Chapter 5

of

Contrary Life and the Technical Fix

from malaria vaccine

to

hormone contraceptive

Alan R. Walker

2015

alanrwalker books, Edinburgh

ISBN 0-9545173-2-6

www.alanrwalker.com

Chapter 5

Retinal detachment and laser surgery

At three weeks old there was little to see of her. So far she had grown from her mother's fertilized ovum into a scrap of tissue that was barely visible to the unaided eye. She was an embryo nestling in the watery cushion of an amniotic sac. Already she was well implanted in the endometrial lining of her mother's uterus, where her umbilical cord and chorion negotiated a delicate alliance with her mother's supply of oxygen and nutrients. Overall she was a lumpy, corrugated plate of translucent and pale white tissues, a little over two millimetres long. Starting as a single cell, an ovum that became a zygote when fertilized, she had grown by repeated division of that original cell. Nuclei of the cells divided by mitosis and new cells developed from the cell cytoplasm and membranes enveloping each new nucleus. Individual cells looked similar to each other. Early on all these cells were motile. They jostled and pushed past each other, or they grouped together as some settled into a destined position. The cells were determined. Individually they knew where to go and what to do when they arrived in these rudimentary tissues. Their determination derived from the vast store of information they each carried in their nucleus. Information that was sufficient to instruct over two hundred widely different types of cell, but from the earliest stages each cell knew which type it had to differentiate into. As the cells grouped into early tissues of the embryo they coordinated their movement, growth, and proliferation. They issued and received chemical messages from each other to induce a particular mass of cells to create a pre-defined shape. One mass of cells of a particular determination might be able to induce a mass of a separate determination to develop in partnership as single a complex organ.

She was still attached to a yolk sac, but more structure became discernible. Along the length of her body a head region and a tail end were developing. In between were signs of the segmentation she shared with all her vertebrate lineage – paired somites running along her back that would grow into the bones and muscles of her spine. When she had been one week younger, a groove had appeared in the mid-line of her back. The tissue forming was her neural plate. This was part of the spread of ectoderm tissue of the upper and outermost surface of the embryonic plate. The groove deepened as it transformed into her neural fold. Now in her third week since fertilization, she could show, in the mid region of her back, a neural tube that had separated off below the ectoderm. The work of this tube now was to grow a spinal cord and associated nerves. At her head region the same neural fold had complex construction work ahead – to construct her brain with its extensions to the outside world in the form of her eyes.

These neural folds grew into paired flaps rising above the surface of the embryonic plate. They consisted of two separate sheets of cells, the outer being ectoderm and the inner layer continuous with the tissue of the neural plate. As she grew to be four weeks old specialized areas of this neural layer started to bulge outwards on both sides. These were the earliest signs of her eyes, her optic grooves or optic sulci. As the grooves pushed outwards each left behind, in the region of her early brain, an optic vesicle. Each vesicle was a fluid-filled hollow, more of a cup shape than a groove. This vesicle showed its open end facing inwards toward the hollow part of her brain whilst its closed end faced outwards to the layer of ectoderm and the amniotic sac.

No longer a vaguely shaped embryo, now in her fifth week, she gained a high-domed head complete with varied bulges destined to grow into eyes, ears, nose and mouth. She grew two pairs of buds as the start of her arms and legs. Her tail remained distinct, like that of her ancestors from an ancient evolutionary past. As a growing member of the family Hominidae she would soon reduce her tail to a mere coccyx tucked in at the base of her spine.

By now the optic vesicle on each side of her head was pressing against the outer layer of ectoderm of the embryonic plate. Contact between these two distinct layers of tissue induced in both layers fundamental changes. Individual cells in the zone of contact replicated by mitotic division and some of them grew in volume greater than neighbouring cells. These cellular expansions folded the layers into further bulging shapes. The optic vesicle, as an outward facing bulge, started to fold in on itself: it invaginated. As it did so the closed end of the cup-like optic vesicle itself took on the form of a cup. This second cup thus became double layered. Another action of these embryonic inductions simultaneously led to the ectodermal cells opposite the optic vesicle to divide and expand into a thickened area, a placode. These placodes would form, one each, the lenses of her eyes.

At the end of her fifth week her eyes were out on stalks. Short stalks but far more than any mere extension, these and the double layered invaginating cups of her optic vesicle remained fundamentally part of her brain. The double layered cup was asymmetrical along its side closest to her neck. The folding was incomplete, leaving an open groove. Into this groove had swarmed millions of spindle shaped cells that came from inner tissue along the crest of her neural tube. These cells were mesenchymal, of the sort that would continue to multiply and spread between the ectoderm and endoderm layers of the embryo and then form blocks of muscle and blood vessels. In the groove of the optic cup these mesenchyme cells gathered and coordinated into an artery to channel blood into the growing eye and a vein to channel spent blood back toward her heart. This pair of vessels comprised the hyaloid system or vasculature, whose task now was to supply with oxygen and nutrients the cells growing into each lens.

