

## MORPHOLOGICAL AND FUNCTIONAL STUDIES OF FETAL THYMUS TRANSPLANTS IN MICE\*

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The thymus gland develops as an epithelial anlage of the third and fourth pharyngeal pouches (1). Detailed ontogenic studies of the developing thymus have been important, not only for understanding its role in the biology of the host's bodily defenses, but also in the immunological analysis of congenital thymic abnormalities and immunodeficiency diseases of man.

The behavior of a thymus graft after transplantation into a secondary host has received much attention (2-11). When a neonatal thymus is transplanted under the renal capsule of a syngenic host rapid and severe necrosis results (7). After this, lymphoid proliferation occurs and restoration of a normal thymus architecture is seen 7-8 days after transplantation (3, 4). The initial regenerative phase is accomplished by donor cells, but by 3 wk after transplantation the graft is repopulated by host cells (8-11). In contrast, lymphoid proliferation and differentiation does not occur in allogenic thymus grafts after the early transplant period of necrosis and rejection is usually complete by 12-14 days (6).

The grafting of thymus tissue under the renal capsule has the distinct advantage of allowing a detailed morphological analysis of both the graft and the host response. Successful immunological reconstitution of neonatally thymectomized mice can be achieved in a high proportion of mice grafted with syngenic thymic tissue (3, 12). Similarly, thymus grafts with minor, non-*H-2* histocompatibility differences are usually successful in reconstituting a significant percentage of neonatally thymectomized mice and the success of such grafting varies with the strains of mice used (12). In contrast, allogenic thymus grafts across major *H-2* histocompatibility barriers often fail to achieve immunological reconstitution and frequently induce a severe and fatal graft-vs.-host disease (GVH)<sup>1</sup> (12). The capacity of thymus grafts to induce GVH was further defined by producing GVH with the implantation of parental thymus grafts into neonatally thymectomized F<sub>1</sub> hybrid mice (13).

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<sup>1</sup> Abbreviations used in this paper: GVH, graft-vs.-host disease; SRBC, sheep erythrocytes; UMC, University of Minnesota colony sublines.

Children with a congenital absence of the thymus have an immunological deficiency similar to that produced by neonatal thymectomy in mice (14, 15). Thymus transplants, taken from fetuses early in gestation, have given apparent successful reconstitution of cell-mediated immunity in two of these patients (16, 17). Concern has been raised as to the capacity of a primitive "wet membrane" of fetal thymic tissue to have any influence in the immunological reconstitution of these patients (18, 19). The following experiments were undertaken to examine the capacity of the murine fetal thymus, taken early in gestation, to withstand transplantation and develop normally under the renal capsule of a syngenic host. Furthermore, the capacity of embryonic thymus grafts with minor and major histocompatibility differences to develop and restore immunologically, neonatally thymectomized mice was studied.

#### *Materials and Methods*

*Mice.*—Inbred mice of the A/Jax, C3H, C57BL/1, DBA/2, CBA/H, and (C3H × A)F<sub>1</sub> strains were used. The inbred strains of mice originated from the colonies of the late Doctors J. J. Bittner and C. Martinez. A detailed description of the strains has been reported (20); they are designated as the University of Minnesota colony sublines (UMC).

*Thymus Grafting.*—Donor thymuses were removed aseptically from 13-day-old fetuses and transferred to cold normal saline. For the morphological studies of thymus transplantation the left kidney of the recipient mouse was exposed through a flank incision under Nembutal anesthesia. A single lobe of thymus was introduced under the renal capsule by means of fine forceps. The skin was closed with wound clips. For the restoration experiments, two to five thymus grafts were injected intraperitoneally into 6-day-old neonatally thymectomized mice. Fetal thymuses were obtained from 14–18-day-old embryos. Adult thymuses were obtained from three 15–30-day-old mice.

Neonatal thymectomy was performed using a standard technique for our laboratory (21). Skin grafting from DBA/2 donors was performed between 75 and 100 days of age using a technique previously described (22). Skin graft rejection in less than 15 days was considered normal. Approximately 30 days after skin grafting the mice were given 0.2 ml of a 20% suspension of sheep erythrocytes (SRBC) intraperitoneally. Sera were titrated for anti-SRBC hemagglutinins in saline 9 days after challenge. These were expressed as the logarithm to the base 2 of the reciprocal of the final dilution showing macroscopically visible agglutination. Titers greater than 7 were considered significant. At 250 days the mice were sacrificed and examined under the dissecting microscope for thymic remnants in the neck. Mice with thymic remnants were excluded.

*Histology.*—The recipient mice were sacrificed at various time intervals after thymus transplantation and the kidneys removed. The tissues were fixed in Formalin and 5- $\mu$  sections were cut and stained with hematoxylin and eosin. Serial sections were prepared on each thymus graft.

#### RESULTS

*Development of Syngenic Fetal Thymus Grafts.*—The growth and development of the fetal thymus grafted into a normal syngenic host had several characteristic stages (Figs. 1–8).

