UNIVERSITY OF LONDON

An Investigation into the Clinical Potential and Applications of Ophthalmic Diode Lasers

A thesis submitted for the degree of Doctor of Medicine

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September 1990
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ABSTRACT OF THESIS

A study has been carried out of transpupillary retinal and of trabecular photocoagulation with infrared diode lasers. There were three phases to the study:

A. Design and construction of instrumentation.

B. Histopathological studies of lesions produced by diode lasers in rabbit retina, human peripheral retina and macula and on human trabecular meshwork. The appearances of the lesions were compared with those produced by lasers which emitted at other wavelengths.

C. Pilot clinical trials in which diode lasers were used in the treatment of the following conditions:
   1. Proliferative diabetic retinopathy
   2. Exudative diabetic retinopathy
   3. Branch retinal vein thrombosis complicated by neovascularisation of the optic disc or of the retina
   4. Central retinal vein thrombosis complicated by established or threatened rubeosis iridis, or by optic disc neovascularisation
   5. Chronic open angle glaucoma

RESULTS

A. INSTRUMENTATION

For initial histopathological and clinical studies, a diode laser emitting at 810 nm and with a power output of 800 mW was constructed, which was incorporated in a modified hand-held direct ophthalmoscope.

In a subsequent phase of development, a diode laser was assembled that could be attached to a standard slit lamp microscope and which had an eventual power output of 1.4 W. The project was completed using this modality, as it was felt that there was greater flexibility and ease of use in the treatment of patients.

B. HISTOPATHOLOGICAL STUDIES

In both the animal and in the human studies of peripheral retinal irradiation with a diode laser, the retinal burns were found to be similar to those produced by argon, and more particularly krypton photocoagulation.

Macular photocoagulation produced burns in which damage was confined to the outer retina, retinal pigment epithelium and the choroid. This was in contrast with the appearances seen following argon blue-green photocoagulation.
of the macula, in which inner retinal damage was observed, which was associated with absorption by macular pigments.

Trabecular photocoagulation with a diode laser produced a pattern of damage to trabecular beams. The histological appearances were similar to those seen in relation to argon blue-green exposures, although the diode laser lesions extended more deeply into the trabeculum.

C. PILOT CLINICAL STUDIES WITH DIODE LASERS

106 eyes in 85 patients were given diode laser therapy for proliferative diabetic retinopathy, exudative diabetic retinopathy, branch and central retinal vein thrombosis and chronic simple glaucoma.

Regression of neovascularisation was observed in 33 of 47 eyes (70%) with proliferative diabetic retinopathy, and in all 11 eyes treated for branch vein thrombosis. Six eyes were successfully treated for established or incipient rubeosis iridis, following central vein thrombosis.

Focal photocoagulation applied to 22 eyes for exudative diabetic maculopathy resulted in a reduction in the number of microvascular abnormalities and partial resorption of exudates.

Laser trabeculoplasty carried out on 20 eyes for glaucoma resulted in a mean ocular hypotensive effect of 10.2 mm Hg, at 2 weeks following treatment and of 9.55 mm Hg, at 6 months.

This thesis will detail the methodology and results associated with each phase of the study. In the context of the histological and clinical results, the discussion will consider the relative advantages of diode laser irradiation compared with treatment with lasers of other wavelengths. This will allow an assessment of the implications of the development of the diode laser with regard to its place in ophthalmic therapy.
ACKNOWLEDGEMENTS

My financial support for this project was provided entirely by the Lady Allerton Vision Research Trust, and I would like to express my appreciation of its generosity.

I am indebted to my supervisor, Professor John Marshall PhD who was an invaluable source of constructive suggestions and critical advice in relation to every aspect of this study.

Mr Timothy ffytche FRCS and Mr Peter Hamilton FRCS, consultant ophthalmologists, allowed me to work in their clinics, from which most of the patients for the clinical trials were recruited. I greatly benefited from their clinical expertise when implementing the trials and their enthusiasm for the project was a great source of encouragement.

I was privileged to collaborate in the technical aspects of the project with Dr Tony Raven and Dr Robin Lee of Scientific Generics, Cambridge and with the team led by Mr CR Keeler of Keeler Holdings Ltd, Windsor.

The histological phase of the study required education in a wide range of techniques to which I was hitherto unfamiliar. I would like to express my appreciation to Professor Marshall's technicians, Mr Steven Rothery and Mrs Ann Patmore for their invaluable help in this regard.

I would like to thank Mr John Hungerford FRCS, Consultant Ophthalmologist for his cooperation in the aspects of this study relating to the patients with ocular melanomas.
SECTION I
INTRODUCTION
CHAPTER 1
HISTORICAL ASPECTS OF OPHTHALMIC PHOTOCOAGULATION
The application of semiconductor lasers to ophthalmic photocoagulation is a relatively novel concept. Before detailing the aims of this project, it may therefore be helpful to outline the historical background and some technical aspects relating to ophthalmic laser therapy.

1.1 SOLAR RETINOPATHY

The damaging consequences of ocular exposure to high energy sources of optical radiation have been recognised for centuries. In Plato's "Phaedo", he records Socrates' advice regarding the potentially harmful effects of sunlight:

"I decided that I must be careful not to suffer the misfortune which happens to people who look at the sun and watch it during an eclipse. For some of them ruin their eyes unless they look at its image in water or something of the sort." (Plato, c. 380 B.C.)

The first description of a central scotoma due to a solar retinopathy is attributed to Theophilus Bonetus (1620-1689) (cited by Hamm, 1947). The development of the ophthalmoscope was followed by several descriptions of the appearance of macular burns which occurred as a result of viewing solar eclipses (Birch-Hirschfeld, 1912; Blessig, 1912; Cords, 1912). Retinal lesions were produced by sunlight, or by a carbon arc by a number of investigators (Czerny, 1867; Deutschmann, 1882; Widmark, 1893).

Maggiore examined the histopathological appearance of radiation burns produced in human eyes due for enucleation and described retinal oedema in the sites of irradiation (Maggiore, 1927).

1.2 THERAPEUTIC PHOTOCOAGULATION

Moran-Salas and Meyer-Schwickerath performed experiments concurrently in the 1940's to examine the therapeutic potential of retinal photocoagulation (Meyer-Schwickerath, 1949; Moran-Salas, 1950).

Meyer-Schwickerath initially used focused sunlight to produce retinal lesions, but this method was superseded by a modified Beck arc. This instrument had the disadvantages of a short photocoagulation time, and it produced gases saturated with carbon and soot particles.
The development of the xenon arc photocoagulator provided a source of broad band optical radiation which was effective in producing full-thickness chorioretinal lesions (Meyer-Schwickerath, 1960). Xenon arc devices are of proven effectiveness in the treatment of proliferative diabetic retinopathy (British Multicentre study group, 1984; Stenkula, 1984) and are still commonly used for retinal therapeutic procedures.

1.3 RUBY LASER

The advent of the ruby laser in 1960 (Maiman, 1960) aroused interest amongst ophthalmologists and this rapidly resulted in the investigation of its potential in the treatment of ocular conditions. Early work on animals by Zaret in 1961 (Zaret, 1961) was followed within two years by therapeutic regimens in humans (Campbell et al, 1963; Zweng et al, 1964). Although the ruby laser (emitting at 694.3 nm) was relatively effective in producing chorioretinal adhesions in detachment surgery, results were disappointing in treating retinal vascular conditions (Campbell et al, 1963; Aiello et al, 1968; Taylor, 1970).

In the mid-sixties the failure of the ruby laser was attributed to an inappropriate wavelength and the resultant lack of absorption of laser energy in retinal vessels. Recent work has emphasised the role of the retinal pigment epithelium in the treatment of retinal vascular diseases (Glaser 1980; Wong, et al, 1987; Miller et al, 1986). The pigment epithelium is a tissue with broad band absorption characteristics and the major site of energy degradation in retinal photocoagulation. The inadequacies of the ruby laser are now thought to be due to the pulse duration rather than wavelength, as the short pulse duration of early instruments produced a high risk of choroidal haemorrhage.

1.4 ARGON LASER

L’Esperance investigated the clinical potential of the argon laser (488-515.5 nm) in 1965 (L’Esperance, 1968), and it became commercially available in 1971. Numerous studies have demonstrated its efficacy in the treatment of common retinal conditions, for example proliferative diabetic retinopathy (Diabetic Retinopathy Study Group, 1978), forms of diabetic maculopathy (Hamilton, 1979) and the complications of retinal vein thrombosis (Campbell, 1973). In addition a number of trials have indicated early beneficial effects in the treatment of subretinal neovascular membranes, although longer term observations have demonstrated
recurrence of membranes and visual deterioration (Macular Photocoagulation Study Group, 1982; The Moorfields Macular Study Group, 1982).

Argon lasers were also found to be useful in the treatment of several forms of glaucoma. The technique of laser trabeculoplasty was suggested by Wise and Witter in 1979 (Wise and Witter, 1979). Several studies have subsequently proved the benefit of this form of technique for the treatment of chronic open angle glaucoma (Wise, 1981; Schwartz, 1981). Laser iridotomies for closed angle glaucoma were performed initially by the ruby laser (Beckman and Sugar, 1973), and then by the argon laser (Abraham and Miller, 1975). In these situations the laser provided a viable alternative to operative intervention.

In recent years concern about the adverse photochemical effects of blue light on retinal photoreceptors of both the patient and the ophthalmologist has led to the development of argon systems in which the blue output can be virtually eliminated. For the patient, this can be achieved either through the use of prisms in the beam path which deflect the argon blue line; for the surgeon it can be minimised by the incorporation of a filter within each eye piece, which attenuates the transmission of shorter wavelengths.

1.5 KRYPTON LASER

In the mid-seventies a new red light emitting laser, the krypton laser (647nm) was introduced and it has been found to be as effective as argon in the treatment of retinal conditions (Blankenship, 1986). It also had advantages when compared with argon blue in that its longer wavelength resulted in virtually no absorption by macular xanthophyll pigment (Marshall and Bird, 1979; Yannuzzi and Shakin, 1982). Further, the lower photon energy at longer wavelengths in the visible spectrum reduced the potential for inducing photochemical damage (Ham et al, 1976).

1.6 DYE LASER

More recently, the continuous wave argon-pumped dye lasers have provided the facility to tune the wavelength of emission. For example, the most frequently used dye, rhodamine-6G permits wavelength tuning over the range, 575-630 nm (L'Esperance, 1985). This in theory allowed the possibility of selectively photocoagulating particular retinal structures. The attractions of this theory have resulted in the dye laser being used in many major centres.
However, because melanin is the prime absorber at every wavelength emitted by the dye laser, thermal damage resulting from the source must be similar at each wavelength. Temperature profiles will only vary with wavelength in the choroid and will only be significant at pulse durations of 1 ms or less. All retinal profiles will be virtually identical at all wavelengths and hence no selective effect can be achieved. Support for this argument has been provided by studies which have demonstrated that the thermal damage resulting from dye laser exposure is widespread throughout the outer retina and have failed to support the concept of selectivity of targets (Smiddy et al, 1988; Brooks et al, 1989). Recent comparisons of the treatment of neovascular membranes with several dye laser wavelengths have not demonstrated any difference in clinical efficacy (Haut et al, 1987; Brancato et al, 1988).

It is probable that the real future of the dye laser lies in the development of much more target-specific chromophores or fluorophores and the use of irradiances and pulse durations that will cause photochemical rather than thermal damage. The possible development of fluorescent, or chromatically labelled monoclonal antibodies offers promise for selective use of dye lasers. The use of the dye laser has already shown promising results in relation to photodynamic therapy. This method involves sensitisation of an intraocular tumour with haematoporphyrin derivative (HPD). Subsequent irradiation of the tumour with light of a wavelength of approximately 630 nm results in activation of the HPD and release of cytotoxic singlet oxygen radicals. L'Esperance has reported successful tumour destruction utilising the wavelength selectivity of a dye laser in conjunction with HPD (L'Esperance, 1985).

1.7 Nd:YAG LASER

The argon, krypton and dye lasers all have (what may be termed) a "thermal" mode of action, in that they induce a temperature rise in the target tissue which results in the phenomenon of photoagulation. The advent of the "Q-switched" neodymium-YAG laser, emitting at 1064 nm (Fankhauser, 1981), introduced the phenomenon of non-linear damage processes, or tissue "photodisruption". The production of high energy pulses of laser energy concentrated in both time and space allowed transparent tissues to be cut within the eye, for example the posterior lens capsule, or vitreous membranes. The Nd:YAG laser has also proved to be more efficient in performing iridotomies and is another example of a laser providing the means to obviate the necessity for invasive surgery.
1.8 CARBON DIOXIDE (CO2) LASER

The CO2 laser (which emits at 10,600 nm) has been used with limited success in the treatment of tumours of the ocular adnexa, and in carrying out glaucoma trephination procedures (Beckman 1971; Beckman, 1979). The use of this laser in ophthalmology still remains restricted to a relatively few centres, because of its lack of precision as a cutting tool.

1.9 EXCIMER LASER

The recently introduced excimer lasers interact with tissues by a process that has been termed "photoablation". They are demonstrating exciting possibilities as a mode of therapy for several anterior segment conditions, for example glaucoma and corneal opacification. The correction of refractive errors has also been carried out with the excimer laser by altering the corneal profile, "photorefractive keratectomy" (Marshall, 1986).

1.10 DIODE LASERS

Continuous wave argon, krypton and dye lasers, while broadly similar in terms of both the damage they induce to the retina, and in their therapeutic efficacy also have several inherent disadvantages.

Laser energy is generated within a relatively bulky gas-filled tube; electrical energy consumption is high, and the efficiency of electrical-optical conversion is low. Many systems require a three-phase power supply and forced cooling facilities dependent on circulating air or water. Heat dissipating factors tend to increase the size of the equipment and these together with their special electrical requirements mean that in most situations rooms need to be adapted for the permanent installation of laser apparatus. Additionally, maintenance costs are high with the average tube life being 2-3 years, and the cost of replacement being about 20% of the total cost of the laser. Advances in semi-conductor technology have allowed the development of infrared diode lasers (750-950 nm) measuring a few millimetres in size. These are used in compact disc players and have important applications in the fields of optical printing and communications.

The recent availability of laser diodes with an output power of 1-2 W has stimulated interest in their potential applications in ophthalmic surgery. As early as 1984, Pratesi postulated some of the possible uses of diode lasers in medicine (Pratesi, 1984). They are compact (9 mm by 2 mm) and easily portable, they may be
powered by either a standard 13 amp power supply or a 6 volt battery and no ancillary cooling facilities are needed.

Currently, most high powered diodes emit in the infrared region of the spectrum (810 nm). This wavelength is just outside the visible spectrum and therefore a permanent protective filter, a dielectric mirror, could be incorporated in a clinical system to protect the operator. This would also remove the requirement for a mechanical shutter and as it would only attenuate invisible wavelengths it would allow the ophthalmologist an uninterrupted, unimpeded view of the retina throughout therapy.

Brancato and Pratesi (Brancato and Pratesi, 1987) and Puliafito (Puliafito, 1987) working independently, successfully produced chorioretinal lesions in rabbit retinas with diode lasers. The former used a transpupillary route while the latter used an intraocular fibre optic. The lesions produced by Brancato were described as being similar to those produced by current clinical lasers. In this early report, the emission of the laser diode was of relatively low power and as a result, an exposure time of six to ten seconds was required even to produce low intensity ophthalmoscopically visible burns. However in a later report intense white lesions were produced in rabbit with an output of 120 mW and exposure durations of between 0.3 and 1 second (Brancato and Pratesi, 1988).

The project described in this thesis resulted in the first histopathological report of retinal photocoagulation by a diode laser in human eyes (McHugh et al, 1988). Microscopic analysis of the lesions demonstrated them to be similar to those produced by conventional clinical photocoagulators and in particular to those induced by krypton lasers. The physical parameters of the exposures such as power levels, exposure durations and spot sizes were also similar.

A further study which examined the histological effect of macular photocoagulation with a diode laser revealed lesions which were confined to the outer retina, retinal pigment epithelium and choroid, with no signs of absorption within the inner retinal layers (McHugh et al, 1990 (I)).

Pilot clinical studies in which a number of retinal vascular conditions were treated with diode lasers have demonstrated comparable results to earlier trials with argon and krypton lasers (McHugh et al, 1989). Further work is in progress to investigate the potential of diode lasers to photocoagulate the trabecular meshwork.
in the treatment of glaucoma (Mchugh et al, 1990 (II)).

Developments of diode lasers include the possibility of diode-pumped Nd:YAG lasers, and of mode-locked diode laser which would themselves have a photodisruptive mechanism of action.

1.11 CONCLUSIONS

The two most recent major developments in laser technology have been the introduction of the excimer laser and the diode laser. There are a number of other devices which are undergoing development, for example the erbium:YAG laser and the Raman and colour centre lasers (Marshall, 1988), which have potential for surgery of the anterior segment. It seems certain that laser technology will play an increasingly important role in the successful management of ophthalmic conditions.
CHAPTER 2
BASIC PRINCIPLES OF LASERS

2.1 GENERAL CONSIDERATIONS

The term "LASER" is an acronym for "Light Amplification by the Stimulated Emission of Radiation". The physical principles underlying the generation of laser energy are related to the quantum theory of radiation, which was originally proposed by Albert Einstein in 1905. According to quantum theory, optical radiation consists of discrete "quanta" of energy called photons, whose energy is given by the equation,

\[ E = h \nu \]

where \( E \) is the energy of the quantum, \( h \) is a proportionality constant called Planck's constant and \( \nu \) is the frequency of the light. According to Einstein, the minimum amount of radiant energy that can interact with matter is equal to the energy of a single photon.

An elaboration of the theory was postulated by Neils Bohr in 1913. He stated that each electron in an atom or molecule occupies a specific energy level. The majority of electrons occupy the lowest energy level available to them and this is called the ground state. This represents the most stable level for a collection of atoms or molecules.

Electrons may move between energy levels by several processes. One way in which this can occur is by optical transition. In this case, a photon of frequency \( \nu \) interacts with an electron. Provided that the energy of the photon is equal to the difference in two energy levels, it can stimulate an electron to undergo transition from one energy level to another via so-called stimulated transition. An electron having undergone such a transition is described as an excited electron. There are several possible consequences to stimulated transition (figure 2.1).

2.2 SPONTANEOUS EMISSION

An electron may be elevated from a stable lower energy level \( E_1 \) to a higher energy level \( E_2 \), by for example absorption of a photon. After a period of time the electron will fall back to its lower energy level, with emission of a photon of light of energy

\[ [E_2-E_1] \]

Each electron makes the transition independently, or out of phase. Thus, although the emitted photons are of the same wavelength and frequency as the absorbed photons, light is emitted at random. Such light is referred to as incoherent light and is one of the typical characteristics of spontaneous emission.
Figure 2.1

The three types of optical transition. In all cases, the photon frequency is equal to $DE/h$, where $DE$ is the energy difference between the two states involved (i.e. $E_2 - E_1$) and $h$ is Planck's constant. In the stimulated emission case, all other scalar and vector properties of the "new" photon are identical to those of the stimulating photon, i.e. exact amplification. (From Melles Griot, 1989)
2.3 STIMULATED EMISSION

An electron which is already in an upper level can be stimulated to undergo transition to the ground state by absorption of a photon. An electron falling to a lower energy level is accompanied by emission of the incident photon and a photon emitted which is of energy

\[ E_2 - E_1 \]

The "new" photon emitted has identical properties to the incident photon in terms of frequency, phase, polarisation and direction of propagation. Such light emitted due to stimulated emission is referred to as coherent light.

In order that stimulated emission occurs within a medium, it is necessary that the majority of electrons are excited or in a higher energy level before light enters the medium. This is a condition referred to as "population inversion". In this situation, the introduction of a beam of light of the appropriate wavelength would result in amplification of the beam following stimulation of the excited electrons into emitting photons which are in phase with the incident photons.

2.4 LASERS

There are three basic requirements for the production of laser radiation:

1. An excitable medium which has transition characteristics which allow population inversion.
2. An energy source to excite the lasing medium.
3. A system for reflecting spontaneously emitted photons repeatedly through the lasing medium (a resonator).

To create population inversion, energy must be supplied to the medium. In the case of gas lasers, such as argon or krypton lasers the external energy is supplied in the form of an electric current passing through the gas. An electrical supply also provides the energy source for diode lasers (vide infra). In the case of the ruby, or neodymium-YAG laser, the energy is supplied in the form of optical radiation by a flash lamp.

In a typical laser, the lasing medium is placed within an optical cavity that acts as a resonator (figure 2.2). The resonant cavity consists of two mirrors, whose separation is an exact multiple of the wavelength of the laser light. The lasing medium occupies the space between the mirrors. One of the mirrors is partially transmitting in order to allow emission of laser light from the system when a
Figure 2.2
Schematic diagram of a typical laser cavity. (from Vassiliadis, 1989)
threshold energy has been reached. After population inversion has been achieved, spontaneous emission will occur from excited electrons. Some of these will be reflected between the mirrors bounding the cavity and these will be of the correct wavelength to effect stimulated emission. Multiple reflections of the emitted photons increase the probability of light amplification. Thus stimulated emission becomes the predominant mechanism of photon propagation and a coherent beam is quickly generated. This represents the basis of laser action.

2.5 GENERAL CHARACTERISTICS OF LASERS

2.5.1 MONOCHROMATICITY

The light that is emitted from a laser is of one or a few individual wavelengths (colours), since there are only a limited number of efficient electronic transitions from excited energy levels in an atom or molecule to lower energy levels. Thus the argon laser emits over several wavelengths (lines) in the blue-green part of the spectrum, with the dominant lines being 488 nm and 514.5 nm.

In the case of clinical dye laser systems, use of a birefringent filter allows tuning of their potentially broad spectral output to an effectively monochromatic range.

2.5.2 DIRECTIONALITY

Since a laser's resonant cavity amplifies only electrons travelling along its long axis, a laser beam is highly directional and it has little divergence compared with conventional light sources. Low divergence permits effective focusing of the beam into a small spot whose irradiance (i.e. power per unit area) is high. This is of clinical relevance, since most ophthalmic laser applications require high focal irradiances.

2.5.3 COHERENCE

The component wave fronts of a laser beam are in phase with one another. Laser light is coherent both spatially and temporally. Spatial coherence means that there is good phase correlation along the laser beam. Temporal coherence means that the wavelength of the laser beam does not change with time, since differences between electronic energy levels do not alter with time. Although a high level of coherence is essential for certain diagnostic applications of lasers, for example retinal interferometry, it is not so important in relation to current surgical applications of lasers.
2.6 MODE OF OPERATION OF LASERS

Depending on the lasing medium and the mode of excitation, a laser may be operated in one of several ways.

2.6.1 CONTINUOUS WAVE LASERS

In continuous wave (CW) mode, there is constant stimulation of the atoms or molecules in the medium and laser radiation is therefore emitted continuously. Examples of lasers that are typically operated in the CW mode are argon, krypton, dye and carbon dioxide lasers. The diode laser is also classed as a CW laser.

2.6.2 PULSED LASERS

Pulsed operation may be obtained when laser materials such as ruby, or neodymium YAG are pumped with flash lamps. The output of these lasers consists of a train of pulses of durations of the order of milliseconds. The duration of the emitted pulses can be made shorter still, with consequently higher energy by either of two processes.

a) Q Switching (figure 2.3)

The "Q", or quality factor of a resonant cavity is related to the ratio of energy storage to energy dissipation in a medium. If a time variable absorbing cell (a "Q-switch") is added to the laser cavity, thereby obscuring one of the mirrors, laser generation is inhibited and a high level of population inversion occurs. If the cell is suddenly made transparent, laser action occurs, resulting in the generation of a high power pulse of light of between 2-14 nanosecond (1 nanosecond = 10^{-9} s) duration. The most commonly used Q-switch in photodisruptors is a "Pockels cell", an electro-optical device which is opaque until an electrical signal switches it to a transparent condition shortly after flash lamp action begins.

b) Mode Locking (figure 2.4)

Despite the theoretical purity of laser light, in the operation of a high powered laser, the output consists of a number of slightly different wavelengths which are slightly out of phase. Ordinarily all these different modes of oscillation operate independently of one another in a "free-running" mode.

In mode locking a layer of a suitable bleachable dye is placed in the path of the beam in the laser cavity. This dye is opaque to the light until the laser intensity builds up to a sufficient intensity to saturate the dye and render it briefly transparent.
This results in the emission of a train of laser pulses in which the longitudinal modes of the laser are coupled together. The duration of these pulses is typically of the order of 30 picoseconds (1 picosecond = $10^{-12}$ s) and the peak power of individual mode-locked laser pulses is approximately one thousand times greater than that of a Q-switched laser pulse. Certain practical differences exist between Q-switched and mode-locked systems. Mode-locked lasers require a longer laser cavity to provide enough longitudinal modes and a dye cell that needs regular maintenance and replacement of dye. The dye tends to bleach unevenly, producing an irregular distribution of energy in the focal spot. The range of energies available in current mode-locked systems is limited to 5 mJ or less and can be varied only by the use of filters. In contrast, Q-switched systems have a greater range of pulse energy, use a solid state Pockels cell that requires little maintenance and are small enough to be incorporated in a slit-lamp microscope. Q-switched lasers therefore tend to be favoured in clinical practice.

2.7 LASER DELIVERY SYSTEMS

The optical delivery systems employed in ophthalmic lasers are typically either a fibre optic cable, or an articulated mirror-arm. These are most commonly attached to a slit-lamp microscope’s objective lens. Lasers adapted for operative endophotocoagulation will have a specialised tip attached to the end of a fibre optic.

2.8 MODE OF ACTION OF DIODE LASERS

The relative novelty of diode lasers in ophthalmology and their many unique aspects indicate a separate consideration of these devices.

2.8.1 SEMICONDUCTORS (figure 2.5)

Laser diodes are special types of semiconductor junctions. Semiconductors are crystalline materials in which at ambient temperatures electrical resistance is mid-way between that of an insulator (e.g. plastic) and a conductor (e.g. a metal). In all materials electrons can exist at a number of energy levels. Electrons at a lower energy level occupy a region called the valence band. There is also a smaller population of electrons which occupy a higher energy band, which is termed the conduction band. Electrons in this band are delocalised and are not associated with a single nucleus. The relative distribution of electrons in these bands confer the properties of a conductor or an insulator. The difference in energies of the two bands, termed the "band gap" is small in a semiconductor. It therefore requires a
Figure 2.3
Laser cavity for Q switched or mode-locked operation. (from Vassiliadis, 1989)

Figure 2.4
Output pulses of a mode-locked laser (from Vassiliadis, 1989)
Energy band diagrams for an insulator, a metallic conductor and a semiconductor. $E_g$ is the band gap, $kT$ is the thermal excitation energy and $E_f$ is the Fermi energy (a measure of the electron population distribution in the crystal). Thermal excitation of electrons into the conduction band in the semiconductor permits limited conduction. (from Melles Griot, 1989)
small input of energy to enable electrons to move to the higher level and for conduction to occur.

The electronic properties of semiconductors can be modified by "doping". Doping refers to the introduction of "foreign" atoms into the crystal lattice during its synthesis. This may have the effect of producing either an excess of electrons, or a relative deficit of electrons in the lattice. In technical jargon, this latter phenomenon is referred to as an excess of "holes". Semiconductors which are doped to produce excess electrons are termed n-type semiconductors and those that are doped to produce an excess of holes are termed p-type semiconductors.

