EXCIMER LASERS IN OPHTHALMOLOGY

FOR A number of years there has been a growing interest in the possibility of changing the focusing properties of the human eye by surgical means rather than the use of spectacles or contact lenses. Surgical procedures to change corneal curvature are basically of two types, those involving the optical zone and those involving the peripheral cornea.

In the central zone procedures, the surgeon decides upon the desired correction and a disc of Bowman's membrane and anterior stroma is then carefully cleaved off the surface of a patient's (keratomileusis) or of a donor's (epikeratophakia) eye and then stained with a vital dye before being frozen. The stain is merely for the surgeon to visualise the specimen. The frozen corneal segment is then placed in a microcryolathe and the stromal surface is turned to the correct curvature to achieve the desired optical correction. The corneal specimen is then thawed and sutured, Bowman's surface outwards, on to either the patient's Bowman's (epikeratophakia) or stroma (keratophakia). In a slight variation of this procedure artificial polysulphone inlays of varying optical powers are inserted into pockets in the patient's stroma. This is high stress surgery for the surgeon and relatively few procedures are undertaken worldwide.

Peripheral zone procedures are currently the most popular refractive surgical modality for both patients and surgeons. Radial keratotomy (RK) involves the surgeon making a series of four, eight, 16, 32 or more radial incisions from the edge of the optical zone outwards to almost the edge of the cornea. These incisions go deep into the stroma penetrating up to 90% of its thickness to cause a collapse or flattening of the central cornea. RK can therefore only be used to correct myopia and certain types of astigmatism.

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Three theories relate this central collapse to peripheral incision (a) that there is a circumferential band of collagen around the peripheral cornea and that cutting through this causes the centre to flatten. (b) The balloon theory which says any weakening in a device under pressure will cause bulging at the weakened part and flattening elsewhere. (c) The gape theory which says the radial wounds gape and by increasing the effective diameter of the peripheral cornea the centre flattens. There is no anatomical evidence for (a), and (b) and (c) would demand a control of predictability over wound healing subsequent to surgery that we do not have.

Even in the absence of a comprehensive theory as to why this type of surgery works, all theories demand a precise control of the depths of incisions. The depth of a given incision depends upon a number of variables including the sharpness of the cutting edge, the surgeon's hand pressure and speed, the tissue resistance and elasticity. Once the blade touches the surface of the tissue the surface deforms and cutting to within an accuracy of a few microns becomes impossible. Ophthalmologists have minimised this by using diamond and sapphire knives and by equipping them with 'blade skis', however, they still cannot cut to the accuracy demanded by refractive surgery and at best manage ±12% of the target depth.

Clinical trials reflect these problems in terms of the numbers of patients under or over corrected[1] but even so a large number of patients are happy with the results and to be free of wearing glasses or contact lenses.

No-touch technique

Four years ago ophthalmologists began to wonder if a no-touch surgical technique could be employed for refractive surgery using lasers. Lasers have long been associated with ophthalmology, being the first sub-speciality in medicine to employ them and still being the field in which the most units and the greatest variety of types of lasers are found. This pre-eminent position has come about because the eye is the only organ of the body that is specialised to allow a portion of the optical radiation spectrum to penetrate deep within it.

In laser surgery it is the wavelength of the laser that determines where the laser energy will be absorbed and therefore which tissues are potential targets. To operate on the surface of the cornea, lasers with emission wavelengths in the UVC (280-100nm) or IRB (1.4-3μm) and IRC (3μm-1mm) holds most promise as they could potentially initiate a superficial effect with no complications of excess energy penetrating into the eye and damaging the retina. A number of infra-red lasers including Hydrogen Fluoride, Colour Centre Lasers, Raman Lasers and Erbium YAG have been considered as suitable candidates but, as yet, most of the experimental work has been concentrated on UVC lasers and, in particular, Excimer lasers.