The lens placode in the ectoderm, responding to strong chemical signals from the optic cup, was induced to invaginate. A bulge inwards toward the optic cup and trailing hollow in the ectoderm rapidly budded off as a hollow sphere. Each sphere then filled with cells of the dividing lens tissue as the diameter of the sphere expanded. These specialized cells would bind together, fill with crystallin protein, lose their nuclei and other structures, and so transform into a clear biconvex lens. The ectoderm remaining outermost to each lens meanwhile developed as the cornea that would cap the anterior chamber of each eye.

Now an embryo of six weeks she was all of ten millimetres long rather than tall, still floating in her amnion, a tiny homunculus in a space-capsule tethered to her mothership. Differentiation was accelerating and her eyes expanded their repertoire of components and skills. The two layers of the cup-shaped neural tissue, contiguous with her central brain, now grew differently. The inner layer, the one nearest the lens, started to develop as a thick sensing and transmitting structure: the neural retina. The outer layer, toward the outer surface of the growing eye, retained its characteristics as an epithelial layer (a layer that lines the surfaces and cavities of body structures). Although derived from neural tissue this layer would not gain a nerve supply. Instead its first of many tasks was to become darkly pigmented. Each cell of this layer synthesized within itself many brown granules of melanin. This layer of her brain became the retinal pigment epithelium. It had many more functions to make ready. The space (often called subretinal space) between these two layers of her optic cup was anatomically still part of the optic vesicle of her brain. This space became squeezed into the merest gap, enough to allow a narrow layer of fluid between the layers of cells.

The melanin pigment of the retinal pigment epithelium would later absorb light to prevent unnecessary back-scattering. At this young age, seven weeks, the pigment simply showed as a dark disc on each side of her head on her otherwise translucent body. The one-cell-thick layer of the retinal pigment epithelium grew laterally with the expanding sphere of the eye. Individual cells packed themselves together as hexagons in a honeycomb. Each cell grew cell-to-cell joints at their outer boundaries, their plasma membranes. These joints were the type called tight-junctions; they bound strongly the cells of the layer and made it impermeable to passage of microbes and even of giant molecules across into the space between the two retinal layers. By the time her blood supply fully developed to this part of the retina the network of tight junctions would become part of her blood-brain barrier; it would reduce risks to her brain of infection or poisoning.

These multi-purpose cells of the retinal pigment epithelium now began to develop a function crucially supporting the operation of the light sensing cells developing in the neural retina. These sensory neurons were growing just across the fluid film above the pigment epithelium. Each cell of this epithelium had, as an ependymal cell lining a

brain vesicle, started life with a cilium facing into the vesicle. On each cell the cilium regressed whilst hollow protrusions of the cell's plasma membrane extended as minute tubular villi and thin veils. These protrusions clasped and wrapped around the outermost segment of each sensory neuron. Every cell of the retinal pigment epithelium became intimately entwined with about forty five sensory neurons of the neural retina. This sheet of epithelium cells spread all over the surface of the growing sphere of the inner eye except for a circular area just off-centre at the back of the eye where the stalk of the eye had formed. This area would be a blind spot, where a thick bundle of nerves ran from the retina down into the central brain.

Meanwhile her neural retina thickened rapidly to a multicellular layer 0.2 millimetres deep. Simultaneously it spread laterally around the growing sphere of the eye. The volumes of these spheres filled with a transparent gel: the vitreous body (or plain vitreous). This was ninety eight percent water, with the remainder consisting of structural and supportive proteins such as collagen and hyaluronan. The vitreous would develop attachments to the inner limiting membrane of the neural retina as these two structures developed.

The neural retina would be where the first two parts of vision would work, the second part would be completed within her central brain. The light sensing cells, the photoreceptors, started life as ependymal cells lining the optical vesicle of her brain. The ependymal cells bore cilia on their open surface facing onto the vesicle. An extremely long time back in her evolutionary history the cilia of these cells gave rise to an intricately folded scaffold within the outer segment of the cells. The cells themselves elongated greatly. Onto the long scaffold the membranes of the cells folded as dense stacks of discs, all interconnected with each other.

Each disc of a photoreceptor cell gained a coating of molecules of a protein called opsin that was reactive to light, that responded to incoming photons. Opsin itself was bound to a pigment component called retinal. This retinal acted as a chromophore, able respond to light by making a conformational change between two isomers of the molecule. The 11-*cis*-retinal, a molecule with a bent shape, straightens out to all-*trans*-retinal. The molecule is bleached by light. This is phototransduction and it stimulates the nerve impulse. After the isomerization retinal is released from the opsin molecule then transported across to the retinal pigment epithelium. There a cascade of enzymes converts the retinal back to its photoreceptive form, ready to be re-incorporated with opsins in photoreceptor cells. This recycling would be constantly and vigorously active when she was born and could see. The photoreceptor cells, deeper into their long bodies, their inner segment, became packed with mitochondria to supply energy, and a large Golgi apparatus to supply proteins necessary for this intense metabolic work.

