes in the paratracheal, paraesophageal, and porta hepatis regions.

The tumor was composed of closely packed, hyperchromic, spindle-shaped cells which were slightly pleomorphic and tended to be arranged in a fasciculated pattern. The cells contained scant and indefinite cytoplasm, formed little reticulum, and had no keratin (Fig 2). Mitoses were numerous. The



2. Donor's tumor at autopsy. A poorly differentiated tumor composed of spindle-shaped cells with scant cytoplasm (×1,450).

massive involvement of the bone marrow was not detected grossly. Small clumps of tumor cells were present in the lymphatic channels and blood vessels of the lungs, spleen, and a few sites in the right kidney. The left kidney was used as the transplant. Slight arteriolar nephrosclerosis was present in the right kidney but morphologically, most of the glomeruli were within normal limits. No site, other than the larynx, was found to be a primary source of tumor.

Comment.—This young woman had chronic glomerulonephritis with uremia, hypertension, and anemia. Despite intermittent hemodialysis, she continued to decompensate with cardiac failure and development of a peripheral neuropathy. Because of her tenuous status, time became an important factor once it was decided to attempt a transplant, and the kidney of a woman who died of a malignancy was used. The patient made a striking recovery after kidney transplantation, and achieved a clinical state of well-being with cardiac recompensation, rehabilitation of the peripheral neuropathy, and hematologic improvement. She did well with adequate renal function until it became apparent eight months postoperatively that other complications were present. Carcinoma diagnosed at that time by a liver biopsy caused her demise.

We were unable to find evidence of tumor in any other organ or tissue to indicate that this was a tumor primary to our patient. The presence of tumor only in the transplanted kidney and in the liver as well as the histologic similarity of the tumor to that of the donor suggest that the tumor was transplanted with the kidney.

Patients with uremia have also been shown to have an altered immunologic response, as manifested by prolonged survival of homografted skins[5] and by suppressed cutaneous hypersensitivity.[6] In renal homotransplantation these uremic patients are placed on immunosuppressive drugs deliberately, further compromising the altered host resistance. The presence of adequate renal function and the histologic characteristics of the homografted cadaver kidney at autopsy eight months after transplantation testify to the adequacy of immunosuppression in our patient.

The striking histologic difference in the donor tumor at the time of autopsy compared to the original specimen suggests that radiation and chemotherapy may have favored the progressive change from a well-differentiated to an undifferentiated cancer, enhancing further its capacity to grow under the conditions imposed in the recipient. The combination of all the factors cited explains adequately the propagation of transplanted tumor cells in our patient.

Renal homotransplantation must be considered an investigative endeavor with commitment of moribund patients to a variety of unique experimental conditions. It is quite clear that innumerable hazards are to be encountered and equally clear

that the ultimate consequences remain to be defined. More observations will be required to enable us to know whether such a case as the one described here is an accident of nature or whether it will be encountered more regularly, interdicting completely the use of cadaver tissues from patients remotely suspected of harboring neoplasm or infection.

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1. Murray, J.E.; Gleason, R.; and Bartholomay, A.: Second Report of Registry in Human Kidney Transplantation, *Transplantation* 2:660-664 (Sept) 1964.

2. Starzl, T.E., et al: Renal Homotransplantation Late Function and Complications, *Ann Intern Med* 61:470-497 (Sept) 1964.

3. Goldman, R., et el: Sixteen Cases of Renal Homotransplantation, *Arch Intern Med* 114:601-609 (Nov) 1964.

4. Couch, N.P., et al: Use of Cadaver Tissues in Transplantation, *New Eng J Med* 271:691-695 (Oct 1) 1964.

5. Dammin, G.J.; Couch, N.P.; and Murray, J.E.: Prolonged Survival of Skin Homografts in Uremic Patients, *Ann NY Acad Sci* 64:967-976 (March) 1957.

6. Wilson, W.E.C.; Kirkpatrick, C.H.; and Talmage, D.W.: Immunologic Studies in Human Organ Transplantation: III. Relationship of Delayed Cutaneous Hypersensitivity to Onset of Attempted Kidney Allograft Rejection, *J Clin Invest* 43:1881-1891 (Oct) 1964.