At 13 days' gestation the mouse thymus is virtually devoid of lymphocytes (23). 24 hr after grafting a 13-day-old fetal thymus under the renal capsule, a healthy-appearing graft was observed. No evidence of the necrosis and hemor-

rhage described for newborn or young adult grafts (7) was encountered. The primary cell at this stage is the stromal reticular-epithelial cell. Occasional lymphocytes and mitotic figures were seen throughout the graft. These probably represent the very early stages of lymphoid stem cell division and differentiation which lead to the development of a normal-appearing thymus.

48 hr after grafting the thymus had increased considerably in size. Microscopic examination showed many more lymphocytes (Fig. 4). These were actively proliferating cells as evidenced by the many mitotic figures seen in the section. Clear evidence of a vascularization was seen in that area of the grafted thymus next to the kidney parenchyma (Fig. 4). In contrast, the area adjacent to the renal capsule did not appear to be vascularized.

7 days after grafting, the fetal thymus contained densely packed lymphocytes and had the characteristic appearance of thymus cortex. Early evidence of lobulation was seen. A peripheral thin layer of large pale-appearing cells was seen adjacent to the kidney parenchyma (Fig. 5).

The thymus graft continued to grow rapidly. 12 days after grafting a well-differentiated cortex and medulla were seen (Fig. 7). Normal-appearing Hassall's corpuscles were present in the medulla (Fig. 8). Mitotic activity remained high. A clear line of demarcation existed between the thymus and kidney. No apparent cellular infiltration was seen in the renal cortex as compared with the normal kidney.

*Thymus Development across Non-H-2 Histocompatibility Barriers.*—Thymuses from fetal (13–15 days) CBA/H mice were grafted into normal 30-day-old C3H mice. These thymus grafts underwent a normal stage of early proliferation and differentiation. No necrosis was seen after transplantation. The lymphoid proliferation continued with differentiation into a normal medulla and cortex, Hassall's corpuscles, lobulation, and normal cellular morphology. No differences between the development of these grafts compared with syngenic grafts were observed until 20–25 days.

In some animals evidence of rejection appeared as early as 25 days post-transplantation (Fig. 9). These signs of rejection first appeared in the periphery of the graft. A round cell infiltrate was present in the area between the thymus and kidney. In addition the renal cortex appeared to contain an increased number of lymphoid cells; however, in some mice evidence of rejection of such thymus transplants did not appear until 50–60 days.

*Thymus Development across H-2 Histocompatibility Barriers.*—When 13-day-old fetal A thymuses were transplanted into normal C3H and C57BL/1 mice, early acute rejection was not seen. During the 1st wk after transplantation the graft underwent early growth and intense lymphoid proliferation. By 8–10 days after grafting growth and development ceased and rejection of the graft began. By 12–14 days graft rejection was extensive and usually complete by 15–20 days. Cell destruction was widespread, and polymorphonuclear leukocytes, cellular debris, fragmented and pyknotic nuclei were seen (Fig. 11).

In contrast to the fetal thymus graft, neonatal A strain thymus grafts trans-

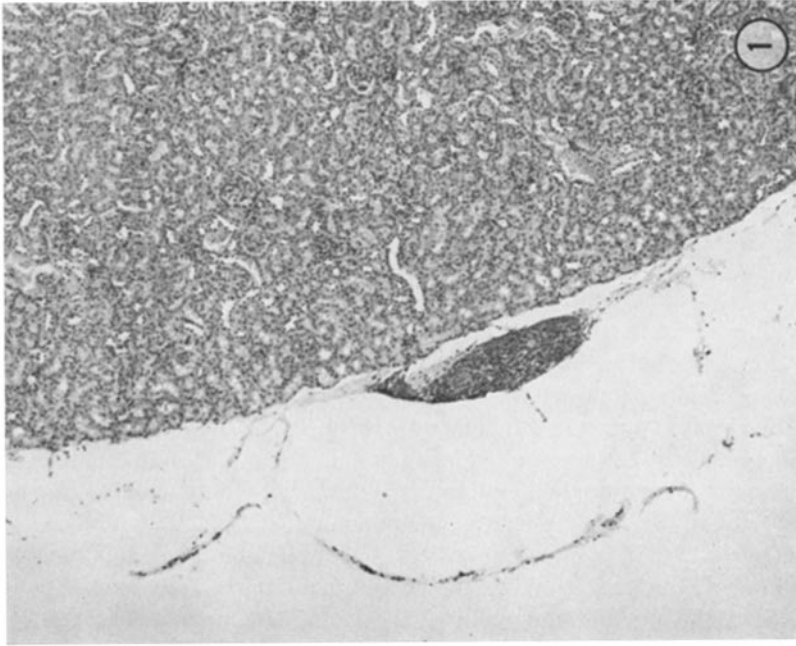


FIG. 1. Subcapsular thymus graft from a 13-day-old A fetal donor 24 hr after grafting into a normal 30-day-old syngenic host. No necrosis is seen. X 50.