Excimer is an acronym derived from the first two and last syllables of the words that describe the physical state of the lasing media used in such lasers *exc*ited di*mers*. Excited dimers are two atoms of an inert gas bound in a highly excited state with atoms of a halogen to form a temporary, highly unstable association as a diatomic rare gas halide. The decay of these unstable molecules is accompanied by the emission of a highly energetic photon of ultraviolet light. The energy of the photons and therefore the wavelength of the light emitted from an excimer laser is dependent upon the particular gas mixture used to fill the laser. For example, the emission from a mixture of argon and fluorine occurs at 193nm and that for krypton fluoride at 248nm. These lasers emit their radiation as a train of individual pulses whose duration is typically about 10 nano-

continued on page 16

continued from page 15

seconds (10^{-9} seconds), with a selectable pulse repetition frequency of between one and 100 pulses per second, and typical pulse energies of 20 to 200mJ.

In the materials and electronic industries excimers are used to etch submicron patterns into the surfaces of plastics and other polymers with no degradation processes being conducted to unirradiated areas.[2] In this situation resolution can be considered both in width and depth of material removed with each pulse of laser energy. In theory, the very best lateral resolution would occur if only those molecules directly irradiated were removed and the best depth resolution would be one layer of molecules removed per laser pulse. In practice more than one layer of molecules is removed with each pulse because photons penetrate through the surface of the target. As previously stated, the penetration depth is a function of the nature of the target material and the wavelength of the incident radiation. In biological tissue, minimum penetration occurs at two wavelengths, 190nm in the ultraviolet C and 2.9μm in the infra-red C. In the former, a penetration depth of one to five μm occurs as a result of absorption of the UV photons by macromolecules, in particular proteins. In contrast, an absorption depth of 20-25μm is observed at 2.9μm and in this case results from absorption of IR photons by water molecules. These respective penetration depths define the maximum amount of target tissue that will be directly affected by each pulse of laser radiation.

There are two theories on the removal of tissue by absorbed photons.[3] The first of these suggests that the photons cause ultrafast tissue heating, so-called photon-phonon interactions, and that the vibration of super-heated molecules causes them to fall apart. The second theory asserts that the target reaction is not thermal but photon-induced molecular decompensation or photoablation. The protagonists of this theory submit that molecules in the target are released as a direct result of rupture of intermolecular bonds whose uncoupling is induced by the absorption of high energy photons. Such a mechanism is possible because in the ultraviolet at 193nm individual photons have an energy in excess of six electron volts and, as this is greater than the binding voltages of some proteins, the photons are capable of disruption valency electrons. As the macromolecules break up the component fragments require a greater space than the original molecules. Fragment expansion can only be facilitated by displacement and as these processes are only occurring at or close to the target surface, such displacement inevitably results in loss of material from the exposed surface. This process is illustrated diagrammatically in Figure 1.

In practice the depth of the tissue removed per pulse is determined by the pulse energy with a maximum set by the penetration depth. At 193nm, varying the pulse energy means that predetermined depths of tissue can be removed at any level between 1/40 and 1μm per pulse. An example of the degree of control is seen in the scanning electron micrograph of excimer excisions in a human hair (Figure 2). The unique nature of the photoablation process becomes even more apparent when excimers are used to incise soft tissues such as the cornea (Figure 3). It is immediately apparent that the walls of the incisions are perfectly smooth and coated by a pseudomembrane rather like a 'shrink-wrap' or 'cling film' covering of food stuffs.[4] This pseudomembrane is thought to arise from the somewhat random recombination of the ruptured bonds of the molecular fragments that remain locked in the tissue matrix of the walls and floor of the excision. Whatever its origin, it creates an optically smooth surface and imparts a limited osmotic integrity to the cut surface. The second quality of excimer incisions is that no damage is apparent *100 to 300nm* away from the region of ablation. This lack of secondary or conductive damage is unique to the excimer lesion.[5]

With such precise control of tissue removal and with such a clean and highly localised wound, an excimer seems an ideal instrument to avoid the procedural limitations incurred during radial keratotomy procedures carried out with steel or diamond knives. However, at a cost in excess of \$100,000 for a clinical excimer laser this would be a very expensive solution to an extremely limited surgical problem.

