pressure the optic nerve can be protected from further damage (that is the essence of glaucoma treatment today). However, there is nothing really new on the horizon at the moment except perhaps unoprostone 0.15% (Rescula, Sucampo).

Moving away from medical therapies, there are new laser techniques that are looking at improving the effectiveness of treatment of the trabecular meshwork by optimising wavelength selection and the use of ultrasound focussed on the trabecular meshwork (to improve outflow of aqueous from the eye) or on the ciliary body (to reduce aqueous production).

We can offer no guidance on how long or whether any or all of these developments will become available for the management of glaucoma, but it is good to know that so much research is underway.

David J Wright FIAM
Chief Executive

Janice Krushner Memorial Lecture 2011

The use of cyclodiode laser treatment in glaucoma - 17 years of the Nottingham protocol

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Firstly, I would just like to give an update on my history with the IGA. I first came to know about them some about 23 years ago when I was setting up an epidemiological study in Nottingham. In fact it was the first one to perform visual fields on every patient in the UK and the IGA gave me £1,000 towards it. That doesn't sound very much these days does it? But 23 years ago that was actually quite a lot of money and it made that project possible. From that project many years later came the Bridlington Eye Assessment Project, which I had the privilege of directing.

I rather hope that you haven't had a talk on the use of Cyclodiode laser in glaucoma before. We've had one of these machines in Nottingham for 17 years now, about the same time as Moorfields Eye Hospital has had theirs. However, we have our own way of doing things and this is known as the Nottingham protocol, so here we go.

For those of you who don't know what Cyclodiode is, it is a laser treatment of the ciliary body (the part of the eye that makes the aqueous) that is aimed at reducing aqueous production and thereby lowering intraocular pressure which is, of course, the aim in many patients who have glaucoma if not most of them.

What other options have we got for lowering intraocular pressure? We have options with medications, both with eye drops and, occasionally, tablets, with laser treatments of the trabecular meshwork known as laser trabeculoplasty originally with the Argon laser and more recently with selective laser trabeculoplasty. We have surgical approaches which may be penetrating as in trabeculectomy or non-penetrating as in deep sclerectomy or visco canalostomy. We have the use of shunt devices, perhaps better known as tubes, and then we have what I am going to talk about today, ciliary destruction. Ciliary destruction was originally done with cyclocryotherapy which is a freezing treatment, but it has now been completely superseded by the use of cyclophotocoagulation.

When we are talking about treating patients with glaucoma we have an overall view of what we are trying to achieve. Many people have attempted to put this into a phrase which I think is particularly relevant for treatment of difficult patients and it is the difficult patients that we have to treat with cyclophotocoagulation. It is 'to prevent significant loss of quality of life from glaucoma or its management within the patient's expected lifespan'. This is important because the management that we attempt in an effort to improve the patient's lot can actually lower their quality of life. In complex glaucoma we need to maintain quality of life by preventing further visual loss either from the visual field (which is primarily through intraocular pressure control), by preserving the visual acuity and we need to reduce the medication load, whether that be by drops or by tablets, because all medications have side effects and people often have a better quality of life without them (if they can do without them). We also need to minimise the number of hospital visits if at all possible. Sometimes that is not possible, but if we have a treatment that can do this, that is our ideal treatment. Now I am not saying that cyclodiode laser treatment achieves all these aims, but in some patients it does go a long way towards them.

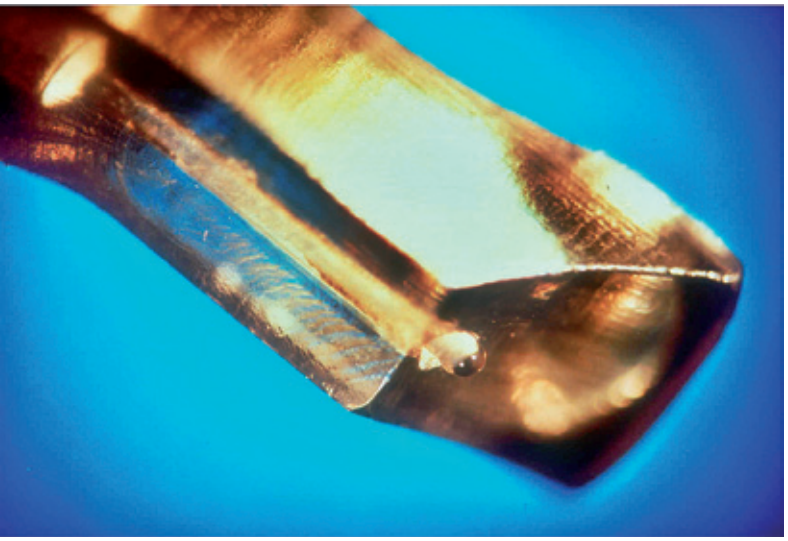
If we look back to the history of destroying the ciliary body, it goes back to the days of the cyclocryotherapy that I mentioned before, and this was really a last resort treatment to lower pressure in hopeless eyes with very high pressures that were very painful. It had a high rate of complications. The