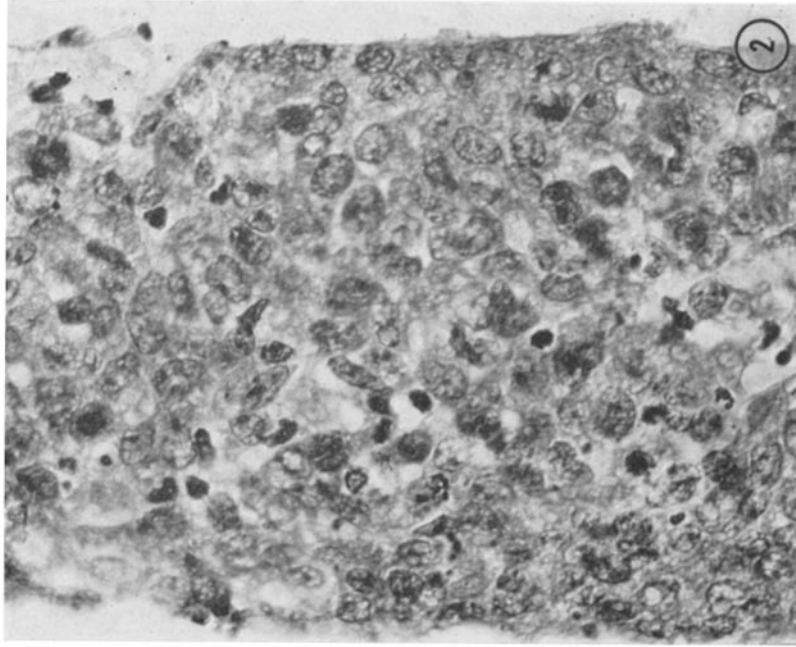


FIG. 2. Higher magnification of Fig. 1. The cellular architecture is intact. Large reticular-epithelial cells predominate and occasional mitotic figures are present. X 600.

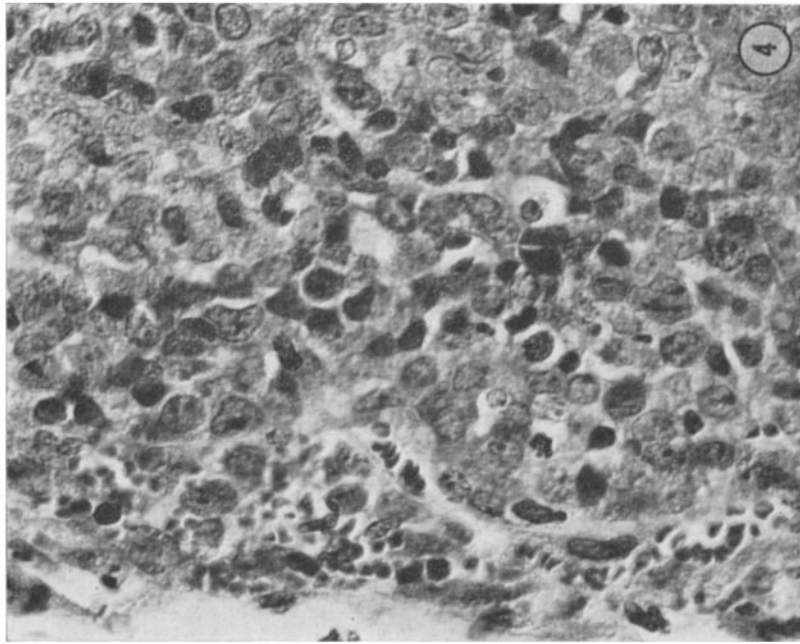


FIG. 3. Subcapsular thymus graft from a 13-day-old fetal donor 48 hr after grafting into a normal 30-day-old syngenic host. Considerable growth of the thymus has occurred. No necrosis is evident. X 50.

FIG. 4. Higher magnification of Fig. 3. The predominant cell is the large reticular-epithelial cell. Thymocytes have appeared. Vessels are seen containing red blood cells. X 600.