2.8.2 SEMICONDUCTOR JUNCTIONS (figure 2.6)

If a p-type and an n-type semiconductor are combined, the interface between the semiconductors is called a p-n junction. If a voltage is applied to the junction, current flows through the junction. Electrons flow into the p-type region and holes move into the n-type region.

This flow can be considered as the recombination of electrons and holes in the junction region. Each electron-hole recombination is accompanied by spontaneous emission of a photon of energy $h\nu$. This is the mechanism by which a light-emitting diode (LED) operates.

2.8.3 LASER DIODES (figure 2.7)

If the n-type and p-type semiconductors at the p-n junction are sufficiently well doped and a high enough current applied, then population inversion of electrons can be induced in the junction region.

For laser production, the junction is enclosed within an optical cavity. The opposite facets of the crystal are optically polished and coated with suitably reflecting dielectric layers. This represents the basic structure of diode lasers.

2.8.4 HETEROJUNCTION DIODES

Since the first laser diode was introduced there have been many advances in device efficiency. The use of heterojunctions has resulted in increased output power, with lower laser threshold current. A heterojunction is a semiconductor junction between two different materials. One heterojunction used in diode lasers is that between gallium arsenide (GaAs) and gallium aluminium arsenide (GaAlAs) (figure 2.8). This is the laser which is currently used in ophthalmology. It can be prepared to emit anywhere in the region 750-950 nm,
although the emission of high power diodes (1 watt) is at present restricted to the near infrared region (780-840 nm).

The active layer of a gallium aluminium arsenide laser diode, is 0.2 microns thick and composed of GaAs and it is sandwiched between two layers of GaAlAs 1 micron thick. The dimensions of a laser diode are typically 0.5 x 0.2 x 0.1 mm- i.e. the size of a grain of salt.

2.9 CHARACTERISTICS OF LASER DIODES

2.9.1 TEMPORAL BEHAVIOUR

Laser diodes can be driven to run in a pulsed or continuous mode. High power laser diodes used in ophthalmology are CW lasers. Ion lasers will be generating laser light continuously throughout any treatment regime. The individual doses applied to the patient’s eye are achieved by a mechanical shutter which opens and shuts in relation to control signals from the foot switch. In the diode laser, the foot switch activates the laser and laser light is generated in CW mode for the selected duration of exposure. The diode laser is not active between exposures and this clearly has implications regarding the working life of such devices in comparison to ion lasers.

2.9.2 CURRENT-OUTPUT CHARACTERISTICS

The output power of a laser diode is a function of the current flowing across the active junction. Figure 2.9 shows a typical plot of beam output power versus input current. Above the lasing threshold, there is a linear region of operation, allowing a high degree of confidence in the ability to modulate the laser output in a controlled fashion.

Linearity of output is also facilitated in laser diodes by the incorporation of an integral photodiode detector (figure 2.10). This photodiode samples the output of the laser diode in situ by collecting the residual emission from the rear facet of the laser diode, which is directly proportional to the output beam intensity. The photodiode signal not only provides a monitor but also facilitates feedback control of the output power.
Idealised band structure of a p-n junction in a semiconductor. When current flows across the junction, holes and electrons recombine: i.e. electrons relax from the conduction band (a higher energy level, which is analogous to excited electronic orbitals of atoms and molecules) to the valence band (a lower energy level, which contains electrons involved in the bonding of the crystal and which is analogous to the ground state in atoms or molecules).

The relaxation energy is released as photons (one per electron). The photon-frequency is equal to $E/h$ where $E$ is the effective band gap and $h$ is Planck's constant. (from Melles Griot, 1989)
Figure 2.7
Structure of a simple gallium arsenide laser diode. (from Melles Griot, 1989)
Figure 2.8
A double-heterojunction laser diode. The carriers are confined to the active region by potential barriers and the laser radiation is confined by the wave guiding of the refractive index gradients. (from Melles-Griot, 1989)
2.9.3 OUTPUT BEAM PROPERTIES

a) Transverse mode structure

Because the junctions in diode lasers have a strange aspect position in that they are extremely narrow in the p-n axis, but relatively extensive in the long axis, the beams of light that they emit tend to be elliptical in cross section. This means that the energy distribution across the beam may be Gaussian on each meridian, but will vary in isoenergy points. The output of laser diodes consists of the lowest order transverse mode. This mode has a transverse intensity profile which is pseudo-Gaussian in shape (figure 2.11), which is analogous to that of many gas lasers.

b) Beam divergence and asymmetry

The divergence of a coherent Gaussian beam is inversely proportional to the radius of the beam waist from which it is diverging. The active region of a laser diode junction is small and asymmetrical. Consequently, the divergence of a laser diode beam is quite high. Beam divergence is typically between 12 and 30 degrees. When collimation of the beam is required, it is necessary to expand the minor axis of the output, in order to eliminate asymmetrical divergence.

2.10 EFFICIENCY AND RELIABILITY OF LASER DIODES

The electrical-optical conversion efficiency of laser diodes is high. Typically, about 20% of input power is converted to laser radiation. By comparison, the efficiency of a Nd-YAG laser is less than 4% and that of an argon or krypton laser is 0.05%. Two implications of the efficiency of diode lasers are that a one watt laser diode can be run by a 6 volt battery and that no external cooling system is necessary, since excess heat production is low.

Semiconductor lasers have a high level of reliability. Manufacturers’ specifications quote a life time of 30,000 hours for a 500 mW laser diode. This would represent several hundred million pulses, at a pulse duration of 0.20 seconds. In a busy ophthalmic department this would probably allow 15-20 years of use for a diode laser, before replacement was necessary.
Figure 2.9
Beam output power versus input current for a typical gallium aluminium arsenide laser diode.
Figure 2.10

Section of a typical laser diode and its integral monitor photodiode. The dimensions of the unit are approximately 9 mm x 2 mm. (from Melles Griot, 1989)
Figure 2.11

Irradiance profile of a Gaussian TEM$_{00}$ mode in a laser diode. The beam radius $w$, is defined as the point at which the irradiance (intensity) has fallen to $1/e^2$ (13.5 %) of the axial value. (from Melles Griot, 1989)
2.11 DEVELOPMENTS AND APPLICATIONS OF DIODE LASERS

The development of mode-locked diode lasers with very high peak powers in the nanosecond or picosecond pulse range may result in exploration of their potential for photodisruptive treatment of ocular structures. Investigations are already being performed into the advantages of diode-pumped YAG lasers over the currently used flashtube as an energising source.

The wavelength of emission of a diode laser is influenced by the band gap within the semiconductor and this in turn depends upon its constituent materials. Compounds are being studied which can produce coherent radiation in the visible spectrum. A Ga/Al/Ind/GaAs system can lase in the 580-680 nm range. A system comprising ZnSSe/GaAs could be developed to emit blue laser radiation. Other compounds are being developed which emit in the near and mid-infrared regions. If high powered lasers were available composed of these alternative compounds, then investigations could be performed into the ophthalmic applications of diode lasers which emit at a range of wavelengths.

2.12 CONCLUSIONS

There are common basic principles underlying the mode of action of all forms of lasers. The nature of the particular lasing medium will determine the wavelength of emission of the laser. The mode of excitation and the configuration of the optical resonator will determine the mode of operation, for example CW, Q-switched or mode-locked. Laser diodes at present represent the most efficient and potentially the most reliable form of production of laser light.
CHAPTER 3
AIMS OF THE PROJECT AND OUTLINE OF THE STRUCTURE
OF THE STUDY
3.1 STUDY AIM

The essential aim of this project has been to develop a clinical diode laser and to examine its effectiveness as a therapeutic device in ophthalmology.

3.2 STUDY DESIGN

The design of this study required consideration of several problems. These problems may be categorised into technological, biophysical and clinical aspects.

3.2.1 TECHNOLOGICAL CONSIDERATIONS

The relative novelty of laser diodes implied the necessity for the design of an optical system that would allow effective transpupillary delivery of laser radiation to particular target structures within the eye. This system had to incorporate a number of features:

a) A visible aiming beam, that was coaxial with the infrared treatment beam.

b) A focusing and illumination system which was either an integral part of the laser device, or which was independently accessible, for example from a slit lamp microscope.

c) A means of preventing exposure of the operator to the treatment beam.

d) The facility to adjust the output characteristics of the laser, for example, laser power, spot size and pulse duration in a controlled fashion.

3.2.2 BIOPHYSICAL CONSIDERATIONS

Data on the histopathology of human ocular laser photocoagulation had been restricted to lasers which emit in the visible wavelengths (488-694 nm) (Marshall, 1967 and 1979) and lasers emitting at 1064nm (Van der Zypen, 1985).

With no information available on ocular beam-tissue interactions of the infrared diode laser within human retina, before commencement of clinical trials it was clearly important to conduct a study into the histological nature of ocular lesions produced by a diode laser. It would then be possible to assess their comparability to burns seen in relation to conventional devices. It would also allow early identification of any excessive non-therapeutic damage which could possibly preclude use of a diode laser in a clinical situation.

With these aims in mind, histological studies in relation to diode laser irradiation were directed at three ocular structures:
a) The retinal mid-periphery  
b) The macula  
c) The trabecular meshwork  

3.2.3 CLINICAL CONSIDERATIONS  

Prior to the present study, no clinical assessment had been performed of the ability of diode lasers to treat ocular conditions. Trials therefore had to be designed which would address the following elements of laser therapy:

a) The suitability and comparability of treatment regimens commonly used with conventional gas lasers, when applied to treatment with diode lasers. These aspects would be assessed by the rate and extent of regression of treated lesions.

b) The visual outcome of therapy.

c) Laser-related side effects.

d) The ergonomics and the general reliability of diode lasers.

This aspect of the investigation was conducted in the form of pilot studies which examined the effects of diode laser photocoagulation in the treatment of the following conditions:

- Proliferative diabetic retinopathy  
- Exudative diabetic retinopathy  
- Branch retinal vein thrombosis complicated by neovascularisation of the optic disc, or of the retina  
- Central retinal vein thrombosis complicated by established or threatened rubeosis iridis, or by optic disc neovascularisation.  
- Chronic open angle glaucoma.

It was felt that such a problem-orientated approach would allow the most favourable conditions under which the aims of this project could be achieved.
SECTION II
DESIGN OF INSTRUMENTATION
CHAPTER 4
INSTRUMENTATION
4.1 RETINAL STUDIES

4.1.1 DIODE LASERS USED IN RETINAL STUDIES

Two lasers were used in the retinal histopathological studies.

a) For the initial exposures in rabbits a model SDL2420-H1 laser diode with 250 mW rated output and wavelength of 810 nm was used.

b) For subsequent rabbit and human exposures the laser was uprated to a SDL2430 laser with double the output power (500 mW). In some cases, to achieve higher power levels two laser outputs were combined to provide 800 mw output.

The diverging output beam from the diode was first collimated and then combined with a helium-neon beam for visual alignment and focusing. A simple lens arrangement allowed adjustment of the vergence of both laser diode and helium-neon beams for retinal focusing. Viewing of the retina was provided by a modified direct ophthalmoscope (figure 4.1 (a) and (b)). The laser diode was driven by a Spectra Diode Labs SDL800M laser diode driver with pulse duration and amplitude controlled by an external pulse generator. Power and energy levels at the eye were calibrated with a UDTS390 photometer and referenced to an EG and G radiometer 581. Both lasers operated in a continuous wave mode and exposure times of between 0.2 and 1.2 seconds were selected. The spot size of the treatment beam at the retina was 200 microns.

4.1.2 ARGON AND KRYPTON LASERS

In a previous study (Marshall and Bird, 1979), from which histological data was re-examined, two different gas laser systems were used, a Coherent Radiation 800 argon laser and a Lasertek krypton laser. Although the Lasertek system may be used to deliver either krypton or argon radiation it was thought that the use of the Coherent Radiation argon system would allow a more useful comparison as this model is widely used in clinical centres. Both of these lasers have integral power monitors and all figures quoted are those registered on the manufacturer’s instruments. No study was undertaken of the relative energy distribution within the laser beams. Exposures were delivered via the integral slit lamp systems in conjunction with a Goldmann fundus contact lens.
4.2 DIODE LASERS USED IN MACULAR AND TRABECULAR
HISTOLOGICAL STUDIES AND IN THE CLINICAL TRIALS

Spectra Physics SDL2430 laser diodes were used with a spectral
emission at 810 nm (figure 4.2), and with a maximum output power of up to 1.4 W.
The laser diodes were driven by a eye were calibrated with a UDTS390 photometer
and again referenced to an EG and G radiometer 581. Measurements demonstrated
that transmission losses within the system were less than 5%. The laser operated in
a continuous mode, but was a power on demand system.

Two forms of delivery system were employed in these phases of the study:

a) A development of the original hand held version, which utilised a direct
ophthalmoscope.

b) A model which could be attached to the tonometer stand of a standard
Haag-Streit 900 slit lamp microscope (figure 4.3 (a)-(d)).

In the slit lamp version an aiming beam was provided by a red-emitting (680
nm) low power (300 microwatts) laser diode. Viewing of the retina was accomplished
with the optics and illumination source of the slit lamp microscope in conjunction
with a fundus contact lens.

In order to establish compatibility with the diode delivery system, three lenses
were used in the clinical studies. These were the Goldmann three mirror; the
Mainster lens; or the Rodenstock panfundoscope lens. Laser spot size was variable
in 50 micron steps between 100 and 500 microns, but as with all lasers the absolute
spot size at the retina varied slightly with choice of contact lens. The maximum
output power of the laser was 1.4 watts. The exposure duration could be varied
between 10 and 990 ms.

All the treatment laser diodes used for this study emitted optical radiation in
the IR-A (around 800 nm). This radiation, whilst just visible to the human eye is
extremely inefficient in initiating the transduction process and therefore if filtered
from the eye its loss is not perceived.
Figure 4.1 HAND-HELD DIODE LASER

(a) Hand-held version of diode laser, utilising a direct ophthalmoscope.

(b) Section through hand-held version of the diode laser showing the major optical elements.

Key to figure 4.1 (b)

IR : Infrared treatment laser diode
Aim : Aiming laser
1 : Illumination source
2 : Collimating lens
3 : Dielectric mirror
Figure 4.3 SLIT-LAMP MOUNTED DIODE LASER

(a) Version of diode laser which is attachable to a standard slit lamp microscope, shown with instrument console.

(b) Diode laser shown mounted on Haag-Streit slit lamp microscope.

(c) Section through slit lamp-mounted diode laser which shows the principal optical components in the assembly (see key).

(d) Top: Optical arrangement of treatment laser diodes. A diverging beam from IR1 passes through a collimating lens (producing a parallel beam), two anamorphic prisms (expanding the beam) and a total internal reflection block. It then passes into a polarising beam combiner, where it joins the beam from IR2.

A diverging beam passes from IR2 and passes through a collimating lens, two anamorphic prisms and a half wave plate (rotating the beam through 90 degrees) and then into a polarising beam combiner. The combined beams are reflected by the dielectric mirror into the vertical telescope.

Bottom: Optical arrangement of treatment and aiming laser diodes. A diverging beam passes from the red laser diode and passes through a collimating lens. It is then reflected by a total internal reflection prism and passes through the dielectric mirror, after which it combines coaxially and collinearly with the infrared treatment laser path and is directed into the vertical telescope.

Key to figure 4.3 (c) and (d)
A1, A2 and A3 : Collimating lenses
IR1 and IR2 : Infrared treatment lasers
Aim : Aiming laser diode
X : Combined aiming and treatment laser beams
1 and 2 : Anamorphic prisms
3 : Half wave plate
4 : Polarising beam combiner
5 : Total internal reflection block
6 : Total internal reflection prism
7 : Dielectric mirror
8 : Glass plate
Figure 4.3 (b)
Figure 4.3 (c)

Protective filters

Patient

Working distance selector lens

View A

X

IR1 IR2

Aim

View B

Laser diodes

Laser head alignment

Cable

Operator

Slit lamp
In the clinical diode laser, anti-reflective coatings were introduced into the laser head to prevent laser irradiation at 1.06 µm from entering the operator's eye. These filters consisted of layers of high and low refractive index dielectric materials which have the property of allowing transmission of all wavelengths shorter than the laser wavelength. The reflection of near-infrared wavelengths is high and, therefore, exhibits a high lens flare. By the incorporation of a hot mirror and a variable density safety shutter during the treatment, the laser beam is blocked from the operator's eye.

A pencil beam of less than 20 micrometers was measured in the eyepieces, which is well within the safety limits for laser exposure.

The power source in each laser was from a standard single phase 13 amp mains supply. Ancillary cooling facilities were not necessary for either instrument since cooling is provided by air convection. The lasers are 39 cm x 15 cm and weigh 85 lb.
In the clinical diode laser, filters with dielectric coatings were introduced into the laser head to prevent laser irradiation at 810 nm from entering the operator's eye. These filters consisted of layers of high and low refractive index dielectric materials which have the property of allowing transmission of all wavelengths shorter than the emission wavelength of the treatment laser and the reflection of near-infrared wave fronts. These wave fronts are rendered in phase with each other by the coatings, which results in constructive interference. Dielectric filters therefore exhibit a high level of reflectance for the incident infrared beam from the treatment laser. A filter designed to produce this effect is known as a "hot mirror". The incorporation of a hot mirror into the laser head obviates the need for a mechanical safety shutter during the treatment exposures and it allows an unimpeded retinal view throughout all treatment sessions.

A photometer was used to monitor the level of infrared radiation passing back through the surgeon's eye pieces during exposure at maximum power. Less than 20 microwatts was measured at the eyepieces, which is well within the safety limits for laser exposure.

The power source in each laser was from a standard single phase 13 amp mains supply. Ancillary cooling facilities were not necessary for either instrument since collateral heat production was extremely low. When not in use, either instrument could be easily stored in a carrying case measuring 46 cm x 33 cm x 15 cm and was light enough to render it easily transportable.
SECTION III
HISTOLOGICAL STUDIES
CHAPTER 5
MATERIALS AND METHODS OF HISTOPATHOLOGICAL STUDIES
5.1 RETINAL EXPOSURES

5.1.1 ANIMAL STUDIES

Three six month old Dutch rabbits were used in this study. Animals were anaesthetised with intramuscular fentanyl and intravenous valium. Cyclopentolate 1% was instilled in both eyes for mydriasis. The animals were placed on a positioning board, with the target eye held open with a lid speculum.

Transpupillary photocoagulation was performed to both eyes using a diode laser at power levels which varied between 100 mW and 400 mW. The laser spot size was 200 microns and the exposure times were varied between 0.20 s and 1.2 s. The position and ophthalmoscopic visibility of all the lesions produced were recorded.

The rabbits were sacrificed immediately following the last exposure with an overdose of intravenous sodium pentobarbitone and after death, the eyes were removed for histological examination.

5.1.2 HUMAN STUDIES

Subsequent to the granting of permission by the relevant local ethical committee, three patients agreed to take part in the diode laser study. All three patients were going to undergo enucleation because of malignant melanoma. Two had ciliary body malignant melanomas and one a juxtapapillary melanoma. All had partial retinal detachments which involved the macula and in two cases the tumour partially obscured the pupil. In these cases the loss of pupillary area would result in a proportional attenuation of the radiation incident upon the retina (because of the large cone angle of the incident beam) and therefore the figures of radiant power in table I may be erroneously high for a given retinal reaction.

Mydriasis of the affected eye was accomplished with cyclopentolate 1%. As human subjects could sustain fixation on request, no form of external fixation of the globe was necessary and because direct ophthalmoscopy was being used, no contact lens was applied. Transpupillary photocoagulation was performed to areas of normal, attached retina. Some exposures were deliberately located over retinal vascular elements. Power levels were varied between 150 mW and 800 mW. The laser spot size was 200 microns and the exposure time was maintained at either 0.25 s or 0.50 s. Between seven and forty three burns were applied to each eye.

The location and observed intensity of the lesions produced were recorded on a retinal diagram. Note was made of the subjective impressions reported by the
patient during photocoagulation. Immediately following treatment, colour fundal
photography was performed. Eighteen hours following laser exposure, enucleation
was performed under general anaesthetic and the eye prepared for histopathological
study.

For comparison, fresh sections were prepared from tissue derived from an
earlier study in which sample argon (200 microns, 300 mW), and krypton lesions,
(200 microns, 600 mW) had been produced with exposure durations of 0.2 to 0.5
seconds in a melanoma eye (Marshall and Bird, 1979).

5.2 HUMAN MACULAR EXPOSURES

A submission was made to the local ethical committee, which gave approval
for the study to proceed. For the diode exposures two patients, each with a choroidal
melanoma which required enucleation were given a full explanation of the nature of
the trial prior to giving consent to the procedure being carried out. The first subject
was a 68 year old male, with a tumour of the left eye which was situated nasal to the
optic disc. Although there was subretinal fluid causing a serous detachment of the
nasal retina, at the time of examination and treatment the macula had a normal
ophthalmoscopic appearance (but see histology section).

Mydriasis was accomplished with cyclopentolate 1% and following topical
anaesthesia, a Goldmann contact lens was applied. A total of 63 exposures were
applied to the macula in a "grid" pattern that was centred on the fovea, although no
burns were applied to the foveola. The spot size was 300 microns and the exposure
duration 0.25 seconds. The output was varied between 400 and 800 mW. Enucleation
was performed five weeks subsequent to the exposures. No discomfort was reported
by the patient during photocoagulation.

The second patient treated with the diode laser was a 65 year old lady with
a right ciliary body malignant melanoma. The presence of associated subretinal fluid
had caused a shallow serous retinal detachment with partial involvement of the
macula. A grid pattern of 25 burns were applied to the macula. The spot size was
100 microns, the exposure duration was 0.20 seconds and power was between 600
and 900 mW. The tumour occluded 25% of the pupil, this resulted in a partial
occlusion of the diode beam and therefore a higher power was needed to produce
a threshold lesion. Enucleation was performed 18 hours following treatment.
In an eye from an earlier study (Marshall and Bird, 1979), sample argon (50 microns, 87 mW), and krypton lesions, (50 microns, 200 mW) had been produced with exposure durations of 0.2 to 0.5 seconds. The argon exposures were made in a line superonasal to the inferotemporal axis and which traversed the fovea. A similar number of krypton exposures were made at similar distances from the fovea at right angles to the line of argon burns. This eye had been enucleated 20 hours after photocoagulation, again due to the presence of a malignant melanoma of the anterior choroid. Microscopic analysis was carried out on ocular tissue from this experiment using an identical preparative procedure to that used for diode-irradiated specimens.

5.3 MICROSCOPIC STUDIES ON RETINAL TISSUE

Immediately following enucleation, a 5 mm penetrating incision was made at the ora serrata and the eyes immersed in 100 mls of fixative. This initial solution contained 2.5% glutaraldehyde buffered in 0.1 M sodium cacodylate containing 10 mg/ml calcium chloride and with a final pH of 7.4. In rabbits the anterior half of the globe was removed, together with the lens, iris and vitreous and discarded. In humans the globe was hemisected, usually obliquely and in such a fashion that the irradiated area was totally isolated from that portion containing the tumour so that routine diagnostic procedures could be carried out on the latter. The retinal lesions of both species were photographed under glutaraldehyde onto Kodak Ektachrome EPY 135 film using a macrophotographic system (Olympus).

Lesions were isolated with a surrounding area of non-irradiated tissue by microdissection under a microscope. A number of retinal lesions were prepared as retinal whole mounts by dehydration in alcohol, clearing in xylene and mounting on microscope slides in depex (Marshall and Mellerio, 1967). The tissue surrounding other sample lesions was trimmed in such a way that its geometry and therefore its orientation could be determined during ultramicrotomy. Tissue was washed briefly in 0.1 M sodium cacodylate buffer containing 7.5% sucrose and post-fixed for one hour in 2% osmium tetroxide buffered in 0.1 M sodium cacodylate. Samples were dehydrated through a graded series of concentrations of ethanol in water and embedded in araldite via epoxyp propane.

Sections for light microscopy (LM) were cut at 1 micron on glass knives mounted in a Huxley Mark 1 ultramicrotome and stained with toluidine blue.
Photography was performed using Kodak Technical PAN 2415 film.

Sections for transmission electron microscopy (TEM) were cut using diamond knives in a Reichert OMU4 ultramicrotome. They were mounted on 200 mesh copper grids and stained with uranyl acetate and lead citrate before being examined in an AE1 801 transmission electron microscope. Sections were photographed onto Ilford Technical Film.

5.4 HUMAN TRABECULAR MESHWORK EXPOSURES

A submission was made to the local ethical committee, which gave approval for the study to proceed. A full explanation of the nature of the trial was given to the patient, who then gave consent for the procedure. The subject was a 65 year old female with a right ciliary body malignant melanoma. Gonioscopy prior to treatment and subsequent microscopic examination confirmed that the tumour did not involve the trabeculum.

Topical anaesthesia was instilled and a Goldmann contact lens was applied to the eye. Three quadrants of the trabecular meshwork were irradiated with the diode laser. A total of 70 burns were applied. The target area was the central, pigmented portion of the trabeculum and the aim was to produce a blanching reaction. The spot size was 100 microns, the exposure duration was 200 ms and the required output power varied between 750 and 1200 mW.

For comparison, an argon blue-green laser was used to apply a further 25 burns to the remaining quadrant of the same eye. In common with the diode exposures, the end point was a visible blanching of the pigmented region of the trabeculum. The spot size was 100 microns, the exposure duration was 200 milliseconds and the power needed to produce a visible reaction varied between 500 and 1000 milliwatts. Gas bubble formation was not observed following either diode or argon irradiation. Enucleation was performed 18 hours following treatment.

5.5 MICROSCOPIC STUDIES ON TRABECULAR TISSUE

Immediately following enucleation, a 5 mm penetrating incision was made at the pars plana and the eye was immersed in 100 mls of fixative. This initial solution contained 2.5% glutaraldehyde buffered in 0.1 M sodium cacodylate containing 10 mg/ml calcium chloride and with a final pH of 7.4. The globe were hemisected in such a fashion that the irradiated areas were totally isolated from the portion containing the tumour so that routine diagnostic procedures could be carried
Meridional sections of the iridocorneal angle were isolated under a dissecting microscope. The samples were trimmed in such a way that the laser employed to irradiate a particular portion of trabeculum and the power that was used could be identified.

Tissue for light and transmission electron microscopy was washed briefly in 0.1 M sodium cacodylate buffer containing 7.5% sucrose and post-fixed for one hour in 2% osmium tetroxide buffered in 0.1 M sodium cacodylate. Samples were dehydrated through a graded series of concentrations of ethanol in water and embedded in araldite via epoxypropane.

Sections for light microscopy (LM) were cut at 1 micron on glass knives mounted in a Huxley Mark 1 ultramicrotome and stained with toluidine blue.

Silver sections for transmission electron microscopy (TEM) were cut using diamond knives in a Reichert OMU4 ultramicrotome. They were mounted on 200 mesh copper grids and stained with uranyl acetate and lead citrate before being examined in an AE1 801 transmission electron microscope.

Specimens for scanning electron microscopy were post-fixed overnight in 2% osmium tetroxide buffered in 0.1 M sodium cacodylate. They were dehydrated through a series of ascending concentrations of acetone before being critical-point dried (Samdri 780). Dried samples were coated with a 30 nm layer of gold in a sputter coater (Emscope) prior to being examined in a Hitachi 520 scanning electron microscope and photographed onto Kodak Tri-X PAN 5-TX 120 film.

