THE AUTOPLASTIC TRANSPLANTATION OF TISSUES INTO THE BONE MARROW CAVITY.

I. The Thymus.

By MAURICE N. RICHTER, M.D., and HENRY L. JAFFE, M.D.

(From the Pathological Laboratory of Bellevue Hospital and the Laboratory Division of the Hospital for Joint Diseases, New York.)

Plates 42 to 44.

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The relation of lymphoid tissue to bone marrow is not definitely known. According to the adherents of the dualistic theory of blood formation these two tissues are independent or even antagonistic to each other. Thus the possibility of a lymphocyte differentiating into a myeloid cell is denied.

The unitarian theory of blood cell development postulates a close relationship between the lymphoid and myeloid tissues, and lymphocytes are considered capable of differentiating, directly or indirectly, into myeloid cells. Maximow (1), Downey (2), and others have reported such findings. Downey has recently published a comprehensive review on this subject. Maximow (3) induced this change experimentally by the addition of cell-free bone marrow extracts to lymphoid tissue cultures.

We transplanted tissues into the bone marrow cavity, in direct contact with actively growing marrow, to study the effects of the marrow on the transplanted tissues, and of the tissues on the bone marrow. Three tissues of lymphoid nature—lymph node, spleen, and thymus—were transplanted. It was thought that if these tissues were genetically and biologically different, different reactions might be produced both in them and in the bone marrow on transplantation.

The lymph nodes are composed almost entirely of lymphocytes and their supporting stroma. Cytologically the spleen differs from lymph nodes, in that a small amount of myeloid tissue may be present, though overshadowed by the lymphocytes. The lymphoid nature of the

thymus is questionable because opinion is not unanimous concerning the "lymphoid" nature of the cortical cells. By the introduction of these tissues into the marrow cavity similarities and differences in their reactions were observed. This paper deals with transplantation of the thymus.

Maximow (4), Danchakoff (5), Hammar (6), and others regard the small thymic cells as lymphocytes. Stöhr (7), Jaffe (8), and others regard them as epithelial elements. In experiments on myeloid metaplasia Danchakoff reported the transformation of thymic cortical cells into granular myelocytes, a change supposedly characteristic of lymphocytes and their precursors.

The literature on transplantation of organs into the bone marrow is scant, and we have found no references to transplants of thymus, lymph nodes, or spleen in this situation.

Methods.

Young guinea pigs 8 to 11 weeks of age were used. These animals were reared in the laboratory under hygienic conditions, and were apparently healthy. Under ether anesthesia with aseptic precautions both lobes of the thymus were removed, and placed immediately in sterile physiological salt solution kept at about 38°C. An osteotomy was then performed on the upper third of each tibia. The marrow cavity of the upper third of the bone was curetted and wiped out with gauze. The thymus was then introduced into the cavity. Thirteen animals, in which the wounds healed by primary union, were used for this study. In six animals several fragments of thymus not more than 2 mm. in diameter were introduced into each marrow cavity, and in seven cases one large piece of thymus sufficient to fill the entire defect was inserted. The bone flap was replaced whenever possible, and the wounds were closed with fine silk.

The animals were killed at intervals of from 1 to 10 weeks after operation. The tibia was sawed through with a fine jeweler's saw at several levels, fixed in Helly's fluid, decalcified in 5 per cent nitric acid, sectioned in paraffin, and stained with hematoxylin and eosin.

The results of the transplantation of several small pieces were essentially the same as those which followed the transplantation of one large piece. Therefore both series of experiments are described together.

OBSERVATIONS.

At the end of 1 week, the transplanted thymus occupied the center of the marrow cavity and showed extensive degeneration of the small thymic cells and the Hassall's corpuscles, the thymic reticulum remaining for the most part intact. At several places in the peripheral portion of the transplant the thymic reticulum was hyperplastic and contained mitotic figures. A layer of loose cellular and vascular granulation tissue, in which new bone was forming, separated the thymus from the bone cortex. (Fig. 1.)

By the 2nd week much of the debris had been cleared away mainly by the process of liquefaction. Phagocytes were present in remarkably small numbers. At this time the outstanding feature in the transplant was the proliferating reticulum, with some round cells and an occasional polymorphonuclear leucocyte scattered in its meshes. During the 2nd week the small thymic cells reappeared and increased in number. The reticulum formed cell masses, the centers of which degenerated resulting in typical Hassall's corpuscles. We found no evidence of Hassall body formation from capillary endothelium as recently described by Jordan (9). In this stage new bone trabeculæ were forming around the transplant. (Fig. 2.)

