MEDICAL PROGRESS:

Ophthalmological Progress: Sight Restoration by Corneal Transplant

JOHN P. LORDAN, Beverly Hills

Of the 250,000 blind persons in the United States today, 22,000 of these have impaired vision due to corneal scarring. Although half of these patients are unsuitable for graft because of the varied causes of this condition, the recent medical and surgical progress which has been made in the field of keratoplasty indicates that many who believed their conditions to be hopeless can successfully avail themselves of operation.

Surveys of the early literature demonstrate that surgeons were concerned with the problems presented by eye tissue therapy as early as 1789. It was in this year that Pellier made the first unsuccessful attempt at the replacement of diseased tissue by a cornea made of glass and supported by a gold band. The real forerunners of today's modern operation, however, were not reported until the years 1823 and 1824 when Meissner conceived the idea of grafting a transparent animal cornea, and Reisinger gave the name "keratoplasty" to an operation in which he experimented with the substitution of a leukemia by a transparent cornea in the rabbit. The first ideas concerning the contemporary theory of the biologic processes occurring in keratoplasty were expressed in 1843 by Pluvier who, after several years of observation, reported his belief that favorable results of corneal grafting were due to the growth of corneal elements in the host. In his opinion, corneas taken from cadavers supplied the best material for transplantation.

During the early half of the Nineteenth Century, all work in keratoplasty which was attempted on human beings consisted mainly in experimentations with single cases of transplantation, none of which succeeded. The operation was indeed a formidable undertaking due to the limitations of instruments and methods of anesthesia. Despite the lack of favorable clinical results and the pessimism of many physicians, attempts at keratoplasty were continued, and several advances in technique were developed, due mainly to the influence of a German investigator, Von Hippel. This physician, who conducted his experiments from 1870 to 1890, emphasized the importance of partial transplantation of the cornea, and developed a technique in which the trephine, which could measure the exact size and shape of the transplant, became widely used.

It was not until 1907 that an Austrian, Zirm, gained international fame through his report of the first successful case of keratoplasty. Using Von Hippel's trephine, this surgeon succeeded in removing a clear disc from the blind eye of an 11 year old boy and transplanting it to the eye of a 45 year old man whose cornea had become opaque due to a burn from unslaked lime. From 1908 to 1930 interest in eye tissue therapy was again fanned by the work of Elschnig and his co-workers in the Prague Clinic. Of the 203 patients on whom corneal grafting was performed, they recorded 20 per cent success among the cases as a whole, and 73 per cent success in those patients whose leukomas had developed following interstitial keratitis. During the years from 1922 to 1938, the work of Filatov and his associates, who reported 435 keratoplasties carried out in their clinic in Odessa, did much to popularize keratoplasty. These investigators not only restimulated interest in the operation through their development of new instruments, a more perfected technique, and the widening of the indications for corneal transplantation, but it was in this school that the use of the preserved cornea originated.

The most outstanding name in the field of keratoplasty today is that of Castroviejo in New York who, in 1932, reported 300 cases of corneal grafts, 80 of which were performed on human eyes. Since this time credit goes to this investigator for having contributed more than any other to the perfection of sound surgical practice in the present-day methods of eye tissue therapy.

SELECTION OF CASES

Whenever a corneal opacity is the major cause of very poor vision, keratoplasty should be considered. Proper selection of cases is most important, however, for the success of any such operation, and the physician must determine whether the case is favorable for improved vision, whether the operation should be advised for cosmetic effect alone, or whether the results would tend to be unfavorable.

The fate of the transplantation of the cornea depends primarily on the histologic nature of the leucoma found within the recipient eye, with the prognosis of such an operation becoming favorable or unfavorable depending on the degree of opacification discovered there. It is important that the physician conduct a thorough examination prior to the operation to determine the nature of the opacity, the thickness of the cornea, the depth of the anterior chamber, the possible presence of anterior or posterior synechiae, and, in general, the extent to which normal corneal elements can be found within the host. This examination can best be carried out by means of an ophthalmoscope and slit lamp, or, if the leucoma is very dense, by transillumination and infra-red photography.
Those cases which generally afford the most favorable results for the patient are those in which normal intraocular tension is present, the corneal leukemia is not dense enough to cause impairment of vision, the diseased tissue is limited to the cornea, and the central corneal opacities, which will be replaced by the transplant, are surrounded by healthy tissue. Keratoplasty is generally advisable when impaired vision has been caused by phlyctenular keratitis, trachoma, rosacea keratitis, familial corneal degeneration, and by interstitial keratitis when the opacity is not too extensive and the transplant remains in contact with fairly healthy corneal tissue.