5.6 RESULTS OF RETINAL STUDIES

5.6.1 MACROSCOPIC FEATURES OF RETINAL BURNS

On ophthalmoscopic examination of the diode exposures it was apparent that lesions of similar appearance were obtained in both human and rabbit retinas (figure 5.1). There was however a difference in the retinal sensitivity between the two species in relation to the irradiance required to produce either a visible or a haemorrhagic lesion (table I). The only subjective effects noted by the human subjects, occurred at a power level of 800 mW when one patient reported a slight "pricking" sensation, which was not particularly uncomfortable. This presumably related to similar responses in other patients when krypton burns are applied to the retina in the region of ciliary nerves (Schulenberg and Hamilton, 1979).
5.6.2 OPHTHALMOSCOPIC APPEARANCES OF RABBIT LESIONS

The radiant power at which lesions were first visible was 100 mW with an exposure duration of 0.25 s. These just supra-threshold lesions were pale greyish areas, showing a slight coagulum of the neural retina. Lesions produced by higher energy exposures demonstrated more extensive coagulation both in area and depth with an intense white reflex (figure 5.1 (a) and (b)).

Correlation between burn dimensions and radiant power were determined both by measuring the lesion diameters on projected images of the macrophotographs and by measurements made on serial histological sections through the lesions. Measurements of burn geometry were also made from whole-mount preparations. Typically lesions were not perfectly circular and a representative small lesion was 185 microns by 160 microns; a large lesion 350 microns by 370 microns.

In order to compensate for any variations in the size of lesions induced by optical imperfections in the rabbit eyes when irradiations were directed off the visual axis a number of paired vertical rows of lesions were made extending from just beneath the area of myelinated nerve fibres to the inferior peripheral retina. In one row of each pair the energy was progressively increased as the lesions became more peripheral and in the second row of the pair energy was increased towards the myelinated area. The results are plotted in figure 5.2 (a) and demonstrate that for any given radiant exposure above that required to produce a faint lesion peripheral burns were always smaller than central ones. This probably results from a drop in irradiance (W/cm²) in peripheral exposures due to an increase in the area of irradiation.

In four lesions, sub-retinal haemorrhages were observed from exposures of 300, 300, 350 and 400 mW at 0.25 s and in the latter, there was disruption of the inner retina and blood in the vitreous.
Figure 5.1

Macrophotographs of diode laser lesions in the eyes of rabbit (a, b) and human (c). Note the typical grey appearance of threshold lesions, which become more intensely white with higher power exposures.
TABLE I
RELATIONSHIP BETWEEN OPHthalMOscopic APPEARANCES AND RADIANT POWER OF DIODE LASER

LASER POWER (mW)

Two cases had at least 25% of the pupillary area occupied and therefore the radiant exposure levels may be in excess of those required to produce a comparable effect in an eye with an unimpeded pupil.
TABLE I
RELATIONSHIP BETWEEN GROSS OPTHALMOSCOPIC APPEARANCES
AND RADIANT POWER OF DIODE LASER

LASER POWER (mW)

<table>
<thead>
<tr>
<th>LESION (ophthalmoscopic appearance)</th>
<th>RABBIT (exposure time 0.37 s)</th>
<th>HUMAN (exposure time 0.5 s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faint</td>
<td>100-200</td>
<td>200-400</td>
</tr>
<tr>
<td>Clearly visible</td>
<td>200-250</td>
<td>400-600</td>
</tr>
<tr>
<td>Intense</td>
<td>300-350</td>
<td>600-800</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>350</td>
<td>-</td>
</tr>
</tbody>
</table>

* Two cases had at least 25% of the pupillary area occluded and therefore the radiant exposure levels may be in excess of those required to produce a comparable effect in an eye with an unimpeded pupil.
5.6.3 OPHTHALMOSCOPIC APPEARANCES OF HUMAN LESIONS

The radiant exposure for producing a visible lesion was 200 mW at 0.5 s. Lesions were clearly observed at power levels of 400 to 600 mW and intense white lesions occurred at exposures of between 600 to 800 mW (figures 5.1 (c). At higher energy levels, greater than 600 mW a transient orange luminescence of the pigment epithelium was observed by the surgeon. At the highest energy levels used in this study we did not produce any form of choroidal or retinal haemorrhage. Figure 5.2 (b) demonstrates how for a given retinal spot size, the diameter of the lesion increases with retinal irradiance. This is due to greater energy dissipation per unit volume with increasing irradiance and thus a larger thermal damage profile in relation to the initial impact zone (Marshall, 1989; Zheltov et al, 1989).

5.6.4 HISTOPATHOLOGICAL APPEARANCES OF RETINAL LASER BURNS

In the following section, a detailed discussion of the histology of the lesions produced by diode lasers is given while those produced by argon or krypton systems are not fully described as they have been previously published (Marshall and Bird, 1979). They will be referred to where they provide a relevant comparison with diode laser burns.

5.6.5 RABBIT

a) LIGHT MICROSCOPY

In all diode lesions there was an abrupt transition between normal and irradiated areas of retina (figure 5.3). The lesions showed cellular displacement and vacuolation together with nuclear pyknosis in both retinal pigment epithelium (RPE) and photoreceptor cells. The RPE cells had either shrunken or swollen outlines and showed disorientation of their apical surfaces and pigment granules. There was also disruption of the outer and inner segments of the photoreceptor cells with elements being radially displaced away from the lesion centre. In the inner segments of the receptor cells, the mitochondria were vacuolated and in most affected cells the receptor nuclei were pyknotic. There was no primary damage to the inner retinal layers.
Figure 5.2 (a)
RADIANT POWER AND LESION SIZE IN RABBIT RETINA

Lesion size (microns)

Radiant power (mW)

- Central lesions  + Peripheral lesions

Spot size = 200 microns; Exposure = 0.25 s
Figure 5.2 (b)
RADIANT POWER AND LESION SIZE IN HUMAN RETINA

Lesion size (microns)

Radiant power (mW)

Spot size = 200 microns; Exposure = 0.50 s
All lesions showed choroidal changes, with closure of vessels of the choriocapillaris throughout the irradiated area. There was evidence of damage to the outer blood retinal barrier, with the resultant fluid movement causing the pooling of oedema either in the sub-retinal space or within the outer nuclear layer. Most of the oedema in low energy lesions was located in an annulus just external to the central plaque of photocoagulated retinal pigment epithelial cells (figure 5.3 (a)). In higher energy lesions the fluid from the initial peripheral annulus collected in the inner nuclear layer internal to the outer zone of coagulated tissue (figure 5.3 (b)). In larger lesions, there was extensive fluid movement between the RPE and photoreceptor layer, resulting in a focal retinal detachment around the site of coagulation (figure 5.3 (c)). The size and clarity of the fracture plane within the tissue is probably a secondary phenomenon resulting from the degree of fluid movement occurring between exposure and enucleation. In several lesions there was evidence of choroidal haemorrhage leading to blood passing to the retina and vitreous.

b) ELECTRON MICROSCOPY

Within the area of irradiation the RPE cells were shrunken, electron dense and showed a flocculent staining pattern particularly over the membranes of remnants of organelles. The melanin granules themselves appeared relatively undamaged in morphology but within the irradiated area each granule was surrounded by microvacuolation. Other loci of vacuolation included mitochondria and the intracellular membrane excursions of the basal convoluted border of the RPE. In the periphery of zones of coagulation large vacuoles were present either beneath or between the RPE cells. In some cases those beneath were sufficiently extensive that a focal RPE detachment was apparent extending centripetally. In other cases spaces between irradiated and non-irradiated RPE cells were sufficiently extensive that perhaps one or more rows of cells had been lost due to fluid movement at the interface zone.

Within the lesion area there was an increase in electron density of Bruch's membrane, which appeared otherwise structurally unaffected. There was damage to the choriocapillaris with the condensation or loss of endothelial cells and the dilatation of their fenestrations (figure 5.4 (a) and (b)). In some vessels the lumen was blocked by fibrin or by blood clots.
Figure 5.3

Light micrograph of diode laser lesions produced by varying levels of radiant exposure in rabbit retina: (a) 200 mW, (b) 300 mW and (c) 350 mW. Note in the medium and high power lesions that an area of outer retina is coagulated and adherent to the underlying area of pigment epithelium. Peripheral movement of fluid has resulted in the artificial separation of the two portions of the outer nuclear layer. In the high power lesions, there is subretinal oedema and an associated area of retinal detachment.

The bar marker is 100 microns.
Figure 5.4 (a) and (b)

Transmission electron micrographs of the basal region of the pigment epithelium, Bruch's membrane and choriocapillaris in rabbit retina at the centre of an area irradiated by a diode laser. In both micrographs the cytoplasm of the pigment epithelium is abnormally electron dense and vacuolated with a flocculent staining appearance. Bruch's membrane is intact, but shrunken and the elastin layer shows abnormal staining properties, as do the endothelial cells of the underlying choriocapillaris. The lumen of the choriocapillaris contains fibrin. P designates the base of the pigment epithelium, B is Bruch's membrane and L is the lumen of the choriocapillaris.

The bar markers are 1 micron.
Two types of damage were present in the photoreceptor cell layer: damage due to heat conducted from the underlying RPE and damage due to fluid flow resulting from a breach in the outer blood retinal barrier. The former resulted in vacuolation and tubular or vesicular breakdown in the membranes of the photoreceptor cell discs whilst the latter induced perinuclear vacuolation and bulk tissue displacement within the outer nuclear layer.

5.6.6 HUMAN
a) LIGHT MICROSCOPY

Similar morphology to that seen in the diode lesions in the rabbit was apparent in human lesions (figure 5.5). On gross observation there was vacuolation and displacement of RPE cells (figure 5.5 (a)); the photoreceptor cells in the irradiated area showed radial displacement of the outer elements and pyknotic nuclei; and there was also vacuolation of the inner segments of the receptor cells (figure 5.5 (b)).

Larger lesions showed the passage of fluid forward into the retina where it pooled at the external margin of the outer nuclear layer. At 18 hours post exposure the passage of fluid was sufficient to induce a horizontal split within the area of irradiation between the coagulated outer retina and the more normal inner layers (figure 5.5 (c)).

No damage was identified in the inner retinal layers other than some disturbance of the outermost nuclei of the inner nuclear layer due to swelling and distortion of the photoreceptor cells, resulting in a slight elevation of the outer plexiform layer. In some few sections a slight and non-specific increase in the density of stain was apparent in the inner retinal layers throughout the area of irradiation but this probably represents an area of disturbed water relationships due to the loss of both the barrier and pumping properties of the damaged pigment epithelium.

Where the major retinal vessels were irradiated the lesions induced by the diode laser were similar in appearance to those produced by krypton laser irradiation (figure 5.6 (a) and (b)). No damage was seen in the various elements of the vessels or in the surrounding nerve fibre layer. This is in marked contrast to the morphological disturbances seen in major retinal vessels irradiated with argon laser where endothelial cell loss was often seen and 18 to 24 hours post exposure swollen axons were apparent (figure 5.6 (c)).
Figure 5.5

Light micrographs of diode laser lesions produced in human retina, (a) 200 mW, (b) 400 mW and (c) 800 mW. Note the progressive involvement of an increasing volume of the photoreceptor cells with increase in radiant exposure. As in rabbit, in the higher exposure (c) a zone of photoreceptor outer segments is adherent to the underlying pigment epithelium and fluid movement resulting from barrier dysfunction at the edges of the lesion has resulted in oedema and splitting of the inner and outer segments of the central photoreceptors from the outer nuclear layer.

The bar marker is 100 microns.
Figure 5.6

Light micrographs of areas of laser exposure located over major retinal vessels, (a) diode, (b) krypton and (c) argon. Note that in the infrared (a) and red (b) exposures, damage is located in the outer retina, pigment epithelium and underlying choroid. There is no damage to the irradiated vessel and no damage in the adjacent neuronal tissue. In contrast, in relation to the argon laser exposure there is a zone of so-called "cytoid bodies" in the nerve fibre layer (arrowed) which results from thermal transients generated within and around the irradiated vessel interrupting axonal flow.

The bar marker is 100 microns.
The axonal disturbances are known to result from the build-up of cellular organelles as a result of interrupted axonal flow caused by thermal transients coagulating portions of axons as they pass adjacent to the target vessel. The accumulation of intra-axonal debris and resultant so-called "cytoid bodies" were asymmetric in relation to many vessels with a greater presence on that side of the vessel adjacent to the optic disc. This asymmetry arises because the orthograde axonal flow may be modulated by the intact undamaged cell bodies whilst retrograde flow has no such capacity for modulation and thus ultimately results in a passive build-up of debris at the border of the zone of thermal damage.

In diode lesions the choroidal damage was again similar to that seen in krypton irradiation, with blood stasis in the choriocapillaris and some deeper vessels in the mid-choroid. A further common finding with both these sources was the loss of vascular endothelial cells and the presence of choroidal oedema (figure 5.7). At 18 hours post-exposure the oedema was sufficient to disrupt choroidal elements such that fluid-filled spaces were apparent and within the area of irradiation choroidal melanocytes displayed an abnormal morphology, being rounded and condensed. In most lesions macrophages were present throughout the depth of the choroid.

b) ELECTRON MICROSCOPY

Transmission electron microscopical preparations of the outer retina showed morphological disturbances in the photoreceptor inner and outer segments very similar to those in rabbit, namely displacement, vesicular degeneration and vacuolation.

In the retinal pigment epithelium three distinct zones of damage were apparent: a central coagulated zone, a peripheral annular transition zone and finally a small circumscribed zone of secondarily damaged cells extending just outside the transition zone.

Within the zone of coagulation the cells were either shrunken apico-basally or grossly vacuolated such that no organelles other than melanin or lipofuscin granules could be identified (figure 5.8 (a)). In lower power lesions cells within this zone had abnormally electron dense staining characteristics and haloes of vacuolation.
Figure 5.7

Light micrographs of pigment epithelium and underlying choroid in areas of (a) diode, (b) krypton and (c) argon laser exposures in human. In all three exposures the choriocapillaris is closed within the area of irradiation. In diode and krypton exposures endothelial cell sloughing is seen within the major vessels of the choroid beneath areas of irradiation (arrowed). This is rarely seen in argon laser exposures. Choroidal oedema is again identified in all three areas of irradiation, but is more prevalent in diode and krypton exposures.

The bar marker is 50 microns.
Figure 5.8

Transmission electron micrographs of outer retina and choroid in humans subsequent to diode laser irradiation. (a) and (b) show pigment epithelium at the edge (a) and at the centre (b) of the area of irradiation. Note that in both cases cytoplasmic detail is lost, although lipofuscin and melanin granules appear to be relatively undamaged. Bruch's membrane is intact, but atypical and the underlying choriocapillaris is completely occluded, having lost its endothelial cells. (c) Control area of choroid showing three choroidal melanocytes. (d) Area of deep choroid, i.e. choroidal/ scleral interface, showing areas of vacuolation in the zone of irradiation. The bar marker is 5 microns.
around both melanin and lipofuscin granules. A further characteristic of coagulated cells 18 hours post exposure was the presence of relatively large vacuoles between the basal border of the retinal pigment epithelium and the innermost aspect of Bruch's membrane. These vacuoles distorted the basal convoluted border of the epithelial cells and separated them from their basement membrane.

Sub-cellular vacuoles were largest and particularly evident within the transitional zone. In this region cells were either totally detached from Bruch's membrane and dissociated from their immediate neighbours within the central area, or they were partially detached and only retained contact with adjacent central cells at the level of their zonula occludens (figure 5.8 (b)). This zone probably represents the junction between irradiated central shrunken coagulated cells and those cells not irradiated and not significantly damaged by heat flow.

As all our human tissue samples were isolated 18 hours after exposure the extensive vacuolation in this region probably results from passive fluid flow in the absence of an area of viable retinal pigment epithelium. The massive expansion of extra-cellular space is supportive of this explanation. Fluid disturbances and morphological changes associated with cellular migration may also account for the slight disturbances in morphology of cells in the secondary damage zone.

Bruch's membrane was not ruptured in any diode exposures in humans although morphological changes were apparent throughout the area of irradiation (figures 5.8 (a) and (b)). These changes consisted of both abnormal electron-dense staining of the collagenous and elastin layer and small vacuoles internal to the elastin layer. In one eye several small vacuoles were also seen within a small drusen fortuitously located within the zone of exposure. With the exception of the microvacuolation all changes were similar to those previously described after argon or krypton irradiation.

Choroidal changes were very similar to those seen in krypton lesions with closure of choriocapillaris; in some cases damage to endothelial cells in the vascular elements of the mid-choroid; a condensation or rupturing of choroidal melanocytes showing either a rounded or fragmented morphology; vacuolation and choroidal oedema and dissociation of elements of the choroidal collagen; and macrophages being seen both within damaged vessels and in the sub-retinal and choroidal tissues (figures 5.8 (c) and (d)). Many small choroidal vessels were still occluded by fibrin.
In some exposures areas of micro-vacuolation and tissue displacement were observed throughout the entire depth of the choroid, but again these findings were consistent with those seen with krypton burns.

5.7 RESULTS OF HUMAN MACULAR EXPOSURES

Detailed comments on the histopathological findings will be confined to the lesions induced by the diode laser. The results of the argon and krypton exposures have been fully described in an earlier study (Marshall and Bird, 1979) and will be referred to only where relevant comparisons may be made.

5.7.1 OPHTHALMOSCOPIC APPEARANCES

Immediately following irradiation with the diode laser, a typical lesion had a greyish-white appearance with an indistinct border (figure 5.9) and thus they were similar to those resulting from krypton laser exposures. No haemorrhagic lesions were observed.

5.7.2 LIGHT MICROSCOPY

Gross observations on both eyes following enucleation revealed subretinal fluid involving a significant portion of the treated areas in shallow retinal detachments. As a consequence, the photoreceptor outer segments were reduced in length and to some extent disordered. These features were particularly apparent in the eye that was studied 18 hours following exposure. There was no evidence of inner retinal damage in either eye, even when irradiation was performed over sites of retinal vessels, or sufficiently close to the fovea to have encountered high concentrations of macular pigment.

a) 18 HOURS POST EXPOSURE

Within the irradiated areas, damage was clearly demarcated and was centred on the retinal pigment epithelium, with spread of damage to involve the photoreceptors and elements of the choroid (figures 5.10 and 5.11). Within the zone of irradiation choroidal melanocytes showed changes throughout the entire thickness of the choroid (figures 5.10 and 5.11). Both internal and external to this zone there was a degree of distortion and swelling due to choroidal oedema. Intravascular changes in the choroid were restricted to the mid-choroidal vessels and the choriocapillaris. In the choriocapillaris there was stasis of the blood column, together with the presence of fibrin, denatured red blood cells and platelets.
Figure 5.9

Fundus photograph of diode laser lesions produced in the macular region of a 68 year old human eye.
Figure 5.10

Light micrographs of the macular region of a 65 year old human retina 18 hours after exposure to diode laser radiation.

Figures 5.10 (a), (b) and (c) show the effects of increasing amounts of retinal detachment in relation to damage to the neural retina. Damage was not observed in the inner retinal layers in any lesion.

(a): A lesion produced at the junction between detached and attached retina, showing damage to the pigment epithelium and underlying choroid, with nuclear pyknosis and damage to the outermost elements of the photoreceptor cells. Note that even though a retinal vessel is present in the ganglion cell layer within the area of irradiation, no damage was seen in the inner retinal layers and therefore no absorption has taken place within the blood pigment.

(b): A region of shallow detachment showing damage to the pigment epithelium and underlying choroid, with significantly less damage to the overlying retina.

(c): A region of more detached retina showing damage to the retinal pigment epithelium and underlying choroid, but no damage to the overlying retina.

(d): A lesion in an area of shallow detachment showing damage to the underlying choroid, but no damage in the adjacent sclera.

The bar marker is 100 microns.
Figure 5.11 (a) and (b)

High power light micrographs of the pigment epithelium and choroid of lesion shown in figures 5.10 (a) and (c). Damage to the retinal pigment epithelium is marked and resulted in cells being displaced from Bruch's membrane throughout the region of irradiation. In both cases, damage to the choroid consists of closure of the vessels of the choriocapillaris and shrinkage or contraction of both fibres and vascular elements in the mid and innermost choroidal layers. The extent of choroidal damage could easily be assessed by a cone of tissue displaying a more marked staining pattern (arrowed) than surrounding tissue. The base of the cone approximated to the area of damage seen in the pigment epithelium and its apex extended almost to the scleral border of the choroid. The bar marker is 100 microns.
There were some indications of endothelial cell loss in affected vessels within the mid-choroid. In one instance, damage to a vessel wall resulted in extravasation of blood and fibrin into the oedematous choroidal stroma but the extravascular blood was confined to within 25 microns of the vessel wall. The only indication of damage within Bruch’s membrane was an atypical staining density. However, the intercapillary pillars of Bruch’s membrane in the adjacent choriocapillaris did show some disruption.

Retinal pigment epithelial cells at the centre of any zone of irradiation were shrunken, densely staining and frequently detached from Bruch’s membrane. At the interface between damaged and undamaged retinal pigment epithelium, areas of denuded Bruch’s membrane could be seen and there was some evidence of further fluid accumulation within the subretinal space. Within the areas of damage, the outer segments of the photoreceptors were shrunken and displaced away from the retinal pigment epithelium. All portions of affected photoreceptor cells were densely stained and their nuclei were pyknotic. Together with nuclear pyknosis, there was an increase of cytoplasmic volume in the outer nuclear layer and inner connecting fibres. There was also a swelling of elements of Muller’s fibres within the outer nuclear layer. Degenerative changes were also seen in the synaptic elements of the outer plexiform layer. This represented the innermost extent of laser induced damage. In some lesions, fluid passing through the broken blood retinal barrier had caused splits between the outer plexiform layer and the inner nuclear layer. Fluid-induced schisis was not observed in any lesion produced in areas of detachment subject to laser exposure.

The appearances of diode laser induced lesions were very similar to those resulting from krypton exposures, with the exception of the severity of changes in the choroid. They did however differ in several important respects from argon laser burns in the macula. Within a typical argon burn, pigment epithelial and outer retinal damage was similar to that seen in relation to diode and krypton lasers, but choroidal damage was less marked. In argon blue-green burns there was however a second damage locus within the inner retinal layers. This was centred on the fibre layer of Henle but also involved the ganglion cell layer and nerve fibre layers.

For any given argon lesion in the macula, examination of serial sections demonstrated that both the inner retinal damage site and that in the outer retina
were discrete (figure 5.12).

b) 5 WEEKS POST EXPOSURE

At this time interval following exposure, cellular repair mechanisms were still active and had not been completed. In the choroid there was resorption of oedema and resolution of swelling. The vasculature was patent in the superficial and mid-choroid, with partial recanalisation of the choroiocapillaris. There were significant changes in the morphology of choroidal melanocytes which both were more rounded and numerous than in the non-irradiated areas (figures 5.13 and 5.14).

Virtually no changes were apparent in Bruch's membrane. Proliferated non-pigmented epithelial cells covered Bruch's membrane throughout the irradiated areas. The subretinal space was crowded with retinal pigment epithelial cells that had become detached from Bruch's membrane, together with pigment laden macrophages and significant amounts of subretinal fluid (figures 5.13 and 5.14).

In the photoreceptor layer there was significant loss of cells as indicated by loss of inner and outer segments, but in some lesions there was a selective survival of cones, whose presence was indicated by their inner segments (figure 5.14 (a)). The loss of photoreceptor cells resulted in a decrease in nuclear numbers and a significantly altered geometry in the outer nuclear layer.

The inner connecting fibres were swollen and the glial elements in this region were enlarged. Within the outer plexiform layer there was loss of rod synaptic spherules and this represented the innermost extent of laser induced damage.
Figure 5.12

Light micrograph of the macular region of a human retina following argon (A) and krypton (K) irradiation. Tissue damage in the krypton exposure is located in the outer retina, retinal pigment epithelium, and the underlying choroid. The argon exposure is also associated with a second damage locus, which is centred on the fibre layer of Henle and involves all the retinal layers central to it. This indicates that there has been significant absorption of radiation within the macular xanthophyll pigment.

The bar marker is 100 microns.
Figure 5.13

Light micrographs of the macular region of a 68 year old human retina 5 weeks following exposure to diode laser radiation.

(a): A region of non-irradiated retina to show the effects of a shallow retinal detachment and of subretinal fluid on the architecture of the photoreceptor cells.

(b)-(d): Areas of retina exposed to various irradiances, showing cellular responses in the photoreceptor cell layer, the retinal pigment epithelial cell layer and in the choroid. In all lesions, some photoreceptor cells had been lost and those remaining showed nuclear pyknosis, together with swelling of their inner connecting fibres. Marked proliferation of the pigment epithelial cell layer was observed, resulting in some cases in multiple layers. The choriocapillaris had reopened and the mid-regions of the choroid were often highly pigmented.

The bar marker is 100 microns.
Figure 5.14 (a) and (b)

High power light micrographs of the outer retina, 5 weeks after diode laser irradiation. The photoreceptor cell inner and outer segments are lost throughout the irradiated area, although in some cases a few inner segments of cones were noted. Pigment epithelial cell proliferation was apparent and virtually all lesions showed that Bruch's membrane had been re-covered by, for the most part, non-pigmented cells. Pigmented cells in the region previously occupied by outer segments of photoreceptor cells were thought to be of pigment epithelial origin. The bar marker is 100 microns.
5.7.3 ELECTRON MICROSCOPY

a) 18 HOURS POST EXPOSURE

Pigment epithelial changes were as seen on light microscopy, with most detached cells showing either gross vacuolation, or shrunken cytoplasm (figure 5.15). No wavelength-specific changes were seen in the photoreceptor cells. Mitochondrial vacuolation was apparent in the inner segments of the cones in the periphery of the lesions and in some cases was associated with autophagic vacuoles. It should be noted that autophagic vacuoles or residual bodies were seen in cones both within and without the irradiated areas. Autophagic vacuoles are thought to occur as a result of cone outer segment degradation subsequent to membrane damage (Reme, 1977). They are found in the retinas of the elderly and in a variety of pathological conditions. In our patient they were probably related to membrane damage caused by the retinal detachment and loss of the glycosaminoglycans cone sheaths.

Choroidal melanocytes showed vacuolation and disruption, with an increased severity of changes in those cells closest to the retinal pigment epithelium. Vacuolation was present within adjacent fibroblasts and oedema was found between them. Vascular changes were most apparent in the deeper choroidal vessels and choriocapillaris. In the choriocapillaris central to the area of irradiation endothelial cells were highly pyknotic or lost. The choriocapillaris within the central area of all lesions showed blood stasis, with the presence of large amounts of fibrin.

b) 5 WEEKS POST EXPOSURE

Within the retinal pigment epithelium there was disruption of the normal orderly cellular arrangement. In most lesions there was a layer of non-pigmented cells adherent to Bruch's membrane and extending across the area of irradiation (figure 5.16 (a) and (b)). As in the light microscopy, pigmented cells together with pigment-filled macrophages were present in the subretinal space.

There was enlargement of the glial cell component in the outer nuclear layer. The few remaining photoreceptors showed vacuolation within the ellipsoid and myoid portions of their inner segments. Glial proliferation and photoreceptor loss resulted in a strikingly prominent outer limiting membrane as it had fewer zones of discontinuity compared with that in normal retinae.