main complication was that it actually worked too well, it would lower the pressure so far that the eye could not maintain its normal shape and it shrivelled up. As a result of that and of pain, in other words, unsuccessful treatment, many eyes had to be removed. From that came the first laser treatment of the ciliary body and this was known as cycloyag, and I think what's a YAG? Well a YAG is a Yitrium Aluminium Garnet laser. Now these lasers came out in 1984 and it was a very exciting time in ophthalmology because for the first time we could actually cut things within the eye without a scalpel. Now, one of the machines had what was called a 'free running mode' which meant that it could produce an entire energy level. People tried this as a treatment for glaucoma by destroying the ciliary body and it was better than cyclocryotherapy, but the success rates were not ideal, and they still had the problem of a significant proportion of patients losing their sight altogether for the same reasons as with cyclocryotherapy. These treatments never really caught on because of their relatively high complication rates. Perhaps they would have continued if it hadn't have been for the cyclodiode, which is a similar idea but with a different wave length of laser and it is the wave length that is important in allowing us to treat externally through the sclera (through the white of the eye) to the pigmented ciliary body and to selectively destroy the cells that produce the aqueous.

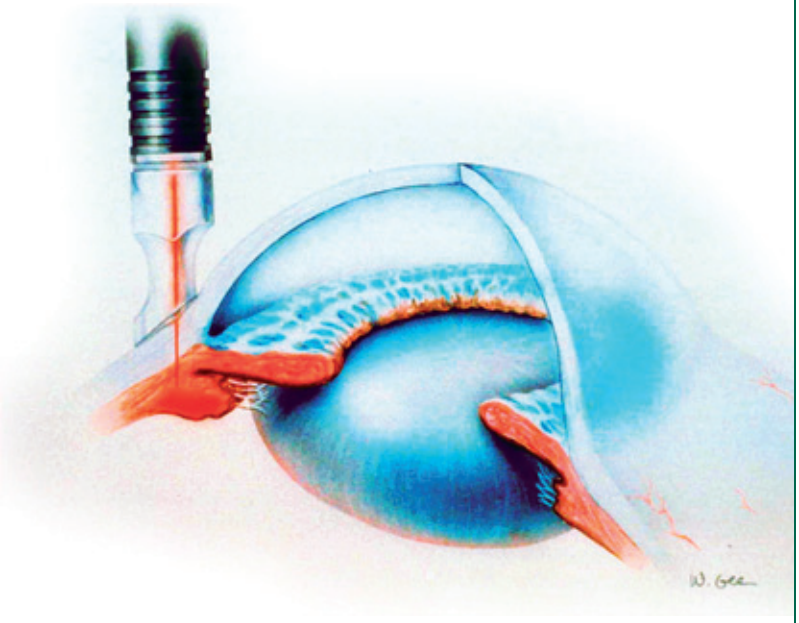
Both we, in Nottingham and Moorfields acquired a cyclodiode laser in 1994 and it is still working perfectly nearly twenty years later.

In a survey that we did in the early 2000's we found that the use of these machines had become very popular and that 92% of UK glaucoma specialists were using the cyclodiode.

