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A Successful Transplant of Embryonic Adrenal Tissue in a Patient with Addison's Disease

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Well documented reports of the successful transplantation of human adrenal cortical tissue cannot be found in the literature. In 1951 we achieved the successful transplantation of human embryonic adrenal gland (cortical tissue) in a patient with symptomatic adrenal insufficiency (Addison's disease), apparently the first instance of histologically documented successful homografting of human adrenal cortex.

Because of its historical pertinence, the authors, many years later, herein report on this case, which appeared in the senior author's medical thesis. The report must be viewed in the context of the existing clinical knowledge and technology available 40 years ago.

The transplantation of endocrine tissues has met with limited success in human beings. No recent reports of successful fetal human adrenal cortical transplants have been identified in carefully conducted MEDLars/MEDLINE searches. Isolated reports of apparently successful human homotransplants [1–7] have appeared in earlier literature, as reviewed by Brooks in 1962 [8]. The transplantation of cortical adrenal tissue, however, has been achieved successfully in the experimental animal.

The successful transplantation of the human embryonic adrenal gland was accomplished at the Yale–New Haven Medical Center in 1951 and was reported initially as part of the senior author's thesis, presented to the Yale University School of Medicine in candidacy for the degree of Doctor of Medicine [9], a thesis which received the Borden Undergraduate Award in Medicine from the Yale faculty in 1952. In the 1962 monograph by Brooks [8] there appears reference to a personal communication from Greene relating to the patient whose experience is now herein reported, many years later. Based upon the pioneer work of Yale Professor Harry S.N. Greene on the transplantation of neoplastic and embryonic endocrine tissue [10–16], experimental work on the transplantation of fetal endocrine tissues in the laboratory animal was initiated under his direction in the academic year 1949–1950; the senior author continued this work during the ensuing years as a medical student and then as a surgical resident at Yale in the period 1950–1957.

Experiments were designed by the authors to determine the capacity of transplanted embryonic tissues to survive, develop, and function permanently in homologous recipients [9]. This capacity was demonstrated to be so for fetal thyroid and adrenal glands, and, for temporary periods of time, for other tissues transplanted into the anterior chamber of the eye of rats and guinea pigs, according to the technique utilized by Greene [9]. Quite normal thyroid and adrenal morphology was

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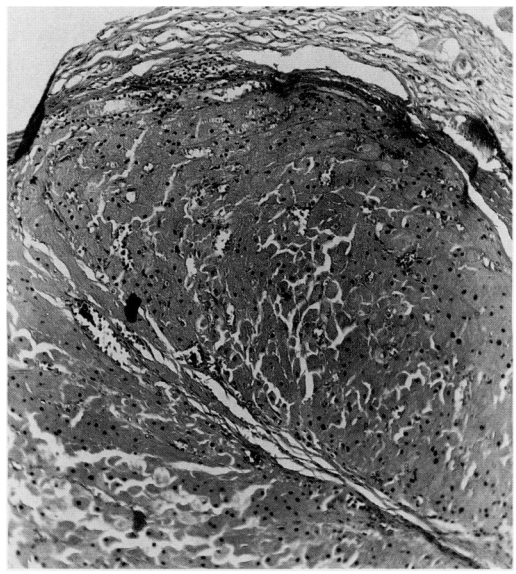

FIG. 1. Histologic appearance of an intraocular homologous transplant of embryonic adrenal gland in an adrenalectomized rat; the animal survived normally, even after being submitted to the stress of electroshock for 16 consecutive days. Note degree of normal cellular differentiation and organization into the normal layers of the mature adrenal cortex.

apparent after a short period of "adaptation," indicating, on the one hand, a remarkable capacity for autonomous growth of the transplanted fetal tissue, and, on the other, a favorable receptor site, i.e., the anterior chamber of the eye [17].

