

By Nick Lane PhD

Pioneers Past and Present – But where are the boundaries of the justifiable?

Their names justly echo down the halls of fame of ophthalmology – Sir Harold Ridley, Peter Choyce, Cornelius Binkhorst, Edward Epstein, Svyatoslav Fyodorov, Charles Kelman, Benedetto Strampelli, José Barraquer, Luis Ruiz, Theo Seiler, Ioannis Pallikaris, to take just a few. Their techniques transformed the world and restored sight for millions. But had it not been for their failures, the successes of today might never have been possible. Failure is an occupational hazard in surgery, but how much failure is too much?

“In society in general there have been many such leaps. Mechanical typewriters were improved to the electric version, but then were unexpectedly supplanted altogether by computers.”

Howard Fine MD

“You can tell the pioneers from the arrows in their backs” joked Marguerite McDonald, MD, clinical professor of ophthalmology at Tulane University, to *EuroTimes*.

Certainly the greatest advances in cataract and refractive surgery have met with vituperative criticism from peers. Dr McDonald herself, after performing the first photorefractive keratectomy (PRK) on a normally-sighted myopic patient in 1987 (following years of research on eye-bank eyes and animals), was accused by a senior colleague, in the letters pages of a journal, of either being irresponsible or lying. And that was the barbed reward for immediate success; initial failure is far more commonly the fate of successful innovation.

History furnishes many examples of how far the disavowal of peers can go, even when an innovative technique proves enormously beneficial in the end (or not as the case may be – see the side bar).

Ridley's own troubles are the stuff of legend. Castigated by Sir Stewart Duke

Elder, his colleagues walked out of early presentations; the very concept of IOL implantations was openly repudiated, and dismissed by the AAO as “not sufficiently proven for use in the US”. Ridley spent years terrified that his early failures would come back to haunt him through the courts. In Barcelona, in 1970, Joachim Barraquer was forced to explant half of the anterior IOLs that he had implanted in 500 patients, as a result of corneal decompensation. And despite his successful anterior IOL designs, the name of Peter Choyce is muddied by the unlicensed manufacture of shoddily produced copies (inadequately sized and finished, and prone to warpage). After 100,000 defective implants in the 1970s, many of which caused the so-called UGH syndrome (uveitis, glaucoma and hyphaema) they were finally withdrawn from the market.

Charles Kelman, too, was subject to scathing criticism for his pioneering of phacoemulsification, not altogether surprisingly given the secretive failure of his first case. After 4½ hours in a room marked ‘contaminated’, with an hour and 19 minutes of ultrasound using his bulky prototype phacoemulsifier, the patient developed endophthalmitis, lost vitreous fluid, and finally had his eye enucleated the following day. Of course, the cumulative technical improvements of phacoemulsification ultimately enabled the successful development of modern microincision cataract surgery, with implantation of foldable intracapsular lenses. Ironically – even pioneers get set in their ways – Ridley and Choyce never accepted intracapsular IOL implantation.

The conceptual leap of innovation

So is there a common theme to these pioneers? According to Howard Fine, MD, clinical professor of ophthalmology at Casey Eye Institute, Oregon Health & Science University, true innovation comes from a conceptual leap, when the current techniques have run up against an immovable barrier. The breakthrough is often an inspired lateral leap from an unexpected quarter, which might seem obvious with the benefit of hindsight. The first attempts may be technically rudimentary, but the conceptual leap forwards is the beginning of a completely new path leading to refinements, until the next barrier blocks the way again.

“In society in general there have been many such leaps. Mechanical typewriters were improved to the electric version, but then were unexpectedly supplanted altogether by computers. Another

example was the supplanting of horse-drawn carriages by cars; there were many people at the time who could see no advantages of cars over horses,” Dr Fine told *EuroTimes*.

Of course pioneers need more than just vision to succeed; they also need the ability to see a technical way through the problem, to convert their vision into action. And they need to be able to get it across to their colleagues in an intelligible way, so that other people can test their ideas properly, and refine the technology. Horses didn't give way to cars before there'd been a lot of engineering improvements.