One further attribute of the excimer laser should be considered. Excimers usually emit beams of rectangular cross section typically 20mm by 10mm. The beam cross section can be made square by passing it through a cylindrical lens and then circular by passing it through an aperture. If an excimer beam of circular cross section and say 10mm in

continued on page 19

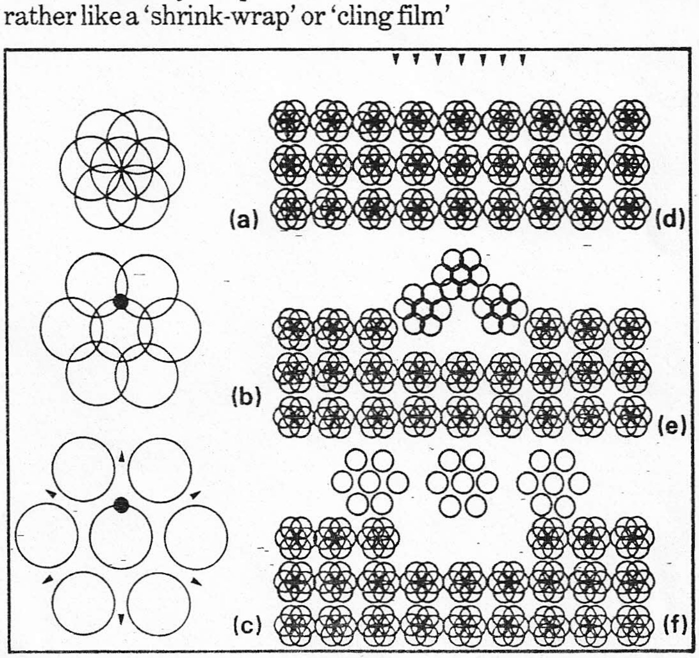

Figure 1—Diagrammatic representation of the molecular events occurring within a biological matrix after irradiation by high energy ultraviolet photons

A A biological macromolecule.
B On absorption of a UV photon (black dot) the bonds of the molecule begin to break up and this is accompanied by an increase in volume.
C Complete breakdown of valency bonds results in molecular fragmentation and fragment displacement with expansion.
D, E, F show the same process but now occurring to three individual macromolecules irradiated at the surface of biological matrix. The net result of molecular fragmentation and expansion is expulsion of destabilised molecules from the target surface.

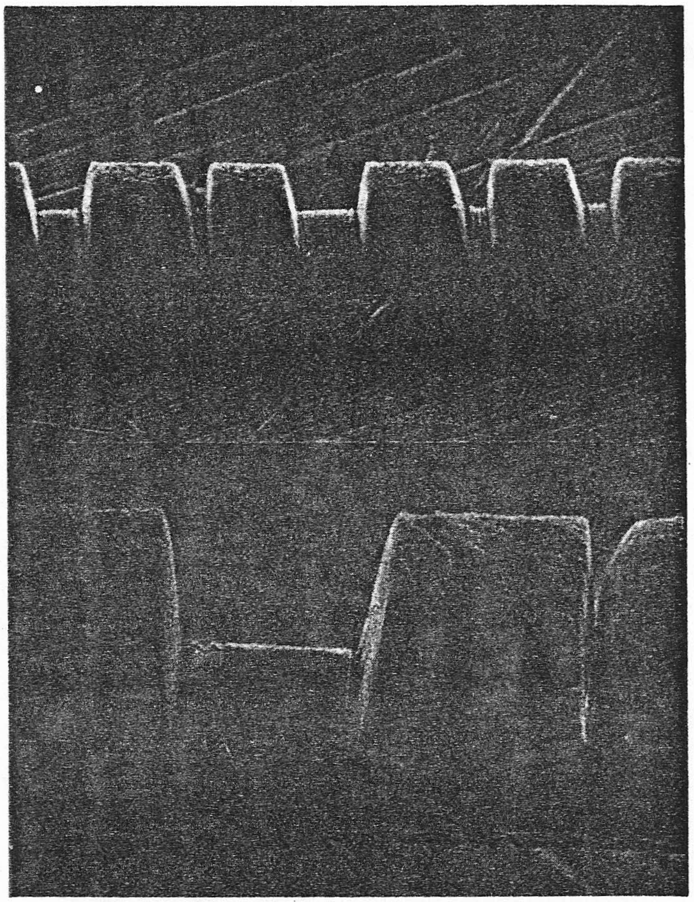

Figure 2—Scanning electron micrograph of excimer laser ablations in a human hair. The scales of the hair can be clearly seen in the higher power picture and the slight ridges on the bottom of the excimer excisions have been caused by diffraction of light through the slit aperture used to make these ablations