Those cases which are less favorable for the achievement of ultimate transparency of the graft, but are still likely to give a high percentage of successful results and considerable improvement in vision, are those caused by certain types of corneal dystrophies, superficial corneal opacities resulting from tear gas burns, superficial opacities extending over the entire area of the cornea when most of the area is normal, and Descemetoceses where the whole opacity may be substituted for a corneal graft. In cases where adherent leukomas are present, it is advisable that keratoplasty be preceded by an iridectomy for a successful result.

Where the eye is amlyopic and there is a dense central leukemia present, it is often advisable to perform a corneal graft for the cosmetic effect alone. Prognosis is usually favorable for these cases where the condition is caused by injury which resulted in blood staining of the cornea, in cases of keratoconus, particularly those where apical corneal changes are present and the patient is not aided by contact lenses, and in cases of central circumscribed corneal leukemia with clear peripheral tissue and in the absence of anterior synechiae. The operation may also be advised for patients with a central superficial or deep leukemia caused by interstitial keratitis whose eyes are "quiet" without underlying pathological change in the iris or the presence of synechiae, and whose Wassermann reactions are negative. The prognosis is usually less favorable and should not be advised for patients whose impaired vision is due to gonorrhea blennorrhea, tuberculosis of the cornea, lipoid degeneration of the cornea, severe lime or acid burns, or the more serious types of corneal dystrophy.

Unless preliminary operations have been performed which have prepared a more favorable soil for the final operation, definitely unfavorable results can be expected should keratoplasty be attempted on patients whose eyes present a dense leukemia covering the entire corneal area, in which (particularly after intra-capsular cataract extraction) aphakia is present, where the intra-ocular tension is increased, or where there is corneal cloudiness with a densely vascularized pannus present. For patients with visual disabilities caused by burns (lime, acid or alkali), glaucoma, or perforating ulcers of the cornea, the operation is ill advised. Again, keratoplasty should not be undertaken for those patients who are very uncooperative and may develop a stormy postoperative period, or for those in whom the corneal opacities have been present for many years, particularly where there is pronounced nystagmus or inflammation present. Experience has demonstrated that cases of corneal opacities caused by pemphigus, corneal opacities with extensive anterior synechiae, large corneal opacities with calcareous degeneration, and those with Fuch's dystrophy have not improved with the grafting procedure.

**BIOCHEMISTRY OF THE TRANSPLANT**

A study of past literature concerning corneal grafts indicates two concepts which have developed relating to the question of the biochemistry of the transplant. The argument which arose centered around the problem of whether the transplant retained its own cellular identity within the recipient eye, or whether it was gradually replaced by the cells of the host. According to the early workers, Lohlein and Salzer, the use of fresh or living tissue was unnecessary since the graft served merely as a temporary framework whose purpose was to guide and support the corneal cells of the host until those cells invaded and gradually replaced the transplant. This theory, which was falsely based on studies of nebulous or opaque transplants in which abnormal corneal elements had been found, has been refuted by modern investigators. Later experimental work in this field has proved that the transplant takes an active part when grafted to the eye of the host by maintaining its own individuality and preserving its separate cellular elements within the parenchyma of the recipient eye.

Castroviejo proved in microscopic studies on transplants removed from six human beings that the original layers of the corneal graft could be recognized as late as several months after the operation had taken place. Fine bears him out in this report when he states that an occasional cross section found in such experimental work would show two layers of Descemet's membrane, the curled edges of one in position, with the new membrane growing across. This proved Filatov's belief that "biologic stimulators" of living tissues can be introduced into a diseased organism by transplantation, and that the regenerative processes of the latter increase while the pathologic disturbances, in turn, diminish or disappear. As Fine has so aptly explained, the cornea is an unusual tissue whose low metabolism determines its small nutritional requirements. While the corneal stroma and endothelium may live indefinitely in aqueous alone, the corneal epithelium has a high metabolic activity which accounts for the rapidity of its regeneration. Castroviejo again found that corneal corpuscular division could take place and that, if the epithelial cells of the graft had been damaged, they might be replaced by the epithelial cells of the host, and likewise a new Descemet's membrane might appear without ensuing nebulousity or opacity. If, however, there was any damage to the stroma of the transplant, it was repaired by the host tissue at the expense of permanent nebulousity or opacity within the graft.
As Fine⁹ points out, the absence of blood vessels is of primary importance in order that the transparency of the graft be permanently insured. Should blood vessels be present within the cornea of the recipient eye, the proliferation of fibrous tissue which invariably follows the implantation of a graft, results in opacity of the transplant. Not only is it imperative, therefore, that fresh, living material be employed as the donor tissue, but the successful transplant must be one which is insensitive and has been grafted to an area which receives protection from the sensitive cornea surrounding it.