In cataract and refractive surgery, Ridley's concept of implanting an IOL was the first such leap. Implanting anything into the eye went against the ethos of the times, when ophthalmologists were taught only to remove things from the eye. Phacoemulsification was a similar leap, making modern microincision cataract surgery possible; and the use of the excimer laser was another lateral leap, which solved many of the problems associated with radial keratotomy, notably the lack of predictive power and the (small but serious) risk of traumatic globe rupture.

The refractive lens exchange revolution

So which of the numerous techniques and ideas being tested today will be seen as a pioneering leap, with the benefit of hindsight? Interestingly, both Dr Fine and Dr McDonald agreed that the most important current conceptual leap is refractive lens exchange.

“I don't think for a moment that we're going to see the end of LASIK or corneal refractive surgery in general, but as the new generations of accommodating IOLs come into their own, we're likely to see more and more people in their fifties and sixties opting for lens exchange, maybe even before they've developed the first signs of a cataract. This is not really a technical leap, at least not surgically – it is in terms of lens technology – but it is certainly a major sea-change in attitudes,” said Dr McDonald.

Innovation versus clinical data

Even so, refractive lens exchange is only one way through the quagmire, and herein lies the problem. What of phakic IOLs? What of the use of advancing wavefront technology in laser ablations, reducing the risk of glare and haloes in more highly myopic patients? These and other techniques are advancing rapidly, and it is



**How much comfort do you want?
It's your decision!**

SOLE WORLDWIDE

- electrically switched image inversion
- microscope independent motorized focus
- ergonomics well-proved for 20 years



Oculus BIOM 3c/SDI 3c –
The fully motorized and most versatile version. Fits to the common microscopes used for vitreo-retinal surgery. Not depending on microscope's brand. Also available for cost-effective retrofitting.

Trust in 20 years experience of the world leader in non contact wide angle observation.

Oculus Optikgeraete GmbH • D-35549 Wetzlar
Tel. +49-641-20 05-0 • Fax +49-641-20 05-295 • www.oculus.de

110 years



hard to say which will provide the best long-term solution. Unless we pursue them all, we'll never know; but equally, some rapidly advancing innovations are likely to do as much harm as good. According to Roger Steinert, MD, data on phakic IOLs (published in *AJO*, November 2004) "shine a bright yellow caution light" on angle-fixated anterior-chamber IOLs

"As the new generations of accommodating IOLs come into their own, we're likely to see more and more people in their fifties and sixties opting for lens exchange, maybe even before they've developed the first signs of a cataract.

Marguerite McDonald MD

and posterior-chamber IOLs. But perhaps this rap across the knuckles is just the stimulus for better innovative design.

On the other hand, cataract and refractive surgeons sometimes seem almost incorrigibly innovative. There are nearly as many different models of IOL as there are surgeons – at least 1,500 different designs registered to 33 companies worldwide. Most of these have never been compared formally; the unsuccessful models simply disappear from the market, or are superseded by new 'improved' marks. Several commentators have complained that negative results are seldom published. In this sense, innovation stands against the ponderous measurement, recording, and the comparison of outcomes.

But while cataract and refractive surgeons have been criticised for their attitude to evidence-based medicine (including by me, in an earlier column), it is also true that too tight an embrace of the 'gold standard' of the double-blind clinical trial may hamper surgical research.

There are two big problems with clinical trials in cataract and refractive surgery. One is that the slow, measured tempo of clinical trials simply can't keep pace with the speed of technical refinements. By the time the National Eye Institute's PERK trial was completed, for example, radial keratotomy had already been effectively replaced by excimer laser treatments. But in the worst case scenario, radial keratotomy was worth the effort because it showed that successful corneal refractive surgery was possible; and in the best case, surgical refinements over the last decade, coupled with its speed and ease, still make RK effective in many situations, especially if laser surgery is not available.

The second drawback is perhaps more profound: conceptual leaps forward almost inevitably begin in a rudimentary fashion, like the earliest cars, and it is the many small obstacles themselves that lead ultimately to the refined and technologically superior product. If the comparison with an existing, moderately

successful but ultimately limiting treatment is drawn too soon, then the negative comparisons may stifle successful innovation. What if Kelman's early attempts at phacoemulsification had been dismissed as disastrous, as well they could? His lasting testament, like Ridley's, was the proof of a concept, not its perfection. It is his vision that stood the

test of time; and the early data were best ignored.