Choroidal vessels were patent in the treated areas, although there were signs of damage to the vascular endothelium (figure 5.16 (c)). There was marked
proliferation of choroidal melanocytes (figure 5.16 (d)). While no breaks were seen in Bruch’s membrane, there were areas of microvacuolation within the collagenous and elastin layers.
Figure 5.15

Electron micrographs of the macular region of a 65 year old human retina 18 hours after diode laser irradiation.

(a): Control area of non-irradiated tissue, showing the outer limiting membrane of retina, inner segments of the photoreceptor cells and the outermost aspect of the outer nuclear layer. Some loss of photoreceptor cells and compensatory glial proliferation had occurred throughout this individual's macula, presumably in response to the subretinal fluid.

(b): A comparable zone to that shown in (a), but from an area of diode irradiation. Extensive nuclear pyknosis had occurred and was associated with marked swelling of pale-staining glial components. Vacuolation of mitochondria within the inner segments of the photoreceptor cells was also apparent.

(c): Retinal pigment epithelium from an irradiated area of macular retina. A shallow retinal detachment had resulted in a reduction or loss of microvilli on the apical surface of these cells.

(d): Retinal pigment epithelial cells from a region of irradiated retina, showing disruption of cytoplasmic architecture and dissolution of intercellular junctions. Melanin and lipofuscin granules were not ruptured, but were often surrounded by haloes of pale-staining cytoplasm. Bruch's membrane (B) was intact throughout all lesions, but was often atypically densely stained. The choriocapillaris showed accumulation of fibrin in the lumen.

(a), (b): The bar marker is 10 microns.

(c), (d): The bar marker is 5 microns.
Figure 5.16

Electron micrographs of retinal pigment epithelium and choroid of the macular region of a 68 year human retina, 5 weeks after exposure to a diode laser.

(a): Poorly pigmented cells cover the surface of Bruch's membrane (B) and at least 3 layers of pigmented cells are interposed between these cells and the neural retina. The pigmented cells are thought to be both pigment epithelial cells that have detached from Bruch's membrane and acted as wandering macrophages within the subretinal space and also some blood-borne macrophages. The poorly pigmented cells are thought to have arisen from cell division within the epithelial layer.

(b): A similar distribution of cells to that seen in (a), also showing the presence of non-pigmented cells covering Bruch's membrane.

(c): Note the reduction of number of lumens in the choriocapillaris and the presence of large pigmented cells (P) in the choroid.

(d): Electron micrograph showing the patency of the choriocapillaris within the area of diode irradiation and the presence of numerous fibroblasts and pigmented cells.

The bar marker is 10 microns.
No evidence was seen of disruption of ameloblastol elements in terms of degeneration of surface cristae or universal involvement were not identified in any of the specimens.
5.8 RESULTS OF HUMAN TRABECULAR EXPOSURES

5.8.1 CLINICAL DATA
The patient experienced no discomfort during either diode, or argon irradiation. She did comment that the diode treatment was subjectively preferable, due to the lack of bright flashes during exposures and the relative silence of the laser system. These findings were typical of the observations that have been noted in association with the clinical trial of diode laser trabeculoplasty currently in progress at St Thomas' and Moorfields Eye Hospitals (McHugh, 1990 (II)).

5.8.2 LIGHT MICROSCOPY (fig 5.17)
Over the energy ranges used in this study, sites of irradiation were difficult to identify in histological preparations, as they were not delineated by gross disturbances in morphology, or by differential staining.

Sites were initially located by gross observation under the dissecting microscope and subsequent trimming of sample blocks. Under the light microscope, the most characteristic changes were seen in relation to the overall geometry of the trabecular elements and of the intervening spaces.

In some areas of irradiation, the trabecula seemed to have contracted, and the intertrabecular spaces therefore became more apparent. In other specimens however, the trabecula appeared swollen and there was a complementary reduction in the intertrabecular spaces. These changes mainly occurred in the uveal and corneoscleral compartments of the trabeculum.

5.8.3 ELECTRON MICROSCOPY
a) SCANNING ELECTRON MICROSCOPY (figs 5.18 and 5.19)
Sites of irradiation could be clearly determined using low power scanning electron microscopy. While both argon and diode exposures produced similar disturbances in the trabecular morphology, those induced by diode irradiation were more obvious and created a more distinctive pattern of disruption. Diode lesions were often ovoid, with a long axis typically 150 microns and a short axis typically 90 microns in diameter and they appeared deeper than those induced by argon. Argon burns tended to be circular and were typically 100 microns in diameter.

No evidence was seen of disruption of trabecular elements in terms of destruction of surface membranes and severed trabeculae were not identified in any
exposure sites. We did not identify fibrin or other surface deposits in any of our specimens.

b) TRANSMISSION ELECTRON MICROSCOPY (fig 5.20)

Transmission electron microscopy of both low power argon and diode lesions showed similar, but limited changes in the morphology of the trabecula. As was seen in light microscope specimens, there was some evidence that lesions produced by the infrared radiation of the diode induced changes to a greater depth than those induced by argon. The most significant changes observed were a contraction of the cross-sectional aspect of individual trabecula, coupled with an increase in electron density. No evidence was seen of rupturing, or fragmentation of trabecula and with the exception of some superficial endothelial cells, most cellular elements appeared relatively normal.

The relatively mild changes induced by both argon and diode lasers could perhaps be attributed to the poorly pigmented nature of our target trabeculum. In the higher power exposures emanating from both lasers, there was a more marked response in the internal aspects of the uveal trabeculum, with some zones of endothelial cell sloughing. Displacement of collagen fibrils was rare and was usually associated with aggregations of macrophages or polymorphs.
Figure 5.17

Light micrographs of the trabecular meshwork 18 hours after irradiation with (a) argon and (b) diode lasers. The presence of red blood cells in both Schlemm’s canal and the juxtacanalicular trabeculum was not related to the laser treatment and was not present at the time of irradiation. In both cases, the beams of the uveal trabecula were slightly swollen and associated with numbers of white blood cells. In the diode, distended trabecula were also seen in the corneo-scleral portion of the trabeculum.

The bar marker is 50 microns.
Figure 5.18

Scanning electron micrographs of sites of argon laser treatment 18 hours after irradiation. In (a) 5 separate areas of irradiation are arrowed and the resultant lesions are roughly circular in shape. A higher power view of the fourth lesion in (a) is seen in (b). Note the presence of white blood cells associated with the trabeculum around the peripheral portion of the lesion.

The bar markers are (a) 100 microns, (b) 50 microns.
Figure 5.19

Scanning electron micrographs of areas of trabecular meshwork 18 hours after irradiation with the diode laser. Two sites of irradiation are seen in (a) (arrowed). In contrast to argon impacts, those of the diode are more readily apparent and are oval in shape. In higher power (b), the more penetrant nature of the wound is apparent and again the site of irradiation shows large number of white blood cells. The bar markers are (a) 100 microns, (b) 50 microns.
Figure 5.20

Transmission electron micrographs of trabecular meshwork 18 hours after irradiation by (a) and (b) argon and (c) and (d) diode lasers. The relatively undisturbed architecture of the trabecular beams is seen in all samples with the exception of the high power diode irradiation in (d), where some dissociated collagen fibres can be seen (arrowed). Figures 4 (b), (c) and (d) also show the presence of numerous cells associated with the surface of the trabecular elements. 
The bar marker is 3 microns.
CHAPTER 6
DISCUSSION OF HISTOPATHOLOGICAL STUDIES
6.1 RETINAL PHOTOCOAGULATION

The histological phase of this project demonstrated that commercially available laser diodes are capable of inducing photocoagulation of the retina. Our observations supported those previously published by Brancato and extended them to include the first lesions produced in human retina. The demonstration of lesions in the human tissue is of particular importance given the relatively limited power output of current laser diodes and the known hypersensitivity of the rabbit retina to laser radiation (Campbell et al, 1966). In comparing our results with those obtained by conventional photocoagulation devices it is perhaps helpful to consider the reaction sequence implicit in all interactions of laser radiation with biological tissues.

This process can be classified into four main sections, which are in sequence, transmission of radiation; absorption of radiation; degradation of radiation and the induced tissue reaction.

a) TRANSMISSION

Optical radiation in the visible (400-780 nm) and in the near infrared (780-1400 nm) is readily transmitted through the ocular media (Boettner and Wolter, 1962; Geeraets and Berry, 1968) and irradiates the retina. Within this spectral domain, light at shorter wavelengths (400-520 nm) is more attenuated by both scatter and absorption than longer wavelengths. Scatter and absorption increase with increasing age in both the cornea and in the lens (Said and Weale, 1959; Allen and Vos, 1967; Stocker and Moore, 1975; Lerman, 1980 and 1983). It has been demonstrated that retinal burns made in the periphery with argon blue light require three times more incident power at the cornea in patients over 50 years old than equivalent burns with argon green radiation (Pomerantzeff, 1976). The difference in required power occurs as a result of the greater attenuation in the media of radiation at 488 nm than at 514.5 nm. The need to use greater power levels in order to induce therapeutic effects in the retina has hazardous sequelae in conventional argon lasers, in that they all use collimated beams of very small cone angles. Thus the higher the required retinal irradiance, the higher the corneal irradiance and hence the greater the risks of both corneal (Pardos, 1981) and lenticular damage.

In contrast, near infrared radiation at 810 nm is close to the wavelength which maximally penetrates all biological tissues, i.e. 1040 nm (figure 6.1). In the eye, very little attenuation occurs in the ocular media at 810 nm and virtually all of the
Figure 6.1
TRANSMISSION OF RADIATION THROUGH THE OCULAR MEDIA
(from Boettner and Wolter, 1962)
radiation incident at the cornea reaches the retina.

For a given irradiance at the cornea, more infrared will reach the retina than will blue or green light. Further, the diode used in this study had a cone angle of 23 degrees and therefore the ratio of irradiances at the cornea and the retina is much lower than with argon lasers. This imparts a further safety factor. Although the spectral reflectance from the human retina is higher at longer wavelengths the total fundal reflectance is so low that it may be ignored in relation to absorption of laser energy (Geeraets and Berry, 1968).

In the present study, although the patients were over 60 years of age and must have had significant amounts of pigment in their lenses, all of the eyes treated had clinically clear media and therefore the advantages of the superior transmission properties of near infrared light were not readily demonstrated. In practice, diabetic eyes often have opacities in the media, either as a result of cataracts, or of blood in the vitreous. Further, in patients with age-related macular disease, lens changes are also often well developed with a prominent loss of transmission in the blue-green portion of the spectrum. In both of these clinical situations the use of infrared radiation would confer significant benefits in relation to minimising transmission losses between the cornea and the retina.

b) ABSORPTION

Photocoagulation is dependent upon the absorption of light and its conversion to heat via linear optical processes (Mainster, 1986). That is to say, there is a linear relationship between the final tissue temperature and the number of photons absorbed. In both the healthy and in the diseased retina, there are a number of pigments whose absorption properties are such that they may be targets for laser radiation. The pigments most commonly identified as primary absorption sites to be utilised in laser therapy are melanin and haemoglobin. The macular pigment is clearly a chromophore that should be avoided and other pigments, while present tend to be ignored, for example lipofuscin and the visual pigments. Of the two primary target pigments, both have a dual distribution. Melanin is present in both the retinal pigment epithelium and in the choroidal melanocytes. Haemoglobin is present in the retinal and in the choroidal vasculature.

For most clinical procedures the pigment epithelium is the prime target and extensive studies have been undertaken on the absorption characteristics of both
isolated melanin granules (Wolbarsht et al, 1981) and upon retinal pigment epithelial cells in enucleated eyes (Gabel et al, 1977).

On isolated granules a flat absorption spectrum is seen with very little variation in the visible portion of the spectrum, but with a slight decrease as the infrared is approached.

In contrast, studies in cell systems show a peak absorption in the blue-green region with a marked decrease in absorption towards the infrared. This latter differential absorption is seen in the increasing retinal irradiance required to produce retinal lesions with increasing wavelength in both studies of retinal damage thresholds for laser safety (Borland et al, 1978) and in clinical exposures comparing argon and krypton lasers (Marshall and Bird, 1979).

In empirical studies of laser induced damage the lesions result from the thermal disturbances generated by the total absorbed energy within the target. This total absorbed dose will receive components from the melanin of both the RPE and the choroid as well as a contribution from energy dissipated within the choroidal blood vessels. The total amount of optical radiation absorbed within the choroid will exceed that dissipated within the RPE because of the larger amount of pigment within the choroid (Lachenmayr et al, 1984). However, although the total pigmentation of the RPE is significantly less than the choroid, all of the pigment in the RPE is confined to a layer some 5 to 10 microns thick, whereas that of the choroid may extend over 200 to 400 microns (Marshall et al, 1975). Thus for any given exposure the absorbed energy per unit path length is far greater within the RPE than that within the choroid and therefore the temperature profiles generated by this energy deposition are greater and of prime importance in defining retinal damage.

c) DEGRADATION OF RADIATION AND INDUCED REACTION

Thermal damage mechanisms predominate in the time domain between 100 microseconds and 1 second (Ham et al, 1979) and in practice for any given image size the longer the exposure time within this temporal domain the more extensive the spread of the thermal profiles and the more damage to adjacent tissues. For typical exposure durations, an increase in temperature within the retinal pigment epithelium of at least 10-20 degrees centigrade is necessary to produce a threshold lesion (Marshall, 1970; Mainster et al, 1970). In most situations heat flow is
anisotropic and favours the choroid because little absorption takes place in the neural retina, whereas with increasing exposure times that occurring in the choroidal melanin assumes increasing importance. Thus within the wavelength region 400-800 nm, spectrally dependent differential absorption within the retinal pigment epithelium becomes of decreasing importance with increasing exposure duration.

The practical aspects of this concept are demonstrated in our histological preparations where in using comparable exposure times of 0.2-0.5 s, choroidal damage is seen in relation to all three laser modalities. The deeper penetration of the longer wavelengths showed more significant choroidal damage with involvement of deeper choroidal vascular elements and more diffuse choroidal oedema. However, in studies of photographs of choroidal histology it was not possible to differentiate between those lesions produced by krypton and those produced by the diode. We conclude that within the time domain of clinical photocoagulation the diode laser at 810 nm produces a retinal lesion extremely similar to that of current krypton (647 nm) systems.

In relation to haemoglobin, the minimal absorption of red and near infrared light (Horeckler, 1943) within retinal vascular elements was demonstrated. When the relative effects of laser irradiation on retinal and choroidal vessels are considered, a second set of parameters are also of importance and that is the spatial extent of the pigment in relation to the cross sectional area of the laser beam. For example, a 200 micron laser spot falling on a 10 micron retinal capillary can only deposit energy into an extremely small volume of the vessel. By contrast, the same spot size falling on the choriocapillaris will have a far greater percentage of its cross sectional area impinging upon the absorbing system.

With the exception of the macula, where the luteal pigment will certainly preferentially absorb the argon blue emission (Marshall et al, 1975; Peyman et al, 1981), wave band changes do not significantly alter the retinal damage profile at therapeutic exposure levels. This has been substantiated in studies using the dye laser where with the exception of one group (Smiddy et al, 1988) no wavelength-specific effects were noted other than at the extremes of blue and red (Borges et al, 1987). When continuous wave YAG lasers have been used to photocoagulate retina with exposure durations of 0.5 s, retinal lesions were produced with damage localised in the pigment epithelium which were still essentially similar to krypton burns (Okisaka
The deeper penetration of red and infrared radiation with the attendant shift in heat flow profiles results in the slight difference in the clinical appearance of the krypton and diode lesions when compared with those produced by argon. Both of the former types of lesions appear greyish and less white than argon lesions in the immediate post-exposure period but within thirty minutes to one hour following exposure all three damage sites appear similar with grey-white centres. The difference in initial appearance probably relates to the volume of retinal tissue initially coagulated, while the developing post-exposure appearance indicates a damage amplification factor due to cell death and oedema. The degree of whiteness is therefore a function of cell damage internal to the RPE.

A further indication of the deeper penetration of the longer wavelengths is the more frequently reported incidence of pain associated with peripheral ablation using krypton lasers (Schulenberg and Hamilton, 1979). The mechanism of pain perception is thought to be related to temperature elevation in the region of the ciliary nerves.

Another treatment complication which has been observed following krypton red laser therapy is delayed perfusion of choroidal vessels, which is related to its relatively greater uptake by the choroid. The subsequent rapid recovery of normal choroidal perfusion suggests that laser-induced vascular spasm rather than choroidal obliteration is the cause of the described changes (Bressler et al, 1988).

There is also a higher incidence reported of retinal pigment epithelial tears with krypton exposures of choroidal neovascular membranes, but this is most often reported in eyes that have a serous detachment of the RPE (Gass, 1984).

Finally, a higher percentage of choroidal haemorrhages in earlier studies using high energy clinical krypton exposures (Yannuzzi and Shakin, 1982) has been cited as a consequence of the penetration depth at this wavelength (Marshall and Bird, 1979). Also of relevance is the increasing risk of haemorrhage with decreasing pulse duration (Borland et al 1978; Birngruber et al, 1977) This is known to be related to the speed at which tissue fluids are converted into gas. Above threshold, the more rapidly the tissue acquires thermal energy the more rapid the phase transitions and volumetric changes. In the outer retina, if thermal episodes are sufficiently fast then the associated volumetric changes may result in bulk physical displacement of tissue.
with tearing or rupturing of structures such as Bruch's membrane or the choriocapillaris.

Choroidal haemorrhages were less frequently encountered in more recent reports and probably occurred in early studies as a result of using too high a power in an unsuccessful attempt to induce burns with a gross appearance like those of argon, in association with too short a pulse duration.

The consequences of damage to Bruch's membrane and the choroid in relation to wound healing has been the subject of at least two reports (Pollack, et al, 1986; Duvall and Tso, 1985). The implication of the title of the Pollack paper, "Cellular processes causing defects in Bruch's membrane following krypton laser photocoagulation" is that the deeper penetration of red laser radiation may give rise to undesirable sequelae. This however is not the intention of the paper whose main thesis is that so-called breaks in Bruch's membrane are not primarily laser induced but the result of subsequent invasion of the structure by cellular processes. This is also the finding of Duvall and Tso whose study used an argon laser. The post-operative times and species varied in these two accounts as did the identification of the invading cell types, Duvall and Tso identifying choroidal pericytes in monkey and Pollack et al claimed an initial invasion by choroidal endothelial cells and then subsequently RPE cells traversing Bruch's and entering the choroid.

The nature of the cells involved in this process must await further studies using cell marker techniques. However it is clear that the process is related to the general mechanism of wound healing and inflammation and is not directly associated with the wavelength of the initiating radiation.

Over the past few years a number of clinical trials have been undertaken comparing the relative efficacy of argon and krypton lasers in treating disciform macular degeneration (Coscas and Soubrane, 1983 (I)) and proliferative diabetic retinopathy (Singerman et al, 1983). All of these studies have demonstrated that both laser wavelengths are equally effective in terms of their beneficial effects. Krypton photocoagulation has been employed to treat the complications of retinal vein thrombosis with similarly encouraging results (Roseman and Olk, 1987).

Coscas has concluded that better transmission can be achieved with krypton red laser in eyes with cloudy media, for example nuclear sclerotic cataracts, or
haemorrhages. The minimal absorption of krypton red light by the macular xanthophyll pigment in comparison with shorter wavelengths was a further stated advantage, especially in relation to the treatment of disciform membranes extending into the foveolar region (Coscas and Soubrane, 1983 (I)). As will be discussed in the next section, infrared diode laser photocoagulation offers similar advantages.

A further advantage of long wavelength lasers may be that their lower photon energy levels avoid the possible collateral photochemical effects from short wavelength exposure. Ham demonstrated that retinal irradiation with light of wavelength of 441.6 nm (blue) resulted in lesions at irradiances below those required to produce a thermal effect (Ham et al, 1976; Ham et al, 1978). This recognition of the "blue light hazard" has received clinical confirmation from the observation that panretinal photocoagulation with argon blue may cause a tritanopic colour defect (Birch and Hamilton, 1981).

The need to avoid repetitive exposure to short wavelength sources is now of great importance as a recent study of the blue cone sensitivity of ophthalmic laser surgeons immediately after performing panretinal ablation show a suppression of blue cone sensitivity lasting for 4 to 6 hours. This phenomenon occurred as a result of reflections of the laser's aiming beam coming back into the operator's eye from the surface of the contact lens or from the patient's fundus. In experienced laser surgeons the suppression of blue cone sensitivity becomes irreversible (Gunduz et al, 1989; Berninger et al, 1989).

The comparable therapeutic effects of argon and krypton lesions together with the potential disadvantages of argon in certain procedures indicate that krypton lasers have a significant role in the treatment of retinal disease. The present study demonstrated many similarities between krypton and diode lasers and implies that similar clinical results would be achieved at either of these two wavelengths.

In conclusion, the data obtained from this early phase of the project clearly indicated that infrared diode laser photocoagulation had a potential role in the clinical management of retinal disease.
6.2 MACULAR PHOTOCOAGULATION

This study demonstrated that macular photocoagulation with the diode laser avoids those complications to the inner retina that result from exposure to argon blue and produces lesions similar to those of krypton red.

Given that laser irradiation has some therapeutic properties in the treatment of macular conditions, the efficacy of treatment with infrared radiation may be examined systematically with respect to the transmission and absorption characteristics of light at 810 nm and the biophysical and metabolic consequences of absorbed radiation by tissue. Transmission and absorption of light within ocular tissue have already received detailed consideration in the previous section. This discussion will therefore concentrate only on the therapeutic implications of absorption within ocular chromophores.

The laser treatment of macular conditions can be broadly divided into two categories: The control of exudates and oedema; and the occlusion of subretinal neovascular membranes (SRNVM). In the former, current theories would suggest that the predominant therapeutic effects emanate from responses to primary damage to the retinal pigment epithelium. In the latter, some groups consider direct absorption of radiation within the SRNVM to be of importance (Gass, 1987), whilst others consider the secondary responses of proliferating retinal pigment epithelium to be of primary relevance (Miller et al, 1986). The close juxtaposition of retinal pigment epithelium to a subretinal membrane means in practice that the thermal profiles generated by absorption and degradation of laser light within the melanin of the retinal pigment epithelium promote temperature elevations of such a magnitude that proteins are denatured within the vascular elements.

Given the broad spectral absorption characteristics of melanin, and given the pre-eminence of melanin as a target during laser treatment, it is apparent that virtually any wavelength in the retinal hazard zone (400-1400 nm) may be used for treatment. The relative absorptions of various commonly used lasers in retinal pigments are expressed as a percentage and are summarised in table II (Boettner and Wolter, 1962; Geeraets and Berry, 1968; Gabel et al, 1977; Horeckler, 1943; Haut et al, 1987). Although absorption of light at 810 nm within the retinal pigment epithelium is about 40% of that at 488 nm (Geeraets and Berry, 1968), it was clearly sufficient to produce visible lesions in the present studies.
From consideration only of relative absorption it is clear that a higher power is required to produce a clinically comparable lesion with the diode laser than with an argon system. However it can be seen from table II that for any given exposure in the older eye, of the energy incident on the cornea about 3 times more reaches the retina in a diode (810 nm) exposure than in an argon exposure (514 nm). Given that there is only a factor of 2 difference between the absorptions at these 2 wavelengths, with argon green (514 nm) being the greater, the transmission and absorption differences may well cancel each other out in the practical situation. Clinical observations have shown that in certain situations such as the presence of nuclear sclerotic cataracts, the superior transmission properties of the diode may allow effective photocoagulation where treatment with an argon system has failed to produce visible lesions. In contrast, in young eyes with clear media, the situation is different. Peyman compared retinal lesions produced in rabbits and monkeys by cw Yag, argon green and krypton red lasers. In order to produce threshold lesions, five to ten times more energy was required with the cw YAG laser (emitting at 1064 nm) than with the argon or krypton lasers (Peyman et al, 1983).

The hyperplasia of the retinal pigment epithelium that was observed 5 weeks following diode laser exposure (figures 5.13, 5.14 and 5.16) may be of importance in understanding the mechanism of action underlying the clinical efficacy of laser therapy for several important conditions. Whatever the wavelength, damage to the retinal pigment epithelium results in death of irradiated cells, together with loss of the blood retinal barrier (figures 5.10, 5.11 and 5.15). The time course of reactions within the retinal pigment epithelium remains relatively constant and again is independent of the initiating wavelength. Blood retinal barrier dysfunction, as shown by fluorescein leakage is apparent immediately after exposure and lasts for 2-3 days following irradiation (Borland et al, 1978). Within 24 hours of exposure, damaged cells begin to detach from Bruch’s membrane and may become phagocytosed by blood-borne macrophages. At 48 hours following irradiation, retinal pigment epithelial cells around the area of irradiation begin to migrate centripetally, to
### TABLE II
APPROXIMATE PERCENTAGES OF TRANSMISSION AND ABSORPTION OF OCULAR COMPONENTS FOR VARIOUS WAVELENGTHS USED FOR RETINAL PHOTOCOAGULATION

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Argon Blue</th>
<th>Argon Green</th>
<th>Dye Yellow</th>
<th>Dye Orange</th>
<th>Krypton Red</th>
<th>Diode</th>
<th>YAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young eye</td>
<td>70</td>
<td>85</td>
<td>90</td>
<td>93</td>
<td>95</td>
<td>97</td>
<td>75</td>
</tr>
<tr>
<td>Old eye</td>
<td>10</td>
<td>35</td>
<td>80</td>
<td>80</td>
<td>90</td>
<td>95</td>
<td>75</td>
</tr>
</tbody>
</table>

**Transmission (%)**

- Melanin (a): 70 72 75 70 60 35 12
- Melanin (b): 55 45 23 20 16 7 2

- Oxyhaemoglobin: 75 75 75 70 25 8 8
- Reduced haemoglobin: 70 75 75 60 15 8 <1
- Xanthophyll: 70 15 2 2 1 <1 <1

(a): Choroid and retinal pigment epithelium: Geeraets et al (1968)

3. Haut et al, 1987. Pigment absorption path length, approximately 100 microns
These figures in are approximate, because the range of measurements quoted in the literature is enormous. In some papers, statements are made concerning reflection and scatter in relation to measurements of absorption, while in others these components are ignored. Measurements of transmission through the ocular media are also relatively sparse, and the effects of ageing have not been clearly defined, other than in studies of isolated specimens.

This table highlights the following:

1. The absorption of short wavelengths by melanin is significantly higher than the absorption of diode radiation at 810 nm. However, transmission of short wavelengths drops off rapidly above the age of 30 and most patients undergoing photocoagulation fall into an even older age group.

2. The apparently high absorption figures of haemoglobin should be put into the context of the calibre of the retinal vasculature—most retinal capillaries are less than 10 microns in diameter.

3. Although xanthophyll is present in a number of retinal cells, its highest concentration is in the fibrous layer of Henle. This fact, coupled with its high absorption coefficient at 488 nm means that sufficient absorption per unit volume may occur to induce retinal damage.

4. The extremely confined distribution of melanin within the retinal pigment epithelial cells means that this tissue has the highest absorption per unit volume of any chromophore in the eye and at all wavelengths.
recover the area of cell loss. By 4-7 days of exposure, an annulus of mitotic division occurs at a distance of 6-10 cell diameters away from the initial edge of the burn.