The success or failure of the numerous methods of grafting technique depends on three factors: the integrity of the host, the use of suitable healthy corneal tissue, and an exact and accurate cutting of the window in order that a perfect, fluid-tight fit be obtained. The two types of transplants employed by present-day surgeons have either round or square perimeters. These in turn, can be classified two ways: by the amount of surface area which is removed, and by the depth or number of layers cut away. Whether the grafts are circular or rectangular in shape makes no difference as long as the edges are smooth and an exact tracing has been made of both the transplant and the defect in order that a perfect fit will be insured. Through frequent experimentation it has been discovered that complete penetration of the full thickness of the cornea, with the removal of a window, variable in area, is not only the most dramatic but the most successful method of replacing the opaque corneal tissue.

All methods of keratoplasty which were employed up to the year 1932 proved that the use of round grafts made with Von Hippel's trephine, as modified, more or less, by the work of Zirm, Elschng, Filatov and Thomas, had given the best results. Castroviejo, who published the reports of his first experiments in 1932, has made a greater number of improvements in the field of keratoplasty than any other ophthalmological surgeon. This investigator advocates the use of square transplants which have points of reference and, he states, are not only easier to cut and place than round grafts, but have a shape which can be less easily seen several months after the operation. Regarding the relative size of the window to be removed from the recipient eye, Fine proved by his experiments with keratoconus that the large corneal graft which must, of necessity, be cut back into relatively normal corneal tissue, had a greater chance for successful union and ultimate transparency. In order to prevent the formation of adhesions within the chamber and the possible rise of intra-ocular tension, rapid reformation of the anterior chamber is essential to the success of the operation. Surgeons have recently demonstrated a method by which an air bubble is injected into the anterior chamber immediately after the graft has been fitted in place, which obviates this hazard by serving to reestablish the chamber successfully.

Not only has there been a wider development of techniques employed in the actual transplantation of corneal tissue, but surgeons have seen the recent introduction of several types of new instruments designed to reduce the difficulties encountered in cutting the tissues, making exact measurements, and fitting the graft into proper position. To surmount the ever-present danger of injury to the lens, and to minimize the pressure upon the ocular structures, a type of corneal punch has recently been devised for both the round and square type of transplants, which, with the double action of its rounded and dull lower cutting blade, reduces the amount of force required to snap the cornea.² Another instrument designed to hold the transplant firmly in place yet relieve the pressure during the grafting procedure is a pillbox type of forceps which is slitted at the ends for entrance of the needles.³ Brown and Nantz,⁴ in an effort to avoid the use of sutures in corneal healing, endeavored to develop a biologic substitute for sutures which would be mechanically strong, non-irritating, and capable of absorption. Through their experiments with fibrin on rabbits, they formed the opinion that it would be unsafe to eliminate sutures completely in operations on human eyes. They demonstrated, however, that the anterior chamber filled immediately when fibrin was dropped on the cornea, and that the substance can act as a reinforcement with which to hold the graft in place as well as a cushion to protect the lens.

DONOR TISSUES

The scarcity of donor material and the difficulties inherent in its preservation have, in past years, presented one of the greatest problems for the eye surgeon. The physician must exercise the greatest care in the evaluation of the donor tissue to be employed. Best results are obtained when the corneal material is fresh and is grafted shortly after its removal from the donor. Transplants can be obtained from various sources: they can be removed from the fellow eye of the patient himself (autotransplant) or from the eye of another individual (homotransplant). Experiments by Castroviejo and Elliott ⁵ with corneoscleral transplants on rabbits proved that the use of any heterogeneous tissue other than that of the cornea was inadvisable because of its tendency to form an imperfect union and to result, invariably, in opacity of the graft. Homotransplants have been found to supply the best material, and these can be obtained either from patients having eye lesions which require enucleation but whose corneas are normal, from cadavers of either adults or children whose eyes are enucleated shortly after death, or from stillborn infants (seven months to full term) whose eyes are enucleated shortly after delivery.