Figures 1 and 2 illustrate the histologic appearance of intraocular transplants of fetal guinea pig thyroid and adrenal glands at four and at eight months respectively. The transplanted thyroid tissue matured and exhibited essentially normal radioiodine uptake, as shown in Fig. 3. In one instance the transplanted block included both

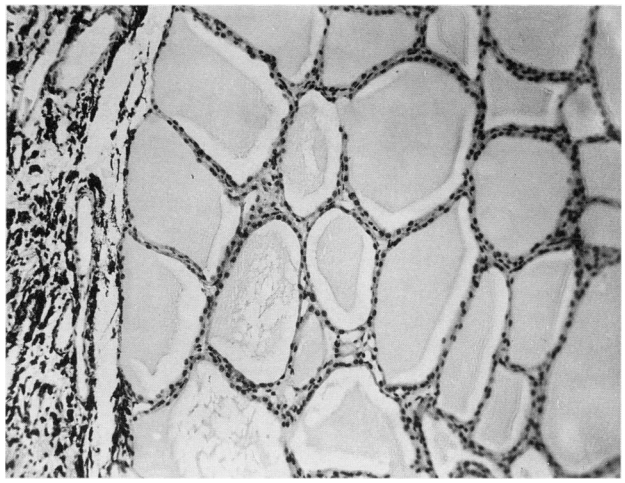

FIG. 2. Histologic appearance of an intraocular homologous transplant of embryonic thyroid gland in a thyroidectomized guinea pig, eight months post-transplantation.

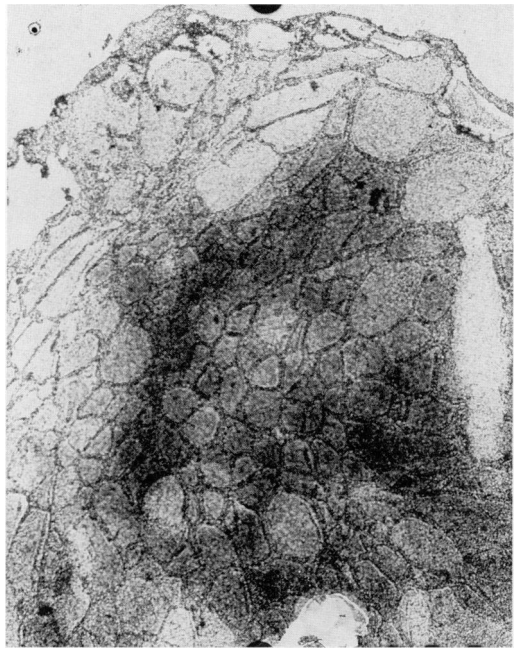

FIG. 3. Mounted 131-I radioautograph of a 5½ months old intraocular homologous transplant of embryonic thyroid in a thyroidectomized guinea pig.

thyroid and parathyroid, with successful engrafting of parathyroid tissue, as can be seen in Fig. 4.

As a result of these successful experiments, several patients being followed at the Yale–New Haven Hospital Clinic were identified as suitable for transplantation of homologous embryonic tissue. Between 1951 and 1956 a series of nine patients was jointly studied by the Departments of Medicine and Surgery, and upon consensus the patients underwent 11 procedures of transplantation of embryonic tissues by the simple technique of implantation of tissue fragments in the substance of the rectus abdominis muscle under local anesthesia. One patient received two transplants of thyroid and parathyroid with a seven-month interval between implants, and one patient, the subject of this report, received two adrenal transplants from two different donors. Table 1 summarizes the characteristics of the recipients and of the tissues implanted.

With the collaboration and support of the late Professors John P. Peters, Louis S. Welt, William T. Salter and Eugene E. Cliffton, the senior author participated either directly as operating surgeon, or as assistant in the performance of each of the transplants. The patients were followed by the Departments of Medicine and Surgery, and the status of their endocrine function was evaluated by the methods available at that time. None of these patients was subjected to immunosuppressive therapy, which was not available then. Of the six fetal thyroid-parathyroid transplants, one pituitary transplant, and four adrenal transplants, only one of the adrenal transplants grew and matured to become a histologically normal gland. Figure 5 shows the appearance of the transplant at the time of examination, eight months post-transplantation. During the time elapsed between transplantation and removal

FIG. 4. Homologous intraocular transplant of embryonic thyroid and parathyroid in a thyroidectomized guinea pig, two months post-transplantation.

of the graft for histological examination, the patient experienced marked clinical improvement in the symptoms of his Addison's disease, according to Dr. Welt, his personal physician.