Some modern examples are more subtle, but still hinge on the play-off between data, on the one hand, and long-term potential on the other.

A recent prospective, comparative trial by Charles Claoue MD, at Hartswood Hospital, Brentwood, is case in point. He compared a multifocal IOL (Array multifocal IOL, Advanced Medical Optics) with an accommodating IOL (ICU accommodating IOL, Human Optics AG). In most respects the multifocal lens proved superior, despite the small size of the trial. Yet as a vision, it is plain that the ultimate goal is an accommodating lens with similar properties to the crystalline lens. Only by trying and failing to produce an effective accommodating lens, and by learning from the mistakes to refine and refine again, can the vision be realised.

This process has recently culminated in the remarkable Smart lens (Medennium), able to change its shape at body temperature from a solid rod to an optically imprinted gelatinous accommodating lens that fills the capsular bag. Dr Fine extolled its virtues to *EuroTimes*:

"This is the closest we've got so far to the crystalline lens. It can be custom made, using MRI measurements of the exact size of the capsular bag, and implanted through an incision as small as 1.0 mm."

Howard Fine MD

"This is the closest we've got so far to the crystalline lens. It can be custom made, using MRI measurements of the exact size of the capsular bag, and implanted through an incision as small as 1.0 mm."

Personalising medicine to individual patients in this way is achievable in surgery, but goes against the grain of evidence-based medicine, which insists on pigeonholing patients into comparable groups with high statistical power. No doubt cataract and refractive surgeons will continue to earn the opprobrium of colleagues in other disciplines. But while monolithic medicine served 20th century science well, it may be that its days are numbered, as the impact of genomics makes itself felt.

The human genome project is set to revolutionise the practice of clinical trials through the application of pharmacogenomics – the tailoring of drug therapies to the genetic makeup of individual patients. By searching for individual single nucleotide polymorphisms (known as 'snips') that influence the pharmacology and pharmacokinetics of drugs, and by tailoring therapies to the specific genotype of individual patients, pharmacogenomics is set to break the stranglehold of both blockbuster drugs and the mega-trials that support them.

Patient-driven innovation

So it is fair in surgical sciences, and in ophthalmology in particular (where refractive endpoints are as objective as any), to tailor novel treatments to patients, rather than insisting on comparators, placebos or, god-forbid, sham surgery. Dr Fine hails the new era as the transition from "high volume, low cost, efficient care, to high-quality, personalised care."

However, there is a balance between the need to innovate, to aspire to a grand vision, and the need to 'first do no harm'. Only the patient can choose between the possibility of perfection, as offered by a perfected accommodating IOL, and the acceptance of a reliable second-best, with a well-established risk profile. And to establish the risks, it is necessary to collect clinical data, ideally on a standardised multicentre basis, and to innovate only on those patients who wish to be 'innovated upon'.

First and foremost, patients are entitled to a clear exposition of the outcomes of new interventions. As Douglas Koch, MD, editor of the *JCRS*, and others have pointed out, the inevitable uncertainty over outcomes in innovative surgery means that it is critical for the integrity of the profession to maintain honest standards in advertising.

Cataract and refractive surgery is leading the way in direct-to-consumer marketing. For LASIK alone, some \$140 is spent on advertising per treated eye. All too often claims are simplistic and misleading ("20/20 for \$2995" or "20/20 promise"), and not supported by data.

Says Koch: "False advertising deceives patients, fosters poor patient decisions regarding having a procedure, demeans

our profession, and is a violation of the implied pact between physician and patient."

Wise words. Yet patient choice is also ultimately the answer, so long as patients are well informed.

"Given that refractive surgery affects quality-of-life, it's reasonable that patients should choose, and pay. But we have a responsibility to educate the patients as honestly as we can."

Howard Fine MD

"Given that refractive surgery affects quality-of-life, it's reasonable that patients should choose, and pay. But we have a responsibility to educate the patients as honestly as we can – we need to be clear about the potential complications of different techniques, and whether they are still experimental. We need to spend a lot of time with patients, talking it through. But if we do that, then innovations will be driven by market forces, and ophthalmologists who over-promise, or mislead, or over-charge for poor outcomes, will be sued or drummed out. It's the market economy at its best," Dr Fine told *EuroTimes*.