It has been found that autolysis of the eye can be retarded several days, and that adult eyes can give normal transparency and no marked thickness during a period of from 48 to 72 hours after enucleation. Stillborn eyes, however, develop a more rapid loss of corneal transparency after enucleation, and 18 hours is the maximum period of time allowed before autolysis is expected. In their efforts to extend the short three-day storage period, investigators ¹⁸ have conducted many experiments to determine the
efficacy of various mediums which could be useful in the preservation of corneal tissue. They soon disproved the belief that rapid freezing of donor eyes in liquid nitrogen presented a hopeful means of preserving the tissue. While the corneas were clear and well preserved under these conditions, with a minimum amount of physical and chemical change taking place, when grafted they became opaque, having lost the vital life-giving quality. Further research along these lines proved to investigators that for best results the eye should be preserved intact in a Ringer's or normal saline solution at a temperature of from 3 to 4 degrees Centigrade.

One of the greatest and most recent steps taken to advance the cause of corneal tissue therapy has been in the creation and establishment of eye banks throughout the nation. Such agencies have been set up to eliminate the difficulty which has so hindered ophthalmologists in the past, the lack of suitable and fresh donor material. The State of California has two such organizations, the Stanford Eye Bank at 2395 Sacramento Street in San Francisco, and the Estelle Doheny Eye Laboratory at 2131 West Third Street (St. Vincent's Hospital) in Los Angeles. These banks, which act as coordinators between those in need of corneas and those wishing to donate them, make it their object not only to establish sources of supply for salvaged eyes and corneal tissue, but to extend the knowledge and skill required to perform keratoplasties through teaching and research. As storehouses and distributing centers for enucleated eyes, the banks conduct pathological studies on all eyes sent to them, and carry on continual research campaigns designed to widen the sources of supply and to develop new and better methods of preservation.

In issuing instructions concerning those eyes which are acceptable, the eye banks require that the corneas be normal, and that the individuals from whom the eyes are obtained must have had no infectious disease and must have had a negative serologic test for syphilis. Eyes of stillborn infants may be used if the mother had a negative serologic test, and eyes with intra-ocular tumors are acceptable if the tumor does not involve the cornea, iris or ciliary body. Eyes to be removed after death should be protected by careful closure of the eyelids prior to enucleation, and the enucleation should be performed within six hours after death.

In an effort to minimize the nuisance to the physician of sending the enucleated eyes off to the bank, these collection centers supply the containers in which the eyes should be transported, and make the handling of the preserved tissue a simple routine which the hospital or a nurse might carry out with little effort. It is necessary that consent for the use of the eyes be obtained on forms which the bank provides, and that a history form be filled out and accompany each bottle used. The bottle supplied must be sterilized, and the gauze at the bottom moistened with sterile saline solution before the eye is placed in the container. After enucleation the eye should be placed in this sterile bottle immediately, the bottle closed tightly, and then kept in a refrigerator at a temperature of from 3 to 4 degrees Centigrade.

It is through such vigorous attempts to make the restoration of sight through corneal grafting a community-wide project, that the eye banks have done much to further interest in this field of surgery, not only among physicians but among the general public as well.

AVOIDANCE OF VASCULARIZATION

Due to the use of present-day modern techniques, 90 per cent of the patients who undergo keratoplasty may expect to have permanently transparent grafts and considerable improvement in vision. Non-union of the graft occurs only as a result of poor technique, infection, or misbehavior of the patient. The complication which the physician must carefully guard against, however, is opacification of the transplant. While this unfortunate result can occur if there is imperfect coaptation of the edges into the cornea of the host, or incarceration of the intra-ocular structures into the wound with a subsequent development of connective tissue behind the graft, vascularization is its main cause. This process usually involves the infiltration of the transplant by lymphocytes and the appearance of wandering cells which should never be present in the healing of a transparent cornea. According to Castroviejo, once these blood vessels have been formed, treatment by x-ray or radium is useless. It is a wise measure, therefore, if the surgeon guards against this latent possibility by administering such therapy prophylactically for a definite period after the operation.

Involving as it does the fundamental biological principle of the reconstruction of living tissue, the modern surgical procedure of keratoplasty has brought new hope to many who would have suffered blindness or ugliness unnecessarily. The first unsuccessful trials in the field of corneal tissue therapy were due mainly to faulty technique and the improper selection of cases. For too long surgical progress was retarded by misconceptions concerning the actual physiological processes within the eye and by the large number of inadequately reported cases which appeared in the literature and served to add to the confusion. Today, as more surgeons become qualified to perform this operation, as newer and more perfected techniques are being advanced, and as a greater number of eye banks are being established to aid in research, physicians and the public alike are being convinced of the greater opportunity which has been extended to the blind for the restoration of their sight through keratoplasty.

9730 Wilshire Boulevard.

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