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THE INFLUENCE OF DONOR-RECIPIENT SENSITIZATION ON CORNEAL GRAFTS*

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The clouding of mechanically successful corneal grafts three to five weeks postoperatively has not been explained adequately in eyes which would be expected to support a clear transplant. Many suggestions have been offered to account for this abnormality of the graft, but none have been substantiated sufficiently by animal experimentation or clinical observation.

It is the purpose of this report to present experimental evidence which will support the theory that one cause of late clouding of corneal grafts is the sensitization of the recipient to material from the donor, and that this type of reaction is dependent on the biologic specificity of individual animals of the same species. A possible method of preventing this type of clouding is also mentioned.

No attempt will be made to refer to all of the suggestions which have been put forward as a cause of the late clouding of corneal grafts. Only a few of the more recent reviews will be cited.

In a symposium on corneal transplants in 1947, Castroviejo[1] stated that the late clouding of keratoplasties was due to a uveitis in the recipient eye and that removal of a focus of infection sometimes would result in a clearing of the graft. At the same symposium,[2] a second suggestion was that this type of opacification was due to an allergic reaction which resulted from a sensitization of the recipient by the homotransplanted material. No experimental data were offered to substantiate this view.

In 1948, Paufique, Sourdille, and Offret[3] divided the cases with technically perfect corneal grafts which became cloudy into three groups according to the time of onset of the opacification. The suggested cause for each of these types of clouding was based on clinical observation.

The first group included those eyes in which the disturbance began by the 10th postoperative day. The etiologic factor in these instances was the sensitization of the recipient by foreign protein in the transplant.

A second group included those cases in which the opacification occurred during the third postoperative week. The clouding of these grafts was caused by a disturbance in the metabolism of the transplant.

The third group included those cases in which the graft became cloudy after the

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third postoperative week. This type of opacification was due to an invasion of fibroblasts and blood vessels from the recipient cornea.

Klima,[4] in 1949, stated that the clouding of corneal transplants was due to an allergic reaction caused by the immunobiologic difference between the host and the donor. He based his opinion on a series of experiments in which he produced a keratitis in rabbits by two injections, given 14 days apart, of 0.05 cc. of homogeneous corneal extract. Corneal inflammation occurred frequently if the material for the two injections came from the same donor, but occurred only rarely if a separate donor was used for each injection. He thought this demonstrated that a sensitization of the recipient to the donor could be produced by material in a corneal transplant.

The only reference to late clouding of grafts in the International Symposium on Corneal Surgery in 1949 was that of Barraquer[5] who stated that this type of opacification was due to a "hypotrophic" change because the graft "may not receive a sufficient quantity of the elements necessary for its metabolism. . . ."

Status of donor-recipient sensitization in tissues other than cornea

If skin is transplanted from one individual to another, it will "take," survive, and show signs of proliferation in the form of migration and mitosis of the epithelial cells. Almost invariably, however, the grafts become necrotic and slough two to six weeks after operation. This destruction of the transplanted material is the result of a sensitization of the recipient by some product of the donor graft.

Underwood,[6] in 1914, on the basis of clinical observation on a patient who had skin homotransplants for extensive burns, suggested that the destruction of the donor material was similar to an anaphylactic reaction. Holman[7] made a similar observation on a child who had had an avulsion of the skin of the leg and developed an exfoliative dermatitis after receiving multiple skin grafts. He also noted that the sensitization produced by the grafts was specific for an individual donor. The skin taken from a second donor remained in excellent condition for four to five days after a second set of grafts from the original donor had completely disintegrated. This occurred even though the second set of grafts from the original donor had been applied several days after those from the second donor.

Medawar[8] in a series of experiments on rabbits has added further evidence to the theory that homografts are destroyed because of donor-recipient sensitization. He has shown that multiple skin grafts are destroyed more rapidly than a single pinch graft, and that a second set of transplants from the same donor disintegrates more rapidly than the original material, even though they are inserted at a point distant from the original operative site.

Skin taken from a second donor and inserted in the original operative site survives for as long as the first set of grafts. The allergic reaction appears to be dependent on a vascular invasion of the donor material.