Generic and Trade Names of Drugs

Azathioprine—*Imuran.*
Dactinomycin—*Cosmegen.*
Cyclophosphamide—*Cytoxan.*
Thio-tepa—*Thio-Tepa.*
Prednisone—*DeHasone, Deltra, Meticorten, Paracort.*

No Comment Department

"Air fluid levels seen on chest roentgenograms may be in the pleural cavity, esophagus, stomach, or lung. The pulmonary differential diagnoses include lung abscess, excavating carcinoma, obstructive pneumonia, and, rarely, tuberculosis."

—from Joannides, M., Jr., MD: Chronic Obstructive Emphysema Position, *JAMA* 192:365-367 (May 3) 1965, p 365.

"Air-fluid levels seen on chest roentgenograms may be in the pleural cavity, esophagus, stomach, or the lung. The pulmonary causes include lung abscess, excavating carcinoma, obstructive pneumonia and, rarely, tuberculosis."

—from Sanford, H.S., MD, and Green, R.A., MD: Air-fluid levels in Emphysematous Bullae, *Dis Chest* 43:193-199 (Feb) 1963.

Program to Conquer Heart Disease

To the Editor:—Reference is made to the AMA staff report titled "A National Program to Conquer Heart Disease, Cancer, and Stroke" (*JAMA* 192:299-301 [April 26] 1965). In my view, the author of the report did a disservice to the American Heart Association and to the public record by inaccurately reporting the testimony given by the Association before Senator Hill's subcommittee. I enclose a copy of the testimony for your information.

The staff report says that the American Heart Association, along with certain other organizations, ". . . accepted the Commission's assumptions and recommendations without comment, confining their remarks to which agency within HEW should administer the program." Actually, only one portion of our testimony had to do with "which agency . . . should administer the program."

Our first point, and the one on which we felt most strongly, was set out as follows:

> If the proposal to establish regional medical complexes is enacted, large numbers of highly trained people—physicians and non physicians; medical and paramedical—will be needed to staff them. At present, these people are not available in sufficient numbers. . . .
>
> We then strongly urged that the most immediate effect of the bill, if enacted, should be to enable existing training centers to expand and upgrade their clinical and paramedical training programs.
>
> To establish such a system (our testimony continued) without first seeing to the expansion of clinical training facilities might, in effect, do more harm than good. It would dilute our existing supply of trained clinical personnel and might well lower, instead of elevating, existing standards of diagnosis and treatment.
>
> The necessity for emphasis on clinical training programs was, in essence, the focus of our comments. But we also indicated that, instead of attempting in one stroke to blanket the nation with Regional Medical Complexes, attention should be given to a series of planning grants and possibly to a few pilot projects. Other recommendations had to do with the proposed basis for use of matching funds, the structure of an Advisory Council for Regional Complexes, and rewording of the proposed bill at several points. And we are, as the author of your report intimated, of the opinion that Regional Medical Complexes should be administered within the National Institutes of Health.
>
> There were other points as well, but the main one had to do with clinical training. It is thus grossly incorrect to say that we confined our comments to an administrative matter, and we are at a loss to understand how the error arose.
>
> I shall be most grateful if you will call the error in your staff report to your readers' attention and will be glad to clarify or expand on our testimony at any time.

CARLETON B. CHAPMAN, MD
President, American Heart Association
Dallas

Both Dr. Chapman, on behalf of the American Heart Association, Inc, and Mr. Kenneth Williamson, of the American Hospital Association, indicated that shortages of physicians and ancillary health personnel make the proposed legislation somewhat unrealistic.

Unfortunately, no transcript of Senator Hill's hearings was available when the staff report was prepared. This transcript suggests that most of those testifying urged passage of S. 596. Supporting statements ranged from:

> You can readily see we are ideally located geographically for a research center.

to the contradictory remarks by Dr. B. F. Madison, of the American Public Health Association, Inc.:

> We applaud the recommended crash approach to these major causes of death, . . . We have some misgivings about the mechanism of application of services to communities as proposed in the legislation. . . .

Even more revealing is the recently issued second volume of the report by the President's Commission. The source papers and subcommittee recommendations frequently fail to support volume one's emotional arguments for drastic changes in the nation's health services and facilities.

What does emerge from all three documents is the compelling need for physicians, sociologists, economists, and political scientists to debate the merit of these proposals and their implications. If the American people are told all the facts, they can be trusted to make this vital decision instead of having the dictates of a shadowy power elite imposed upon them.—ED.