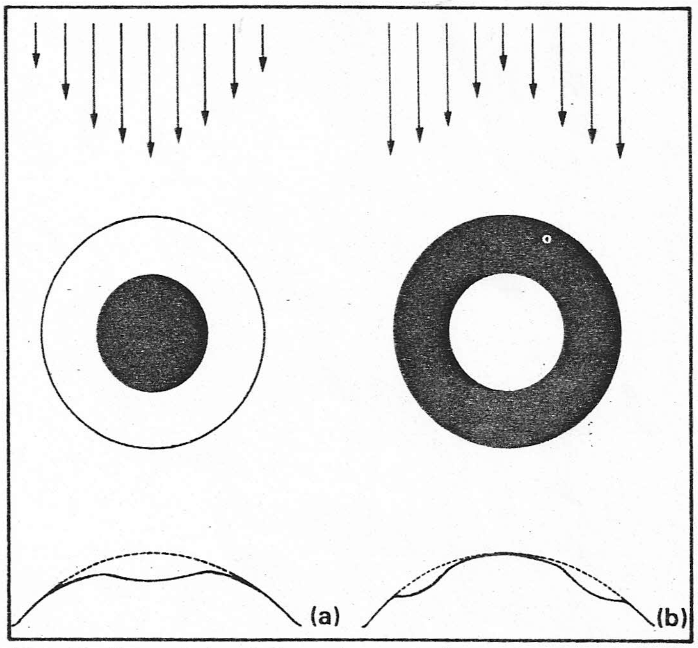

Figure 3—Transmission electron micrograph of an excimer laser incision through the stroma of a rabbit cornea. The individual collagen fibres can be seen running diagonally across the photograph. The dark line running vertically is the juxtaposition of two layers of pseudomembrane and outside this an electron dense zone can be seen in relation to excimer laser exposures

continued from page 16

diameter is allowed to fall upon a biological surface then at a given pulse energy a 10mm diameter disc 1μm deep will be ablated with each laser pulse. If the tissue were the cornea, then a perfectly round smooth surface excavation would be created to a predetermined depth and this is precisely the configuration desired for preparing the recipient eye in corneal graft procedures. Similarly, if instead of using a beam of circular cross section one was obtained which was an annulus or ring shape, then the corneal button to be grafted could also be cut from the donor eye and the bed and button would match with submicron accuracy. An annular beam cross section can be obtained by using a combination of prisms and lenses called an Axicon.

Circular beams

The facility for producing large beams

continued on page 20

continued from page 19

of circular cross section also has profound implications for refractive surgery. If, for example, a beam was produced in which the energy distribution across it was variable in a controlled fashion, then the beam could be used to sculpt or shape the surface of the target. This is shown diagrammatically in Figure 4 where two examples are considered. In Figure 4(a) the highest concentration of energy is located at the centre of the beam and energy per unit area decreases towards the periphery. Such a configuration of energy would result in a concave erosion of the target or in the case of the cornea the production of a negative lens. Conversely, in Figure 4(b) with the highest concentration of energy at the edges of the beam and the lowest at its centre the resultant erosion would produce a convexed surface or a positive lens.

In practice it is easier to control the number of pulses falling upon a given area of surface rather than varying the energy per unit area. By varying the number of pulses different areas can be ablated to different depths. If for example, an iris diaphragm is placed concentric with the laser beam and then progressively opened or closed with a given number of laser pulses being directed through the aperture in the diaphragm at each aperture size, then the target surface will be ablated to give rise to a series of concentric circular steps (Figure 5). If the aperture is motorised and suitably integrated with the laser control system then the steps could become infinitely small and thus in practice a smooth curve would be generated. This is the principle employed in the two ophthalmic excimer laser systems that are commercially available, one produced by CooperVision, the other by Summit Technology.

Such systems can cut optically smooth curves on to the surface of the cornea[6] and an example of the optical quality of the ablated zone is shown in Figure 6. Computer predictions showed that greater than 90% of all myopia throughout the population of the world could be corrected by ablating curves which maximally removed 25μm or less of stromal material. Subsequent experiments on animals have shown these predictions to be correct in terms of the refractive power of the initially ablated surface.

