Intra-ocular Transplantation of Heterologous Tissues

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Since Van Dooremaal's (35) report in 1873 concerning the suitability of the anterior chamber as a site for transplantation of tissue, there have been many conflicting reports on the intra-ocular transplantation of heterologous tissues. A few investigators have recently reopened the question and have submitted reports of successful heterologous transplants into the anterior chamber of the eyes of animals with tumor tissue from human beings and other animals. Greene (11) has expressed the opinion that only malignant invasive tumors have the characteristic of heterotransplantability, which serves as a biologic test of malignant disease.

The purposes of our investigation were to determine whether we could successfully transplant tissue from a tumor of a human being into the anterior chamber of the eye of an animal and, if so, to learn (a) whether the method could be used as an aid in the diagnosis and prognosis of malignant disease, (b) the essential factors for successful transplantation, and (c) the biologic factors for growth of the transplant. Our objectives have been partially achieved.

DEFINITIONS

In our study we defined a homologous transplant as a transplant from one member of a species into another member of the same species.

A heterologous transplant was a transplant from a member of one species into a member of an alien species. The criteria for successful transplantation of tissue should include: (a) vascularization of the transplant by the vessels of the host, (b) definite growth of the transplant within a reasonable period after transplantation, and (c) morphologic and cytologic similarity of the transplant and the tissue originally transplanted. Some observers might also require, and probably justifiably so, eventual metastasis in the host as a necessary criterion of successful transplantation of malignant tumors.

Vascularization of a transplant by the host associated with regression of the tumor cannot be considered evidence of successful transplantation.

RÉSUMÉ OF LITERATURE

Intra-ocular heterologous transplantation of tumors.—The history of intra-ocular heterologous transplants may be divided logically into three eras.

The first era, 1884–1912, was a period of agreement among investigators on the nontransplantability of tumors from one species to another. Zahn (37), in 1884, was the first to attempt intra-ocular heterologous transplantation of a tumor. A hyaline enchondroma from a human being was infiltrated with lymphocytes and absorbed after transplantation into the anterior chamber of the eye of the rabbit.

Herzog (16) reported, in 1902, that he had tried for years, without success, to accomplish heterologous intra-ocular transplantation of carcinomas and sarcomas from human beings. Subcutaneous and intraperitoneal heterotransplants were also unsuccessful.

In 1912, Ruben (32) was successful in making homologous transplantation of sarcoma of rats into the anterior chamber and vitreous body, but heterologous transplants into rabbits regressed and failed.

The second era, 1913–1937, was a period of dissension. Hegner (15) and Keysser (20), in 1913, were the first to report successful heterologous transplantation into the anterior chamber. Transplantation of sarcoma of a patient was described as successful in four rats; however, regression occurred later after an unstated period. Transplantation of carcinomatous tissue from human beings failed to take.

Woglom (36), in 1915, was unable to substantiate Hegner's and Keysser's observations. Mouse sarcoma 180 failed to grow in the eyes of any of 88 rats, while 45 takes occurred among 54 control mice.

The third era, 1937 to the present, has been a period of general agreement on the heterotrans-
plantability of malignant tumors, with views diametrically opposed to those of the first era. Smirnova (34) in 1937 described successful heterotransplantation of carcinomatous tissue from the breast of a human being and of Ehrlich’s mouse sarcoma.

Lucké and Schlumberger (23–25), in 1939 and 1940, were the first to report on heterotransplants into the eyes of cold-blooded animals. Carcinomatous tissue from the kidney of the leopard frog was successfully transplanted into members of an alien species. The more closely related the species, the higher the percentage of takes which resulted.

Greene (4), in 1941, reported successful heterologous transplantation of mammary and endometrial carcinomas of the rabbit into the anterior chamber. In the next two years Greene (5, 6) described successful heterotransplants into the anterior chamber of a few tumors from human beings. In 1944, Greene and Lund (8) expressed the opinion that heterotransplantability might be characteristic of cancer. They reported the successful heterologous transplantation of several tumors of human beings into the anterior chambers of guinea pigs.

Greene and Murphy (9), in 1945, reported that heterotransplants of several mouse tumors into the anterior chambers of guinea pigs were successful only after the tumors became invasive in the donor.