The treatment protocol that we have in Nottingham (and that we have kept to for the vast majority of eyes) is that we restricted our treatment to only 14 shots. We picked an energy level and a time period that we thought was likely to be the most effective and we stuck with it. It was a bit like a recipe book so if you told one of the other doctors to do the treatment they would do pretty much the same as you did. For the first treatment there would be 14 shots and if you placed the probe appropriately and



you indent and then you put the next position of the probe with the edge of the probe on the previous indentation, on an average eye you deliver 14 shots over ¾ of the of the eye leaving ¼ untreated. If you needed to re-treat the patient then we would use the



same number of shots and we would again do 270 degrees but spanning a different 90 degrees (so we would treat the zone that we left the first time) and we would give whatever treatment we needed afterwards and that would vary depending on the patient.

A really important part of this treatment is to not to make it so awful the patient will never come back for another treatment and I do hear stories of patients who have really hit the roof when this treatment is delivered because if you do this without adequate anaesthesia it is very painful indeed. In my view there are two ways of anaesthetising an eye properly for this treatment. That is either for the patient to sleep so they can't feel anything at all (a general anaesthetic) or to give them an appropriate injection behind the eye with a local anaesthetic so they don't feel anything. Other forms of local anaesthetics such as those used for cataract surgery are not appropriate, in my view, for this treatment.

The other thing that is really important is getting the position in the right place. The probe is designed so that for an average eye you just had to put the edge of the probe on the edge of the cornea and the treatment would be directed in the right place. The problem is that many of the eyes that we treat are not an average, they are often very large eyes and the position of the ciliary body can vary enormously so you have to do something called trans-illumination where you shine the light on the eye so that you get a sort of gap of lightness between the cornea and the start of the ciliary body. In this way you can see the ciliary body and how it varies around the eye and in

this way we can make sure that the treatment is applied accurately.

In the nineties tubes didn't do well, certainly in our hands. I stopped using tubes altogether when this laser came out because we were getting good results with it. We published our first paper in 1999 from my initial treatment of 58 eyes and as you can see from (Fig 1) the intraocular pressure started at a mean of 33 mm Hg and, following treatment, the mean pressure of the group of eyes was much lower and at the last visit for this particular study it was about half the pressure that it was at the start.

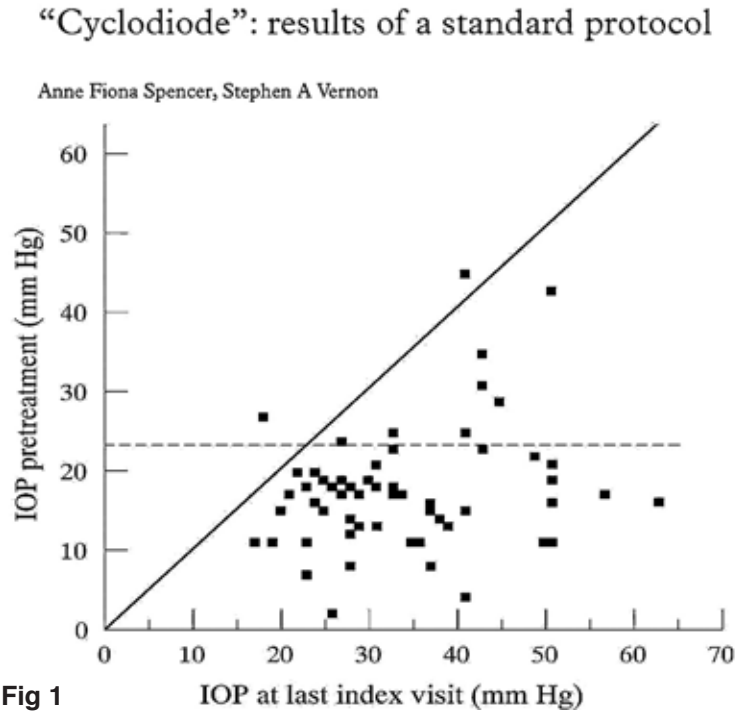


Fig 1

In 2001 the American Academy of Ophthalmology did what they call an ophthalmology technology assessment and this is where they look at a particular mode of treatment in terms of the evidence in the literature and decide how, at least in America, it should be used. They came to the conclusion that for cyclophotocoagulation the cyclodiode laser was the best combination of effectiveness, portability, expense and ease of use. They also said that it should only be used on eyes with limited visual potential or where glaucoma surgery had failed or for those who were refused surgery. It is this first statement, 'limited visual potential' that I wish to take a bit further.