Usually within 2 months of laser damage, new epithelial cells are present throughout the entire area of irradiation. These cells may be non-pigmented and multi-layered and they frequently do not develop tight junctions. Pigment epithelial cells that had budded off Bruch's membrane are often found in the proliferated glial scar in the neural retina (Marshall and Mellerio, 1967; Marshall, 1981). There are a number of different theoretical concepts which attempt to relate damage to retinal pigment epithelial cells to beneficial changes in retinal vascular diseases. These concepts include:

a) The destruction of damage-compromised or malfunctioning retinal pigment epithelial cells.

b) The destruction of the outer blood retinal barrier, thus allowing plasma-derived metabolic factors into the neural retina.

c) The proliferation of retinal pigment epithelial cells and the simultaneous release of inhibitors of vasoproliferation.

d) The proliferation of retinal pigment epithelial cells with rejuvenated pumping mechanisms.

e) The proliferation of retinal pigment epithelial cells and incarceration of subretinal neovascular elements.

The above theoretical concepts may each relate to a given aspect of the epithelial response and the healing process, and several examples are discussed in the literature.

a) There is some evidence from animal models of streptozocin-induced diabetes that the pigment epithelial barrier and transport functions may be compromised long before disease-related manifestations occur in the retinal capillaries (Kirber et al, 1980; Tso et al, 1980). There is also some indication that macular oedema may arise through a disturbance in the balance between the two blood retinal barriers. For example, leaky capillaries may overwhelm a normal pigment epithelial pump. Equally, an abnormally weak retinal pigment epithelial pump would result in the accumulation of fluid in the retina even in the presence of a normal retinal capillary system. In diabetes, macular exudates and oedema clearly arise as a result of a primary malfunction in the retinal capillaries, but again animal
models would suggest that the situation is exacerbated by an insidious malfunction in the retinal pigment epithelium.

The differential contribution of capillary endothelial cell or retinal pigment epithelial cell malfunction have recently been clearly demonstrated in a clinical study by Cox et al (Cox and Bird, 1988). In this study, the effect of acetazolamide in the management of macular oedema in a series of 41 patients was examined. The patients were divided into 2 clinical subtypes, which were those where the source of leakage was thought to be the retinal capillaries and those where malfunction was thought to reside in the retinal pigment epithelium. Only in those patients with presumed retinal pigment epithelial malfunction could a beneficial effect be demonstrated. Although the mode of action of acetazolamide is not clearly understood, this study clearly demonstrated that retinal pigment epithelial malfunction can contribute to fluid disturbance in the retina.

b) Both in vivo and in vitro studies indicate that subsequent to photocoagulation of the retinal pigment epithelium, factors that inhibit vascular endothelial cell division are released into the vitreous (Glaser, 1988; Boulton et al, 1988). These inhibitory factors may be associated with plasma leakage into the neural retina as a result of blood retinal barrier breakdown. They may also be related to the diffusion of breakdown products of deranged cells.

c) During migration or proliferation of the retinal pigment epithelium, factors may be released from the cells themselves, which again may have stimulatory (Marshall et al, 1984), or inhibitory effects on vascular endothelium (Glaser et al, 1985).

d) In grid photocoagulation, a significant population of retinal pigment epithelial cells are killed and large numbers of cells proliferate in their place. It is suggested that these newly formed cells have more efficient pumping mechanisms and also have the potential of re-establishing a non-leaky outer blood retinal barrier (Bresnick, 1983; Wallow, 1984)

e) A further beneficial effect of proliferation of retinal pigment epithelial cells in relation to subretinal neovascular membranes has been suggested by Miller (1986). This proposes that natural involution of a disciform membranes is the result of proliferation of retinal pigment epithelial cells that tightly envelope the vessels and effect resorption of subretinal fluid. Laser photocoagulation may therefore work via
this route, rather than as a consequence of direct closure of the membrane (Miller et al, 1986). Another study has shown that laser treatment of choroidal neovascular membranes can either result in closure or atrophy of the new vessels or in the resolution of leakage of vessels which remain physically intact. The latter observation is confined to areas of retinal pigment epithelial proliferation and has been confirmed both by clinical and histological observations (Guyer et al, 1986).

The presence of melanin in the choroid, coupled with the deeper penetration of infrared radiation resulted in choroidal damage in all of our exposures. This was almost indistinguishable from that produced by krypton red radiation. The one factor that differentiated diode laser damage to the choroid from that of krypton irradiation was the absence of choroidal haemorrhages occurring with the former modality. This may relate to a more diffuse distribution of absorption of radiation at the longer wavelength, thus resulting in less acute thermal gradients across vessel walls, together with the utilisation of a sufficiently long pulse duration that would minimise the chance of an explosive effect occurring in the choroidal vasculature (Birngruber et al, 1977).

The reperfusion of the choriocapillaris and larger choroidal vessels which was observed at 5 weeks following exposure has been previously described in a series of cat experiments by Perry and Risco (1982). By using a cast technique and scanning electron microscopy, they observed that after argon photocoagulation of cat retina, obstruction of the choriocapillaris was present immediately following irradiation, but that there were early signs of repair at 10 days and almost complete recanalisation of the choriocapillaris at 30 days (Perry and Risco, 1982).

Diode laser radiation at 810 nm is not well absorbed by haemoglobin. We do not consider this of significance in the treatment of vascular lesions of the macula. In essence, macular vascular abnormalities may occur beneath the retina, in the form of disciform membranes, or within the neural retina, in the form of microaneurysms. These are the only two conditions which are treated focally, but in both cases the major portion of the incident energy is deposited in the retinal pigment epithelium and therefore is independent of the absorption characteristics of haemoglobin.

Haemoglobin strongly absorbs blue, green and yellow light well, but absorption is low at 647 nm and 810 nm (Mainster, 1986). It has been argued that argon green and dye laser yellow (577 nm) are the most appropriate wavelengths for
macular therapy, since there is low absorption by xanthophyll pigment and high absorption by haemoglobin. However studies of photocoagulation of disciform membranes with light of different wavelengths have failed to show any significant differences in the clinical outcome (Brancato et al, 1988; Haut et al, 1987).

Moreover, in certain situations, the superior absorption by haemoglobin of green and yellow light could render treatment difficult if the presence of a thin retinal haemorrhage impeded transmission to the target area. Penetration of thin layers of blood is much better by red light (Folk et al, 1985) and the present studies have shown that diode laser irradiation of major retinal vessels is not associated with significant intravascular absorption.

In situations where it was felt that enhancement of uptake of light at 810 nm within a vascular structure was desirable (for example, in order to effect the direct closure of retinal new vessels) this could be achieved by the use of an intravascular dye such as indocyanine green which has a peak absorption in the near infrared region of the spectrum. Preliminary experiments using this agent have been conducted and have demonstrated positive results (Destro and Puliafito, 1989).

There have been a number of claims of unidentified chromophores being present in the inner retinal layers, and that such chromophores give rise to wavelength-dependent absorption events in the neural retina. For short-pulse systems, an elaborate absorption spectrum in the infrared has been described by Lund (Lund et al, 1987). However, these observations have yet to be substantiated by other groups.

For continuous wave laser exposures in the orange-yellow region of the spectrum, absorption in the inner retinal layers has been suggested by Smiddy (Smiddy, 1988). As yet, no clinical correlates of absorption sites for the first two spectral bands have been identified and a recent histopathological study of dye laser irradiation showed no evidence of wavelength-specific damage (Brooks et al, 1989). In contrast, clear histological and clinical evidence has been presented for the inner retinal absorption of argon blue laser light within the xanthophyll pigment of the macula (Marshall and Bird, 1979).

In this phase of the study, we had a unique opportunity to evaluate the presence of any chromophore absorbing at the diode wavelengths in the inner retinal layers, as in both of the eyes that we treated there were areas of retinal detachment.
Where the retina was sufficiently detached from the retinal pigment epithelium to ensure that thermal profiles generated within the retinal pigment epithelium did not reach the neural retina, no damage was identified within it. As the detachment shallowed, damage to the outer retinal layers became proportionately more marked, due to thermal transfer from the retinal pigment epithelium. We concluded that there were no absorption sites for 810 nm radiation within the retina. This concurs with the experimental findings of Juarez and associates (1982), in which argon blue-green and krypton red photocoagulation of experimentally detached retinas did not show signs of damage other than that associated with absorption of argon blue in the macular pigment (Juarez et al, 1982).

In the human retina, luteal pigment absorbs approximately 60% of the incident energy at 488 nm. Absorption at 514 nm is much lower and at krypton red and near infrared wavelengths there is less than 1% absorption (Nussbaum et al, 1981). This differential in spectral absorption properties accounts for the second damage locus seen within the inner retina following irradiation with argon blue (Marshall and Bird, 1979; Juarez et al, 1982; Smiddy, 1984). In photocoagulation of the macula there may be several advantages in using longer wavelength radiation and avoiding inner retinal damage. For example, any loss of retinal transparency such as occurs with argon blue reduces the visibility of the area treated and thus compromises the observation or possible retreatment of residual or recurrent lesions. Secondly, the absence of inner retinal absorption with diode lasers removes the possibility of damage to the papillomacular bundle and the resultant sector visual field defects.

The histological results arising from this phase of the study have demonstrated the great potential of the diode laser in the treatment of macular conditions. It offers the combination of ergonomic efficiency together with a clinically satisfactory tissue reaction, good media transmission and a lower incidence of non-therapeutic side effects compared with irradiation with short wavelength light.
6.3 HUMAN TRABECULAR PHOTOCOAGULATION

Although numerous clinical and laboratory studies have been undertaken to examine the effects of laser irradiation on the trabecular meshwork, the mechanisms underlying this therapeutic regime remain unclear.

Before reviewing current concepts of cellular responses, the underlying biophysics of beam-tissue interactions within the trabecular tissue will be examined and an attempt made to define the radiation dose and the site of its absorption. In order to relate the present findings to those of previous studies, a comparison will be made with the parameters of beam-tissue interactions at both the wavelength of the diode laser (810 nm) and of the argon laser (488-514.5 nm).

In common with the situation implicit in retinal irradiation, when one considers the interaction of laser energy with trabecular tissue, four sequential and interactive processes have to be evaluated. These are transmission, absorption, degradation and radiation. The first two of these processes, transmission and absorption are tissue properties which are wavelength-dependent. In relation to intraocular irradiation via the cornea, only those wavelengths between 400 nm and 1400 nm need be considered.

The cornea transmits slightly more effectively in the near-infrared (780 nm-1400 nm) than in the visible region of the spectrum (Boettner and Wolter, 1962). At shorter wavelengths (400-520 nm), optical radiation is more attenuated by both scatter and absorption than at 800 nm. These attenuation properties of the cornea increase with increasing age (Lerman, 1980). However, given the limited absorption by the cornea and the relatively long path length (560 μm) over which such absorption takes place, then from consideration of the Beer-Lambert law it can be seen that laser damage will only occur in this tissue in very few cases.

In contrast with retinal photocoagulation, in irradiation of the trabecular meshwork laser beams are brought to a focus relatively near to the corneal endothelium. However, the focus is always on the opposite aspect of the cornea to that through which the beam passes as it is being reflected from the mirror of a gonioscope lens. With a typical argon laser, the beam cone angle is about 3 degrees. With the diode, the cone angle is 23 degrees. It has been reported that using an argon laser at high levels of irradiance may result in corneal endothelial damage (Pardos, 1981). This damage arises because of both a higher absorption in the blue-
green region of the spectrum and a relatively high irradiance in the cornea as a result of a narrow laser cone angle. Both the transmission properties and the beam geometry of the diode will avoid this complication.

The absorption of laser energy in the trabecular meshwork is a difficult concept to understand in that linear optical processes and thermal damage require the presence of a pigmented absorption system. All previous reports assume that argon laser trabeculoplasty results from thermal transients generated by absorption in melanin within the trabecular meshwork. In reality, in most individuals this tissue is extremely poorly pigmented and what melanin exists tends to be present in isolated cells. This is in contrast to the pigmented sheet that is within the retinal pigment epithelium.

Most current clinical procedures adhere to the parameters that have been defined by Wise and Witter and practised in subsequent studies (Wise and Witter, 1979; Glaucoma Laser Trial, 1989). These parameters are: a spot size of 50 microns, a pulse duration of 50 ms and a power of approximately 1 watt. Clinically this exposure results in blanching of the trabeculum and frequently in the formation of a gas bubble. These features are assumed to result from the thermal degradation of laser energy and the conversion of liquid cell contents to the gas phase. The small spot and short pulse duration are thought to result in a very rapid change of energy content of tissue in a relatively confined space. This in turn is considered to generate the cellular responses which are a prerequisite to lowering intraocular pressure.

In reality it is extremely difficult to define boundary conditions of exposure to optimise the required tissue response, if the mechanisms underlying such a response are unknown. The treatment parameters for the clinical trials of argon laser trabeculoplasty were set on the basis of limited pilot studies and of largely hypothetical mechanisms of action.

In examining the absorption characteristics of melanin it can be seen that for a uniform absorbing monolayer, 55% of argon blue, 45% of argon green and only 7% of diode irradiation at 810 nm will be absorbed (Gabel et al, 1977). These are maximal figures. Melanin distribution in the trabeculum is discontinuous and therefore the percentage of incident energy absorbed will be less. The depth of tissue to which radiation penetrates increases with increasing wavelength in the visible and the near-infrared and therefore radiation at 810 nm penetrates to a greater depth
than argon. Current physiological and experimental studies indicate that 97% of tissue resistance to aqueous outflow is in the 10 microns of tissue adjacent to the canal of Schlemm (Seiler, 1990). It therefore follows that diode laser irradiation of trabecular tissue will penetrate deeper into the trabeculum and may exert a more immediate effect on the tissue responsible for outflow resistance.

Given that the optimal tissue reaction underlying argon laser trabeculoplasty is unknown, it is difficult to understand why a gas bubble is a prerequisite of the current protocol. The presence of a gas bubble indicates that a phase change within the tissue has occurred, which in turn identifies a very rapid change of energy content and adiabatic expansion of cellular constituents. This implies a two stage damage mechanism to the target cells, the first resulting from the passage of thermal transients and the second from mechanical displacement due to the expanding gas bubble. In diode exposures, heating takes place as a more gradual process, resulting from absorption and energy conversion over a greater volume of tissue. The more diffuse absorption and less marked rate of change of energy did not result in a gas bubble in the present study and therefore such damage only involved a thermal mechanism.

The lower tissue absorption and greater penetration depth of the diode are comparable to those of cw-YAG laser irradiation. With both of these laser wavelengths, higher energy levels have to be used compared with those of argon. Typically in this study, power levels of greater than one watt were required with diode exposures, whereas lesions resulted from powers of 900 mW or less with the argon system. The more diffuse zone of tissue reaction was also perhaps responsible for the less defined nature of the diode lesions. Clinically, in some patients it is difficult to perceive any change in the trabeculum, other than a slight altered light reflex.

The tissue reaction to laser irradiation is also poorly understood. Human trabecular meshwork is composed of beams of collagenous tissue, which are lined by endothelial cells and which have an extracellular matrix of glycosaminoglycans, non collagenous protein and fibronectin (Tawara, 1989). The initial effect of trabecular photocoagulation is one of protein denaturation. The rate of thermal denaturation of protein is influenced by the temperature of the tissue (Birngruber 1980). Studies have shown that shrinkage of collagen fibres in cornea (Shaw and Gasset, 1974) and
iris (Van der Zypen et al, 1979) occurs at 60-70 degrees centigrade and one would predict that a similar temperature is necessary to induce such changes in the trabeculum. The conversion of light to heat within melanin (Mainster, 1986), and the production of thermal transients passing over the trabecular beams may thus result in denaturation of protein if equilibrium temperatures are of sufficient magnitude.

The tissue changes observed in this study with both laser wavelengths were similar and were also comparable to those identified in studies of the free running YAG (Rodriguez et al, 1982; Van der Zypen and Fankhauser, 1987). All of these studies have identified some thermal damage to trabecular beams and cells, but none comment on the mechanical displacement that must result from gas bubble formation.

In our analysis of the acute effects of laser irradiation of the trabecular meshwork, little difference could be seen in the tissue responses other than that in the diode exposures, deeper penetration had resulted in more damage to deeper tissues. Clinically, a therapeutic effect should ensue from a successful treatment within 2-3 weeks of irradiation, with a maximal ocular hypotensive effect occurring within 6-9 months of treatment (Fink et al, 1988). It is difficult to extrapolate from acute tissue effects to chronic effects and ultimately to beneficial physiological changes. However, from the similarity of the results obtained at two laser wavelengths in this study, it may be inferred that similar long term tissue responses would be seen with diode laser trabeculoplasty.

Currently, there are three basic concepts which attempt to explain the beneficial effects of laser trabeculoplasty. Wise and Witter proposed that heat-induced shrinkage of collagen fibres caused a reduction in the circumference of the trabecular ring, and an opening of the trabecular spaces (Wise and Witter, 1979). Some experimental evidence for this theory has been provided by Weber (Weber, 1983).

Van der Zypen and Fankhauser proposed an alternative mechanism to explain the ocular hypotensive effect of photocoagulation. Laser burns applied to the posterior trabecular meshwork in monkeys induced a widening of trabecular spaces adjacent to the burn site, due to primary disruption of collagen fibres. In addition over a time course of 8-12 weeks, there was a secondary degenerative effect which extended beyond the primary impact zone, and as deep as Schlemm's canal. The
result of this process was further widening of the trabecular spaces (Van der Zypen and Fankhauser, 1984).

Studies by Van Buskirk and colleagues (Van Buskirk, 1984; Acott et al, 1988; Bylsma et al, 1988 (I) and (II); Bylsma et al, 1989) suggest that in addition to the above mechanical mechanisms of action, photocoagulation may also promote beneficial cellular and biochemical processes within the trabecular meshwork. In Van Buskirk's studies it has been shown that trabecular cell loss following irradiation was accompanied by trabecular cell hyperplasia. It was hypothesised that these newly formed cells were able to perform the functions which contributed to the re-establishment of a normal outflow resistance. The complexity of the situation is increased by the observation of Fink that laser trabeculoplasty to one eye was often associated with a reduction in pressure in the contralateral eye, indicating the possible influence of neurogenic or biochemical mediators released by cellular elements and initiated by laser irradiation (Fink et al, 1982).

Although the data obtained in the present study only relate to the primary effects of laser radiation, the close correlation of initial clinical results with observations at a corresponding period in other studies of argon laser trabeculoplasty suggests that diode laser trabeculoplasty is directly clinically comparable (see section 7.4).

Current protocols suggest a spot size of 50 microns for argon LTP (Mandell and Terry, 1982), while the minimum available spot size with the diode laser was 100 microns. This did not appear to have a detrimental effect and in practice a given spot size with any laser probably results in a wide range of burn diameters as a consequence of variations in focus and power settings.

The results of this histological study have indicated that the diode laser is an effective instrument to perform photocoagulation of the trabecular meshwork. The similarity with lesions produced by current laser modalities, and the further advantages of diode lasers with regard to their portability and reliability is certain to stimulate future interest in their therapeutic potential for the treatment of glaucoma.
SECTION IV
CLINICAL STUDIES
CHAPTER 7

METHODS AND RESULTS OF DIODE LASER CLINICAL TRIALS

7.2 DIODE LASER THERAPY FOR RETINAL VASCULAR CONDITIONS

A number of retinal vascular conditions for which laser photocoagulation had become an accepted mode of therapy were treated in this study. These conditions were:

a) Proliferative diabetic retinopathy

b) Exudative diabetic maculopathy

c) Branch retinal vein occlusion complicated by neovascularization at the retinal or at the optic disc

d) Central retinal vein occlusion with threatened or established retinal neovascularization

7.2.1 TREATMENT AIMS

The aims of photocoagulation therapy for retinal vascular conditions had been established, but in summary these were as follows:

a) The aim of treatment of proliferative retinopathy in either diabetes or vein occlusion was closure, or regression of any areas of neovascularization.
7.1 STUDY DESIGN

All clinical work was carried out in either the Department of Ophthalmology at St Thomas' Hospital, or the Retinal Diagnostic Department at Moorfields Eye Hospital. Prior to commencement of the study, a detailed protocol was submitted for approval to the ethical committees of each institution.

The design of this initial study took the form of a series of pilot clinical trials. There were strict inclusion criteria relating to admission of patients to the trials. The diode laser was the only instrument used to perform photocoagulation. If it were felt that an inadequate response to therapy was being observed, or that unacceptable side effects were occurring with the diode laser, the patient would be withdrawn from the trial and the treatment complete with an argon system.

The rationale of performing pilot studies lay in the requirement of gaining initial clinical data on a new laser modality over a reasonably short time course. Longer-term randomised trials are being constructed that will compare infrared diode lasers with lasers that emit at other wavelengths. There were two classes of ocular conditions that were treated in the trials:

• Retinal vascular conditions
• Chronic open angle glaucoma

7.2 DIODE LASER THERAPY FOR RETINAL VASCULAR CONDITIONS

A number of retinal vascular conditions for which laser photocoagulation is an accepted mode of therapy were treated in this study. These conditions were:

a) Proliferative diabetic retinopathy
b) Exudative diabetic maculopathy
c) Branch retinal vein occlusion complicated by neovascularisation at the retina or at the optic disc
d) Central retinal vein thrombosis with threatened or established rubeosis iridis

7.2.1 TREATMENT AIMS

The aims of photocoagulation therapy for ocular vascular conditions have been established, but in summary these were as follows:

a) The aim of treatment of proliferative retinopathy in either diabetes or vein occlusions was closure, or regression of any areas of neovascularisation.
b) The aims of photocoagulation for exudative diabetic maculopathy were closure of intraretinal microvascular abnormalities and the resolution of macular hard exudates.

c) In those patients with established rubeosis iridis secondary to central retinal vein occlusion, photocoagulation attempted to cause regression of the rubeosis and forestall the onset of rubeotic glaucoma.

7.2.2 INCLUSION CRITERIA

The inclusion criteria for the study were:

a) The patient should have one of the above conditions and be able to provide informed consent to participate in the study and be willing and able to attend for follow-up visits;

b) The absence of significant media opacities, for example, a cataract that precluded an adequate retinal view;

c) No previous photocoagulation in the study eye, if a maculopathy was to be treated;

d) In conditions requiring panretinal photocoagulation, previous photocoagulation had to have been carried out more than one year previously and have been confined to the macular region.

7.2.3 PATIENT EVALUATION

Pre-treatment evaluation of the patient consisted of the following:

a) Corrected visual acuity with an illuminated Snellen chart.

b) Biomicroscopic examination of the anterior segment, which included intraocular pressures; pupillary reflexes and fundoscopy.

c) Colour fundal photography, using Ektachrome CRR 64 film and fluorescein angiography, using FP4 125 ASA film and 5 ml of 10% sodium fluorescein were performed at the pretreatment visit. A set of standard fundal photographs and the Hammersmith classification was used to grade those eyes with proliferative and exudative diabetic retinopathy (Oakley et al, 1967; Appendix II). Eyes with retinal vein thrombosis and new vessels were assessed on the basis of retinal ischaemia and fluorescein leakage from neovascular elements prior to and following therapy.

7.2.4 TREATMENT PROTOCOL

All patients were given a full explanation of the treatment modality and possible side effects before signing consent forms (Appendix I). Included in the
discussion was a statement that some discomfort may be associated with the treatment.

Therapy was carried out on a separate day from that of the pretreatment assessment and if possible all treatment was completed at one sitting. In those patients where the slit lamp system was employed, after instillation of a topical anaesthetic (amethocaine 1%), a fundus contact lens (Mainster or Rodenstock panfundoscope lens, or a Goldmann 3 mirror lens), was applied to the eye. The pattern of laser treatment administered varied according to the condition.

a) Eyes with diabetic retinopathy and papillary neovascularisation had panretinal therapy (Hercules, 1977), with the application of 1500-2000 burns, while peripheral new vessels were given either sector or panretinal photocoagulation depending on the extent of the lesions and area of ischaemia (Hamilton and Blach, 1979).

b) Exudative maculopathy had focal treatment to regions of microvascular abnormalities (Hamilton, 1979).

c) In those eyes with branch retinal vein occlusion, sector ablation was administered to the area of ischaemic retina indicated by fluorescein angiography (Archer and Michalopoulos, 1981).

d) Central retinal vein occlusions were treated with panretinal photocoagulation, with typically 500 burns applied to each quadrant (Magargal et al, 1982).

In all conditions the immediate aim of photocoagulation was to produce a mild blanching of the retina with each burn.

During treatment careful note was made of any subjective sensations remarked on by the patient and the operator recorded his own observations. Immediately following treatment colour fundal photography was carried out.

7.2.5 POST-TREATMENT REVIEW

Patient review was at two weeks, six weeks and twelve weeks following treatment and at three monthly intervals thereafter. At each visit the ocular examination included visual acuity, anterior segment examination, intraocular pressures and fundoscopy.

Colour photographs were taken at each visit and fluorescein angiography performed at six weeks. The severity of the retinopathy was graded at each visit, with
reference to comparable photographs taken prior, and subsequent to therapy.

In some instances further therapy was administered if it was felt on review that inadequate treatment had been given initially. All results were entered on standard pro-formas (Appendix I). The information was then transferred to a computer database for analysis.

7.3 RESULTS OF TREATMENT OF RETINAL VASCULOPATHIES

Over a period of 25 months, diode laser photocoagulation was performed on a total of 86 eyes in 71 patients who were included in the pilot studies. Approximately 100 further patients were treated with the diode laser over this period who were not eligible for inclusion in the trials. Although the clinical results from the latter group could not be analysed, important data was obtained regarding the use of the laser in a routine clinical setting.

7.3.1 USE OF INSTRUMENTATION

The hand-held, direct ophthalmoscope version was used for the first six patients treated (all with retinal vein occlusions) while the slit lamp model was employed for all subsequent cases. Both forms could be quickly and easily set up for use in the clinic and no difference was found in the type of lesions produced with either instrument.

The greater magnification and smaller field of view made treatment with the hand-held device a lengthier procedure, and poor target fixation made macular photocoagulation difficult. In contrast the slit lamp instrument allowed more accurate aiming, the patient being stabilised through the contact lens and the head rest of the microscope. The greater field of view and the better retinal illumination were also perceived advantages by the operator. Patient comments indicated a strong preference for the direct ophthalmoscope modality mainly related to the fact that no contact lens was required and that they could assume a more relaxed posture.

In each instrument the red aiming beams were usually clearly visible, but where there was extravascular blood in either the vitreous or the retina, the retinal image of the aiming beam tended to fade in sharpness and brightness. The absence of an occluding safety shutter allowed an uninterrupted retinal view during photocoagulation, and therefore it was possible to visualise the full process of development of a retinal burn. This uninterrupted view also expedited treatment, as the operator never lost his retinal orientation during procedures, as sometimes occurs.
in response to eye movements during shutter closure using conventional systems.

An additional feature of a system not requiring a mechanical shutter, was that retinal treatment was a much quieter procedure than with conventional lasers, the only sound being that of the faint click of the foot switch during each exposure. As only the aiming beam was visible there were no bright flashes during photocoagulation, although at higher power levels a faint transient orange luminescence of the retinal pigment epithelium was visible. Several patients who had been treated previously with an argon laser stated that these features made diode laser photocoagulation a less stressful experience.