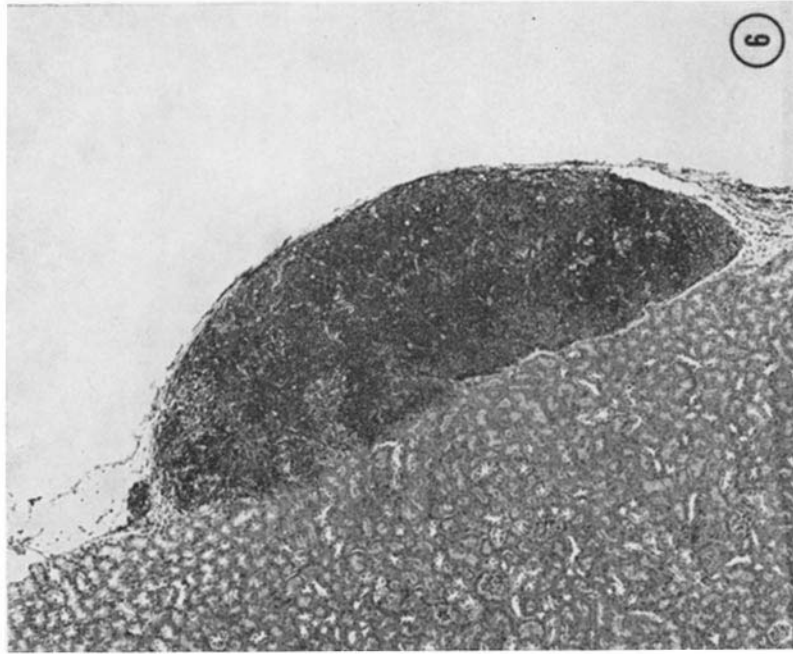
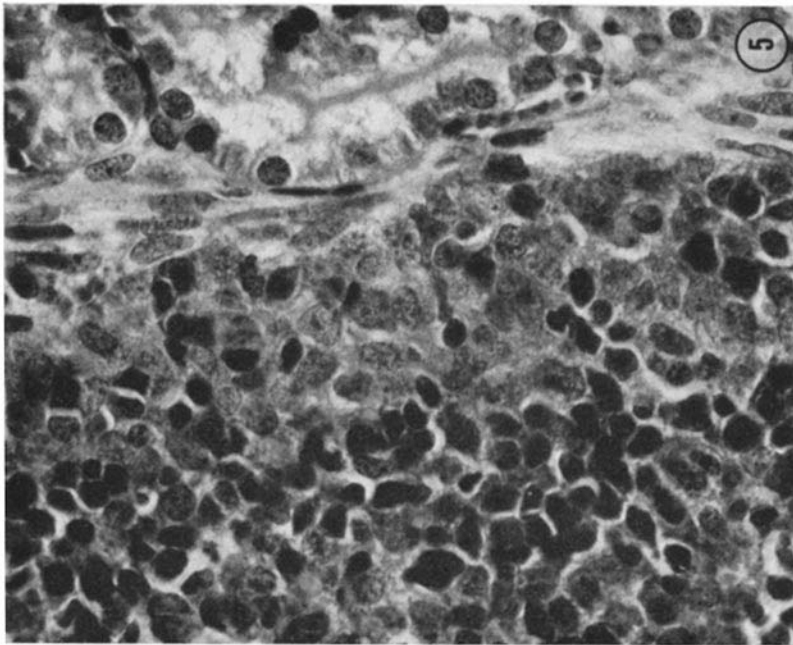


FIG. 5. Subcapsular thymus graft from a 13-day-old A fetal donor 72 hr after grafting into a normal 30-day-old syngenic host at the junction of thymus graft and kidney cortex. Many large, medium, and small thymocytes are packed within the reticular-epithelial framework (large clear nuclei). X 600.

FIG. 6. Subcapsular thymus graft from a 13-day-old A fetal donor 7 days after grafting into a normal 30-day-old syngenic host. The thymus, primarily cortex, shows early differentiation into a medullary zone. X 50.

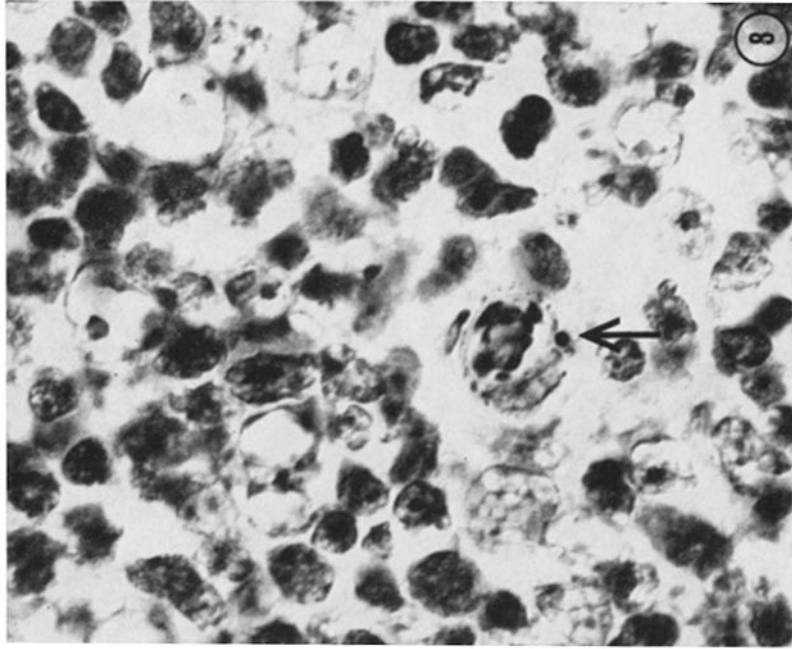
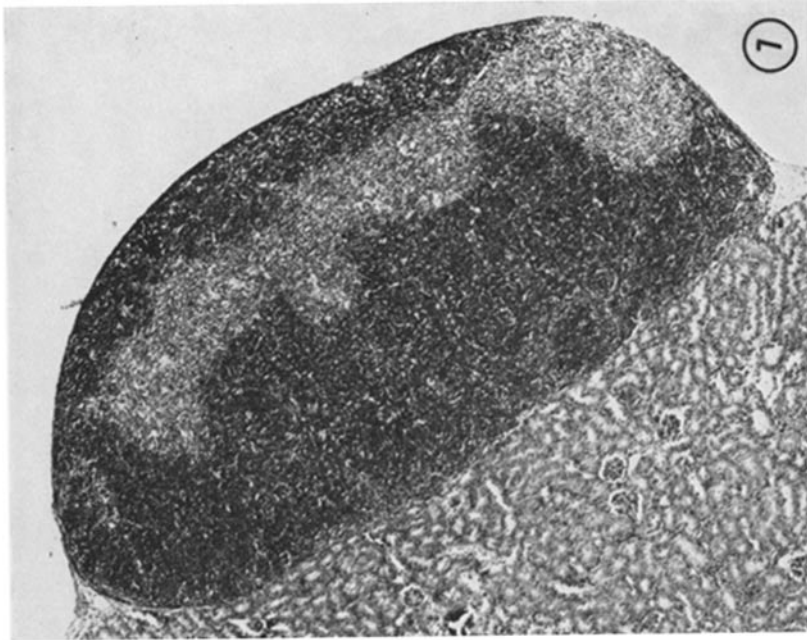