In 1946, Greene (10) reported adoption of heterologous transplantation into the anterior chamber as a routine procedure in his laboratory. He suggested that the guinea pig was superior to the microscope as an aid in the classification of tumors.

Hovenanian, Deming, and Greene reported successful heterologous transplantation into the anterior chamber of two vesical tumors and two urethral carcinomas (2, 17).

Masina (28), in 1947, recorded successful heterotransplants of two renal neoplasms into the anterior chamber. One of his transplants was described as surrounded by a pseudo-capsule. Blake (1) described successful transplantation of a single fibrosarcoma into the anterior chambers of guinea pigs.

Finally, Greene (11) criticized the present concept, which is generally accepted, of diagnosis of neoplasms based on morphologic and cytologic criteria. He suggested that tissues should be assessed according to their behavior as transplants.

Schilling, Snell, and Favata (33) reported successful heterologous transplants of cancerous tissue from human beings into the anterior chamber in 8 of 36 animals, but ultimate regression of these transplants ensued.

Recently Lushbaugh and Steiner (27) reported unsuccessful heterologous transplants into the anterior chamber of several animals of malignant lymphomas from human beings and animals. These transplants underwent rapid necrosis and partial absorption followed by organization of the debris.

Homologous intra-ocular transplantation of tumors.—Happe (14), in 1913, achieved successful homologous transplants to the anterior chamber and vitreous body of a round-cell sarcoma of the rabbit which eventuated in metastasis in one animal. In the same year Hegner (15) and Keysser (20) reported metastasis after successful homologous transplantation of mouse carcinoma and sarcoma into the anterior chamber.

In 1928, Gyotoku (12, 13) described successful homologous transplantation into the anterior and posterior chambers of Kato rabbit sarcoma with metastasis to the liver, lungs, and kidneys in some instances.

Greene (3) reported that intra-ocular homologous transplants of mammary tumors of rabbits were successful only after an invasive tumor had developed in the donor. Three years later Greene and Brown (7) described similar results after homotransplantation of a squamous-cell carcinoma of the rabbit.

Lushbaugh and Steiner (27) achieved successful homologous transplants of lymphatic leukemia into the anterior chamber of mice. Local infiltration and distant metastasis occurred in mice of homologous strain, while regression of transplants occurred in most of the mice of heterologous strain.

While not an example of intra-ocular transplantation, one of the most remarkable experiments in homologous transplantation of a tumor was reported by Kurtzahn (21). He transplanted portions of a mammary adenocarcinoma from a human being into the subcutaneous tissue of his own thigh. The transplants became necrotic, infiltrated with lymphocytes and giant cells, and finally were completely destroyed.

Tissue culture.—Some appreciation of the behavior of tissue culture is essential for the proper evaluation of the results of this study. Lambert and Hanes (22) demonstrated that various tumors of animals would grow in the plasma of alien species. In 1914, Murphy (29) substantiated the findings of Lambert and Hanes. Lumsden (26) achieved successful tissue culture of several tumors from animals and one carcinoma from the...
breast of a woman in the plasma of normal rabbits and sheep. However, tissue cultures were killed by immune serum of an alien species.

MATERIALS AND METHODS

Tissue from four malignant tumors and one specimen of benign tissue from human beings were transplanted into the anterior chamber of sixteen guinea pigs and within the lens of the eye of five animals. Tissue from 36 malignant tumors, three benign tumors, and one specimen of placental tissue from patients were transplanted solely into the anterior chambers of 170 guinea pigs. All of the specimens were removed surgically from living patients. Carefully selected portions of each specimen were placed in a sterile Petri dish which was kept in the refrigerator until shortly before the transplants. The period of refrigeration was usually one to four hours' duration. Immediate study of frozen sections of tumor tissue contiguous to the portion selected for transplantation was made in order to evaluate the character of the transplant.

TECHNIC OF TRANSPLANTATION

A sterile technic was employed in all phases of the experiments.

The animals were anesthetized with sodium pentobarbital administered intraperitoneally.