CASE HISTORY

A 30 year old male (D.W. B37944) with a well-documented history of symptomatic Addison's disease had been followed by the Metabolism Service, Department of

TABLE 1
Clinical Material in the 1952–1956 Yale Series of Human Embryonic Endocrine Transplants

Identification	Diagnosis	Tissue Transplanted
R.N., A91724	Addison's disease	Adrenal, 14-week fetus, March 22, 1951
D.W., B37944	Addison's disease	Adrenal, two-month fetus, and adrenal, 5.5 cm embryo, April 4, 1952
M.M., C14244	Hypothyroidism	Thyroid, 14 cm fetus, January 24, 1952
C.D., 378236	Addison's disease	Adrenal, 13.5 cm fetus, October 6, 1952
R.J., B19319	Hypopituitarism	Pituitary, 8 cm fetus, November 13, 1952
E.K., A12504	Hypoparathyroid	Pre-tracheal block, three-month fetus, May 27, 1953
J.A., A21448	Hypothyroid and hypoparathyroid	Thyroid and parathyroids, premature baby, January 2, 1954, and thyroid and parathyroid, premature baby, August 5, 1954
F.A., 2407	Hypoparathyroid	Pre-tracheal block, three-month fetus, January 16, 1954
A.A., 91369	Hypoparathyroid	Pre-tracheal block, December 17, 1956

Of the 11 transplants performed on nine patients, only one patient, D.W. (B37944), who was the recipient of two simultaneous transplants from two different donors, exhibited growth of normally appearing endocrine tissue.

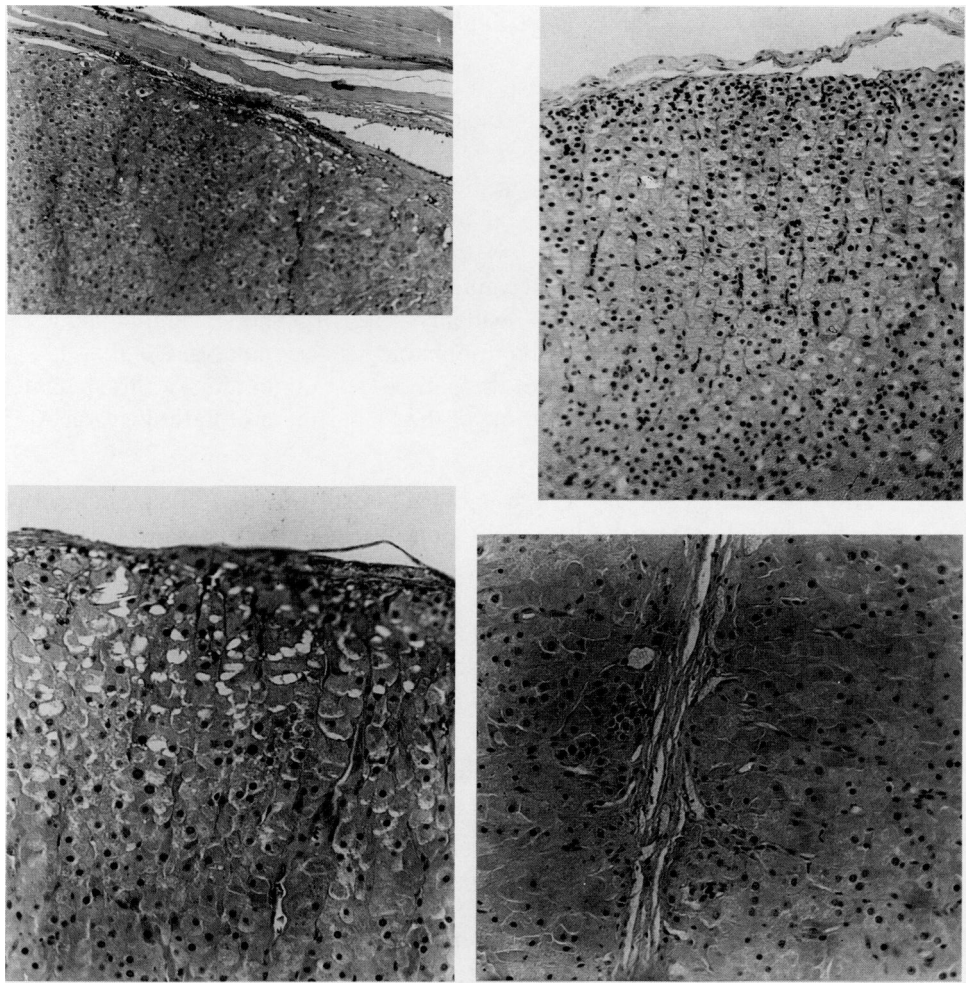

FIG. 5. Different zones of a homologous transplant of embryonic adrenal tissue in a man with Addison's disease. The tissue was implanted in the substance of the rectus abdominis muscle. Muscle fibers can be seen in the figure at the upper left, eight months post-transplantation.