When we produced our second paper on cyclodiode looking at the long term results of the treatment on our standard protocol, we also reviewed the literature and this was published in the New Zealand and Australian Journal of Ophthalmology in 2006. We particularly wanted to look at the long term follow-up because there wasn't much in the literature on what happens to these patients over time. For this reason we took all the eyes with first treatment dates between April 1994 and May 1995, (our first group of eyes that we treated when we first had the laser) and looked at them again. We had 42 eyes of 39 patients, who had a mean average age of just under 60, a mean number of treatment sessions of 2.17 with a range of 1 – 6 treatment sessions. The mean average follow-up was five and a half years with a minimum of three years and a maximum of seven years.

What sorts of glaucoma did we have? Well, the first thing to point out is that ¾ of these patients have come to Nottingham from elsewhere. They came for a second opinion from Consultants who were in trouble with the treatment, it is a bit like Moorfields who have that same sort of group of patients and they are a mixed bunch. Some of them have aphakic glaucoma (that means no lens), some inflammatory glaucoma, some open angle glaucoma with surgery that's failed, some have had severe trauma, some have had retinal detachments with silicone oil in their eye and some have rubeotic glaucoma. They are a mixed bunch.

What about the pressure? Well, pre-treatment on medication the average pressure was 31½ mm Hg and at their last visit the mean pressure was about half that which was very similar to that first study. Here is a similar graph (Fig 2) comparing the IOP listing with the intraocular pressure at last follow-up. As you can see, almost all of the eyes, apart from one,

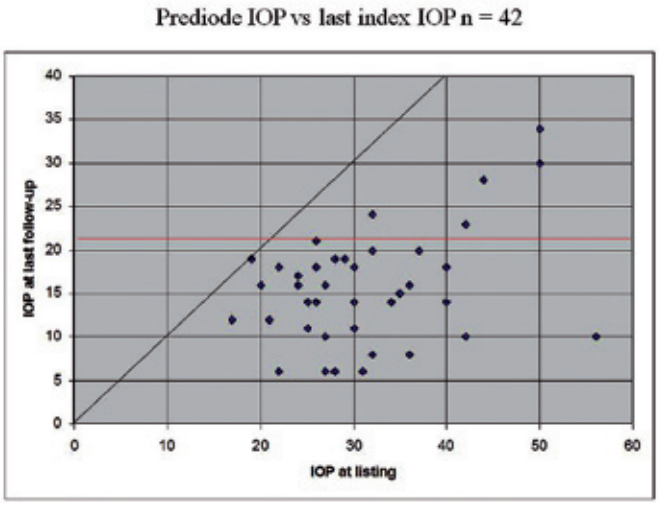


Fig 2

are on the right hand side of the line, showing some treatment effect and most of them are below 21 mm Hg. Here is a graph (Fig 3) of the intraocular pressures all the way along from before treatment right the way to seven years afterwards.

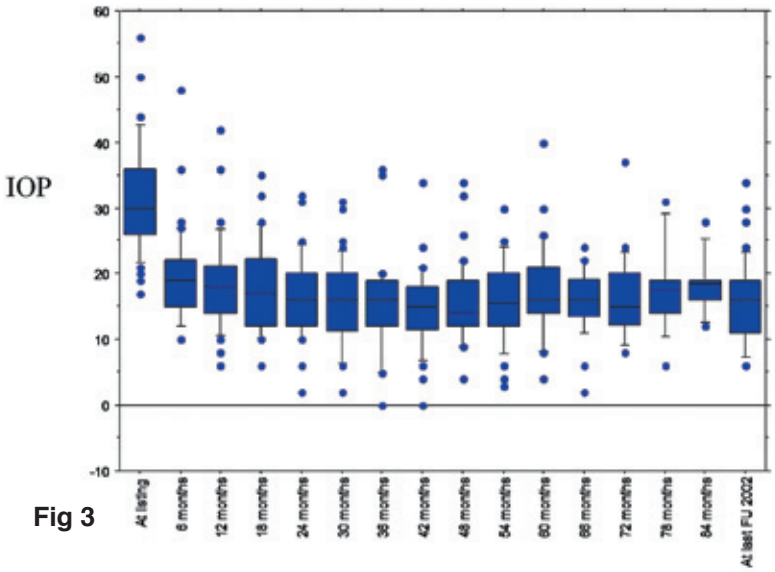


Fig 3

There weren't many patients that got to seven years, but you can see that on the whole the pressure stays quite low right the way along.