A small piece of tumor is loaded in a trocar. The nictitating membrane is grasped with forceps, which serve to immobilize the globe of the eye. An incision is made in the cornea, near the sclero-corneal junction. The loaded trocar is inserted and advanced to the angle on the opposite side of the anterior chamber. The obturator is depressed, depositing the transplant in the desired location. A cotton applicator stick rolled gently from the incision site across the surface of the cornea toward the site of the transplant secured the transplant in the angle.

Intralenticular transplantation may be accomplished by directing the trocar beneath the capsule of the lens. One eye in each animal was used as the site of the transplant. No further treatment of the eye was necessary, and the animals were kept under ordinary conditions of cage life.

Fixed sections were made of the tissue contiguous to the portions used as transplants as a final control of the character of the tissue transplanted.

The experiments were usually terminated after about 60-70 days of observation. In several instances one member of the series of animals harboring transplants of a given tumor was observed for several months.

Complete necropsies were performed on all animals.

RESULTS

An appreciation of a few facts concerning the lens of the eye is essential in evaluating the results of this study. The capsule of the lens is a hyaline membrane secreted by a single row of cuboidal cells covering the anterior surface of the lens (30). The capsule is described, in part, in Gray's Anatomy (18) as follows: "It is brittle but highly elastic, and when it is ruptured the edges roll up with the outer surface innermost." Small wounds of the capsule may be closed with the formation of a small cataract. Varying amounts of the lenticular fibers may be extruded and may become free masses in the anterior chamber if the wound is large. These masses are gradually dissolved by the aqueous humor and pass out with it through the angle of the chamber. In this manner a large part of the lens, with the exception of the capsule, may be absorbed (31).

Tissue transplanted both into the anterior chamber and into the lens of the eye.—The results of this group of transplants are summarized in Table 1. Four intralenticular transplants of malignant tumors and one of benign tissue survived and in some cases grew. The capsule of the lens which surrounded the transplants protected them from vascularization. Consequently, the host could not react to the alien transplants, which were nourished by imbibition of nutrient material through the capsule, just as the lens is normally nourished.

On the other hand, transplants into the anterior chamber were completely absorbed, or showed residual reactions of the host in and about remnants of the stroma of transplant. The tumor cells were destroyed. One exception will be described later.

Thus the fundamental difference observed between transplants into the anterior chamber and intralenticular transplants was vascularization of the former. Avascular transplants within the lens
Fig. 1.—Tissue 1. a. A squamous-cell epithelioma of the bronchus (hematoxylin and eosin, X350). b. Sixty-four days after transplantation of tissue into the anterior chamber. The cornea appears above, the iris below. The tumor has been destroyed. Note residual lymphocytic infiltration in the angle (hematoxylin and eosin, X45). c. Intralenticular transplant of tissue 1, 63 days after transplantation. The tumor is entirely within the lens. On the left note the characteristic sinuous conformation and rolling of the edge of the ruptured anterior capsule of the lens (hematoxylin and eosin, X27). d. Higher magnification of c (hematoxylin and eosin, X80). e. Higher magnification of d (hematoxylin and eosin, X350).
survived and grew as in vitro tissue cultures. They are thus comparable somewhat to in vitro tissue cultures grown in the serum of alien species.

A squamous-cell carcinoma of the bronchus (Fig. 1, a) was transplanted into the anterior chambers of three animals and within the lens of one animal. None of the transplants into the anterior chamber survived. Figure 1, b, illustrates the residual lymphocytic infiltration of the remnant of one of the transplants. No tumor cells remained 64 days after transplantation. On the other hand, the intralenticular transplant of the tumor survived 63 days and had grown around the periphery of the lens just beneath the capsule (Fig. 1, c, d, and e). A sinuous conformation and rolling of the edge, characteristic of a fractured lenticular capsule, were present in the left portion of the lens (Fig. 1, c). Only a small portion of the lenticular fibers was lost, and the posterior capsule appeared to have closed the defect in the lens.

A papillary adenocarcinoma of the endometrium (Fig. 2, a) was transplanted into the anterior chambers of four animals and within the lens of one animal. Three of the transplants in the anterior chamber were completely absorbed, while one underwent calcification and osteogenesis (Fig. 2, b). The intralenticular transplant survived 68 days (Fig. 2, c and d). There was neither vascularization nor cellular infiltration of this transplant. Most of the lenticular fibers were extruded and absorbed by the aqueous humor. The anterior capsule demonstrated the characteristic sinuous outline of a fractured capsule. The fine posterior capsule can hardly be traced, which is usual, in Figure 2, c. However, it can definitely be identified in the higher magnification (Fig. 2, d).