FIG. 7. Subcapsular thymus graft from a 13-day-old A fetal donor 12 days after grafting into a normal 30-day-old syngenic host. A well differentiated cortex and medulla are present. X 50.

FIG. 8. Subcapsular thymus graft from a 13-day-old A fetal donor 12 days after grafting to a normal 30-day-old syngenic host. A normal Hassall's corpuscle is seen surrounded by epithelial-reticular cells and thymocytes. X 100 oil.

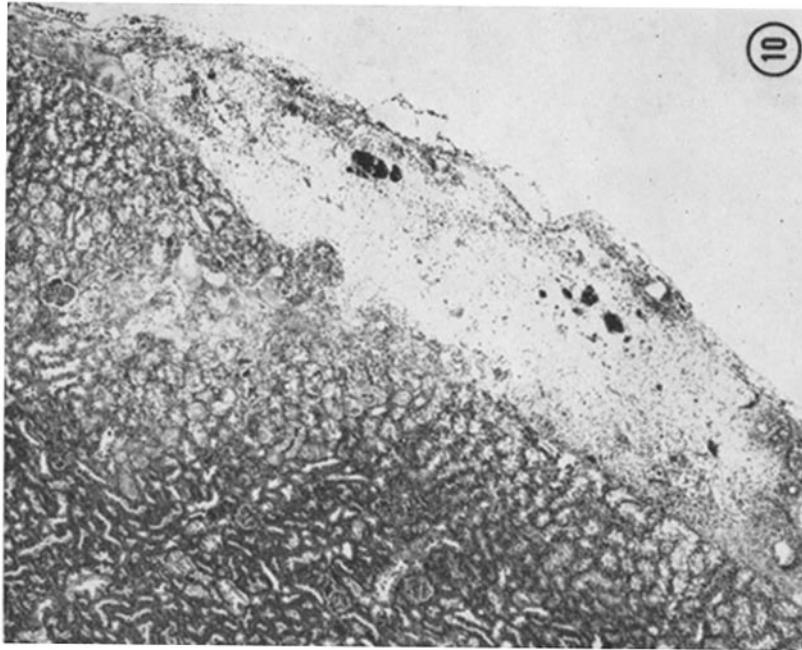
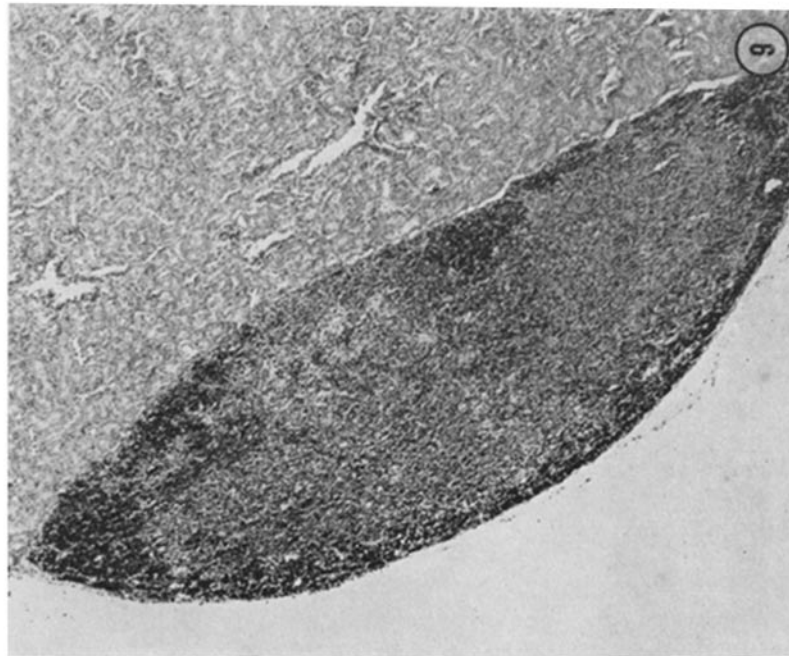


FIG. 9. Subcapsular thymus graft from a 13-day-old CBA/H fetal donor 180 days after grafting into a normal 30-day-old C3H host. The thymus shows evidence of rejection with preservation of thymic architecture. X 50.