Grafts to the anterior chamber survive for a much longer time if they remain free in the aqueous or attached to the avascular posterior surface of the cornea than if they adhere to the anterior surface of the iris and become vascularized.

Donor-recipient sensitization is not organ specific, however, for the accelerated destruction of homografted skin can be produced by previous injections of leukocytes. The sensitized state cannot be demonstrated by tests for agglutinins in the blood, nor can it be elicited by the use of tissue cultures and serum from the sensitized animal.

These observations and many others have adequately demonstrated that almost any tissue transplanted from one individual to another will be destroyed due to the results of sensitization of the recipient to the donor material.

There are instances, however, in which tissue can be transplanted from one individual to another and appear to survive. These are grafts from one identical twin to another and cartilage grafts. Grafts between identical twins survive because of the biologic similarity of the donor and the recipient. Cartilage transplants are probably not destroyed because there are not enough cells in the material to elicit an allergic reaction and the cells are protected by the cartilaginous matrix from the blood vessels of the recipient.

There are other conditions in which grafts are not destroyed for several weeks or months after transplantation. These are grafts to the anterior chamber of the eye, the uterus (pregnancy), and the brain.

Transplants to the anterior chamber of the eye are not destroyed so rapidly as elsewhere in the body because the blood vessels of the recipient do not invade the donor material for several days to a week, thereby allowing the grafted material to become acclimated to the host.

In pregnancy, the embryo survives in the uterus because of the lack of vascular invasion from the host and because of the weak antigenic properties of the embryo.

It is not known why grafts to the brain survive, but it has been suggested that the absence of lymphatics in the brain prevents tissue transplanted in this area from causing a donor-recipient sensitization.

The status of corneal grafts in relation to donor-recipient sensitization has never been clearly defined. In recent studies[9, 10] which were made to determine the fate of the donor material in corneal grafts to rabbits, it was concluded that the epithelium and endothelium of the transplants were replaced. The corneal nerves degenerated. The stromal fibers and glassy membranes were not replaced. The stromal cells did not undergo a massive dissolution at any time, but it could not be determined whether or not the keratocytes were gradually replaced.

On the basis of these histologic observations, it can be suggested that clear grafts do not show a donor-recipient reaction similar to that found in the skin for there is no massive destruction of stromal cells at any one time after operation. The poor antigenic properties of corneal transplants may be accounted for by the relatively small number of cells in a corneal transplant, and the avascular bed into which it is inserted. In these respects, corneal grafts may be compared to cartilage grafts.

The following studies were designed to show whether or not sensitization of the recipient to the donor material would affect the clarity of a corneal graft.

Experimental studies

Young albino rabbits weighing approximately two to four Kg. were obtained from a single dealer. No attempt was made to determine whether the animals used in a single experiment were from the same litter or were genetically related.

Keratoplasties were performed with a mechanical trephine. Three to four grafts, 4.5 mm. in size, were obtained from one eye of the donor and a single transplant was inserted into an eye of the recipient. Transplants were held in place by criss-cross sutures inserted in the recipient cornea.

The eyes were cleansed every day for the first week after operation and every other day during the second week. The sutures were removed on the seventh postoperative day. The reactions of the eye and the transplant were recorded twice a week.

Grafts which are clear or only slightly edematous two weeks after operation pass through the following sequence of events. The recipient cornea and transplant are edematous during the first seven to 10 days. The iris is hyperemic and thickened.

Blood vessels invade the cornea to a varying degree depending on the extent of the postoperative reaction. They usually advance to the margin of the donor material, and occasionally will invade the edge of the transplant for approximately 0.5 mm.

The anterior chamber is usually present at all times and anterior synechias occur only rarely. The eyes show a slight to moderate inflammatory reaction two weeks after operation, and are almost quiescent at three weeks after the operation (fig. 1).

With this technique, approximately 50 percent of the homotransplants to normal rabbit corneas remained clear. If the transplant was clear or only slightly hazy, the inflammatory reaction mild and the pannus not extensive, two weeks after operation, then only one graft in 60 eyes became cloudy at a later date. This is in marked contrast to human grafts which not infrequently appear successful two weeks after operation only to become cloudy a few weeks later.