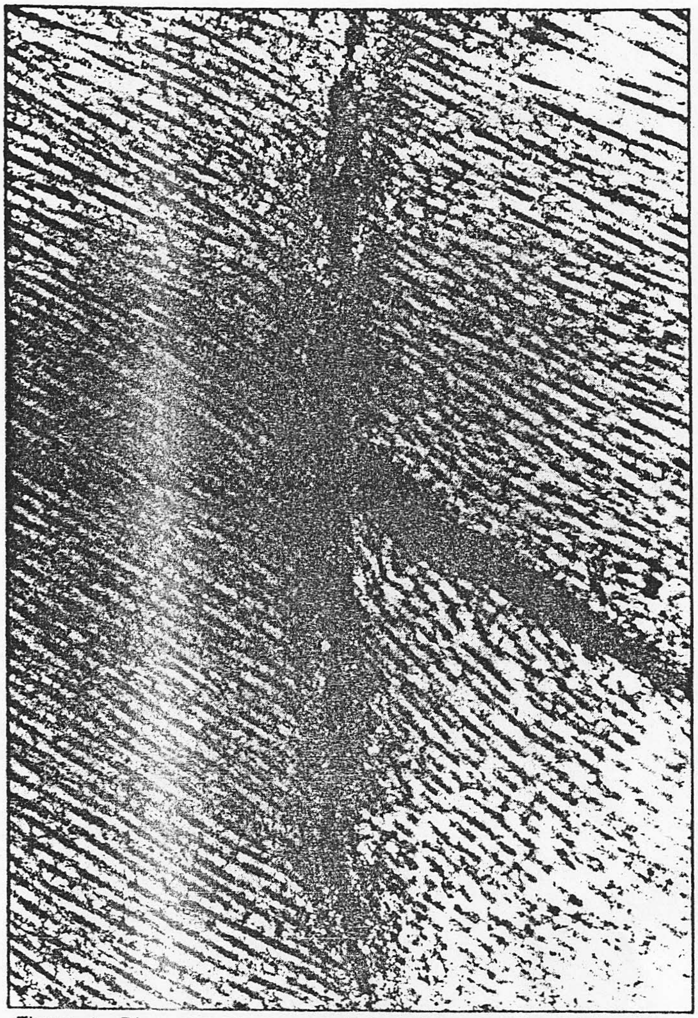

Figure 4—Diagrammatic representation of the ways in which excimer lasers could be utilised to cut (a) negative or (b) positive lenses on to the surface of the cornea

Figure 5—Scanning electron micrograph of corneal surface showing a series of steps cut into the surface by progressively opening the aperture of an iris diaphragm. Note that each step in this case is not perfectly circular, but has a segmented boundary which is due to the movement of leaves within the iris diaphragm

Long-term survival experiments are currently being conducted to examine the healing characteristics of these large area ablations. Studies with animals and tissue culture systems indicate that excimer induced ablations do not exhibit a latency in wound healing and that the ablated area is recovered by epithelial cells within 12 hours of exposure. The cells migrate along the pseudomembrane from peripheral unirradiated areas and because the pseudomembrane is so smooth they re-establish a perfectly parallel optically brilliant epithelial system.

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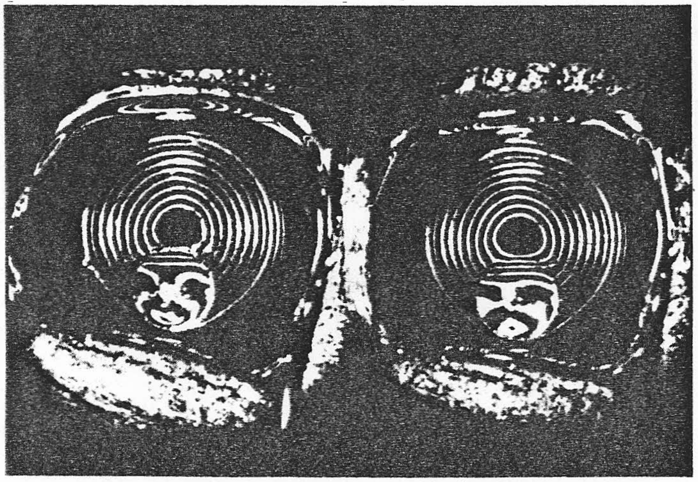