FIG. 10. Subcapsular thymus graft from a neonatal A donor 48 hr after grafting into a normal 30-day-old C57BL/1 host. Extensive necrosis and loss of thymic architecture is evident. X 50.



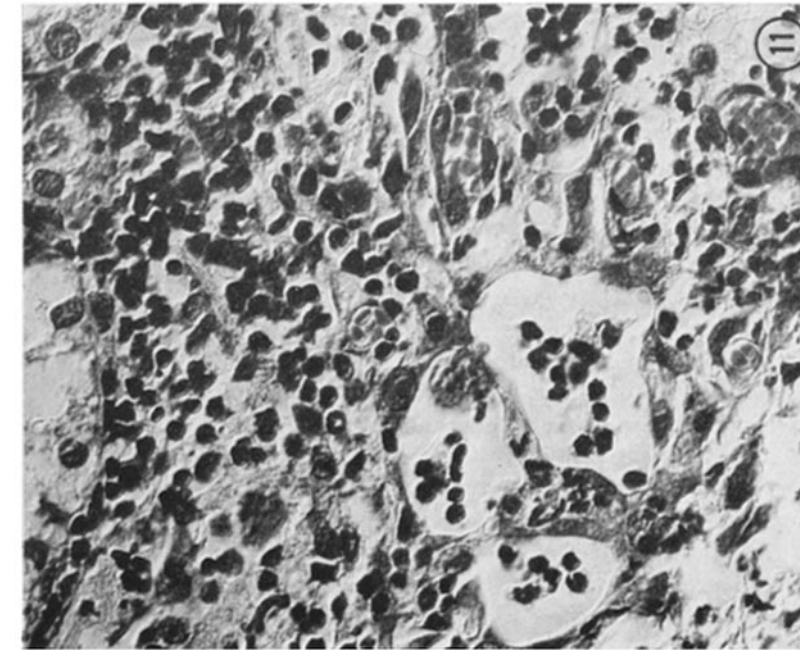
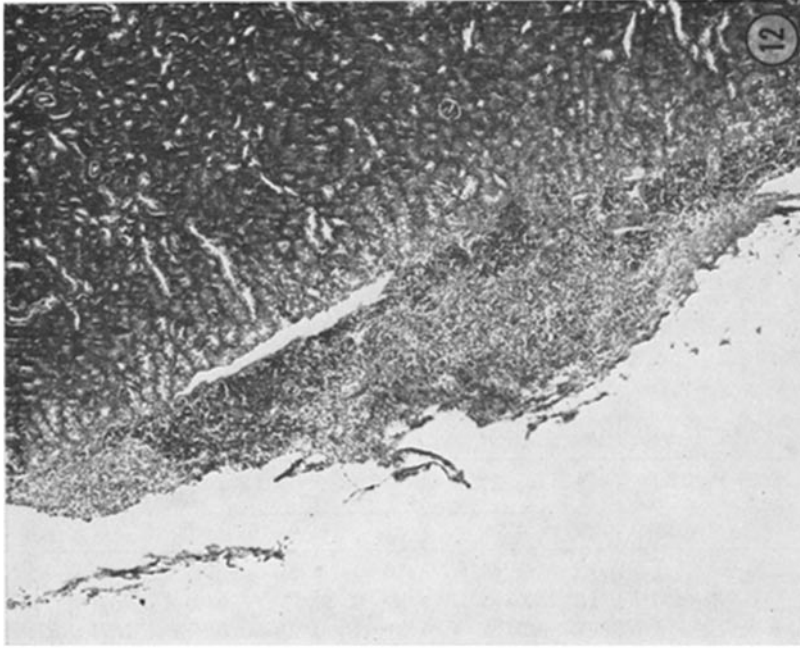


FIG. 11. Subcapsular thymus graft from a 13-day-old A fetal donor 15 days after grafting into a normal 30-day-old syngenic host. Cell destruction is extensive. Pycnotic lymphocytes, polymorphonuclear leukocytes, fragmented nuclei, cellular debris, and hemorrhage are present. X 600.

FIG. 12. Subcapsular thymus graft from a neonatal A donor 12 days after grafting into a normal 30-day-old C57BL/1 host. No repopulation of the graft is evident and rejection is almost complete. X 50.

planted into normal 30-day-old C3H or C57BL/1 hosts underwent rapid and acute necrosis (Fig. 10). 24–48 hr after grafting intense hemorrhagic necrosis was seen. Pycnotic lymphocytes, polymorphonuclear leukocytes, fragmented nuclei, cellular debris, and hemorrhages were present. An intense round cell infiltrate of small lymphocytes and histiocytes was seen in the renal cortex and at the junction of the thymus graft and kidney cortex. Progressive fibrosis and scarring ensued. Rejection was complete by 8–12 days (Fig. 12). Morphological analysis of thymus grafts under the renal capsule is summarized in Table I.