A possible explanation for the absence of this type of late clouding in rabbit corneas is that they are not as susceptible to donor-recipient sensitization as man, and that the 4.5-mm. grafts which were used do not supply enough antigen to produce this reaction.

An attempt was therefore made to increase the dose of antigen in these rabbits by inserting a 2.0 by 2.0 cm. piece of skin from the same donor into a pocket flap under the panniculus carnosus of the recipient abdominal wall. It has been shown that skin grafts of this type survive and produce a sensitization as well as those place on a prepared surface bed.[8c]

In the first set of experiments, skin was inserted two weeks before the corneal transplant in 12 animals. This was done to allow the sensitization produced by the skin to have its greatest possible effect on the corneal tissue. Operations done in this manner resulted in opaque grafts in every instance. In several eyes, the donor material became very edematous, appeared necrotic, and sloughed.

In the next set of grafts, the skin and corneal material were inserted at the same time in eight rabbits. Again all of the transplants became cloudy but, in two instances, the grafts were relatively clear at the end of 14 days before they became opaque during the third postoperative week.

These two sets of animals indicated that the donor-recipient sensitization so produced had a deleterious effect on the grafts. However, there are so many uncontrollable variables which might produce an opacification of a corneal graft in rabbits during the first two postoperative weeks that it was thought desirable to perform an experiment in which more exact controls could be obtained.

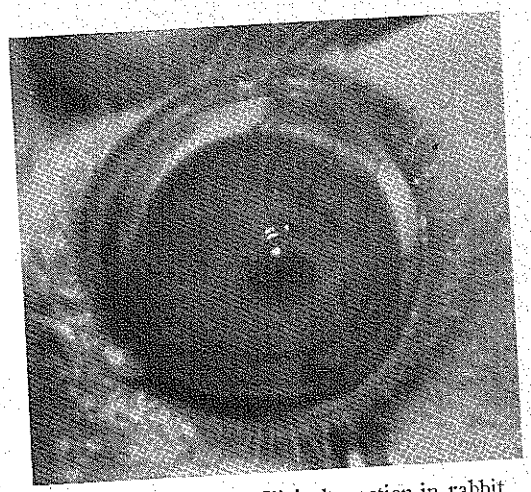

Fig. 1 (Maumenee). Clinical reaction in rabbit eye 10 days after corneal graft.

To this end, the corneal operation was performed first and only those animals which had a clear or only slightly cloudy graft in a relatively uninflamed eye two weeks after the operation were used.

Skin from the same donor which supplied the corneal material was then inserted into the abdominal wall of the recipient, two to four weeks after the ocular operation. Twenty-eight grafts in 30 animals so treated became cloudy two to four weeks after the insertion of the skin transplants. This clouding of the grafts is in striking contrast to the late clouding of only one graft out of 60 animals in which a booster skin graft was not given.

Further control experiments were done to determine whether the deleterious effect of skin transplants on the corneal grafts was due to an organ or an individual specificity.