Internal Medicine, since 1943. Subcutaneous implantation of desoxycorticosterone acetate (DOCA) pellets was periodically done, and the patient required high salt intake, the established therapeutic regimen at the time. The patient was considered an excellent candidate for transplantation, and simultaneous grafting of fragments of the adrenal glands from two different fetuses that became available simultaneously was performed on July 28, 1951. A member of the surgical faculty, Dr. E.E. Cliffton, acted as operating surgeon, and the senior author (JFP), a medical student at the time, acted as assistant. The first donor human embryo was 8 cm long and had been kept in refrigeration for 12 hours, the product of a spontaneous abortion that occurred at a nearby hospital. The second donor human embryo became available unexpectedly as the grafting procedure was being terminated, the product of a therapeutic abortion performed in an adjoining operating room. It measured 5.5 cm. in length. The recipient's incision which had already been closed was reopened and

the second fetal adrenal gland was implanted in the substance of the rectus abdominis muscle.

The only significant finding in the post-operative follow-up was the rise of the 24-hour urinary excretion of 17-ketosteroids, from a pre-transplantation level of 10.4 mg, to a level of 15.5 mg on September 9, 1951, two months after transplantation. The excretion returned to 12.0 mg on January 21, 1952. On April 4, 1952, the transplantation site was explored. A viable mass of tissue, measuring 2.0 cm in its longest diameter, was found just below the rectus sheath, with a good vascular pedicle entering through one pole and connecting to the muscle mass. The tissue was interpreted by the surgeon (a surgical resident) "as a lymph node," and he made the unfortunate decision to remove it *in toto* for histological examination.

The report (S.P. No. Special 669) of the pathologic examination of this specimen issued by the late Dr. Wilhelm S. Albrink, of the Department of Pathology, on April 4, 1952, read as follows:

> This specimen consists of a roughly elliptical mass of tissue measuring approximately 1.5 cms. All excepting inferior margin appears to be covered with a smooth and glistening capsule. At the one pole of the specimen there is a well developed pedicle of blood vessels. Immediately below the main tissue mass is some irregular tissue which appears to be striated muscle. The main tissue mass has the color and consistency similar to that of a lymph node. Representative sections are sent for histological examination.
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> *Microscopic*: All Sections on Special Section 669 are essentially the same. These show at the inferior border a small amount of striated muscle which has no foreign body reaction or no lymphocytes. The muscle abounds on one margin of the capsule of the main tissue mass. This tissue mass appears to be well encapsulated and consists of large numbers of cells with pale eosinophilic cytoplasm, some of which is foamy. There are no foreign body reactions, no lymphocytes, or other untoward phenomena. Main tissue mass is well vascularized. This main tissue has the appearance of adrenal cortex. There is, on this section received, no evidence of any medullary tissue whatsoever.
>
> *Diagnosis*: Well organized group of cells consistent with adrenal cortex.

Following removal of the graft the patient suffered return of his symptomatology and became DOCA-dependent again, as he had been before transplantation. A DOCA pellet was subcutaneously implanted on May 1, 1953. At that time exploration of the transplantation site was performed and biopsies taken. Only old areas of scar tissue and silk sutures were found, but nowhere was any residual viable adrenal tissue encountered, over one year after removal of the apparently functioning and histologically normal graft.

Dr. R. Andrade of the Pathology Department of the Centro Médico de los Andes, Fundación Santa Fe de Bogotá (Colombia), has reviewed the histology sections of 1952. He concurs with Dr. Albrink's original report, adding in his own report that the cells resemble an infantile adrenal cortex; the so-called fetal zone is present and constitutes 90 percent of the glandular tissue; towards the periphery there appears a population of smaller cells, corresponding to the so-called provisional zone or adult-type zone.