Figure 6—Photokeratoscope pictures of the corneas of a rabbit one month after a PRK procedure carried out with an excimer laser

continued from page 20

Providing the ablations were executed with suitable laser exposure parameters and providing they were shallow, *ie* less than 50μms, then scar tissue and loss of transparency were not found to be significant problems in 18 month follow-up studies in monkeys. Exposures in which the entire volume of ablated material was restricted to Bowman's layer were particularly notable for a virtual absence of scar collagen and in such cases the initial curvature of the ablated surface remained virtually unchanged.

In deeper exposures where stromal collagen restructuring was apparent the new collagen formation followed the new radius of curvature of the ablated surface and therefore the induced refractive change seemed to remain relatively stable within the limits of measurement.

Finally, although studies have been carried out to try to detect both unscheduled DNA repair and true mutagenic changes in cells adjacent to areas of ablation, as yet at 193nm such changes either do not occur or are of a magnitude that cannot be detected in the cornea.

To date all the experimental evidence supports the concept of excimer laser surgery for corneal refractive errors and as a result human exposures are beginning to be undertaken in a number of countries. The fundamental requirement is an excimer laser specifically designed for clinical environments, being small, highly mobile and self-contained in terms of gas supplies and cooling and with adequate safety interlocks both in relation to chemical and radiation hazards. Four further components would be required for photorefractive ablation and these are:

1 A measuring system capable of determining the refractive error and astigmatism axis in the patient's eye.

2 A beam delivery system with optical components that allow programming of the energy distribution across the beam in time or space.

3 A computerised means of inter-relating (1) and (2) such that the required correction is ablated.

4 Some means of locking the laser delivery system to the eye so that the target area remains located throughout the exposure period.

As stated, two commercial systems are addressing these delivery problems but only the Summit system has a purpose-built clinical laser (Figure 7).

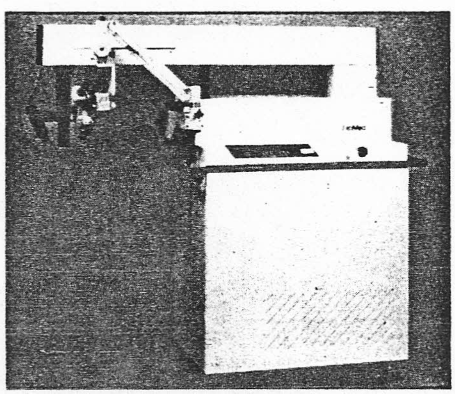

Figure 7—Photograph of the clinical prototype of the Summit ophthalmic excimer laser system. The laser and microprocessor are housed in the box to the right of the photograph whilst the delivery optics are located in the horizontal boom. The laser energy is delivered via the vertical nozzle seen on the extreme left of the boom and viewed via the integrated operating microscope

As far as the patient is concerned a typical visit for a photoablative keratectomy procedure should consist of the following. First the patient's refraction is determined by whatever method the practitioner favours, then the procedure is repeated using the integrated refraction system in the excimer laser delivery system. If the surgeon is satisfied there is a good agreement he can lock the refraction into the laser's microcomputer and it will automatically set the laser delivery optics. If the surgeon is dissatisfied he can enter whatever he feels is the required correction manually and again the microcomputer will set up the delivery optics to his specification.

The patient is given a miotic to close the pupil and a local anaesthetic. The delivery system is then locked to the eye by a vacuum ring located on the sclera and the refraction is again checked to ensure that the vacuum coupling has not altered the curvature of the cornea. If satisfied the surgeon fires the laser and for most corrections the laser exposure will last less than 12 seconds. The system is uncoupled from the sclera and, after the instillation of further topical anaesthesia and antibiotics, the eye would be padded overnight. The whole visit as an out patient should be no longer than 20 to 30 minutes. The next morning the site of ablation will have re-epithelialised and the patient should be free of any discomfort and visually active.

We would predict if all goes well with current trials that systems may be in clinical use in two years.

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