To this end, in 14 animals, skin from sup-

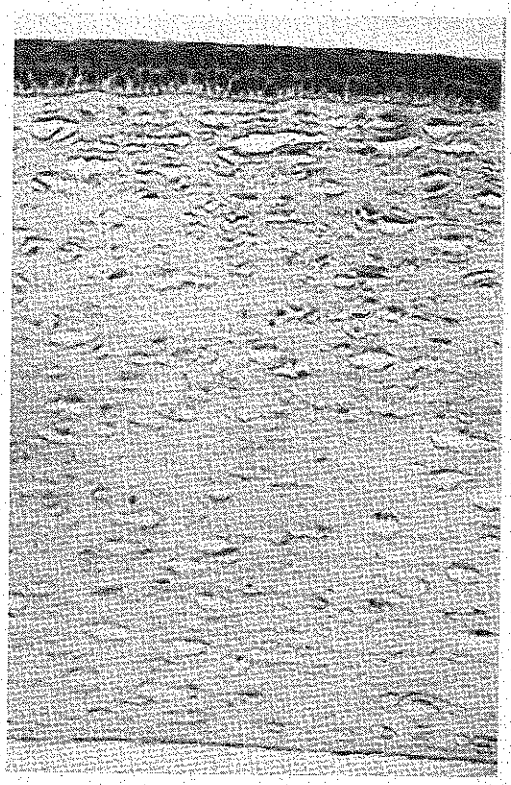

Fig. 2 (Maumenee). Clear corneal graft two weeks after operation, showing slight edema of the stroma, normal stromal cells, epithelium and endothelium. (×100.)

posedly genetically unrelated donors was inserted two to four weeks after the ocular operation. Twelve grafts remained clear. In eight of these animals, one eye was grafted and two weeks later skin from the donor of the first eye was inserted under the abdomen. At the same time a corneal transplant was inserted into the unoperated eye from an unrelated donor.

In six instances the unrelated cornea remained clear and the related cornea became cloudy. Thus, it seems that the clouding of the corneal transplants produced in these animals by the insertion of skin from the same donor is due to an individual hypersensitivity.

It is not possible to state with any degree of certainty why the two grafts in the sensitized animals did not become opaque. Possible explanations are: (1) That sensitization cannot be established in every animal by this technique, or that not all grafts will be influenced by this sensitization, (2) the donor and recipient animals may have been litter mates, (3) or the graft survived because of the lack of functioning blood vessels in the recipient cornea.

It is interesting that when the corneas of these two animals were examined with the aid of a strong light and a loupe which magnified approximately 1.7 times, blood vessels could not be seen in the recipient cornea for more than a millimeter or two.

The clinical appearance of the ocular reaction in these eyes was extremely consistent. On the day before or on the same day the graft became cloudy, the corneal and circumcorneal vessels became congested, and the iris hyperemic and thickened. The stroma in

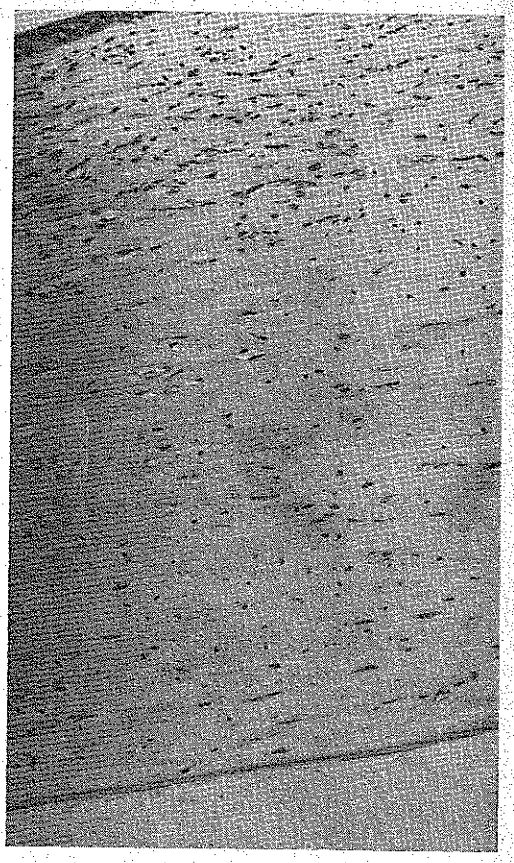

Fig. 3 (Maumenee). Corneal graft which was clear for five weeks before opacification due to sensitization. Note edema of stroma, scarcity of stromal cells, and detachment of endothelium.

the graft adjacent to the largest group of vessels became edematous and cloudy.

During the next day or two the clouding spread throughout the entire graft and not infrequently the adjacent recipient cornea became slightly edematous. The blood vessels invaded the graft and, in the most severe reactions, the keratoplasty became opaque and vascularized.