Reliability of the instruments was high. The slit lamp version has performed over 200,000 exposures to date, without malfunction.

7.3.2 THE LASER BURNS

In a sequence of initial exposures the power level was set to produce a grey-white chorioretinal lesion, corresponding to a mild burn (typically 550-650 mW). The immediate post exposure appearance of the lesion was similar to that seen in relation to krypton laser irradiation: that is a slightly less distinct burn than that typical of argon irradiation.

The degree of retinal pigmentation influenced the power level at which a clinical threshold lesion could be obtained. Generally, highly pigmented fundi required lower power settings for photocoagulation (450-650 mw) than lightly pigmented fundi (650-850 mw) (figures 7.1 (a) and (b)). Lesions were made with an exposure duration of between 0.20 and 0.50 seconds. Within one month of treatment the burns had become pigmented scars essentially identical to those produced by other forms of laser irradiation (figure 7.2). No complications were seen such as choroidal haemorrhages, or tears in the retinal pigment epithelium. The presence of media opacities required an increase in power to produce a burn, but it is noteworthy that the laser radiation at 810 nm was observed to be able to penetrate a thin film of preretinal haemorrhage (approximately 150 microns in thickness) in sufficient concentration that a burn ensued at the retinal pigment epithelium.
Figure 7.1 (a)
Appearance of diode laser-induced burns in a heavily pigmented fundus (power = 455 mW).

Figure 7.1 (b)
Note the paler appearance of acute lesions produced in a lightly pigmented fundus (power = 750 mW).
Figure 7.2

Diode laser burns 6 weeks following treatment. Note the typical pigmented appearance of the lesions, which is common to all retinal laser burns at this stage.
7.3.3 CLINICAL RESULTS
(i) PROLIFERATIVE DIABETIC RETINOPATHY

47 eyes were treated in 38 patients, who had either optic disc or retinal neovascularisation. 17 eyes were of patients with insulin-dependent (type 1) diabetes and 30 eyes were of non-insulin dependent (type 2) diabetics. 26 patients were male and 12 female. The mean age was 53 (range 26-76) and the mean period of follow-up was 11 months (range 2 months to 19 months). 2 patients died from cardiovascular causes during the study.

Prior to treatment, 9 eyes had disc new vessels (NVD) alone and 28 eyes had peripheral new vessels (PNV). 10 eyes had both NVD and PNV.

a) NEOVASCULAR REGRESSION

Total closure of the new vessels was observed in 33 of 47 (70%) eyes during the review period. Partial neovascular regression occurred in 13 eyes (28%). In one eye, there was further proliferation at the optic disc in spite of photocoagulation. Figure 7.3 shows the change in the extent of new vessels following treatment in each eye of the series.

b) VISUAL ACUITY

During the period of follow-up, the visual acuity was unchanged compared to the pretreatment level in 32 eyes, improved in 12 eyes and was reduced in 3 eyes (figure 7.4).

In 2 of the latter eyes, haemorrhage from the neovascular elements had occurred. This largely resolved in one eye. In the other eye it has persisted, despite multiple treatments. A vitrectomy is being considered in this patient. In the third eye that had experienced visual deterioration, cystoid macular oedema occurred within one week of photocoagulation. The oedema resolved within 4 weeks, but there has been a persistent visual deficit.

c) NUMBER OF TREATMENTS

The mean number of treatments performed on each eye in the series was 2 (range 1-8). 17 eyes had only one episode of therapy, and the remaining eyes had more than 1 treatment.

d) TREATMENT PARAMETERS

The spot size was varied between 300 and 500 microns and the pulse duration was between 0.20 and 0.50 seconds. The mean power used in
Figure 7.3 (a)
Effect of diode laser treatment on diabetic disc new vessels

Figure 7.3 (b)
Effect of diode laser treatment on
diabetic peripheral new vessels

The scale of the axes in 7.3 (a) and (b) refers to the extent of neovascularisation, on a scale from "0" to "5" (Appendix II). In the majority of eyes treated, there was a reduction of at least one grade, representing partial, or complete regression of the new vessels.
Figure 7.3 (a)

DIODE PHOTOCOAGULATION
Effects on optic disc new vessels (NVD)

NVD pre Rx

NVD post Rx

* Eyes treated (n=19)
Figure 7.3 (b)

DIODE PHOTOCOAGULATION
Effect on peripheral new vessels (PNV)

PNV pre Rx

4

2

1

PNV post Rx

1. Eyes treated (n=38)
Figure 7.4
Visual acuity and diode laser treatment in proliferative diabetic retinopathy
With 2 exceptions, visual acuity in the treated eyes remained unchanged, or improved over the period of review.
VISUAL ACUITY AND DIODE PHOTOCOAGULATION
PROLIFERATIVE DIABETIC RETINOPATHY

Snellen acuity pre Rx

Snellen acuity post Rx

* Eyes treated (n=47)
### TABLE III

**DIODE LASER PANRETINAL PHOTOCOAGULATION FOR PROLIFERATIVE DIABETIC RETINOPATHY**

Mean number of burns applied in single and multiple treatments

<table>
<thead>
<tr>
<th>No. of treatments</th>
<th>No. of eyes</th>
<th>Mean no. of burns applied</th>
<th>Total closure</th>
<th>Partial closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>2257</td>
<td></td>
<td>2292</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>3430</td>
<td></td>
<td>2233</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
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<td>8692</td>
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<tr>
<td>8</td>
<td>1</td>
<td>-</td>
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<td>12,094</td>
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</tbody>
</table>
### TABLE IV

**DIODE LASER PANRETINAL PHOTOCOAGULATION**

Success and distribution of new vessels (NV)

<table>
<thead>
<tr>
<th>Distribution of NV following Rx</th>
<th>Total closure</th>
<th>Mean no. of burns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic disc</td>
<td>5/9 (56%)</td>
<td>5087 (range, 3027-8633)</td>
</tr>
<tr>
<td>Retina</td>
<td>22/28 (80%)</td>
<td>2921 (range, 189-8266)</td>
</tr>
<tr>
<td>Optic disc and retina</td>
<td>6/10 (60%)</td>
<td>5416 (range, 2020-7494)</td>
</tr>
</tbody>
</table>
photocoagulation was 620 mW (range 400-1270 mW). The mean number of burns applied in all treatments was 4020 (range 189-12094). Table III shows the mean number of burns applied in eyes requiring single, or multiple treatments. Table IV shows the success of photocoagulation in effecting regression of the various patterns of neovascularisation. The highest success rate and the fewest burns were required in those eyes with peripheral new vessels.

e) COMPLICATIONS OF THERAPY

In none of the patients were treatment-related anterior segment complications observed, such as corneal or lenticular changes.

9 patients, in common with several from the other groups occasionally reported symptoms of discomfort during treatment. Comments were encountered most often at higher power levels, or where photocoagulation was applied to areas of lightly pigmented retina. In no instance was it found necessary to discontinue therapy due to unacceptable levels of discomfort, but in 2 cases retrobulbar anaesthesia was administered when further treatment was carried out. One of these patients had previously required argon laser therapy to the other eye, also under retrobulbar anaesthesia.

Other patients who had undergone argon therapy to the fellow eye favoured diode treatment. In particular patients commented upon the absence of both noise and the intense and repetitive flashes of light.

The only posterior segment complication that can be attributable to the diode laser is in that patient who developed transient cystoid macular oedema.

CASE REPORT 1

A 38 year old insulin dependent diabetic male presented with optic disc and retinal neovascularisation in the right eye (figure 7.5 (a) and (b)). Diode laser panretinal photocoagulation was performed, a total of 3,280 burns being applied with an exposure duration of 0.20 seconds, a laser spot size of 500 microns and power of 535-700 mW. No problems were encountered during treatment apart from the patient experiencing mild discomfort at higher power levels of exposure.

On review at four weeks the laser lesions showed the typical appearance of pigmented scarring and the disc new vessels showed signs of regression (figure 7.5 (c)). At six weeks, fluorescein angiography showed an absence of leakage from the previously patent new vessels (figure 7.5 (d)). Subsequent examination has shown
Figure 7.5: Case report 1

(a) Fundus photograph showing papillary neovascularisation in the right eye of an insulin-dependent diabetic.

(b) Pre-treatment fluorescein angiogram of same eye demonstrating leakage from the disc new vessels.

(c) 4 weeks following diode laser panretinal photocoagulation, there are signs of closure of the optic disc new vessels. Several laser scars are visible nasal to the optic disc.

(d) Six weeks following treatment, fluorescein angiography shows an absence of leakage at the optic disc, confirming regression of the new vessels.
no recurrence of the treated lesions.

(ii) EXUDATIVE DIABETIC MACULOPATHY

22 eyes in 16 patients were treated in this group, 9 males and 7 females with a mean age of 61 (range 49-75). The mean period of review was 11 months (range 3 months to 19 months).

Focal photocoagulation was administered to microvascular abnormalities (MVA) within the areas of hard exudate. The MVA were principally microaneurysms but in one case was a macroaneurysm. No immediate alteration in the appearance of the treated vascular lesions was seen, the infrared laser energy being transmitted through the vascular lesions and being absorbed by the underlying retinal pigment epithelium and choroid.

a) REGRESSION OF LESIONS

A reduction in the number of vascular lesions in the treated areas of each eye has been observed in 20 of 22 eyes. This has been associated with evidence of resorption of hard exudates. No alteration in the clinical appearances was observed in the other 2 eyes.

b) VISUAL ACUITY

11 eyes had an improvement in visual acuity over the period of review. In 7 eyes vision was unchanged and in 4 eyes there was a deterioration in vision (figure 7.6).

c) NUMBER OF TREATMENTS

The mean number of treatments performed was 2 (range 1-3).

d) TREATMENT PARAMETERS

The laser spot size in all eyes was 100 microns and the pulse duration was varied between 0.20 and 0.30 seconds. The mean power used in all treatments was 530 mW (range 340-800 mW). The mean number of burns was 120 (range 20-410).

e) COMPLICATIONS OF THERAPY

Only a few patients were aware of any sensation during macular laser therapy. In no case was it necessary to perform retrobulbar anaesthesia. There were no other laser-related anterior, or posterior segment related side effects.

CASE REPORT 2

A 63 year old West Indian Lady, with insulin dependent diabetes presented with a circinate area of hard exudates in the left macula. Central to the exudates were several retinal microaneurysms (figure 7.7 (a)). Visual acuity was 6/24. 61 burns were
Visual acuity improved, or was unchanged in the majority of eyes following treatment.
VISUAL ACUITY AND DIODE PHOTOCOAGULATION
EXUDATIVE DIABETIC MACULOPATHY

Snellen acuity pre Rx

Snellen acuity post Rx

Eyes treated (n=22)
applied to the region of the microaneurysms. The laser power was 350-400 mW, the spot size was 200 microns and the exposure duration was 0.25 seconds (figure 7.7 (b)). No adverse symptoms were reported by the patient.

20 weeks following treatment, there was a reduction in the number of microaneurysms and the area of exudates had resorbed considerably (figure 7.7 (c)). Fluorescein angiography confirmed that there was reduced leakage within the macula. It was also interesting that a marked degree of retinal pigmented hyperplasia had been induced by the photocoagulation to the extent that in some areas it was difficult to identify the treatment sites (figure 7.7 (d)). The visual acuity had improved to 6/9.

(iii) BRANCH RETINAL VEIN OCCLUSION AND NEOVASCULARISATION

11 eyes in 11 patients were treated in this group. 4 eyes had optic disc new vessels (NVD) and 7 eyes had peripheral new vessels (PNV). 8 patients were being treated for hypertension and one patient had ischaemic heart disease. 9 patients were female and 2 were male. The mean age was 66 (range 51-81) and the mean follow up period was 12 months (range 9 months to 19 months).

a) NEOVASCULAR REGRESSION

11 out of 11 (100%) of patients had closure of the vessels following treatment.

b) VISUAL ACUITY

The visual acuity remained unchanged in 8 eyes during the period of review. Vision improved following therapy in the remaining 3 eyes.

c) NUMBER OF TREATMENTS

The mean number of laser treatments performed was 2 (range 1-4).

d) TREATMENT PARAMETERS

The laser spot size was varied between 200 and 500 microns and the pulse duration was between 0.20 and 0.30 seconds. The mean power used in all treatments was 590 mW. The mean number of burns applied was 1565 (range 290-3164, the latter being in an eye with a hemispheric vein occlusion).

e) COMPLICATIONS OF THERAPY

No patients complained of excessive feelings of discomfort during therapy and no laser-related complications were observed.
Figure 7.7: Case report 2.

(a) Fundus photograph of a patient with insulin dependent diabetes, which shows a left exudative circinate maculopathy surrounding several microvascular abnormalities.

(b) Appearance of diode laser lesions immediately following treatment.

(c) 4 months following focal photocoagulation the central lesions have resolved and there is considerable resorption of surrounding exudates.

(d) Fluorescein angiography taken at the same interval following treatment demonstrates areas of increased pigmentation in several of the sites of irradiation.
CASE REPORT 3

An 81 year old hypertensive lady presented with a left inferotemporal branch retinal vein occlusion. There were several tufts of forward retinal neovascularisation surrounded by areas of intra-gel haemorrhage (figure 7.8 (a) and (b)).

235 burns were applied to the area of ischaemic retina. Power was 500-650 mW, spot size 200 microns and exposure duration 0.5 seconds. Apart from a slight "pricking" sensation the patient reported no adverse symptoms and no other side effects were observed. Eight weeks later, the new vessels had regressed, closure being confirmed on angiography (figure 7.8 (c) and (d)). No recurrence of the vessels has been observed subsequently.

(iv) CENTRAL RETINAL VEIN THROMBOSIS

6 eyes in 6 patients were treated for central retinal vein thrombosis. 5 eyes had established rubeosis irides and 2 of these eyes also had optic disc neovascularisation. The remaining eye had widespread areas of vascular closure on fluorescein angiography, and therefore was considered at risk of development of rubeosis. All of the patients were female. The mean age of the patients was 68 (range 57-75). The mean period of review was 13 months (range 6-19 months).

a) REGRESSION OF NEOVASCULARISATION

There was total disappearance of rubeosis following treatment in 4 of 5 eyes. There was also complete closure of the disc new vessels that had been observed in 2 of these eyes. Partial resolution of rubeosis occurred in the fifth eye. The eye that had been given prophylactic therapy has not developed rubeosis during the period of review. None of the patients has developed rubeotic glaucoma.

b) VISUAL ACUITY

The visual acuity remained unchanged following therapy in 4 eyes and there was a slight improvement in vision in 2 eyes.

c) NUMBER OF TREATMENTS

The mean number of sessions of photocoagulation performed was 1.5 (range 1-2).

d) TREATMENT PARAMETERS

The laser spot size used was either 300 or 500 microns. The pulse duration was varied between 0.20 and 0.50 seconds. The power required ranged from 450 mW to 1.0 W. The presence of extensive areas of retinal and preretinal haemorrhage in
Figure 7.8: Case report 3.

(a) Pre-treatment fluorescein angiogram of a left inferotemporal branch retinal vein occlusion with retinal neovascularisation, which demonstrates several areas of leakage from the neovascular complexes.

(b) Fundus photograph in the same patient, immediately following laser sector ablation. Areas of neovascularisation are indicated by arrows.

(c) 8 weeks following laser therapy, the new vessels have regressed and the laser burns have become pigmented scars.

(d) Closure of the retinal new vessels is confirmed by fluorescein angiography.
the majority of eyes treated generally necessitated a higher power setting, although the infrared radiation appeared to have good transmission through layers of blood. The mean number of burns applied was 2030 (range, 1200-3059).

e) COMPLICATIONS OF THERAPY

Only one patient experienced any symptoms of discomfort during therapy, but not to the extent that retrobulbar anaesthesia was required. There were no other side-effects of laser therapy.

CASE REPORT 4

A 75 year old lady presented with a left central retinal vein occlusion (figure 7.9 (a)). Several months previously she had developed left acute angle closure glaucoma, which was successfully treated with peripheral iridotomy with a YAG laser.

2 months following the onset of the vein occlusion, the patient developed rubeosis iridis and optic disc neovascularisation (NVD) (figure 7.9 (b) and (c)). Visual acuity was hand movements only. The intraocular pressure was normal, but there was atrophy of the optic disc, which was presumed to be related to her episode of narrow angle glaucoma.

Panretinal photocoagulation was carried out with the diode laser. The spot size was 300 microns, pulse duration was 0.25 seconds and the power was 500 mW. A total of 3059 burns were applied in 2 treatment sessions.

On review 6 weeks following treatment, the NVD and the rubeosis had entirely resolved (figure 7.9 (d) and (e)). There has been no change in visual acuity, but the intraocular pressures have remained normal and the eye comfortable.
Figure 7.9: Case report 4

(a) Fundus photograph of a left central retinal vein occlusion in a 75 year old lady.

(b) Fluorescein angiogram performed 2 months after presentation showing the presence of early rubeosis iridis.

(c) Angiography also indicated that optic disc neovascularisation had developed in this eye.

(d) 6 weeks following treatment, there was no evidence of rubeosis.

(e) Fluorescein angiography at the same interval showed regression of the optic disc new vessels.
7.4 DIODE LASER THERAPY FOR CHRONIC OPEN ANGLE GLAUCOMA

7.4.1 AIMS OF STUDY

The purpose of this study was to evaluate the ocular hypotensive action of diode laser trabeculoplasty (DLT) in the treatment of patients with chronic open angle glaucoma. In this preliminary investigation, randomised comparison with argon laser trabeculoplasty was not performed.

7.4.2 INCLUSION CRITERIA

The following inclusion criteria were established for the study:

a) The patient should have chronic open angle glaucoma for which medical therapy has failed to satisfactorily control intraocular pressures (IOP).

Because the emphasis of the study was directed at the effect on IOP, individuals with poorly controlled ocular hypertension were also admitted to the study. Patients with forms of secondary glaucoma, for example resulting from uveitis, or aphakia were excluded.

b) The pre-treatment IOP should be 22 mm Hg or greater.

c) The patient should be able to provide informed consent to participate in the study and be willing and able to attend for follow-up visits.

d) The absence of significant corneal opacities, for example band keratopathy, that precluded adequate visualisation of the trabecular meshwork.

e) No previous photocoagulation or operative surgery should have been performed on the trabeculum.

7.4.3 PATIENT EVALUATION

Pre-treatment evaluation of the patient consisted of:

a) Corrected visual acuity with an illuminated Snellen chart at 6 metres.

b) Biomicroscopic examination of the anterior segment, including:

Intraocular pressure measurement with a Goldmann applanation tonometer. All measurements of IOP were performed in the morning.

Gonioscopy using a Goldmann 3 mirror contact lens. The width of the anterior chamber angle was estimated on a scale of 0-4, using the Shaffer grading.

Fundoscopy included an examination of the optic discs, with an estimation of the cup:disc ratio and the degree and extent of pallor.
Colour stereo photographs of the optic discs were taken in those eyes without pharmacologically induced miosis.

### 7.4.4 TREATMENT PROTOCOL

All patients were given a full explanation of the treatment modality and possible side effects before signing consent forms. Included in the discussion was a statement that some discomfort may be associated with the treatment.

Therapy was carried out on a separate day from that of the pre-treatment assessment. After instillation of a topical anaesthetic (amethocaine 1%), a Goldmann or Ritch contact lens was applied to the eye in order to allow visualisation of the anterior chamber angle. The pattern of treatment consisted of applying approximately 50 burns to 180 degrees of the trabecular meshwork. The laser spot size was 100 microns and the pulse duration was 0.20 seconds. The target area was the pigmented portion of the trabecular meshwork. The power was adjusted in order to produce a mild blanching of the trabeculum.

The intraocular pressures were measured 2 to 3 hours after therapy. A transient rise in pressure would be treated with a drop of timolol 0.5%. The patient was asked to continue with their current glaucoma medication.

### 7.4.5 POST-TREATMENT REVIEW

Patient review was at 2 weeks, 6 weeks and 12 weeks following treatment and at 2 to 3 month intervals thereafter. At each visit the ocular examination included visual acuity, anterior segment examination, intraocular pressures and fundoscopy, including examination of the optic discs.

If a satisfactory ocular hypotensive effect was achieved, with an IOP of less than 22 mm Hg, a reduction of the patient’s ocular medication was considered.

An unsatisfactory response to treatment was considered to be failure to reduce the intraocular pressure to less than 22 mm Hg at 6 weeks following laser therapy. In this case, laser trabeculoplasty was repeated to the other 180 degrees of the angle. Continued failure to control the IOP would lead to consideration of operative intervention.

### 7.5 RESULTS OF DIODE LASER TRABECULOPLASTY

#### 7.5.1 USE OF INSTRUMENTATION

A slit-lamp version of the diode laser was used throughout the study. No problems were encountered using this instrument in conjunction with a
Goldmann 3 mirror, or a Ritch lens. Visualisation of the angle of the anterior chamber was not difficult, and the red aiming beam was easily focused on the trabeculum.

7.5.2 THE LASER BURNS

The tissue reaction that was commonly observed following laser exposure was a blanching of the pigmented portion of the trabecular meshwork. This generally occurred at power settings of between 800 and 1200 mW. In eyes with poor pigmentation of the trabeculum, this response was more difficult to identify. Gas bubble formation at the site of laser irradiation was not observed.

7.5.3 CLINICAL RESULTS

20 eyes in 13 patients were treated. 16 eyes had chronic open angle glaucoma, 3 eyes had ocular hypertension and one eye had pseudoexfoliation glaucoma. 8 patients were female and 5 were male. 2 patients were black, the others were Caucasian. The mean age was 65 (range 57-76). The mean period of review was 9 months (range 6-12 months). 7 patients had bilateral DLT performed, and 6 patients treatment to one eye only. 16 eyes had one treatment with the diode laser; 4 eyes had 2 treatments.

a) INTRAOCULAR PRESSURES

The mean pre-treatment intraocular pressure was 28.3 mm Hg (range 22-36). The mean IOP 2 weeks following laser trabeculoplasty was 18.1 mm Hg (range 14-22). It was noted that of those 6 patients who had treatment to one eye, in 3 patients the intraocular pressure was lower in the untreated eye compared to pretreatment levels (by 3, 4 and 8 mm Hg). In the remaining untreated eyes, there was no change in intraocular pressure.

Table V shows that the ocular hypotensive effect of laser therapy was maintained in the treatment group over a period of 6 months following treatment. The paired t test, which determines the difference between matched samples was used to assess changes in IOP, compared to the baseline pretreatment level and the results indicate that a significant effect was achieved and maintained following therapy. Figures 7.10 and 7.11 illustrate the IOP's before and at 2 weeks and at 6 months following treatment in each of the eyes. Of the 5 eyes which have been reviewed for longer than 6 months, 4 have had IOP's of less than 22 mm Hg. One eye had a measured pressure of 25 mm Hg at 10 months and evidence of further loss
of visual field. It was therefore decided to perform a trabeculectomy on this patient.

In this small series, no particular factors were identified which would tend to reduce the success of treatment. One of the black patients treated had an initial reduction in IOP from 28, 22 mm Hg, to 16, 18 mm Hg at 2 weeks. At 12 weeks and 24 weeks following treatment, the pressures have been 20, 18 and 21, 18 mm Hg. If the IOP in the right eye should increase any further, retreatment will be carried out.

2 patients had adjustment of their hypotensive medication. One patient had returned 4 weeks following treatment to both eyes. She had suffered a myocardial infarction and all her ocular medication had been stopped. On examination, her intraocular pressures were 36 and 38 mm Hg. DLT was repeated to each eye and the patient was commenced on guttae pilocarpine 4%. Two weeks later, her intraocular pressures were 22 mm Hg in each eye and on subsequent review her IOP has continued to be within normal limits. The second patient had pre-treatment pressures of 28 mm Hg bilaterally and was being treated with guttae adrenaline 1%, guttae timolol 0.5%, B.D. to each eye in addition to acetazolamide 250 mg, QID. 3 months following treatment his IOP's were 15 mm Hg and 14 mm Hg. His adrenaline drops were stopped and the dose of acetazolamide was reduced to 250 mg BD. At 5 months, his pressures were well controlled at 16 mm Hg in each eye.

b) VISUAL ACUITY

There was no change in visual acuity in any of the patients during the period of review.

c) OPTIC DISCS

During the relatively brief follow-up period, there was no change in the appearances of the optic discs in the eyes treated.

d) COMPLICATIONS OF THERAPY

In 4 of the eyes treated, a mild cellular reaction in the anterior chamber was noted 2 hours following therapy. This was not considered to require anti-inflammatory therapy.
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<td><strong>Mean pre-treatment IOP</strong></td>
<td>28.30</td>
<td>(SD=3.63)</td>
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<tr>
<td><strong>Mean IOP at 2 weeks following DLT</strong></td>
<td>18.10</td>
<td>(SD=2.53)</td>
<td>(n=20)</td>
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<td><strong>Mean reduction in IOP at 2 weeks</strong></td>
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<td>(SD=3.25)</td>
<td>(p &lt;0.001)</td>
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<td><strong>Mean IOP at 6 weeks following DLT</strong></td>
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<td>(SD=2.88)</td>
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<td><strong>Mean reduction in IOP at 6 weeks</strong></td>
<td>9.20</td>
<td>(SD=4.48)</td>
<td>(p &lt;0.001)</td>
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<td><strong>Mean IOP at 3 months following DLT</strong></td>
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<td>(SD=3.63)</td>
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<td><strong>Mean reduction in IOP at 3 months</strong></td>
<td>9.30</td>
<td>(SD=4.70)</td>
<td>(p &lt;0.001)</td>
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<td><strong>Mean IOP at 6 months following DLT</strong></td>
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<td>(SD=3.11)</td>
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<td><strong>Mean reduction in IOP at 6 months</strong></td>
<td>9.55</td>
<td>(SD=3.36)</td>
<td>(p &lt;0.001)</td>
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</table>
Figure 7.10
Intraocular pressures before and at
2 weeks following diode laser trabeculoplasty (DLT)

Treatment was associated with a reduction in intraocular pressure ranging from 4 to 14 mm Hg.
Figure 7.10

DIODE LASER TRABECULOPLASTY
CHANGE IN INTRAOCULAR PRESSURE (IOP)
2/52 FOLLOWING TREATMENT

IOP pre Rx (mm Hg)

IOP post Rx (mm Hg)

* Eyes treated (n=20)
Figure 7.11
Intraocular pressures before and at 6 months following DLT

The ocular hypotensive effect of diode laser trabecuoplasty appears to have been maintained over this period of review.
Figure 7.11

DIODE LASER TRABECULOPLASTY
CHANGE IN INTRAOCULAR PRESSURE (IOP)
AT 6 MONTHS FOLLOWING TREATMENT

- Eyes treated (n=20)
In no eyes was there an acute increase in IOP compared with pre-treatment levels. In 6 eyes there was a small decrease in IOP. This was attributed to the effect of the contact lens pressing on the eye and resulting in expulsion of aqueous.

Several patients noted a mild "pricking" sensation during therapy, but no patients complained of excessive discomfort.

CASE REPORT

A 69 year old man presented with chronic open angle glaucoma. He was being treated with guttae pilocarpine 4% and timolol 0.5%. His visual acuities were 6/36, right eye and 6/9, left eye. Intraocular pressures were 23 mm Hg right and 26 mm Hg left. There were bilateral arcuate scotomas. That on the right approached visual fixation.