During the 3rd week the thymus was usually completely regenerated, forming large cellular lobules, some of which showed differentiation into cortex and medulla. The thymic lobules were richly cellular and the small round thymic cells predominated. The Hassall's corpuscles were well developed. The regeneration of the thymus was complete in that all the structures of the normal thymus in their normal morphological relationship were reproduced. The regeneration, however, fell short of reproducing as active and cellular a thymus as was introduced. This is in marked contrast to the results obtained when thymus is autoplastically transplanted into the abdominal wall (8). The bony trabeculæ observed in the previous stage formed an incomplete bony capsule around the thymus. Where the bony wall was lacking, a thin layer of fibrous tissue separated the thymus from the marrow. (Figs. 3 and 4.)

By 6 weeks the bony capsule was fully developed and completely enclosed the thymus. The development of this bony capsule not

only prevented further growth of the thymus, but led to its atrophy. As the gland atrophied there was replacement fibrosis and Hassall's corpuscles disappeared. (Fig. 5.)

By $8\frac{1}{2}$ weeks only a tiny fragment of thymus remained which was separated from the marrow cavity by a capsule of newly formed bone (Fig. 6). The thymus was markedly atrophic, the cortical cells had almost completely disappeared, and practically nothing remained but a stroma consisting mainly of connective tissue, in the center of which was a small group of round cells. Reticulum cells, if present, could not be differentiated from the cells of the fibroblastic stroma. No Hassall's corpuscles were seen. A few foreign body giant cells were present in the stroma.

In sections made at the end of 10 weeks, no thymic tissue was found.

SUMMARY.

When the thymus is autoplastically transplanted into the marrow cavity of the tibia of a guinea pig, the transplant degenerates, regenerates, and finally atrophies. The degeneration and regeneration of the thymus when so transplanted are similar to the homologous changes occurring when it is autoplastically transplanted into the abdominal wall. For comparative study the material used in previously published work on transplantation into the abdominal wall was reviewed. A difference in the final result of transplantation of thymus in these two situations is observed. In the abdominal wall the thymus regenerates and persists apparently indefinitely. Abdominal wall thymus transplants more than a year old have been observed. In the bone marrow cavity, the regeneration, which is slower and less abundant, is followed by an atrophy of the gland, and finally its complete disappearance. This atrophy is, we believe, the result of the encasement of the thymus in a bony capsule. That the genetic character of the transplanted tissue has much to do with the success of the transplantation in the marrow, is evident from the fact that some other tissues regenerate without encapsulation, even though they may finally disappear.

The blood clot about the thymus which fills the rest of the curetted cavity, is quickly vascularized and replaced by regenerated cellular bone marrow and newly formed bony trabeculæ.

The difference in the fate of the thymus when transplanted in the abdominal wall and in the marrow, is probably due to differences in the reciprocal relations of the thymus to the tissues in those situations. From experience gained in the transplantation of other tissues into the marrow cavity, we have learned that encapsulation of the transplant does not occur with all tissues. The reaction of the marrow to transplanted thymus is similar to its reaction to any tissue foreign to it.

CONCLUSIONS.

1. The thymus when transplanted autoplastically into the bone marrow undergoes complete but not abundant regeneration.
2. The histological structure of the regenerated thymus is the same as that of the normal thymus despite its situation in the marrow cavity.
3. We have noted no metaplasia of the thymic round cells into myelocytes.
4. The regeneration of the bone marrow in the curetted cavity is not influenced by the presence of the thymus.
5. The regeneration of the thymus is accompanied by its enclosure in a fibrous and bony capsule which prevents extensive development and causes pressure atrophy of the transplant.

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EXPLANATION OF PLATES.

PLATE 42.

FIG. 1. 7 days. Cross-section of the tibia at the level of the transplant showing several lobules of degenerated thymus. The section also shows the replaced bone flap. Hematoxylin and eosin. ×18.

FIG. 2. 14 days. Regenerating thymus is surrounded by newly formed endosteal trabeculæ. Hematoxylin and eosin. ×18.

PLATE 43.

FIG. 3. 24 days. The regeneration of the thymus has reached its maximum. Hassall's corpuscles and medullary centers are seen. Marrow has regenerated between the trabeculæ, and the bony encapsulation is progressing. Hematoxylin and eosin. ×44.