In several instances in which the reaction

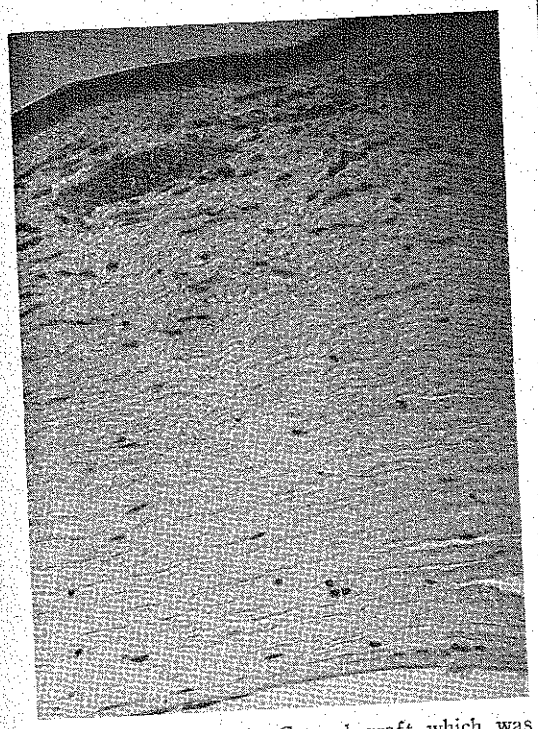

Fig. 4 (Maumenee). Corneal graft which was clear for five weeks before opacification due to sensitization. Note edema of stroma, absence of stromal cells and endothelium, and invasion of blood vessels in superficial stroma.

was not so severe, the edema in the keratoplasty subsided leaving either a nebulous opacity in the superficial portion of the transplant or a thin white sheet of tissue on the posterior surface of the graft.

These latter reactions seemed to occur more frequently when the skin was inserted three to four weeks after the corneal graft rather than two weeks after the operative procedure. The course of events in these transplants was extremely similar to that

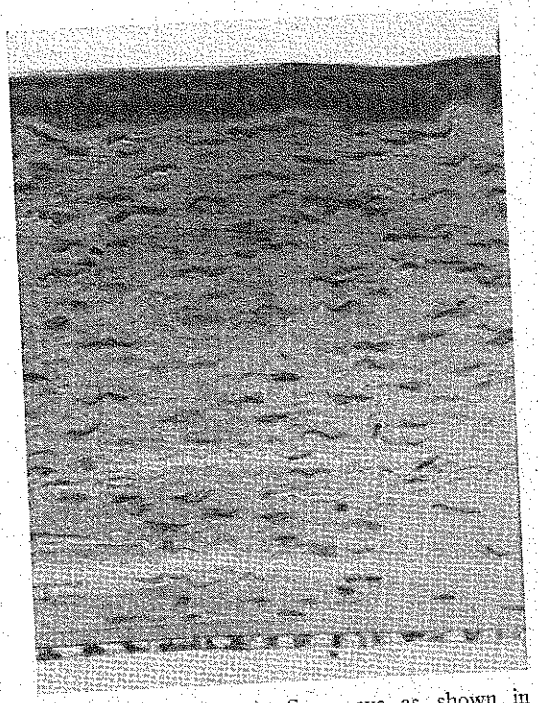

Fig. 5 (Maumenee). Same eye as shown in Figure 4. Recipient cornea adjacent to corneal graft. Note normal appearance of cornea as compared to graft.

seen in the late clouding of human keratoplasties.

A histologic examination has been done on only eight eyes in which corneal grafts were clear and then became opaque due to an induced allergic reaction. Material for this part of the study is, therefore, not sufficient to give a detailed chronologic description of the sequence of pathologic changes which occur.

Histologic sections of clear grafts two to three weeks postoperatively usually show the transplant to be the same as a normal cornea except for a slight edema of the stroma (fig. 2). There are few, if any, polymorphonuclear cells in the material and the stromal cells are normal in appearance and number.

Corneal transplants which remain clear for four to six weeks after operation before they become cloudy due to a sensitization, show many changes which are not found in clear grafts. In eyes removed two to six days after the onset of the clouding, the stroma of the graft is edematous, and the endothe-

Fig. 6 (Maumenee). Corneal graft which was clear for six weeks before opacification due to sensitization. Note infiltration with leukocytes and increased number of stromal cells.

lium is detached from Descemet's membrane (fig. 3).