The animal harboring an intralenticular transplant of fibrosarcoma of the forearm died thirteen days after transplantation. Figure 3 illustrates the surviving transplant completely protected from vascularization and cellular infiltration by the lenticular capsule. Most of the fibers of the lens have been lost to the aqueous humor and absorbed. The serpentine anterior lenticular capsule can be traced, on careful study, throughout its course.

More than 90 per cent of the adeno-acanthoma of the ovary was composed of adenocarcinomatous tissue (Fig. 4, a). An intralenticular transplant of this tumor partially survived for 60 days. The transplant was incompletely inclosed by the capsule, and consequently a large part of the tumor was infiltrated with lymphocytes and destroyed. A transplant into the anterior chamber partially survived for 60 days (Fig. 4, b). The anterior chamber was filled with an exudate of lymphocytes and some polymorphonuclear leukocytes. Resistant islands of squamous cells survived (Fig. 4, b and c).

One intralenticular transplant contained tissue from a small-cell carcinoma of the bronchus, as well as normal bronchial elements: cartilage, ciliated columnar epithelium, and mucous glands (Fig. 5, a). Sixty-four days after transplantation, an island of viable, benign cartilage and a single space lined with ciliated columnar epithelium (Fig. 5, b and c) was evident. Almost all of the lenticular fibers were lost. The capsule of the lens had collapsed and inclosed most of the transplant. On the right, where a free edge of the capsule was curled on itself, early cellular infiltration from without was observed. Anteriorly, the damaged lens was adherent to the posterior surface of the cornea. The lenticular capsule could be differentiated readily from Descemet's membrane.

Results of transplant solely into the anterior chamber.—Of transplants from 36 malignant tumors, 3 benign tumors, and 1 placenta in the anterior chamber, none survived. The results of the 170 transplants into the anterior chamber are summarized in Table 2.

Usually transplants in the anterior chambers were completely absorbed in all animals harboring a given tumor. Occasionally, one animal in each series showed some residual host reaction. Cellular infiltration, with either lymphocytes or plasma cells predominating, was observed in remnants of thirteen transplants into anterior chambers. Vascularization and destruction of the tumor tissue had occurred (Fig. 6). In four cases these reactions were incorrectly interpreted as tumors while the animals were living. Fibrosis and hyalinization were observed as residual changes in eleven transplants. None were interpreted as tumors in the living animals. Residual fibrosis and calcification were present in remnants of six transplants, one of which was interpreted as tumor growth before necropsy (Fig. 7). Calcification with osteogenesis occurred in thirteen remnants of transplants, of which six were erroneously interpreted as tumor tissue in living animals.

Residual lymphocytic or plasma-cell infiltration of the iris was observed in 23 animals.

Early observations after transplantation.—Early observations after transplantation were limited, since they were not the primary purpose of the study.

The transplant into the anterior chamber from a sarcoma (tumor 10) appeared viable when the animal died, one week after transplantation. Early vascularization was present, but cellular reaction had not occurred around the transplant at this early stage. All the tumor cells in tissue from a semi-
FIG. 2.—Tissue 3. a. A papillary adenocarcinoma of the endometrium (hematoxylin and eosin, X120). b. Transplant of tissue 2, 68 days after transplantation into anterior chamber. Evidence of residual fibrosis, calcification and osteogenesis of tumor in the angle (hematoxylin and eosin, X45). c. Intralenticular transplant of tissue 2, 68 days after transplantation. Most of the lenticular fibers have been extruded and absorbed, leaving a collapsed lenticular capsule. The tumor is just beneath the posterior capsule on the left (hematoxylin and eosin, X80). d. Higher magnification of c. Note the very fine posterior capsule (hematoxylin and eosin, X450).
Fig. 3.—Tissue 3. A fibrosarcoma of the forearm. a. Intralenticular transplant thirteen days after transplantation. Most of the lenticular fibers have been extruded and absorbed. The clearly defined anterior capsule is protecting the tumor tissue from vascularization and cellular infiltration (hematoxylin and eosin, ×32). b. Higher magnification of a. Note avascularity of tumor transplant. There is some vacuolation of anterior capsular epithelial cells (hematoxylin and eosin, ×125). c. Higher magnification of b (hematoxylin and eosin, ×450).
Fig. 4.—Tissue 4.  