*Immune Restoration of Thymectomized Mice using Different Thymus Grafts.*—Table II shows the capacity of the various thymus grafts to restore neonatally

TABLE I  
*Morphologic Analysis of Renal Subcapsular Fetal and Adult Thymus Grafts\**

	Syngenic		Allogenic non- <i>H-2</i> different		Allogenic <i>H-2</i> different	
	Fetal	Adult	Fetal	Adult	Fetal	Adult
Early necrosis	0/7	5/5	0/5	5/5	0/5	5/5
Acceptance graft‡	9/11	9/10	9/10	10/10	0/10	0/10
Normal rejection§	0/10	0/10	0/10	0/8	5/9	10/10
Late rejection	0/5	0/5	5/5	5/5	0/8	0/5

\* Morphological studies were done on renal subcapsular thymus grafts examined at various time intervals. Recipients were normal C3H and C57BL/1 mice who were transplanted with syngenic, allogenic non-*H-2* different (CBA/H into C3H), and allogenic *H-2* different (A into C57BL/1) thymus grafts.

‡ Normal-appearing thymus 60 days after transplantation.

§ Rejection of thymus graft in less than 15 days.

|| Rejection of thymus graft in greater than 30 days.

thymectomized mice. The parameters of restoration studied were the capacity to form antibodies in response to an antigenic challenge with SRBC, the capacity to reject a third-party skin graft, and to survive 250 days. The 250-day survival of mice grafted with syngenic fetal thymuses was almost equal to that of mice grafted with adult thymuses (75 vs. 85%, respectively). A high percentage of mice given fetal grafts had a good SRBC response (80%) and normal skin graft rejection (100%). When parental strain thymus grafts were given, the fetal thymus proved to be far superior in immunologic reconstitution than were grafts of adult thymuses. 72% of the mice grafted with parental fetal thymuses survived 250 days whereas only 33% of the mice grafted with parental adult thymuses survived that long. Furthermore, the results of syngenic fetal and parental fetal grafts were similar.

When thymus grafting was across a major *H-2* histocompatibility barrier (A to C3H) the fetal thymus again was more effective than the adult thymus. 43% of the mice given fetal grafts survived 250 days. All these mice had normal skin graft rejection and 47% had a good antibody response to SRBC. These

results stand in marked contrast to those of mice given adult allogenic thymus where only 5% survived 250 days.

## DISCUSSION

The observations presented here clearly demonstrate that a fetal thymus transplanted under the renal capsule of a syngenic host develops into a morpho-

TABLE II

*Restoration of 6-Day-Old Neonatally Thymectomized Mice Grafted with Fetal or Adult Thymus\**

Thymus donor	Recipient	No. surviving 250 days	No. with normal SRBC response†	No. with normal skin graft rejection‡
(C3H × A) <sub>1</sub> F <sub>1</sub> adult	(C3H × A) <sub>1</sub> F <sub>1</sub>	12/14 (85%)	10/12 (84%)	12/12 (100%)
(C3H × A) <sub>1</sub> F <sub>1</sub> fetal	(C2H × A) <sub>1</sub> F <sub>1</sub>	44/59 (75%)	12/15 (80%)	12/12 (100%)
A adult	(C3H × A) <sub>1</sub> F <sub>1</sub>	5/13 (33%)	Not done	4/5 (80%)
A fetal	(C3H × A) <sub>1</sub> F <sub>1</sub>	31/43 (72%)	11/15 (74%)	12/12 (100%)
A adult	C3H	1/20 (5%)	Not done	0/1 (0%)
A fetal	C3H	19/44 (43%)	9/19 (47%)	10/10 (100%)
None	(C3H × A) <sub>1</sub> F <sub>1</sub>	0/20 (0%)	3/20 (15%)	1/18 (5.5%)

\* Neonatally thymectomized (C3H × A)<sub>1</sub>F<sub>1</sub> and C3H mice grafted intraperitoneally at 6 days of age. Fetal thymus was obtained from 15–18-day-old embryos. Adult thymus was obtained from 30–40-day-old mice. Recipients were given two to five thymuses.

† SRBC agglutination titer (log<sub>2</sub>) greater than 7 was considered normal.

‡ Rejection of DBA/2 skin grafts in less than 15 days was considered normal.

logically normal thymus. At 13 days of gestation, the thymus is comprised primarily of reticular-epithelial stromal cells derived from the third and fourth pharyngeal pouches (1, 23). These stromal cells have a round or oval irregular nucleus and a spherical nucleolus. The nucleus is surrounded by abundant cytoplasm which contains small vacuoles (24). When a neonatal or adult thymus is grafted under the renal capsule of a syngenic host, rapid and massive necrosis occurs throughout the graft during the first 24–48 hr. Only a small number of epithelial and lymphoid cells remain in the periphery (3, 7–11). After phagocytosis of nuclear debris, intense mitotic activity is apparent and normal thymic architecture is restored by 7–8 days (3, 4). The fetal thymus graft on the other

hand, appears healthy, contains viable cells, and is free of overt necrosis in the early posttransplant period. The absence of necrosis may be related to the graft size (25), the absence of rapidly dividing thymic lymphocytes, qualitative and/or quantitative differences in cell surface antigens, or to the relative avascularity of the 13-day-old embryonic thymus. 48 hr after transplantation, considerable growth and evidence of vascularization had occurred. The vessels first appeared in the area next to the kidney parenchyma. Active cell proliferation was seen. The lymphoid cells proliferating at this time are probably progeny of stem cells present in the graft at the time of transplantation (25).