In some instances there is an almost complete loss of stromal cells in the transplant (fig. 4). In other grafts there is a marked infiltration by polymorphonuclear and lymphocytic cells (fig. 6). The blood vessels adjacent to and in the transplant are congested and dilated.

In eyes which have been removed a week or so after opacification, the tissue is still infiltrated with polymorphonuclear and lymphocytic cells which are migrating to the graft. The endothelial and stromal cells in the recipient cornea remain normal (fig. 5).

It may be concluded from these experiments that sensitization of the recipient to a specific donor will produce an opacification of the graft if the reaction occurs before the fifth to seventh postoperative week. The histologic response of the donor material is essentially the same as that seen in homogeneous skin grafts.

The severity of the reaction in the eye and the permanency of the opacity is in part dependent on the time of onset of the sensitization after the insertion of the corneal graft. The clinical appearance of the opacification when it occurs three to seven weeks after the ocular operation in rabbits is very similar to the late clouding of corneal grafts in man.

Evidence for survival of donor cells in grafts

Many attempts have been made to determine whether or not the donor stromal cells in homogeneous grafts survive or if the transplant merely acts as a framework for the recipient cells. This question cannot be definitely answered by routine histologic studies, for it is impossible to determine by this method if there has been a gradual replacement of the stromal cells. Likewise, introduction of some foreign substance into the cells of the recipient or donor to identify them is subject to error, for it is possible that the marked cells may be destroyed and their identifying substance phagocytized by the surviving cells of the host or the donor.

The use of the biologic individuality of the animal would seem to offer a solution to the problems of identifying the donor material. Sufficient studies have not been done as yet to state with certainty whether the individual sensitivity is due to the stromal cells or fibers. However, work on other tissues suggests that it is the cells and not the framework which causes the sensitization.

If this is correct, it appears that the donor cells either survive or maintain their identity for a month or six weeks after grafting and then die or assume the nature of the host. Thus, 28 grafts in 30 instances became cloudy if sensitization was produced before the sixth to seventh postoperative week.

On the other hand, when skin from the same donor as the corneal transplant was inserted into seven animals from six weeks to

four months after the ocular operation, in no instance did opacification of the cornea occur.

It is possible that atrophy and obliteration of the blood vessels in the cornea prevented sufficient antibodies from reaching the graft to cause an allergic reaction in these cases. To test this, one eye was kept in an irritated state and the blood vessels of the conjunctiva engorged, for two months after skin grafting, by injecting hypertonic sodium chloride under the conjunctiva twice a week. The corneal transplant in this animal did not become opaque.

Prevention of opacification of corneal grafts caused by donor-recipient sensitization

The discovery of the response of allergic reactions to cortisone and ACTH[11] suggested that these compounds might be useful in preventing the clouding of corneal grafts which occurs as a result of donor-recipient sensitization. It seemed that these substances might be of value even though they prevented the allergic reaction only during their administration and for a short time thereafter, for it has been shown, in this study, that sensitization after the seventh postoperative week had no influence on the clarity of the corneal grafts.

In six rabbits a keratoplasty was performed and skin from the same donor was inserted at least two weeks later. These animals were treated with intramuscular injections of 15 mg. cortisone per Kg. of body weight each day. This is approximately 15 times the dose used in man.

In three animals the drug was begun after the graft became cloudy as a result of sensitization.

In the first rabbit, skin was inserted three weeks after the corneal operation and the transplant became cloudy and the eye hyperemic 22 days after the skin graft. Cortisone was started on the second day of clouding of the graft and was continued for six days. The hyperemia subsided in two days and the graft cleared to translucency in 11 days. Three weeks after the cortisone was discontinued, and eight weeks after the skin operation, the transplant was clear. Unfortunately, at this time the rabbit died.

In a second animal, skin was inserted 28 days after the ocular surgery and clouding of the graft occurred in 15 days. Cortisone was started and continued for six days. Both the hyperemia of the eye and the graft cleared in four days. The eye has remained unchanged for 8.5 weeks since the cortisone was discontinued and 11.5 weeks since the skin graft.