1. An adeno-acanthoma of the ovary. More than 90 per cent of the tumor was composed of adenocarcinomatous tissue, as illustrated (hematoxylin and eosin, ×250).  

2. Transplant of tumor 4, 60 days after transplantation into anterior chamber. The anterior chamber is completely filled with an exudate of polymorphonuclear neutrophils and lymphocytes which surround several small islands of resistant squamous-cell carcinoma (hematoxylin and eosin, ×25).  

3. Higher magnification of 2 (hematoxylin and eosin, ×200).
FIG. 5.—Tissue 5. Normal bronchial elements: cartilage, mucous glands and ciliated columnar epithelium, as well as small-cell carcinoma. a. Section made from tissue from which portions for transplantation had been removed. b. Sixty-four days after intralepticular transplantation. An island of benign cartilage and ciliated columnar epithelium lie within the lenticular capsule. Note the characteristic sinuous conformation of a ruptured lenticular capsule and rolling of the free edges of the capsule. Practically all of the lenticular fibers have been lost. Scar tissue binds the damaged lens to the posterior surface of the cornea (hematoxylin and eosin, X35). c. Higher magnification of portion of b. Note the benign ciliated epithelium (hematoxylin and eosin, X800).
nomma which was transplanted into the anterior chamber of an animal which died eighteen days later were destroyed. Lymphocytes, plasma cells, and a few foreign-body giant cells had infiltrated the remnant of the tumor (tumor 16). Three transplants of malignant tumors (tumors 6, 8, and 9) into the anterior chamber were completely absorbed within three weeks after transplantation.

**COMMENTS**

The results of this study offer good evidence that heterotransplants of malignant tumors of human beings into the anterior chamber of the eye can seldom be accomplished. Opinions were based on the observation of 167 transplants of 40 malignant tumors. Eleven transplants of three benign tumors, four transplants of placental tissue, and four of normal bronchial tissue were also observed, but the tissue in each case was destroyed by the alien hosts.

The survival of benign as well as malignant heterologous tissues when transplanted within the lens was a unique observation. Although only five intralenticular transplants were observed, their survival suggests that similar results might be expected in a larger series. Successful heterologous intra-lenticular transplantation of normal tissue seems especially significant.

The fundamental difference between anterior chamber and intralenticular transplants was vascularization of the transplants into the anterior chamber as compared with the lack of vascularization of intralenticular transplants. Subsequent invasion of the transplants in the anterior chamber by lymphocytes, plasma cells, and occasionally foreign-body giant cells destroyed the transplant.

Lambert and Hanes (22) and Lumsden (26) demonstrated that tumors as well as normal tissue would grow in the plasma of alien species. These intralenticular transplants survived as in vivo, avascular tissue cultures nourished by imbibition of nutrient material from the intra-ocular fluids.

As indicated in the introduction and résumé of the literature, there have been many conflicting reports concerning heterologous tumor transplantation into the anterior chamber. Zahn (37), Herzog (16), Ruben (32), Woglom (36), and recently Lushbaugh and Steiner (27) were unable to achieve success, and the reports by Hegner and Keysser of successful heterotransplantation of sarcoma of human beings into the anterior chamber were brief and did not contain illustrations. They failed to achieve successful transplants of carcinomas. Furthermore, actively proliferating granulation tissue might be confused with sarcomas.

Since 1941 Greene (4-8) has made reports of successful heterotransplantation of several tumors from animals and human beings into the anterior chamber. Apparently metastasis has not occurred in the animals harboring heterotransplants of

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TABLE 2

Tissue from Tumors of Human Beings Transplanted Solely into Anterior Chambers of Eyes of Guinea Pigs

malignant tumors. On the other hand, metastasis has been described in animals harboring heterotransplants of tumors in the anterior chamber (12, 14, 15, 20). It seems reasonable to expect metastasis to occur if vascularization of heterotransplants
FIG. 6a.—Transplant of tissue 13, 60 days after transplantation into anterior chamber. The tumor cells have been completely destroyed. The remnant of the tumor is vascularized and infiltrated with plasma cells and lymphocytes (hematoxylin and eosin, ×50). b. Higher magnification of a. Note vascularization and character of cellular infiltrate in remnant (hematoxylin and eosin, ×400).