The laser doesn't necessarily get you off treatment, it is not designed to do that, it is designed to get your pressure lower without having disastrous things happen in difficult eyes. What is really important is that many patients have been able to stop using Diamox which can cause difficult side effects.

As part of this paper we also looked at all the other papers that had reported on their results with this treatment. Ours is on the top and everybody else is lower down (Fig 4).

Fig 4

All others under three yr mean follow up

	No of Eyes	No of Burns per Session	Diode Laser Dose	Max No of Treatment Sessions	Mean Follow-up (months)	Mean Pre-op IOP (mmHg)	Mean Post-op IOP (mmHg)	% Drop in IOP	% with IOP <22mmHg
Vernon et al (our study)	42	14	2.0W x 2.0 sec	Up to 6	65.7	31.4	15.6	50.3%	88.1%
Shah et al (12)	28	40	1.5W x 1.5 sec	Up to 4	31.1	35.7	16.5	51.2%	82.1%
Pucci et al (16)	120	8 to 15	1.6 - 2.0W x 2 sec	Up to 5	26	30.4	20.3	34.7%	NA
Walland Group A (13)	22	40	1.5W x 1.5 sec	1	20.7	49.4	28.5	42.3%	45.5%
Walland Group B (13)	8	20	1.5W x 1.5 sec	1	22.9	29.4	18.3	37.8%	62.5%
Brancato et al (seeing) (10)	48	16 - 20	2.6W x 1.5 - 2.5 sec	Up to 4	20.7	37.1	19.5	44%	70.8%
Brancato et al (blind, painful) (10)	20	16 - 20	2.6W x 1.5 - 2.5 sec	Up to 4	20.5	50.7	20.6	56.3%	?
Kosoko et al (8)	27	17 - 19	1.5 - 2.0W x 2.0 sec	Up to 2	17.9	36.4	20.3	NA	59%
Murphy et al (17)	263	NA	Total Energy per session 104.1J	Up to 7	17	40.7	17.7	52.6%	NA
Kramp et al (18)	193	24 - 30	1.4 - 1.8W x 2.0 sec	Up to 6	13.9	24.6	19.3	21.5%	76.4%
Hawkins et al (2)	30	40 - 45	1.2W x 0.99 sec	Up to 2	12	32.5	20.8	NA	NA
Schlote et al (19)	93	10 - 15	1.5 - 2.0W x 1.5 - 2.0 sec	Up to 4	12	30.7	20.6	32.8%	74.2%
Yap-Veloso et al (20)	43	18.4	1.4 - 2.75W x 2.0 sec	Up to 3	11.9	37.2	17.7	50%	68%
Martin et al (21)	30	40	1.5W x 1.5 - 2.0 sec	Up to 3	10.8	51	22	NA	NA
Bloom et al (7)	210	20 - 40	1.5W x 1.5 sec	Up to 5	10	34.1	20.1	41%	69%%
Izgi et al (9)	41	18 - 20	1.7 - 2.0W x 2.0 sec	Up to 4	10	34.5	12.1	29%	NA
Mistlberger et al (22)	206	Mar-40	1.5 - 3.0W x 2.0 sec	Up to 6	9.2	42.1	20.3	NA	72.7%
Wong et al (11)	33	30	1.8 - 2.0W x 0.3 - 0.5sec	Up to 3	9.4	40.6	24.4	NA	38%
Threlkeld et al (23)	47	NA	1.5 - 2.5 x 2.0sec	Up to 3	9 (median)	38	16	NA	81%

Next to lowest mean final IOP

All the others had less than a 3 year mean follow-up. Ours is double that so we have the longest series by far. We had the next to the lowest mean trial intraocular pressure and we have the highest percentage of pressures less than 22 mm Hg. What was really interesting was when we looked at the complication rates, the significantly blinding complications of very low pressure. We found that if you could divide the study into two the group where the laser energy level was less than 60 joules and those above, there was a significant difference in complication rates (Fig 5).