In the third animal, skin was grafted 32 days after the corneal transplant and the keratoplasty became cloudy 11 days later. Cortisone was started on the second day of the opacification and was continued for nine days. The hyperemia of the eye responded in four days and the graft cleared in nine days. The transplant is still clear and it has been five weeks since cortisone was last used and eight weeks since the skin operation.

In three other animals, a homograft was inserted in one eye and, two weeks later, skin from the same donor was placed under the panniculus carnosus of the abdominal wall and a corneal heterograft from a cat was inserted in the opposite eye. Cortisone, 15 mg. per day, was begun on the eighth day after the last operation and was continued for 14 days.

One rabbit died two days after the cortisone was discontinued. This was 17 days after the skin graft.

A second rabbit died two weeks after the cortisone and five weeks after the skin graft. Again, the grafts in both eyes remained clear throughout the postoperative course.

In the third animal, the heterograft was an operative failure. The homograft, however, remained clear for three weeks after the cortisone was discontinued and six weeks after the skin operation (fig. 7). During the seventh week after skin graft, nine weeks after the keratoplasty, the transplant became slightly hazy and vascularized.

It is realized that cortisone has not been

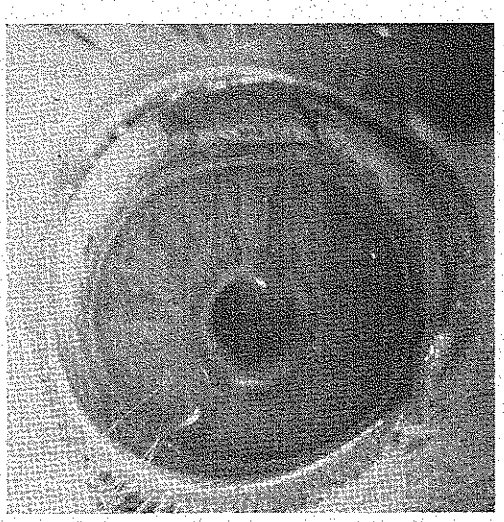

Fig. 7 (Maumenee). Clear corneal transplant six weeks after skin graft. Animal treated with cortisone.

used in enough animals in this experiment to allow definite conclusions to be drawn, but it does seem that this drug has had some beneficial effect on the clouding of corneal grafts which results from a donor-recipient sensitization.

Summary

1. Corneal transplants performed in the manner described in this paper have remained clear in approximately 50 percent of the grafts.

2. Only one graft in 60 instances became cloudy at a later date if the graft was clear or only slightly cloudy two weeks after the corneal operation.

3. When skin from the same donor was used as an antigenic supplement, two weeks after the corneal operation, the corneal transplant became cloudy in 28 out of 30 eyes within two to three weeks after the insertion of the skin.

4. The clinical appearance of the ocular reaction in these eyes was similar to that observed in the late clouding of corneal grafts in man.

5. Histologic sections of the grafts which became cloudy as a result of sensitization in rabbits show an inflammatory reaction similar to that which occurs in homogeneous skin grafts.

6. The biologic individuality of a corneal transplant appears to last for only six to eight weeks after corneal grafting.

7. The opacification of corneal grafts which resulted from a sensitization to the donor material may be influenced by the prophylactic use of cortisone.

Discussion

It is readily admitted that the method used to produce a donor-recipient sensitivity and a clouding of the graft in these experiments differs from a keratoplasty in man in that skin and cornea are never transplanted from the same donor in man. There are two points of similarity, however, in the clouding of the grafts which strongly suggests that it may be of the same origin in both species. First, the clinical appearance of the grafts and the reaction in the eyes are remarkably alike. Second, the time of onset is approximately two to seven weeks after the insertion of the donor material in both cases.

It has been previously stated that one of the reasons why corneal homografts do not always elicit an allergic reaction is that a relatively small number of cells are transplanted to an avascular area. However, it seems reasonable that, if almost every other tissue in the body produces a sensitization when transplanted from one individual to another,[12] corneal transplants would at least occasionally cause a similar response.