FIG. 7.—Transplants of tissue 15, 64 days after transplantation into anterior chamber. The tumor cells are completely destroyed. Residual calcification of some tumor remnant and lymphocytic infiltration of the ciliary body are present (hematoxylin and eosin, ×50).
of malignant tumors into the anterior chamber was successful.

It might not be amiss to suggest that investigators might re-examine their material in view of the results of intralenticular transplants reported herein. Masina (28) described a "pseudocapsule" around one of his transplants into the anterior chamber. This might represent the lenticular capsule. As indicated in the results, most lenticular fibers may be extruded, leaving only the capsule collapsed around some tumor tissue. Furthermore, this inclosed avascular transplant may be displaced to the vicinity of the angle.

Greene's criticism of the generally accepted methods of microscopic diagnosis of neoplasms hardly seems admissible. The evaluation of biologic characteristics of neoplasms based on histopathologic characteristics is a sound principle. Since the days of Virchow, pathologists have been correlating the behavior of tumors with their morphologic and cytologic characteristics and have thus established well-founded criteria for the evaluation of neoplasms. It is, of course, desirable for the pathologist to classify accurately all neoplasms studied. While it is occasionally difficult to classify accurately the highly malignant, completely undifferentiated tumors, still the biologic implications are clear in such instances to physicians and laymen alike. Even if infiltrative or metastatic tumors were transplantable to the anterior chamber of alien species, the clinical value of such a procedure would be limited. The present goal in diagnosis of tumors is to discover neoplasms while they are still largely or completely in situ, not after they are widely infiltrative or have given rise to distant metastasis.

The technic of intra-ocular transplantation is not difficult. The transplants into the anterior chambers were accurately placed with few exceptions. The tissue transplanted was carefully evaluated both by frozen sections before transplantation and by fixed sections of the tissue contiguous to the portions transplanted. The period of refrigeration was not excessive.

Evaluation of transplants by gross examination is unreliable.

The element of time has entered into several reports of heterotransplants. One animal died 1 week after transplantation of tissue into the anterior chamber. Transplantation should not be considered successful in this case even though early vascularization was evident. Although meager, the early results which were available suggested that between 1-3 weeks after transplantation, destruction of the anterior chamber transplant begins.

There is a need for more early post-transplantation observations.

Greene has indicated that he has observed growth beginning several months after transplantation into the anterior chamber. In none of the transplants which were observed for several months was there any evidence of survival or growth of the transplant.

It seems reasonable to suggest that careful attention to the technic of transplantation and careful choice of material for transplantation should obviate the necessity of using unduly large numbers of animals in a series for a given tumor.

An instance of only partial survival incident to partial protection of a transplant by the lenticular capsule has already been cited. Another factor which might delay vascularization and reaction of the host to the heterotransplant is the possibility of the transplant's lying free and unattached in the aqueous humor of the anterior chamber for a period. Such an avascular transplant should also probably be considered an in vitro tissue culture and not a successful transplant.

These results indicate that successful heterotransplantation of tumorous tissue as a biologic test of malignant disease is not a feasible procedure.

SUMMARY AND CONCLUSIONS

Transplants of 40 malignant tumors of human beings into the anterior chambers of 167 guinea pigs did not survive, with one exception. In this single exception partial survival of resistant squamous-epithelial elements occurred with a marked reaction of the host.

Transplants of four malignant tumors and one specimen of normal tissue from human beings into the lens of the eyes of five guinea pigs survived, and in at least one case the transplant grew. The lenticular capsule prevented vascularization, infiltration, and destruction of the intralenticular transplants which were nourished by imbibition of nutrient material from the intra-ocular fluids through the capsule. Thus the avascular, intralenticular transplants are tantamount to in vitro tissue cultures.

Intralenticular transplantation is probably of limited value in assessing the biologic characteristics of neoplasms, since these limited observations suggest that any heterologous tissue, benign or malignant, will survive within the lens.

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