FIG. 4. Higher magnification of the regenerated thymus shown in Fig. 3. Typical Hassall's corpuscles are seen. Hematoxylin and eosin. ×100.

PLATE 44.

FIG. 5. 41 days. The encapsulation of the thymus has excluded it from the marrow cavity. The organ lies between the osteotomy flap and the newly formed endosteal trabeculæ which separate it from the regenerated marrow. Retrograde atrophy of the thymus has set in. Hematoxylin and eosin. ×22.

FIG. 6. 63 days. The thymus is completely surrounded by a bony capsule connected with the cortex. There is almost complete atrophy of the thymus. Hematoxylin and eosin. ×25.

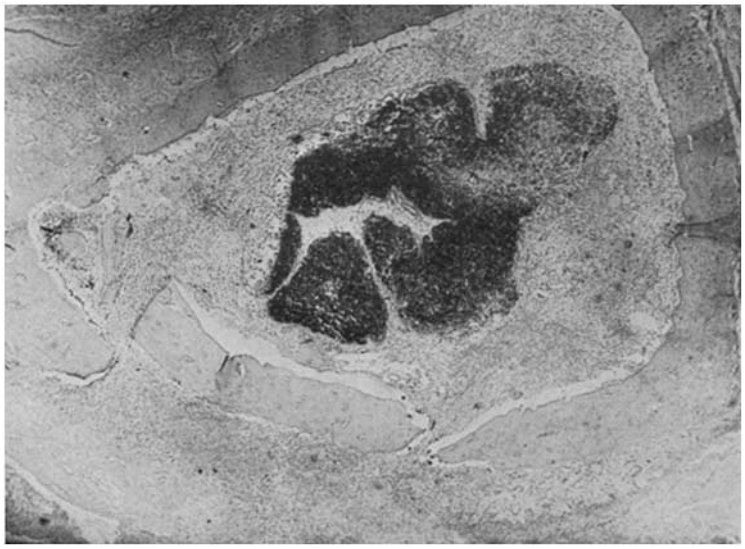

FIG. 1.

FIG. 2.

(Richter and Jaffe: Transplantation into bone marrow cavity. I.)

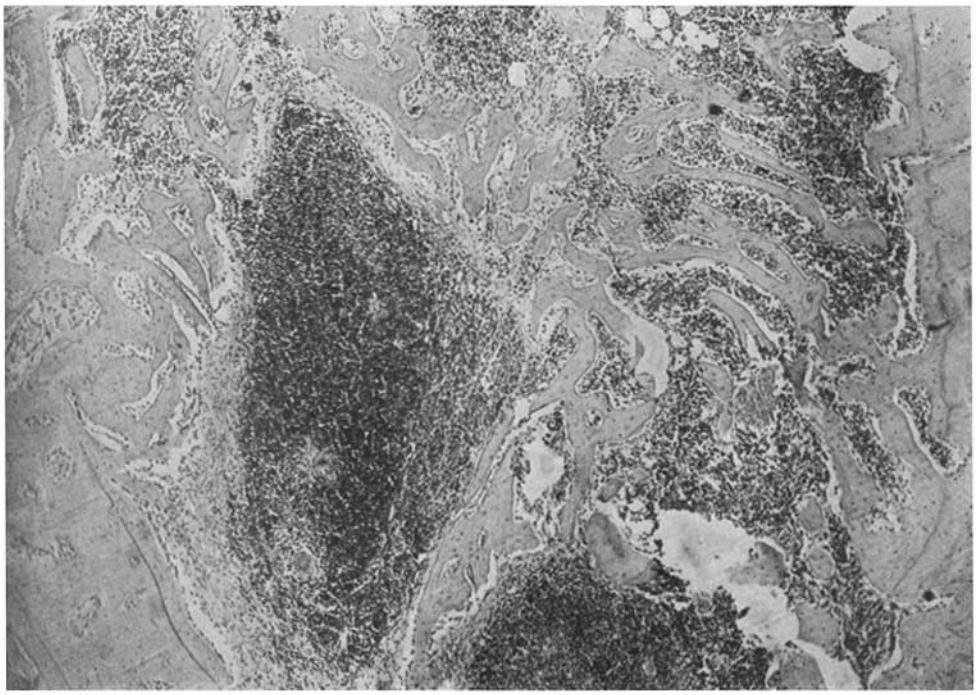

FIG. 3.