The graft continued to grow and to be populated with densely packed lymphocytes. These varied in size and had a deeply stained nucleus surrounded by a small rim of cytoplasm. By 7 days, islands of reticular-epithelial cells were distinguishable as medullas. Contained in these medullary islands were larger lymphocytes with deeply staining nuclei, containing central nucleoli and large clumps of chromatin attached to the dense nuclear membrane. The nucleus was enclosed by a rim of cytoplasm. 12 days after grafting the medullary region appeared to be fully developed and to contain Hassall's corpuscles.

These observations indicate that the primitive fetal thymic anlage, at a stage when reticular-epithelial stromal cells predominate, can withstand the trauma of transplantation. Furthermore, these studies clearly demonstrate that fetal thymus is capable of restoring neonatally thymectomized mice as well as the adult thymus and is superior to the adult thymus when allogenic grafting is done (Table II). The relevance of these data to the treatment of thymic deficiency syndromes in man (16, 17) is obvious. If the thymus graft had been significantly traumatized by the surgical manipulation, delay in its growth and development in the transplanted host would have occurred. The thymus tissue transplanted in these experiments appeared to develop and mature at a rate very similar to that of a normal fetal thymus.

When allogenic thymus was grafted into mice with non-*H-2* histocompatibility differences (CBA/H into C3H), a similar early period of rapid growth and development was observed. These grafts appeared to be healthy mature thymuses until approximately 20–25 days after transplantation. At this time, progressive lymphocyte infiltration appeared at the periphery of the graft. The central portion of the grafted thymus remained intact. Progressive cellular infiltration and cellular destruction ensued. By 60–80 days, only a small island of normal-appearing thymus remained. Complete rejection and fibrosis followed; however, in some mice, complete rejection was as late as 180–200 days.

Allogenic fetal thymuses grafted across a major histocompatibility barrier (A into C3H) were rejected a little more slowly than were thymus grafts taken from neonatal donors. The thymus grafts from allogenic neonatal donors failed to develop after the early period of necrosis (3, 6, 12). The degree of lymphoid proliferation and graft repopulation related to the immunological capacity of the host. Neonatally thymectomized mice apparently accepted these allogenic non-*H-2* identical grafts at the times studied. That nonimmune factors might

also influence the capacity of lymphoid cells to proliferate in the adult thymus after transplantation was suggested by the occurrence of acute and severe rejection phenomenon with virtually no latent period (3, 7).

Fetal allogenic thymus grafts were not rejected as rapidly as were the neonatal grafts. These grafts clearly underwent lymphoid proliferation in the early stages after transplantation. By 8–10 days, an intense cellular infiltrate appeared in the renal cortex and the process of rejection followed. The early lymphoid development within the allogenic fetal thymus graft, as compared with the neonatal thymus graft, may be related to quantitative and/or qualitative differences in the tissue-specific surface antigens of fetal cells. Fetal cells are known to contain less *H-2* specificity than do similar cells from newborn mice (26). Similarly, surface isoantigens, for example TL, are expressed on thymus cells towards the latter part of gestation (25). Fetal tissues early in gestation might then be expected to reflect the weak antigenic stimulus to the immunocompetent host and a delay of the rejection phenomenon.

These studies have shown that the fetal thymus, obtained early in gestation when it is primarily a reticular-epithelial structure, can withstand the surgical manipulation of transplantation and undergo apparently normal differentiation and maturation under the renal capsule of a secondary syngenic host. It seems possible therefore that a similar process of development and restoration could occur in the patients with a congenital absence of the thymus who are transplanted with fetal thymic tissue (14, 15). Hematopoietic pluripotential pre-thymic stem cells would migrate to the thymus graft and, under its influence, thymus cell maturation processes and immunocompetence would be achieved (27). These immunologically competent lymphocytes could then traffic from the thymus and restore the peripheral lymphoid tissues. When major histocompatibility differences exist between the donor thymus and host, these developing immunocompetent, thymus-derived lymphocytes could conceivably recognize the grafted thymus as being foreign and thus reject it. Evidence of such a phenomenon has been observed in mice (12, 28). If a similar process applies to man, a patient restored with an *HL-A*-incompatible thymus graft might be expected to reject that same thymus which restored his cell-mediated immune deficiency. Such a patient might then slowly develop deficiencies of cell-mediated immunity similar to those present before transplantation and thus require retransplantation.

#### SUMMARY

The fetal thymus at 13 days of gestation withstands transplantation and develops normally under the renal capsule of a syngenic host. Distinct differences were observed between the fetal thymus grafts and grafts from neonatal or adult thymus donors. The fetal thymus graft did not undergo the rapid and severe necrosis observed when adult thymus was grafted. Furthermore, when thymuses were transplanted into allogenic recipients, rejection was delayed.

The fetal thymus was as effective as the adult thymus in restoring syngenic

neonatally thymectomized mice and far superior to adult thymus when grafted into allogenic recipients. These observations seem relevant to clinical efforts to restore immunocompetence in patients with congenital absence of the thymus.

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