Diode laser trabeculoplasty was performed to each eye. The treatments were applied to the inferior 180 degrees of the angles. Power was between 1.1 and 1.2 watts, with a spot size of 100 microns and an exposure duration of 0.20 seconds. A few cells were noted in the anterior chamber 1 hour following treatment, but there was no increase in IOP.

Two weeks following treatment, the intraocular pressures were 14 mm Hg right and left. At 6 weeks, they were 17 mm Hg and 16 mm Hg. Three months following therapy, pressures were 13 mm Hg in each eye. There was no change in visual acuity during the period of review. The patient is being maintained on his current ocular therapy.
In the clinical study, the maximum period of follow up was 25 months. This allows initial conclusions to be drawn concerning the ergonomic and the therapeutic efficacy of the diode laser in relation to retinal vascular diseases and glaucoma.

8.1 RETINAL VASCULAR DISEASES

8.1.1 PROLIFERATIVE DIABETIC RETINOPATHY

Diabetic retinopathy is the commonest cause of blindness in England and Wales in patients between the ages of 30 and 64 years (Sorsby, 1972; Government Statistical Service, 1988). Blindness is caused by neovascular proliferation complicated by haemorrhage or retinal detachment, or by maculopathy. The prevalence of proliferative diabetic retinopathy among diabetics in one survey has been found to be 8% and that of diabetic maculopathy to be 6.8% (McLeod, Thompson et al, 1988).

Neovascularisation is known to occur in the presence of ischaemic areas of retina and is believed to be mediated via an angiogenic factor which may be elaborated by the inadequately perfused retina (Michaelson, 1948; Ashton, 1957; Boulton et al, 1988). Panretinal photocoagulation has been found to induce neovascular regression, although the mechanism of action is not known. Several hypotheses have been advanced to explain this association.

1) The elimination of the source of angiogenic factor through destruction of ischaemic retina (Patz, 1982).

2) Increased availability of oxygen to the retina, following photoreceptor destruction (Wolbarsht and Landers, 1980).

3) The release of an inhibitor of neovascularisation which is derived either from the retinal pigment epithelium (Glaser et al, 1985), or from the plasma (Boulton et al, 1988).

Although the biological mechanisms of action remain unclear, several clinical trials have demonstrated the efficacy of photocoagulation in the treatment of proliferative diabetic retinopathy. The first indications of the benefits of panretinal laser photocoagulation were provided by use of the ruby laser (694.3 nm). Beetham and colleagues produced total regression of neovascularisation in 60% of diabetics treated, although patient selection also included those which apparently only had pre-proliferative changes (Beetham et al, 1969). Subsequent studies which were more carefully controlled, have confirmed these findings.
The Diabetic Retinopathy Study (DRS) recruited 1758 patients with proliferative diabetic retinopathy to a study in which eyes were randomly assigned to treatment with either argon blue-green, or xenon photocoagulation, or to no treatment. The DRS identified a number of "risk factors" which put eyes at increased danger of visual loss, which included optic disc new vessels, peripheral new vessels of one half disc diameter or more, and the presence of vitreous or preretinal haemorrhage (Diabetic Retinopathy Research Group, 1978).

The DRS found that photocoagulation (PRP) to eyes with the above risk factors effected neovascular regression and reduced the overall rate of severe visual loss over a 2 year period from 26% in untreated eyes to 11% in treated eyes (Diabetic Retinopathy Research Group, 1981).

Other studies have confirmed that photocoagulation for proliferative retinopathy confers a significant reduction in the risk of visual loss following regression of neovascularisation (Hercules et al, 1977; Plumb et al, 1982). A recent review calculated that PRP reduced the risk of "blindness" (defined as reduction in visual acuity to < 6/60) by 61% (Rohan et al, 1989). In early trials, attempts were made to assess the respective merits of argon all-line laser photocoagulation versus xenon arc treatment. Similar rates of neovascular regression were demonstrated with each modality and in both cases, photocoagulation was associated with a better prognosis than the natural history of the disease (Hercules et al, 1977; Plumb et al, 1982).

A similar beneficial effect has been observed following krypton red photocoagulation. Schulenberg performed PRP on 12 eyes with optic disc neovascularisation. 6 eyes were treated with an argon laser and 6 with a krypton red laser. Partial or complete resolution of the new vessels occurred following treatment in both groups (Schulenberg and Hamilton, 1979). A larger series published by Blankenship reported complete optic disc neovascular regression following treatment occurring in 56% of eyes treated by a krypton red laser and in 67% which had argon blue-green photocoagulation (Blankenship et al, 1989).

It may be concluded from these studies that the wavelength of emission of the photocoagulation device is not relevant to the effectiveness of therapy. All that is required is the ability to produce a lesion in the outer retina. The present study with the infrared diode laser has a relatively short review period. It is therefore difficult
to derive firm conclusions from diode laser treatment of proliferative diabetic retinopathy. The underlying metabolic abnormality is complex and may continue to exert an effect on the retina despite apparently successful laser photocoagulation. It is clear, however, that historical comparison with previous trials using argon and krypton lasers does demonstrate similar rates of regression at comparable periods following treatment (Table VI).

With regard to the functional outcome of treatment, there was little observed change in visual acuity following treatment and this is comparable to visual results following treatment with other wavelengths (Table VII).

The mean number of burns applied was 4023, with a maximum of 12,094. This is higher than that recommended by the DRS, which stated that 1200 burns reduced the risk of severe visual loss in patients. There are two reasons why the number of burns used in the present study was higher than the DRS recommendation. First, the aims in the present study, which were consistent with current practice in the United Kingdom are different from those of the DRS. An attempt was made to effect total neovascular regression, or fibrosis and thus eliminate the risk of haemorrhage, or traction retinal detachment. Thus it would be predicted that a greater number of burns would be applied to the treatment group. The second factor is that certain individuals require more extensive photocoagulation in order to promote neovascular regression. Singerman and Weaver concluded that the application of 2000-3000 burns to the eyes of juvenile onset diabetics with proliferative diabetic retinopathy reduced the risk of severe visual loss to a greater extent than that achieved by the DRS (Singerman and Weaver, 1981). Vine (1985) treated 23 eyes with severe proliferative retinopathy with an average of 7767 burns (range 4296-15,356), but failed to elicit a satisfactory response in 11 eyes. Aylward reported 28 eyes with proliferative retinopathy that was refractory to treatment. The mean number of burns that were applied to this group was 7225 (range 5136-11,513), with total neovascular regression occurring in 89% of cases (Aylward et al, 1989).

A final consideration is that retinal exposure does not necessarily result in a visible lesion. The presence of cataract or of other media opacities, together with variations in the degree of retinal pigment epithelial and choroidal pigmentation may alter the power required for a threshold effect. Variations in the power density at the retina due to the operator's accommodation, the depth of focus of the observation
### TABLE VI
DIABETIC NEOVASCULAR REGRESSION INDUCED BY DIODE LASER
IN COMPARISON WITH ARGON AND KRYPTON PHOTOCOAGULATION

<table>
<thead>
<tr>
<th>LASER MODALITY</th>
<th>REGRESSION OF DISC OR RETINAL NEW VESSELS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIODE (n=47)</td>
<td>33 (70%)</td>
</tr>
<tr>
<td>'ARGON (n=36)</td>
<td>23 (63%)</td>
</tr>
<tr>
<td>'KRYPTON (n=35)</td>
<td>24 (68%)</td>
</tr>
</tbody>
</table>

* Observations made 6 months following argon and krypton therapy and a mean of 11 months following diode photocoagulation

<table>
<thead>
<tr>
<th>LASER MODALITY</th>
<th>POST TREATMENT SNELEN ACUITY WITHIN ONE LINE OF PRE-TREATMENT VALUE *</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIODE (n=47)</td>
<td>44 (92%)</td>
</tr>
<tr>
<td>ARGON (n=36)</td>
<td>22 (62%)</td>
</tr>
<tr>
<td>KRYPTON (n=35)</td>
<td>24 (69%)</td>
</tr>
</tbody>
</table>

* Observations made 6 months following argon and krypton therapy and a mean of 11 months following diode photocoagulation

system (Pomerantzeff and Schepens, 1975) and astigmatism and magnification induced by the contact lens (Mainster et al, 1990) may also result in difficulties in obtaining an optimal lesion.

The number of treatments performed in the present study ranged from 1-8. If PRP was performed, an attempt was made to apply a minimum of 1600 burns in a single session. Doft and Blankenship found that there was a greater incidence of exudative retinal detachment, choroidal detachment and of angle closure in patients given 1200-1290 burns in a single session, compared to those treated over 3 sessions. These effects were transient, and there was no difference in the long-term effects of treatment (Doft and Blankenship, 1982).

Apart from the patient who developed transient cystoid macular oedema (which is a recognised complication of PRP: McDonald, 1985), which occurred following application of 2400 burns in a single session, no complications occurred which were attributable to excessive diode laser therapy. There therefore seems to be no justification for limiting the number of exposures in a single treatment session to 500 or less as suggested by Doft and Blankenship.

8.1.2 EXUDATIVE DIABETIC RETINOPATHY

Diabetes may affect the macula in a number of ways. Ischaemic retinopathy is not amenable to treatment, but oedematous and exudative maculopathy have been shown to benefit from photocoagulation. Several researchers reported that macular therapy with a xenon arc photoeoagulator resulted in closure of microaneurysms and resolution of hard exudates (Spalter, 1971; Rubinstein and Myska, 1974). The efficacy of argon laser therapy to the macula has been confirmed by the results of subsequent studies (Reeser et al, 1981; Early Treatment Diabetic Retinopathy Study Group, 1987). A recent report has found that good vision (defined as 6/12, or better) was maintained over a 10 year period in 60% of eyes treated (Davies et al, 1989).

Currently the preferred technique for the laser treatment of diabetic exudative maculopathy is to focally irradiate microaneurysms with argon laser radiation (Early Treatment Diabetic Retinopathy Study Group, 1987). The underlying concept in such treatment is that closure of these discrete sources of leakage result in eventual resorption of exudates. There are few clinical studies of krypton radiation for such treatment because of the assumption that poor absorption of red laser light in retinal
blood vessels will not result in a therapeutic effect.

In the present study the use of an infrared system correlated with a protocol demanding focal irradiation of microaneurysms may seem illogical, as even less radiation at 810 nm will be absorbed within microaneurysms than at krypton red (647 nm). In argon laser irradiation, if the microaneurysm is large then significant amounts of energy will be focally deposited within the abnormal vessel and the resulting thermal gradients may produce an acute thrombosis. Clinically this is frequently observed as the vascular lesion changes in colour from red to greyish white. In diode treatment the transparency of the vascular lesion to this wavelength precluded the generation of significant thermal disturbance in the aneurysm and therefore acute spasms or thrombosis were not observed. However at review several weeks post treatment microaneurysms within the areas of focal treatment had resolved together with resorption of exudates.

Recent laboratory studies employing tissue culture techniques on both human retinal pigment epithelial cells and retinal capillary endothelial cells are beginning to demonstrate possible biochemical mediators which induce beneficial tissue responses secondary to photocoagulation (Glaser, 1980; Wong et al, 1987). Such factors may be relatively acute such as relating to opening of the blood retinal barrier or death of pigment epithelial cells (Marshall et al 1984), or may be somewhat delayed and depend upon a body of pigment epithelial cells proliferating (Glaser, 1988). In the former case, newly proliferated capillary endothelial cells may result in retinal vessels with a lower permeability and therefore less leakage of plasma constituents, while in the latter the newly formed retinal pigment epithelial cells may increase the removal of fluid from the retina.

Proliferating retinal pigment epithelial cells have also been shown to be correlated with the presence of factors in the vitreous which are seen to inhibit retinal vascular endothelial cell division in vitro and may play a role in the effect of panretinal ablation (Glaser, 1988). From our observations and these laboratory studies it seems that much of the beneficial effect of photocoagulation in retinal vascular disease derives from processes dependent upon energy deposition in the retinal pigment epithelium rather than in retinal vessels themselves. If this is the case then the match of emission wavelength of clinical lasers in relation to the haemoglobin absorption spectra is relatively unimportant.
A recent clinicopathological study tends to confirm the concept that closure of microaneurysms is not due to direct absorption of laser energy within the lesion. Wallow performed histological examination on a human retina, that had been given focal photocoagulation for exudative diabetic retinopathy. It was found that the majority of retinal burns involved the retinal pigment epithelium and photoreceptor layer. In all but a few heavy burns, there was sparing of the inner nuclear layer, within which microaneurysms tend to be located. It was observed, however that focal treatment had resulted in successful closure of many of the microvascular abnormalities (Wallow and Bindley, 1988). It therefore appears to be likely that the current protocol in relation to focal macular therapy demands power levels in excess of those necessary to produce the therapeutic effect.

8.1.3 RETINAL VEIN THROMBOSIS

The risk of neovascularisation following retinal vein thrombosis seems to be positively correlated to the degree of retinal ischaemia. Branch retinal vein occlusion (BRVO) tends to be complicated by preretinal or papillary new vessel formation; central retinal vein thrombosis is complicated by rubeosis iridis and secondary glaucoma. Posterior segment neovascularisation is relatively uncommon following central vein thrombosis (Magargal et al, 1981).

The beneficial effects of photocoagulation in treating neovascularisation complicating BRVO have been firmly established. The Branch Vein Occlusion Study Group discovered that photocoagulation reduced the risk of neovascularisation in affected eyes and that treatment would reduce the risk of vitreous haemorrhage in eyes with established neovascularisation (Branch Vein Occlusion Study Group, 1986). Magargal performed argon laser therapy on 75 cases of proliferative BRVO and caused neovascular regression in the majority of eyes treated, with an 89% success rate in preventing vitreous haemorrhage (Magargal et al, 1986). Archer carried out argon laser treatment on 50 eyes with branch vein thrombosis complicated by preretinal or papillary neovascularisation. He reported total neovascular regression in 42 of 48 eyes with preretinal new vessels and in 17 of 21 eyes with papillary neovascularisation (Archer and Michalopoulos, 1981).

A similar success rate has also been demonstrated in relation to red laser light from krypton lasers. Roseman performed krypton red photocoagulation on 5 eyes with retinal or optic disc neovascularisation complicating BRVO. Total regression of
neovascularisation was observed in all the eyes treated (Roseman and Olk, 1987). The studies have all demonstrated that regression usually begins within a few weeks following laser treatment and that there is a low incidence of recurrence. The mechanisms by which laser treatment exerts its beneficial effect are not known. It has been speculated that photocoagulation may work by destroying ischaemic retina and thus a possible source of angiogenic factor (Magargal, Donoso et al, 1982).

Given the temporal basis of this therapeutic effect and that our average follow up time was 12 months we can draw significant conclusions from our 11 patients suffering from branch vein thrombosis. The diode laser emission was in the infrared and the clinical effects in the treatment of neovascularisation appear exactly comparable to those previously observed with the argon blue-green and the krypton red laser.

None of the patients treated with the diode laser for BRVO had any significant level of visual loss due to macular ischaemia, or oedema. It was therefore not possible to assess the efficacy of diode laser treatment for macular oedema that has been claimed for argon laser treatment (Finkelstein, 1986).

The efficacy of prophylactic panretinal photocoagulation in the treatment of central retinal vein occlusion (CRVO) is well documented. Magargal treated 100 eyes with ischaemic CRVO with argon laser panretinal ablation. Only 3 eyes developed early iris neovascularisation and none of the eyes developed neovascular glaucoma (Magargal, Brown et al, 1982). Laatikainen has successfully treated established rubeosis with photocoagulation therapy (Laatikainen et al, 1977). Although the number of patients who had been treated for central vein retinal occlusion with the diode laser was small, the observed resolution of rubeosis following treatment and the absence of onset of thrombotic glaucoma in any eye were encouraging results.

### 8.2 GLAUCOMA

It is difficult to draw clear-cut conclusions from this study, due to the small size of the treatment group and the limited period of review. Historical comparisons may be made with results from previous studies, in order to gain some indications of the efficacy of diode laser trabeculoplasty compared with other laser modalities.

Lasers were initially employed to create small drainage fistulas in the trabeculum and thus increase outflow of aqueous. This procedure was termed "laseropuncture" and was first reported by Krasnov, who used a Q-switched ruby laser.
A similar technique in which argon lasers were used was reported by Hager (Hager, 1973) and Worthen and Wickham (Worthen and Wickham, 1973). The treatment parameters implicit in argon laser treatment required relatively high power exposures of 1-3 watts, with exposure durations of up to 3 seconds. This tended to result in anterior segment inflammation, with eventual formation of anterior synechia and poor long-term control of intraocular pressure.

The technique of laser trabeculoplasty (LTP) for the treatment of uncontrolled glaucoma was first described by Wise and Witter (Wise and Witter, 1979). Their treatment protocol described applying 100 burns with an argon laser to 360 degrees of the trabecular meshwork. They recommended treatment parameters of a spot size of 50 microns, a pulse duration of 100 ms and a power of 1-1.5 watts. This resulted in less energy being delivered to each individual area of the trabeculum than had occurred with the previous technique, with the production of partial thickness thermal lesions, rather than full thickness holes.

In the pilot study of Wise and Witter, the mean reduction in IOP at 3 months following treatment was 10.29 mm Hg and a subsequent report confirmed these early favourable findings (Wise, 1981). LTP has since become an established treatment modality, with several studies demonstrating its effectiveness (Schwartz et al, 1981; Pollack et al, 1983).

The treatment protocol for LTP has remained essentially unchanged, although initial treatment is now directed to 180 degrees of the angle, in order to reduce the degree of acute post-treatment elevation in IOP, (Thomas et al, 1982).

Although LTP is usually performed with an argon laser, a similar ocular hypotensive action has been demonstrated with lasers emitting at other wavelengths. Spurney reported performing laser trabeculoplasty using a krypton red (647 nm) or krypton yellow laser (Spurney and Lederer, 1984). There was a mean reduction in IOP of 9.6 mm Hg following krypton red therapy and of 7.0 mm Hg after krypton yellow treatment.

A study in which the effects of LTP were compared using a cw-neodymium YAG (1064 nm) laser and an argon blue-green laser demonstrated similar therapeutic effects, although the short pulse duration of the YAG laser (20 ms) rendered the results not strictly comparable (Belgrado et al, 1988).
Table VIII compares the results of the present study with those reported in previous trials at up to 2 months following treatment. It shows that the early therapeutic effects of LTP are similar and that they do not appear to be dependent on the wavelength of the laser employed; although there is some indication that diode infrared irradiation tends to effect a greater early reduction in pressure than argon blue treatment.

The precise mechanism for the pressure-lowering effect of LTP is unknown. A more detailed discussion is presented in section III, but briefly, one theory suggests that photocoagulation results in contraction of trabecular fibres, which opens Schlemm’s canal by drawing the attached trabecular fibres inward towards the anterior chamber (Weber et al, 1983). Another proposes that laser irradiation causes degenerative decay of the trabecular fibres, with a secondary widening of the intertrabecular spaces (Van der Zypen and Fankhauser, 1984). Whatever the mechanism of action, it is agreed that the beneficial effect of LTP is to cause a decrease in resistance to aqueous outflow (Brubaker and Liesgang, 1983) and an improvement in aqueous outflow facility (Schwartz et al, 1980; Wilensky and Jampol, 1981). This then results in an ocular hypotensive effect. There is also evidence to suggest a more complex biological response to irradiation, with an increase in trabecular cell division, which may also influence the outflow facility (Bylsma et al, 1988 (I) and (II)).

The observation of a comparable hypotensive effect of diode laser trabeculoplasty with treatment using lasers of other wavelengths implies a similar mode of action. The deeper penetration of infrared into the relatively poorly pigmented trabeculum compared with argon blue was observed in the histological study. It may be that this results in a more marked effect on intraocular pressure, by involving a larger volume of tissue in the initial damage process. This would lead to secondary responses such as a greater degree of opening of the trabecular spaces, or the promotion of more widespread division of those trabecular cells which may play an active role in aqueous outflow (Bylsma et al, 1988 (I) and (II)). The validity of this speculation awaits the results of further investigations.

The desired visible end point of a trabecular exposure was a mild blanching of the pigmented portion of the trabeculum. This was based on the responses noted during the histopathological study. Gas bubble formation was not a feature of any
### TABLE VIII
**MEAN REDUCTION IN IOP FOLLOWING DIODE LASER TRABECULOPLASTY IN COMPARISON WITH TREATMENT WITH OTHER LASERS**

<table>
<thead>
<tr>
<th>LASER MODALITY</th>
<th>REDUCTION IN IOP AT 2-4 WEEKS (mm Hg)</th>
<th>REDUCTION IN IOP AT 4-6 WEEKS (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIODE</td>
<td>10.2 (n=20)</td>
<td>9.2 (n=20)</td>
</tr>
<tr>
<td>ARGON</td>
<td>6.9 (n=26)</td>
<td>9.7 (n=34)</td>
</tr>
<tr>
<td>ARGON</td>
<td>4.0 (n=61)</td>
<td>5.5 (n=61)</td>
</tr>
<tr>
<td>cw.Nd-YAG</td>
<td>6.2 (n=33)</td>
<td>6.3 (n=33)</td>
</tr>
</tbody>
</table>


reaction. This may be related to the characteristics of the tissue response to infrared irradiation, in that the dissipation of energy over a greater path length results in a lower possibility of phase changes, or of explosive tissue disruption. Alternatively, it may be due to the powers selected being below the threshold required for gas bubble formation.

It is a feature of the treatment protocol of several series that gas bubble formation should be caused, as part of the end point (Schwartz et al, 1981; Wilensky and Jampol, 1981). The rationale for this has never been satisfactorily explained. Indeed, there is some evidence that it has an adverse effect on the eye. It is recognised that LTP is often accompanied by a transient rise in intraocular pressure (Thomas et al, 1982; Weinreb, et al, 1983 (I)). This phenomenon may put an eye which is already compromised at risk of further loss of visual field (Thomas et al, 1982; Levene, 1983).

The Glaucoma Laser Trial examined the acute effects of argon laser trabeculoplasty on intraocular pressure. They found a strong association between pigmentation of the trabecular meshwork and the likelihood of a rise in IOP. It was also noted that those eyes in which greater than 80% of the burns resulted in bubble formation had a greater tendency to a rise in pressure (The Glaucoma Laser Trial, 1989). An excessive tissue response, due to selecting an excessively high power thus seems to exacerbate the risk of a potentially dangerous increase in IOP. There is histological evidence for this. Glaucoma has been produced in the eyes of monkeys in which the entire trabecular meshwork has been irradiated with a laser (Gaasterland and Kupfer, 1974). Other studies have found evidence of accumulation of cellular debris within trabecular spaces immediately following irradiation (Melamed et al, 1985; Rodrigues et al, 1982). The reduction in outflow which then occurred would then provide an explanation for a rise in IOP following therapy.

A reduction in the amount of energy applied to the trabeculum may reduce the post-treatment pressure rise (Rouhiainen et al, 1987). Various pharmacological strategies to reduce the incidence of a rise in IOP, such as prophylactic therapy with acetazolamide have also been adopted with some success (Brooks et al, 1987; Metcalfe and Etchells, 1989).

The present study with the diode laser found no acute rise in IOP following therapy in any of the eyes treated, even in those eyes with deeply pigmented
trabecula, for example in black patients. As the desired reaction was to produce a mild blanching of the trabecular meshwork with each burn and bubble formation was not a feature of the exposures, it seems clear that the lesions were only just above threshold. There would then be a reduced likelihood of excessive damage to trabecular fibres and of obstruction to aqueous outflow. One final contributory factor may be that in diode irradiation, the diffuse path length over which absorption takes place may result in a more homogeneous tissue response and avoid any coagulated surface lamination which could contribute to outflow obstruction. The mildness of anterior segment inflammation following therapy may also be related to the lower powers employed in treatment.

Without a detailed knowledge of the mechanisms underlying laser trabeculoplasty, it is difficult to optimise the procedure, but clearly the beneficial effects of laser trabeculoplasty do not depend upon excessive irradiation of the trabeculum. One study treated patients with argon LTP, with one group being treated with 100 burns at 1 W, and the other group being treated with 65 burns at 850 mW. No significant difference was found in the rate of success for each group (Fink et al, 1988). Tissue culture experiments have been performed in which cat trabecular meshwork was irradiated with an argon laser at power settings of 300 mW and at 1000 mW, with no differences being found in the rate of induced cell division between the 2 groups (Bylsma et al, 1989).

The powers used in the present study were of the order of 1 W and therefore similar to those used with argon LTP. However, the lower absorption of infrared (810 nm) within melanin compared with that of argon blue-green radiation (488-514.5 nm) (Gabel et al, 1977), implies less energy deposition with diode irradiation at comparable power levels. This should lead to less tissue damage with diode exposures, but clearly a similar clinical response was observed.

Another controversial topic, is the extent of trabecular irradiation that is necessary to obtain optimal results. The established protocol of treatment to 180 degrees of the trabeculum appears to be based on successful precedent, rather than on scientific investigation. A significant reduction in intraocular pressure has been achieved in studies in which there has been treatment to 90, or even 45 degrees of the trabeculum (Klein et al, 1985; Schwartz et al, 1983; Weinreb et al, 1983 (II); Wilensky and Weinreb, 1983). Evidence of this nature may result in revised
treatment protocols which promote a beneficial response, and yet obviate the occurrence of excessive tissue destruction.

It was interesting that in several patients, a reduction in pressure was noted in the contralateral, untreated eye. This was described by Fink, in his series of 34 eyes. He found an average decrease of 4.2 mm Hg in the untreated eyes, compared with 9.9 mm Hg in the treated eyes (Fink et al, 1982). This raises the possibility of the influence of neurogenic factors, or systemically disseminated chemical mediators.

The limited review period of the present series does not allow any conclusions to be drawn regarding the longer term efficacy of diode laser trabeculoplasty. Previous studies of argon LTP report a maximum pressure lowering effect occurring between 2 months (Schwartz et al, 1985) and 6-9 months following treatment (Fink et al, 1988).

It is well documented that there is a gradual reduction of the hypotensive effect of LTP with time. Grinich observed that of patients in whom LTP was initially successful, the failure rate was approximately 10% per year (Grinich, 1987). Schwartz calculated that the median time before intraocular pressures increased to greater than 21 mm Hg following treatment was 60 months for white patients and 12 months for blacks, resulting in an overall success rate over 5 years in the 82 eyes studied of 46% (Schwartz et al, 1985). Wise reported more favourable results in a 10 year review of his initial group of patients treated with LTP. The intraocular pressure was maintained within normal limits in the majority of patients treated, although about one third of those who were followed up for 6 years, or more were found to have required filtering surgery (Wise, 1987).

Opinions differ on the effects of repeat LTP (i.e. therapy to an area already treated). Fink found that repeat LTP was successful in only 25% of patients treated (Fink, et al, 1988). A similar rate of success for retreatment has been reported by Brown and by Sarita (Brown et al, 1985; Sarita et al, 1984). This differed from the results of Jorizzo, who observed a sustained hypotensive response to repeat argon laser trabeculoplasty in 8 of 11 eyes treated (Jorizzo et al, 1988). They suggest that more favourable results can be obtained provided that the initial treatment does not irreversibly destroy the trabecular meshwork and its regenerative capacities. This is therefore a further argument in favour of selecting a laser power which produces only a mild response.
Apart from the reduced long-term ocular hypotensive action of LTP, there is also a question regarding its ability to prevent visual field loss. Pohjanpelto found that 20% of patients treated with argon LTP continued to have progressive field loss (Pohjanpelto, 1983). Fink described 8 of 11 eyes showing continued field loss despite the pressures being below 22 mm Hg (Fink et al, 1988).