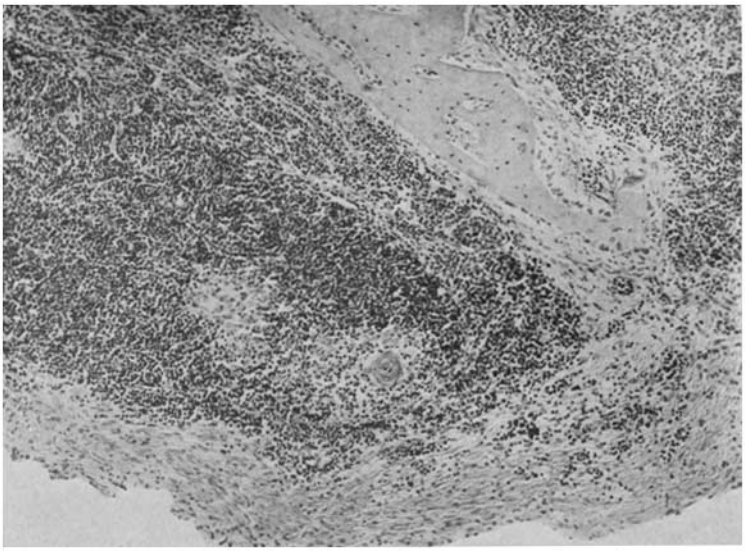

FIG. 4.

(Richter and Jaffe: Transplantation into bone marrow cavity. I.)

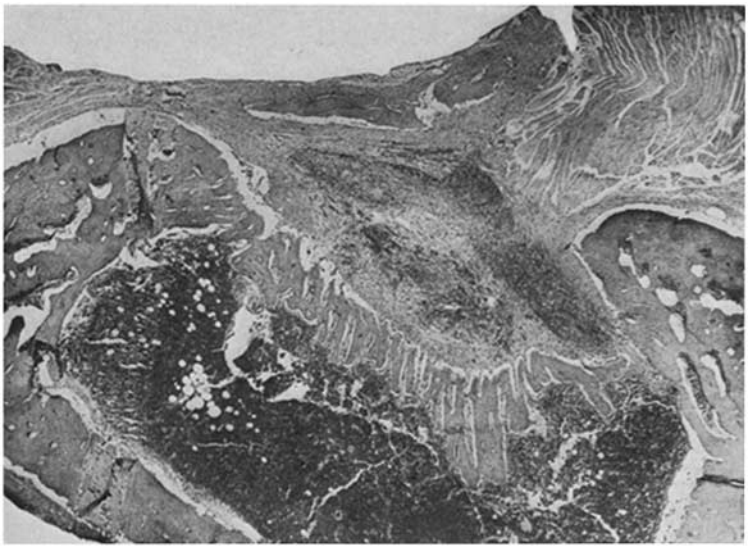

FIG. 5.

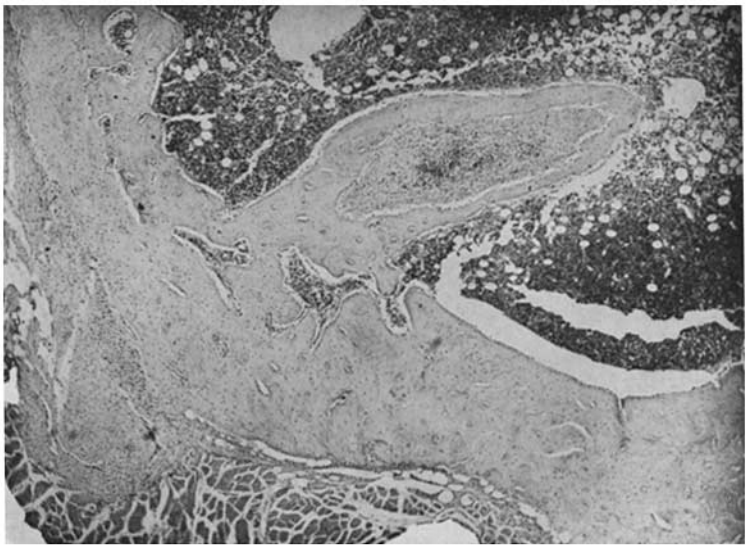

FIG. 6.

(Richter and Jaffe: Transplantation into bone marrow cavity. I.)