COMMENT

The subject of human homografts of endocrine tissues in the light of successful animal homografts was evaluated by J.R. Brooks in a monograph published in 1962 [8]. In reviewing the status of adrenal transplantation, he stated that "Homografts have apparently been transiently successful only in certain animals, particularly mice and rats and to a certain degree guinea pigs and rabbits. . . . No proven successful human homografts of cortical tissue have been obtained".

Our work of the 1940s and 1950s, conducted in Greene's laboratory at Yale's Department of Pathology, was based on Greene's postulates regarding the inherent "autonomy" of embryonic tissues; when grafting of embryonic tissues is performed, the supporting stroma provides such tissue with the environment to grow and develop into morphologically, and in some instances, functioning cells [9]. The possibility of creating a favorable recipient organism by the inbreeding of the laboratory animals (guinea pigs, rats, and some rabbits were utilized) was considered, but this theory seems to be negated by the failure observed when transplanting *adult* homologous endocrine tissues utilizing the same technique and in the same animals. The lack of methods for histocompatibility studies at the time precluded specific testing before transplantation. The only proof of success of the homografting of a human adrenal in our patient with Addison's disease resides in the histological demonstration of apparently viable adrenal cortical tissue in the substance of the recipient's rectus abdominis muscle, just over eight months later, when the patient was doing well without the support therapy that had previously been required. Adequate methods of evaluating function were not available, but based on the results of the existing ones, and the clinical course, the late Dr. L.G. Welt believed that the graft was functional. And the matter must rest there.

CONCLUSION

The case of an apparently successful transplantation of human fetal adrenal cortical tissue in a patient with well-known Addison's disease, performed in 1951, is reported here. We believe this is the first instance of histologically documented successful homografting of human adrenal cortical tissue.

REFERENCES

1. Eiseman B, Hughes R, Summers W, Travlor F: Human adrenal cortical autografts into the portal circulation. Ann Surg 142:961–966, 1955
2. Beer E, Oppenheimer BS: Transplantation of the adrenal cortex for Addison's disease. Ann Surg 100:689–703, 1934
3. Katz F, Meinzer F: Successful grafting of adrenal gland in a case of Addison's disease. Brit Med J 1:617–618, 1941
4. Goldzieher MA, Barishaw SB: Transplantation of adrenal tissue in Addison's disease. Endocrinol 21:394–400, 1937
5. Thiersch JB: Intrasternal bone marrow grafts in foetal organs in man: a new method of adrenal cortical grafts in the treatment of Addison's disease. Med J Austral 1:249–251, 1943
6. Woodruff MFA: The transplantation of homologous tissue and its surgical applications. Ann Roy Col Surg (England) 11:173–194, 1952
7. Mainzer F: Siebenjähriges funktionelles Überleben einer überpflanzten Neberniere bei Addisonscher Krankheit. München Med Wscr 101:2310–2311, 1959
8. Brooks JR: Endocrine Tissue Transplantation. Springfield, IL, Charles C Thomas Publisher, 1962
9. Patiño JF: The Transplantation of Embryonic Endocrine Tissues. A Thesis, presented to the Yale

University School of Medicine in candidacy for the degree of Doctor of Medicine. New Haven, CT 1952
10. Greene HSN: Heterologous transplantation of embryonic mammalian tissues. Cancer Res 3:809–822, 1943
11. Greene HSN: Biological differentiation of benign and malignant growth. Bull N Y Acad Med 20:595–598, 1944
12. AAAS Research Conference on Cancer. The occurrence of dependent and autonomous phases in the development of cancer. p. 154–161. Gibson Island, Maryland, 1944. Edited by FR Moulton. Washington, DC AAAS Smithsonian Institution Bldg, 1945
13. Greene HSN: The production of carcinoma and sarcoma in transplanted embryonic tissue. Science 101:644–646, 1945
14. Greene HSN: The microscope or the guinea pig? Yale J Biol Med 18:239–244, 1946
15. Greene HSN: Identification of malignant tissues. J Am Med Assn 137:1364–1366, 1948
16. Greene HSN: Evidence for eye chamber tissue tolerance for homografts and heterografts. Ann N Y Acad Sci 59:311–318, 1958
17. Dameron JT: Anterior chamber of the eye for investigative purposes: Site for transplantation of fetal endocrine tissue. Surgery 30:787–799, 1951