Furthermore, the reactions would be more likely to occur if the recipient cornea was heavily vascularized. It has been shown that homografts of skin to the anterior chamber of the eye survive only when they are not in contact with the blood vessels of the iris.[8c]

Clinical studies of corneal transplants are compatible with this suggestion for it has been shown that a higher percentage of grafts will remain clear in patients with keratoconus or central corneal scars where

no blood vessels, or only occluded vessels, are present than if the cornea is heavily vascularized.

It may be asked why a spontaneous sensitization to corneal grafts does not occur in rabbits, if one is expected to believe that this can happen in man. This cannot be answered with certainty at this time, but there are several possible explanations.

First, only normal avascular rabbit corneas were used for recipient eyes. Next, the size of the specimen transferred was small as compared to the rabbit cornea. The grafts were 4.5 mm. in diameter and the cornea 14 to 15 mm. in diameter. In man the grafts are usually 5.5 to 7.0 mm. in diameter as compared with the corneal diameters which are 11 to 12 mm.

Finally, it is possible that rabbits require a larger dose of antigen to produce sensitization than is required in man. This is supported by the findings that nerve grafts survive in rabbits and other lower animals but they are invariably replaced by fibrous tissue in man.[13]

This presentation is not intended to convey the idea that the only cause of clouding of corneal grafts is the sensitization of the recipient to the donor material. There are other obvious causes for clouding of the grafts during the first two postoperative weeks. These are defects in the donor material, poor apposition of the donor-recipient tissues, and pyogenic postoperative infections.

There are also other factors which can cause an opacification of the graft after the second postoperative week. Some of these are well established and others have only a theoretical basis. Thus, it has been observed many times clinically that grafts will become opaque due to an extension of a disease process. This is true in eyes which have an endothelial dystrophy, a lipoidal dystrophy of the stroma, or an active corneal inflammation.

There are also two other possible causes that might account for the late opacification of grafts in some cases. These are foci of lymphocytes in old corneal scars and the destruction of some hypothetical enzymatic system in the cornea or at the limbus which produces a chemical essential for the clarity of the cornea.

It does seem, however, that there are many instances of opacification of grafts where none of the factors just mentioned apply. In this group of cases, it is felt that a donor-recipient sensitization is the genesis of the clouding of grafts.

On the basis of experimental work presented at this time, it seems reasonable that cortisone or ACTH should be used in a clinical study to determine if they will prevent late clouding of corneal grafts after the second postoperative week. In this study it has been shown that cortisone is capable of preventing the allergic response which occurs from the transplantation of tissue from one individual to another if a dose of 15 mg. per Kg. is used for 10 days.

Further, it seems that if corneal tissue can be protected from a donor-recipient sensitization for approximately six weeks, the graft will assume the individuality of the recipient. Thus, the opacification of grafts which would result from this type of allergic reaction might be averted even though the effect of cortisone lasts only while the drug is being administered.

Finally, these experiments are still further evidence that the mechanism of destruction of tissue when transplanted from one individual to another is the result of a sensitization phenomenon. They also demonstrate that this type of reaction is not one of tissue specificity, but individual specificity, because skin transplanted from the same donor caused an allergic reaction in corneal tissue.

Conclusions

1. It has been shown that an opacification of corneal grafts can be produced in rabbits by a donor-recipient sensitization.
2. The clinical appearance of the reaction

in these eyes is very similar to the clouding of mechanically successful corneal transplants in man, where the graft becomes opaque two to six weeks after operation.

3. The donor cells in a corneal graft appear to survive for about six to seven weeks after transplantation when the biologic individuality of an animal is used as a means of identifying the tissues.

4. The clouding of corneal grafts which results from a donor-recipient sensitization can be influenced by the use of cortisone.

5. The clouding of corneal grafts produced in these experiments by the supplemental transplantation of skin is further proof that the destruction of homotransplanted material is the result of a donor-recipient sensitization. It also demonstrates that an allergy so produced will affect more than one type of tissue from the same animal.

Stanford University Hospitals (15).

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