The Fruits of Innovation

The kind of derision that greeted Sir Harold Ridley's invention of the intraocular IOL has by no means been restricted to ophthalmology. It's always been difficult to judge the lasting value of innovative treatments. Here are a few examples from outside ophthalmology that incurred similar wrath from peers, and went on to greater things – or not, as the case may be.

Crazy innovations that worked...

In vitro fertilisation

The first successful in vitro fertilisation was performed in 1978 by Robert Edwards (an embryologist) and Patrick Steptoe (a gynaecologist) in England. Since then more than 20,000 test-tube babies have been born worldwide. The possibility of a continuing pregnancy being achieved by IVF has improved from practically zero to around 20% at top IVF centres.

Organ transplantation

The first corneal allograft was performed in 1837 in a gazelle model, and the first successful human transplant by Eduard Zirm in Austria in 1905. The first successful kidney transplant was carried out by Joseph Murray and David Hume at Brigham Hospital, Boston in 1954, and the first heart transplant by Christiaan Barnard in South Africa in 1967. The advent of cyclosporine, approved by the FDA in 1983, made transplantation the successful treatment it is today.

Blood transfusion

Blood transfusions have been attempted since ancient times, with Pope Innocent VIII apparently receiving the blood of three boys on his deathbed (all of whom died). After centuries of failure, the discovery of blood groups early in the nineteenth century led to the first successful transfusion by James Blundell in 1818, to treat a patient for postpartum haemorrhage, and later, in 1840, to treat haemophilia.

Irradiation of tumours

Roentgen discovered X-rays in 1895, when experimenting with a vacuum tube; he noticed a fluorescent screen glowing on the other side of the lab. He tried to block the unknown rays by holding out cardboard and was shocked to see an image of the bones in his own hand. Weeks later, Chicago medical student Emil Grubbé became the first person to use radiation to treat cancer. Early radiotherapy consisted of a single, massive one-hour dose of radiation, and side effects were severe. In 1922, Claudius Regaud proved that fractionated therapy was as effective as a single-dose, but caused fewer side effects.

And a few that didn't...yet

Frontal Lobotomy

The first attempt at human psychosurgery was a series of prefrontal lobotomies performed by Egas Moniz, who received the Nobel Prize in 1949. The idea was popularised by Walter Freeman, who invented the 'ice-pick lobotomy', hailed as a great advance in 'minimally invasive surgery.' Freeman travelled the US in his 'lobotomobile' during the '40s and '50s, and his treatment was carried out on some 50,000 patients, even misbehaving children. The era is now regarded as a barbaric episode in psychiatric history.

Hysterectomy for hysteria

The ancient Greeks considered hysteria to be 'womb fury' and advocated manipulation of the genitals to orgasm as the cure. By the 1800s, the uterus was considered the origin of women's psychological neuroses, said to be the most common of all diseases except fever. The obvious cure for distress was hysterectomy, which was perfected in the 1870s. Even today, one in three women have a hysterectomy by the age of 60, a procedure found to be unnecessary in at least 50% of cases by the AMA.

Blood-letting

The history of phlebotomy goes back to ancient Egypt at least 3000 years ago, and was based on the four humours, blood, phlegm, black bile and yellow bile. Health was restored by purging, starving, vomiting or bloodletting. Phlebotomy was used specifically to cure spiritual or physical weaknesses (as blood carried the vital force) from tumours to tonsillitis. Modern phlebotomy is still used to treat erythraemia and congestion following acute heart failure.

Transplantation of goat testicles for virility

In 1889, French physiologist Charles Brown-Sequard reported he had rejuvenated mind and body by injecting himself with an extract from the testicles of dogs. By the 1920s, Leo Stanley, surgeon at San Quentin, was implanting boar testes into willing prisoners, and in Paris Serge Voronoff transplanted monkey glands to extend the lives of wealthy clients. John Brinkley eventually transplanted hundreds of sliced goat testicles into elderly patients in Kansas, before fleeing to Mexico and succumbing to poor health and endless lawsuits.