Fig 5

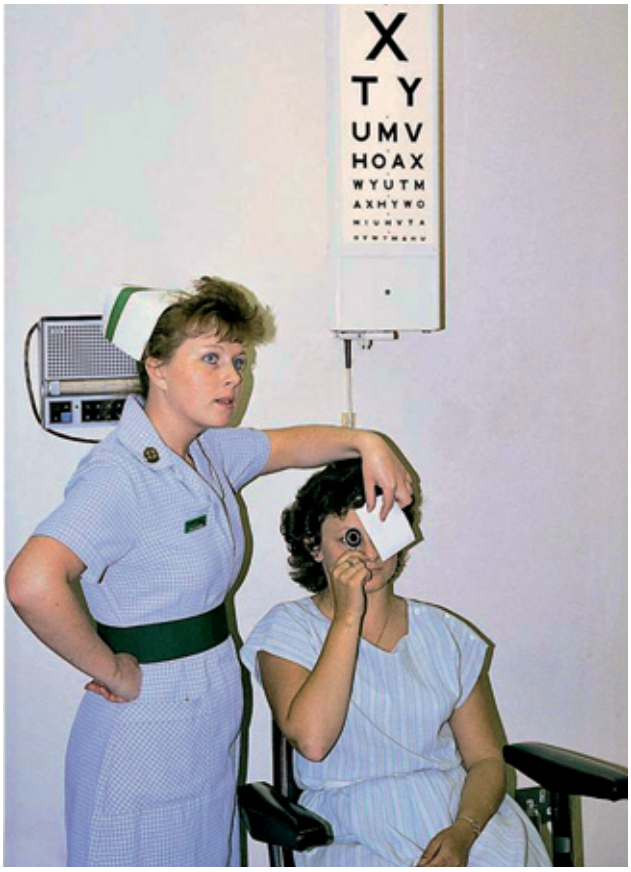
Cyclodiode and hypotony/phthisis

Study	Hypotony (%)	Phthisis (%)	Energy per treatment (J)
Laser energy > 60 J			
Murphy *et al.*[15]	9.50	5.30	104.1 ± 37.5
Martin *et al.*[19]	10	Nil	90–120
Brancato *et al.* (seeing)[11]	2	Nil	62.4–130
Brancato *et al.* (blind, painful)[11]	5	Nil	62.4–130
Mistlberger *et al.*[20]	NA	1.90	55.8–111.6
Kramp *et al.*[16]	NA	1.60	67.2–1.8
Yap-Veloso *et al.*[18]	NA	2	51.5–101.2
Walland Group A[14]	18	NA	90
Shah *et al.*[12]	3.60	Nil	90
Bloom *et al.*[8]	1.50	0.50	45–90
Izgi *et al.*[10]	NA	Nil	61.2–80
Kosoko *et al.*[9]	3.70	Nil	51–76
Laser energy < 60 J			
Vernon *et al.* (our study)	Nil	Nil	56
Schlote *et al.*[17]	Nil	Nil	22.5–60
Hawkins and Stewart[2]	Nil	Nil	47.5–53.5
Walland Group B[14]	Nil	Nil	45
Pucci *et al.*[13]	Nil	Nil	32–40
Wong *et al.*[21]	Nil	Nil	16.2–30

Vernon SA et al. Clin. Experiment Ophthalmol. 2006 34: 411-29.

If you keep each treatment below this level you have no severe sight complications. If you go above this energy level then you start getting problems and the higher the treatment power the more likely you are to get a severe complication.

These findings led us to look at all of the eyes that we have done with good vision throughout our time with the laser. We started looking at this in about 2008 and we had to get enough of a follow-up so we allowed entry into this particular study from April 1994 (when we got the laser) to December 2006. We found that we had 51 eyes of 46 patients which we treated. The mean age was a bit older than the previous study at 65 years. The median acuity is good at 6/9, with a range of 6/5 to 6/18 (because that was our top limit). Our mean average follow-up again is five years. Mean treatment sessions 1.57 with a range of 1 – 6 with 32 having just 1, 10 had 2, 4 had 3 and 5 had more than 3. Nearly 90% of these eyes had previous intraocular surgery of one form or another. They are a mixed bag once again as you would expect, some had their natural lens in place, some had artificial lenses in and some had no lenses in. 50% of them had previous filtration surgery, 20% had previous cataract operations and a similar sort of range of glaucomas as in our first study. The average acuity five years later in this group of patients is only one line lower on the Snellen Eye Chart, that's the average acuity. 90% of our eyes have a pressure of less than 21 mm Hg and even more importantly for these particularly badly damaged eyes nearly ¾ of them have a pressure less than 16 mm Hg, on treatment of course.