The ability of laser trabeculoplasty (as with other treatment modalities) to slow the sight-threatening consequences of glaucoma has still not been fully established. The present study has however shown that diode laser trabeculoplasty is effective in control of intraocular pressure and that it is a treatment with minimal ocular side effects. It thus represents a viable adjunct, or replacement to pharmacological therapy and a means of deferring drainage surgery, with its attendant risks of sight-damaging consequences (Watson and Grierson, 1981).

8.3 USE OF INSTRUMENTATION

In this report of the use of diode lasers in the treatment of clinical conditions, in addition to specific information being gained on its therapeutic efficacy, valuable data has been collected on the ergonomic aspects of these systems when in routine clinical use.

The pilot studies were constructed to investigate the therapeutic potential of the diode laser and also to allow a measure of comparison with conventional lasers from the view point of ease of utilisation and patient tolerance.

Both versions of the laser were reliable, no malfunction being encountered during the period of study. Their portability and simplicity of use conferred a flexibility of operation not allowed with current laser systems, which are restricted by reason of their size, power requirements and cooling facilities. These factors, together with the projected lower capital and maintenance costs of diode lasers will allow their use outside the major ophthalmic centres and also enable deployment in those third world countries which have at present only a few ophthalmic lasers to serve whole populations.

The absence of the need for a safety shutter is a novel feature of the diode laser. In current laser apparatus it is not possible to view the formation of retinal lesions during exposure. Recent reports of failure of the shutter during argon laser therapy resulting in at least one instance in retinal damage to the surgeon highlight the disadvantages of the necessity for a safety system that relies on moving parts,
with the potential for malfunction (Dept of Health, 1988).

The hand held version proved effective in producing retinal burns and in treating retinal vein occlusions, although comparatively few patients were treated. The relative disadvantages of limited field of view, reduced illumination and unsuitability for macular photocoagulation tends to mitigate against it gaining widespread acceptance and are similar to many of the criticisms of the ergonomics of the early ruby laser ophthalmoscopes. There are however certain situations where it could be of advantage. Patients who for reasons of physical disability cannot sit at a slit lamp microscope could be treated while lying on an examination couch. Those patients who would need a general anaesthetic due to exceptional intolerance of laser treatment, or for reasons of extreme youth might also be suitable for this mode of therapy. Such hand-held systems may also be of value in the third world where the absence of slit lamp systems in field conditions may result in patients being denied therapy.

The advantages conferred by the slit lamp model in terms of retinal imaging and illumination and ease of targeting allow a greater versatility of use in a variety of conditions, including macular photocoagulation, and in the presence of significant media opacities. The visibility of the red aiming beam was satisfactory apart from in the presence of intravitreal haemorrhage, when the retinal view itself tended to be compromised.

In conclusion, it was found that an experimental diode laser system mounted on a conventional Haag Streit slit lamp was extremely easy to use and was very reliable. To date the clinical results are compatible with those obtained from the use of conventional laser systems.
SECTION V
CONCLUSIONS ARISING FROM THE FINDINGS OF THE PROJECT
CHAPTER 9
OPHTHALMIC DIODE LASERS- CURRENT WORK AND FUTURE PLANS
9.1 DISCUSSION OF THE STUDY FINDINGS

The results obtained have achieved the principal aims of the three major phases of the study:

(a) Laser design and instrumentation

It has proved possible to construct an ophthalmic diode laser, which allowed good visualisation of the target tissue, accurate placement of the laser burn and which was reliable and easy to use.

Loss of power following transmission of laser energy through the optics of the device was low. The dielectric mirror proved to be safe and satisfactory in restricting the reflection of harmful radiation towards the operator, while allowing the transmission of visible radiation.

The theoretical ergonomic advantages of diode lasers with regard to their compactness, efficiency and reliability have been confirmed throughout the study.

(b) Biophysical studies

These studies demonstrated that diode laser irradiation of ocular tissue resulted in lesions that were similar to those produced by other wavelengths, with the primary site of damage being the melanin of the retinal pigment epithelium and thus the presumed source of any beneficial effects must reside in this layer. This provided sound theoretical grounds for believing that diode laser therapy at 810 nm would be clinically effective. It also provided more evidence against the concept of the selective effects of wavelength and tissue specific damage in clinical practice. There were two potential advantages over argon blue-green. The first was in relation to the minimal absorption of infrared radiation within xanthophyll, with the implication of non-therapeutic damage to the nerve fibre layer. The second was the effective removal of the possibility of photochemical damage due to the blue light hazard.

This phase of the study also identified two aspects of diode laser irradiation which could have disadvantages in clinical practice:

(i) The lower absorption of infrared within melanin compared with shorter wavelengths necessitated generally higher powers being used to produce a threshold lesion. Although adequate burns were obtained in the histological studies, there remained some uncertainty as to whether this success could be reproduced in clinical practice.
(ii) While poor absorption within haemoglobin could be of advantage in preventing accidental damage to a retinal vessel during therapy, it could result in difficulties where it was necessary to treat vascular elements distant from a melanin-containing structure, for example retinal microaneurysms.

(c) Clinical trials

The pilot clinical studies demonstrated that within the review periods of the trials, infrared laser photocoagulation is effective in the treatment of a wide range of retinal vascular conditions and for the treatment of glaucoma.

There did prove to be adequate power available in the units employed to produce clinically satisfactory burns.

The treatment of exudative maculopathy also demonstrated that the poor absorption of infrared radiation within blood did not preclude the successful closure of microvascular abnormalities. The implication of an indirect mechanism of action runs counter to accepted tenets, which usually require a radiant energy sufficient to thrombose the lesion directly, with the danger of damage to adjacent normal structures. The present findings provide persuasive evidence to the contrary and suggest that regardless of wavelength, the visible end-point of treatment need only be a mild blanching of the retinal pigment epithelium.

The principal disadvantage of the diode laser was that irradiation resulted in a generally higher level of discomfort than has been noted with argon laser therapy. However, only a small number of patients complained of significantly painful sensations during treatment and only two felt the need for retrobulbar anaesthesia. My clinical impression is that diode laser therapy provokes less discomfort than krypton red irradiation. It may be that the relative silence of the treatment and the lack of a visible light during laser exposure tends to counterbalance the adverse effects of any painful stimuli.

9.2 CURRENT STUDIES

a) Clinical trials have been implemented to compare the efficacy of diode and argon laser photocoagulation for proliferative diabetic retinopathy (Appendix III) and for chronic open angle glaucoma. In each study, patients have been randomised to treatment with either diode infrared, or argon blue-green irradiation. With standardisation of the selection criteria for inclusion, and of the treatment protocols, it is anticipated that analysis of the results will allow a
statistically valid comparison of the effectiveness of the two laser modalities.

b) The influence of infrared radiation on visual function in comparison with treatment with blue-green is being examined. Psychophysical tests are being performed on a series of patients with proliferative diabetic retinopathy before and following panretinal photocoagulation. Standard tests are being performed to measure distance and near visual acuity, colour vision and visual fields. In a parallel study, the effects of diode and argon therapy on colour vision is being measured using the colour contrast sensitivity test that has been developed by Arden and associates (Gunduz, 1989). This work will test the hypothesis that infrared therapy does not have the adverse effects on blue perception that has been observed with short wavelength radiation.

9.3 FUTURE PROJECTS

a) A project is being devised to investigate the use of indocyanine green (ICG) in diode laser therapy. As the peak absorption of ICG (805 nm) is close to the emission wavelength of diode lasers (Puliafito, 1988; Destro and Puliafito, 1989), enhanced absorption of laser energy within disciform membranes may be effected by prior injection with ICG. Thus a lower radiant energy would be required to produce a threshold lesion and there would be less risk of non-therapeutic damage to adjacent structures.

b) Alternative delivery systems which incorporate laser diodes may be deployed in the future. Such alternative modalities include a laser indirect ophthalmoscope, a fibre optic endoscope and transscleral photocoagulation of the retina and the ciliary body using contact probes. The transmission properties of infrared radiation with respect to the sclera have already been established with the cw-YAG laser (Fankhauser et al, 1986) and initial studies have suggested that infrared diodes may be similarly effective (Okamoto et al, 1990).

9.4 CONCLUSIONS

The inherent physical advantages of diode lasers in comparison to current systems, together with these promising early clinical results suggests that semiconductor lasers will eventually supersede ion lasers. The advent of diode laser photocoagulators therefore has profound implications for ophthalmic practice in the next decade.
SECTION VI
REFERENCES


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APPENDIX I

(A) Explanation and consent form for patients with diabetic retinopathy, or retinal vein thrombosis who are entering the diode laser clinical pilot studies.

(B) Pro formas used in relation to data collection in the clinical trial of diode laser treatment of proliferative diabetic retinopathy.
EXPLANATION AND CONSENT FORM FOR SUBJECTS ENTERING A TRIAL OF THE EFFECTIVENESS OF THE DIODE LASER

You are at present under the care of the Ophthalmic department of this hospital for the treatment of a condition which affects the retina. One of the established forms of treatment is therapy to the retina using a device called an "argon laser".

A new form of laser, known as a diode laser has been developed for the treatment of various eye conditions. Work which has been carried out so far promises beneficial effects from the use of this laser and there are several potential advantages over the argon laser. However, more information needs to be gained on the efficacy of this laser and you are being asked to take part in a clinical trial to assess this.

The new form of laser therapy is not expected to produce any side effects other than those that occasionally occur with conventional laser therapy. One such side effect which you may notice is some discomfort at times during the treatment session. If you should be experiencing a level of discomfort which you feel to be unacceptable, treatment will be stopped and before completion of therapy, medication will be given, either in tablet form or as an injection in order to render the therapy pain-free.

There will be a number of tests which will need to be performed prior to and following treatment. One of them is a standard investigation, called fluorescein angiography. This involves an injection, followed by retinal photography. The other tests only require a degree of patience and concentration.

In order for the investigations, treatment and the post-treatment evaluation to be carried out, several trips to St Thomas' Hospital, or Moorfields Eye Hospital will need to be made.

CONSENT

I, (name) _______________________________
of (address) ____________________________
consent to retinal treatment with a diode laser to the ____ eye, the nature of which has been explained to me. Any questions which I have wished to ask have been answered to my satisfaction. I understand that I may withdraw from the investigation at any stage without giving any reason for doing so and that this will not in any way affect the care that I receive as a patient.

SIGNED
Participant _____________________________ Date _________
Doctor who gained consent for participation:
____________________________ Date _________

Witness (where appropriate):
____________________________ Date _________
**FORM 1 PREOPERATIVE REPORT**

<table>
<thead>
<tr>
<th>Patient Last Name</th>
<th>F.I. M.I.</th>
<th>Patient ID Number</th>
<th>Log No.</th>
<th>Investigator Last Name</th>
<th>F.I. M.I.</th>
<th>Institution</th>
</tr>
</thead>
</table>

**DIODE LASER CLINICAL STUDY**

<table>
<thead>
<tr>
<th>Operative Eye (check one only)</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser Therapy (check one only)</td>
<td>Diode</td>
<td>Argon</td>
</tr>
</tbody>
</table>

**LIGIBILITY CRITERIA**

<table>
<thead>
<tr>
<th>(Check one)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Has clinically obvious disc vessels or neovascularization elsewhere along the vascular arcades.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Has no, or minimal, lens opacities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 If maculopathy is present, visual acuity is 6/18 or better</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Has had no previous photocoagulation therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Absence of conditions that would prevent adequate visualization of the treatment site.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Absence of conditions that would prohibit transmission of laser beam.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Is willing and able to adhere to study protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Will return for follow-up visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Has signed informed consent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All items must be answered "yes" to permit study participation.

**HISTORY-OPERATIVE EYE**

<table>
<thead>
<tr>
<th>(Specify)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Surgical History — No previous ophthalmic surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Cataract extraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. IOL insertion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Corneal surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Glaucoma surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Retinal detachment surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Other (specify)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MEDICAL HISTORY**

<table>
<thead>
<tr>
<th>(Check one)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diabetes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Year diagnosed</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>2. Is patient insulin dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Other (specify)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please Review Form to Ensure All Items Have Been Completed.

Physician Signature

Date / /
**FORM 2 TREATMENT REPORT**

**DIODE LASER CLINICAL STUDY**

<table>
<thead>
<tr>
<th>Patient Last Name</th>
<th>F.I.</th>
<th>M.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient ID Number Log No.

Investigator Last Name F.I. M.I.

<table>
<thead>
<tr>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Treatment Date**

<table>
<thead>
<tr>
<th>D</th>
<th>M</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Temples MUST BE COMPLETED. MISSING OR INCORRECTLY COMPLETED ITEMS WILL REQUIRE ADDITIONAL FOLLOW-UP.**

**TREATMENT PARAMETERS**

- **Treatment pattern:** (Check one)
  - Local ablation ...........................................  □  1
  - Sector ablation ...........................................  □  2
  - Pan-retinal ablation ....................................  □  3

- **Treatment number:**
  - One .....................................................  □  1
  - Two ......................................................  □  2
  - Other (specify) ........................................  □  3

- **Duration of exposure** ................................ (sec)

- **Spot size** ................................................ (μm)

- **Laser power** ............................................ (mW)

- **Number of burns/quadrant**

<table>
<thead>
<tr>
<th>Quadrant</th>
<th># of Burns</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL** ........................................................................  □  □

- **Pupillary dilatation (mm)** ................................  □  □

**Completion of Treatment**

8. **Was treatment interrupted prior to completion of therapy?** .................................. Yes □  1  No □  2

   a. **If yes, indicate reason.** (Check all that apply)

   - Laser malfunction ...........................................  □  1
   - Medical problem with patient ..................................  □  1
   - Patient experienced excessive symptoms of discomfort ..................................  □  1
   - Other (describe) ......................................................................  □  1

   b. **If interrupted, was treatment discontinued?** .................................. Yes □  1  No □  2

**IMMEDIATE POSTTREATMENT RESULTS (OPERATIVE EYE)**

9. **Distance vision**

   - Operative Eye
     - Best corrected — 6/ (meters)
       - or check one:
         - Finger counting □  1 □  1
         - Hand movements □  2 □  2
         - Light perception □  3 □  3
         - No light perception □  4 □  4

   - Fellow Eye

10. **Was fundal photography performed?** .................................. Yes □  1  No □  2

    If yes, attach photograph and describe

11. a. **Were there any significant adverse effects?** .................................. Yes □  1  No □  2

    If yes, describe

11. b. **Were additional procedures performed?** .................................. Yes □  1  No □  2

    If yes, specify

Please Review Form to Ensure All Items Have Been Completed.

Physician Signature

Date / /
### FORM 3 FOLLOW-UP REPORT

<table>
<thead>
<tr>
<th>Patient Last Name</th>
<th>F.I.</th>
<th>M.I.</th>
</tr>
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<tbody>
<tr>
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<table>
<thead>
<tr>
<th>Patient ID Number</th>
<th>Log No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigator Last Name</th>
<th>F.I.</th>
<th>M.I.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

**DIODE LASER CLINICAL STUDY**

**Operative Eye**  
* (check one only)  
- Right □ 1  
- Left □ 2

**Laser Therapy**  
- Diode □ 1  
- Argon □ 2

---

### RESULTS

<table>
<thead>
<tr>
<th>Distance vision</th>
<th>Operative Eye</th>
<th>Fellow Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

**Best corrected — 6/ (meters)**  
- or check one:  
  - Finger counting □ 1  
  - Hand movements □ 2  
  - Light perception □ 3  
  - No light perception □ 4

**Field of vision (Goldmann Analyzer)**  
- Mean centripetal constriction (degrees)  
  - Target: V4 □ 1  
  - I4 □ 2  
  - 12 □ 3

**Visible corneal laser damage**  
- None □ 1  
  - (Check all that apply)  
    - Endothelium □ 1  
    - Stromal □ 2  
    - Epithelium □ 3

**Fundal Examination**  
- Absent → Severe

**Posterior vitreous detachment**  
- □ 0 □ 1 □ 2 □ 3 □ 4 □ 5

**Grading of retinopathy:**  
- Haemorrhages and microaneurysm □ 0 □ 1 □ 2 □ 3 □ 4 □ 5

**Safety**

### SAFETY

13. Were there any significant complications noted?  
- Yes □ 1  
- No □ 2

| If yes, indicate:  
<table>
<thead>
<tr>
<th>Check all that apply</th>
</tr>
</thead>
</table>
| Haemorrhage:  
  - Choroidal □ 1  
  - Retinal □ 1  
  - Vitreous □ 1  
| Oedema:  
  - Macular □ 1  
  - Peripheral □ 1  
| Significant Pain (specify) □ 1  
| Other (specify) □ 1

---

Please Review Form to Ensure All Items Have Been Completed:

**Physician Signature**  
- Date / /
APPENDIX II
THE HAMMERSMITH HOSPITAL SYSTEM FOR
GRADING DIABETIC RETINOPATHY
(Oakley et al, 1967)

1) Each standard is a Zeiss retinal photograph (30 degree field), and should only be compared to a similarly defined area of retina.

2) Such defined photographic fields are graded by direct comparison with the standards in the manner described below. A grading for a whole fundus may be arrived at by averaging all the fields studied; if this is done, care must be taken to avoid assessing any part of the fundus more than once.

3) The set of standards comprises 20 Kodachrome transparencies; these enable each of the important features of diabetic retinopathy to be graded into five degrees of severity.

4) In the case of each retinopathy feature, standards A-D enable five grades to be defined as follows:

   Grade 0. . . . . No lesion
   Grade 1. . . . . Less than standard "A"
   Grade 2. . . . . Equal or worse than "A" but better than standard "B"
   Grade 3. . . . . Equal or worse than "B" but better than standard "C"
   Grade 4. . . . . Equal or worse than "C" but better than standard "D"
   Grade 5. . . . . Equal or worse than "D"

5) The five retinopathy features for which standard photographs have been prepared are:

   a) Microaneurysms and haemorrhages
   b) Hard exudates
   c) Peripheral new vessels
   d) Venous irregularities
   e) Retinitis proliferans

   In addition, neovascularisation of the optic disc is graded according to a set of established criteria (vide infra).

6) The following definitions, covering the features themselves and the principles by which their severity are assessed are used:

   a) Microaneurysms and haemorrhages
This includes all "dots and blots" in the retina, but excludes vitreous haemorrhages. The grading is according to the number of lesions present in the field, regardless of their size.

b) Hard exudates

As confluent lesions are common, the area of retina involved, rather than the number of lesions, is used for grading.

c) Peripheral new vessels

All abnormal vascular channels, except those in relation to previously established retinitis proliferans. Grading according to the area of field involved.

d) Venous irregularities

All venous irregularities, including dilatation and segmental irregularities. Grades 1-3 thought to be abnormal. Grades 4 and 5 are reserved for fields in which all the veins present are thought to be abnormal, distinguished from one another by the severity of the abnormality.

e) Retinitis proliferans

Any fibrotic lesion in front of the retina, regardless of its vascular associations and including any detectable diffuse veiling over the retinal surface. Grading according to the area of field involved.

f) Neovascularisation of the optic disc

Grade 1. On disc or <\(\leq\) 1 disc diameter from disc
Grade 2. <\(\leq\) 1 disc diameter from disc in 2 quadrants
Grade 3. <\(\leq\) 1 disc diameter from disc in 3 quadrants
Grade 4. <\(\leq\) 1 disc diameter from disc in 4 quadrants
If >\(\geq\) 2 disc diameters from disc, add one grade

Assessment of optic disc and peripheral neovascularisation was augmented by inspection of the relevant fluorescein angiograms.
APPENDIX III
PROTOCOL FOR A CLINICAL TRIAL TO COMPARE DIODE AND ARGON LASERS IN THE TREATMENT OF PROLIFERATIVE DIABETIC RETINOPATHY

STUDY OBJECTIVES

1. To assess the relative efficacies of infrared diode laser and argon green photocoagulation in the treatment of proliferative diabetic retinopathy.

2. To monitor the relative incidence of laser-related side effects and the effects of photocoagulation on various aspects of visual function.

STUDY DESIGN

The trial will be carried out on diabetic patients presenting to the retinal clinics at one of the five designated centres. Eyes will be randomised to treatment with argon green photocoagulation, or with the diode laser and followed for twelve months during the course of the study. It is suggested there be a minimum sample size of a total of 100 patients in each group. An independent centre will assess the effects of treatment by grading of fundal photographs. At the conclusion of the trial, patients will be returned to the referring clinic for long-term management. Their future progress will continue to be monitored closely.

INCLUSION CRITERIA

a) The patient should be diabetic and aged at least 18.

b) There be clinically obvious disc new vessels, or neovascularisation elsewhere along the vascular arcades (>\(=\) 1/2 disc area, or associated with haemorrhage);

c) The patient should be able to provide informed consent for entry to the trial;

d) The patient should live close enough to the hospitals to be able to attend for up to six out-patient visits.

e) No previous photocoagulation should have been performed.

f) Maculopathy, if present should not reduce visual acuity below 6/18. Previous macular photocoagulation is not a criterion for exclusion.

g) There should be no, or minimal lens opacities.

h) If vitreous haemorrhage is present, it obscures less than 25% of the fundus.

i) No traction retinal detachment.
g) Final selection for the trial will be agreed by one of the supervising specialists.

PRE-TREATMENT EVALUATION

Patients will be randomised to receive either diode, or argon laser photocoagulation. If both eyes of the patient require treatment, one eye will receive argon and the fellow eye will receive diode laser therapy. The best corrected distance visual acuities of the patients (following refraction) will be measured using a standard ETDRS chart (which shall be provided for each centre, if not already available). Visual fields will be measured with a Humphrey 30-2 analyser. Slit lamp biomicroscopy will be performed, together with retinal examination by direct and indirect ophthalmoscopy.

Pre-treatment evaluation will also include fundal photography, using a 30 degree field to obtain a retinal survey. Fluorescein angiography will also be performed. The fundal photographs will be graded according to the Hammersmith classification.

TREATMENT

Eyes with disc neovascularisation will be treated with pan-retinal photocoagulation. The laser used will be either a Keeler Microlase diode laser, or an Argon green laser.

Topical anaesthesia will be applied (although particularly sensitive, or anxious patients may require retrobulbar anaesthesia). Treatment will be performed through a contact lens, either a Goldmann 3 mirror, Rodenstock, or Mainster lens. A total of between 1500-2000 burns will be applied to the retina. Completion of therapy may require several separate sessions. A record will be made of spot size, duration and intensity of the burn. In each form of treatment the aim will be to produce a "mild" retinal burn, i.e. a burn which is just supra-threshold in appearance.

New vessel formation elsewhere in the retina will be treated with either sector photocoagulation or panretinal ablation, depending upon the extent of neovascularisation and the degree of retinal ischaemia.

The patient will be questioned regarding their tolerance of the respective forms of treatment, in relation for example to pain, or dazzle. Excessive symptoms of discomfort will lead to exclusion from the trial.
POST-TREATMENT EVALUATION

A. VISUAL FUNCTION

The patients will be examined at intervals of two weeks, six weeks and twelve weeks following therapy and then at one year following treatment. Visual acuity will be measured at each visit and visual field examination carried out at two weeks and twelve weeks following treatment.

B. FUNDOSCOPY

Clinical examination of the treated fundi will be directed towards evaluation of the retinal burns produced by the diode laser and comparison with those from argon photocoagulation. The presence of any side-effects (for example, choroidal haemorrhage) will be noted. The rate and extent of regression of neovascularisation in the treated eyes will be assessed, together with the results of the various parameters tested.

Fundal photography will be repeated at each visit and fluorescein angiogram will be performed at twelve weeks. If further treatment is deemed necessary, the sequence of post-treatment assessments will be repeated. If the diode laser is found to be having little demonstrable effect in a particular case, consideration will be given to changing to conventional laser therapy. A consultant supervisor will be responsible for such decisions. The post-treatment fundal photographs will be graded by an independent assessor.

C. STATISTICAL ANALYSIS

1) NEOVASCULAR REGRESSION

The appropriate statistical tests will be applied to the data. A 20% difference in neovascular regression in eyes treated with a diode and in those given argon therapy would be considered significant.

2) VISUAL FUNCTION

Any alterations in visual acuity, or fields will be quantified and the appropriate tests of significance applied.

On the basis of the data analysis, it is anticipated that it will then be possible to make a judgement as to the efficacy of the diode laser in the treatment of proliferative diabetic retinopathy in comparison with argon laser therapy.
CENTRES PARTICIPATING IN TRIAL
PARIS: Professor G. Coscas, Dr G. Soubrane
MILAN: Professor R. Brancato
MUNICH: Professor P. Gabel
SWEDEN: Professor P Algvere
LONDON: Mr AM Hamilton, Mr JDA McHugh
APPENDIX IV

PUBLICATIONS RELATED TO THE DIODE LASER PROJECT

The data in this thesis provided the basis of the first publications of the histological and clinical effects of diode laser irradiation in human eyes.


McHugh JDA, Marshall J, ffytche TJ, Hamilton AM, Raven A: Diode laser trabeculoplasty (DLT) for primary open angle glaucoma and ocular hypertension. Accepted for publication, British Journal of Ophthalmology, September, 1990

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CASE REPORT 3

An 81 year old hypertensive lady presented with a left inferotemporal branch retinal vein occlusion. There were several tufts of forward retinal neovascularisation surrounded by areas of intra-gel haemorrhage (figure 7.8 (a) and (b)).

235 burns were applied to the area of ischaemic retina. Power was 500-650 mW, spot size 200 microns and exposure duration 0.5 seconds. Apart from a slight "pricking" sensation the patient reported no adverse symptoms and no other side effects were observed. Eight weeks later, the new vessels had regressed, closure being confirmed on angiography (figure 7.8 (c) and (d)). No recurrence of the vessels has been observed subsequently.

(iv) CENTRAL RETINAL VEIN THROMBOSIS

6 eyes in 6 patients were treated for central retinal vein thrombosis. 5 eyes had established rubeosis irides and 2 of these eyes also had optic disc neovascularisation. The remaining eye had widespread areas of vascular closure on fluorescein angiography, and therefore was considered at risk of development of rubeosis. All of the patients were female. The mean age of the patients was 68 (range 57-75). The mean period of review was 13 months (range 6-19 months).

a) REGRESSION OF NEOVASCULARISATION

There was total disappearance of rubeosis following treatment in 4 of 5 eyes. There was also complete closure of the disc new vessels that had been observed in 2 of these eyes. Partial resolution of rubeosis occurred in the fifth eye. The eye that had been given prophylactic therapy has not developed rubeosis during the period of review. None of the patients has developed rubeotic glaucoma.

b) VISUAL ACUITY

The visual acuity remained unchanged following therapy in 4 eyes and there was a slight improvement in vision in 2 eyes.

c) NUMBER OF TREATMENTS

The mean number of sessions of photocoagulation performed was 1.5 (range 1-2).

d) TREATMENT PARAMETERS

The laser spot size used was either 300 or 500 microns. The pulse duration was varied between 0.20 and 0.50 seconds. The power required ranged from 450 mW to 1.0 W. The presence of extensive areas of retinal and preretinal haemorrhage in