What about these patients who did badly? (We always need to look at our failures to see if we can learn from them.)

Well progression of glaucoma, yes I am afraid that we felt that 8 eyes did get worse, 4 of them had very advanced disease to begin with and had good pressure control all the way through, and there are some people who are on what I call 'the slippery slope' unfortunately.

Once they have got to a certain level with their glaucoma, whatever happens to them even if their pressures are very good, it can get worse because they are just getting older and this is a long term follow-up. We felt that was the case in 4 patients, but there were 4 patients where, in retrospect, we should have controlled their pressure better. We should have perhaps had delivered more treatment or put in more medication, something for us to learn from. Four eyes had what's called macular oedema. Now that's fluid in the central part of the retina, which we considered was the cause of their reduced vision. One of them had no lens in their eye and one of them had had cataract surgery with vitreous loss that was a complication of the operation and one occurred after one week on their second treatment from what is called cystoid macular oedema. That one we can blame on the treatment, but the rest we can't and of the others, one had a retinal detachment spontaneously much later after the treatment and the other eye had a spontaneous retinal detachment. One had a vitreous haemorrhage and then a cataract and the patient refused surgery, so they might have done better in terms of their vision if they had had surgery in that eye, and one had dry macular degeneration. So there is not a high rate of severe complications that we could have avoided.

Unfortunately diode treatment can have lots of complications and you have to do it carefully and here is a big list of all of the complications that have been reported with this treatment.

Cyclodiode - complications reported -

Retinal detachment

pain

Uveitis/necrotising scleritis/phthisis

hyphaema and/or vitreous haemorrhage

Neurotrophic keratitis

CME/epiretinal gliosis

pigment dispersion

lens subluxation

Conj/scleral burns/ staphyloma formation

transient and permanent pupil ovalisation

scleral perforation

choroidal haemorrhage

sympathetic ophthalmia

Aqueous misdirection syndrome

By delivering a smaller amount of treatment and being careful when you deliver it you can reduce the risk, but not eradicate the risk of these complications, and that's the message I am trying to get across. Now, do we always do these 14 shots? Well not always because we have learnt as time has gone on there are certain eyes that are at high risk

of very low pressure so we decrease the number of shots in these eyes down to 10. In patients who have advanced rubeotic glaucoma 14 shots is probably not enough so I up it to 20. For larger eyes with a previous poor response I treat with a double row of shots because the ciliary body seems to be stretched over a larger area and that by doing that we deliver 28 shots in two rows and that seems to be very successful.

So to summarise, cyclodiode with a standard protocol is reasonably effective in controlling pressure in the long term in difficult eyes. It is not the best thing since sliced bread but it's certainly comparable with many of the other treatment modalities that we've got and it doesn't have some of the dangers of some of the other treatments. It is very cost effective, it's quite quick to do this treatment, it takes about 5 minutes, if that. We have to do all of ours in theatre because that's where the laser is and it can't be moved, but I schedule 15 minutes in total for one of these treatments, which is not a very large cost to our Health Service for one of the treatments and it is even cheaper if you have the laser out of theatre. Only one treatment was required in our series in approximately 40% of our long term follow-ups, that does mean that most people require more than one treatment, but that is what we expected when we started off all those years ago. If the pressure is controlled and your glaucoma is not advanced and you don't have anything wrong with the central part of your retina or any other eye disease then the chance of retaining your vision is higher after this treatment. Treatment however does still require a fair amount of operator's skill, in fact you can't really do it as a 'cook book' you do need to look at the eyes carefully before your treatment, measure carefully how far the ciliary body is back and deliver it carefully. It is not a quick 'oh well, anybody can do it'. Once you have been taught to do it properly it's pretty safe.

Thank you for listening to me and we got to the end of the talk.