Two types of photoreceptor cells developed: long tubular rods and slightly shorter pointed cones. In rod cells the combination of opsin and retinal, called rhodopsin, developed for detecting illumination between light and dark. A rod can detect a single photon, one quantum of energy. The opsins in the cone cells developed together with retinal into photopsins sensitive to wavelengths of light, in descending order of wavelength: red, green and blue. Both rhodopsin and photopsin molecules on these cell membranes developed to transduce signals of light energy into signals of electrical energy.

When fully developed and functional her eyes would each contain about seven million cones and one hundred million rods. The signals from the rods and cones in turn transmitted deeper into the neural retina along the inner part of each photoreceptor cell to nerve junctions, synapses, with many more neurons. They formed synapses with the common bipolar cells that continued directly toward the inner surface of the retina, facing the vitreous. Less common connections were with horizontal cells that traversed this layer of the retina laterally. Both rods and cones in her retina developed synapses with these transmitting neurons variously: one-to-one, one-to-many, many-to-one. Further inward there were more horizontally connecting neurons called amacrine cells. Finally connections were made with ganglion cells which developed toward the innermost part of the neural retina axons long enough to reach into the optic nerve and down into the brain.

The optic stalk was where nerves led from the neural retina to the brain, and blood vessels led toward the neural retina. The area of retina above it would develop without photoreceptors; it would be blind. A related inefficiency had developed. Light would not only have to traverse many layers of neurons before reaching the outer segments of photoreceptors. A fine network of retinal blood vessels now developed on the inner surface of the neural retina and its capillaries penetrated down to just above the photoreceptor layer. Light would be blocked where it hit the dense pigment of haemoglobin in red blood cells.

When she entered the world of light neither deficiency would be apparent. The business of high definition vision would be conducted at an area of the retina called the fovea, just 0.2 millimetres across. This was at the centre of focus of the eye, close to the off-centre blind spot. At the fovea the nerve layer was destined to develop as the thinnest possible area of connections between the photoreceptors and inner retina by displacing the inner bulk of each photoreceptor cell peripherally to connect with bipolar and horizontal cells beyond the fovea. Also the fovea lacked the retinal blood vessels that elsewhere covered the area between the neural retina and vitreous. Instead the fovea gained its oxygen and nutrients from the dense network of blood vessels external to the retinal pigment epithelium. Only cones would develop in her fovea; exceptionally densely packed here at two hundred thousand cones per square

millimetre. When she needed to make visual sense of her new surroundings her eyes would dart back and forth, scanning her surroundings by imperceptible movements called saccades. The high definition information at the centre of where she directed her attention would be sorted and compressed by her neural retina, then analysed for use by her central brain. Meanwhile, the rest of her retina would feed in vague, low definition information about what was happening at the margins of her attention. Her peripheral vision would provide alerts of danger or other possibilities needing attention. The muscles that developed in her eye orbits would do all the work of these minute saccade movements and eyeball swivels needed for both modes of vision.

Nerves continue to grow out of the innermost surface of the neural retina, out next to the gel of vitreous. Growing and stretching, from there they headed direct for the optic stalk to converge in a dense mass of nerve fibres. These fibres developed tightly packed around the hyaloid artery and vein. Thence they connected to the vision centres of her brain. This retinal part of her brain was growing as densely and complexly interconnected as her central brain tissue.

Eight weeks old and approximately twenty five millimetres long, she was grown up enough now to now be called a foetus. Her fingers and toes were visible and thankfully her tail nearly disappeared. With her big brained domed head, a miniature human was clear to see arising from these seething trillions of cells, all individually going about their concerted multicellular business. Each cell had its own purpose to cooperate in a sum far greater than its parts.

For her eyes the retina was now the component demanding most resources from her mother. Soon after birth, bathing in light, and with years more work needed to fully interconnect, integrate and train all these nerves for full vision, her retina was going to need a prodigious supply of oxygen and nutrients, and passage away for wastes. On both sides of her retina, by her eighth week, mesenchyme cells streamed toward her eyes, multiplying as they travelled. These became angiogenic, capable of growing into new blood vessels. Redundant hyaloid blood vessels, no longer needed to supply the developed lens, transformed into the retinal artery and vein. As they exited from the optic stalk into the chamber occupied by the vitreous they spread over the inner surface of the neural retina as a fine network of interconnected, anastomosed, capillaries. In turn these capillaries penetrated down into the layer of the neural retina where the bipolar and horizontal cells bore their nuclei and main bulk.

Separately blood vessels grew around the globe of her eyes as a dense network of wide vessels stretching from the optic stalks to the rim of the cornea. This was the choroidal vasculature, the choroid. It was squeezed between the basal membrane (Bruch's membrane) of the retinal pigment epithelium and the tough outer coat of the eyeball (the sclera). This network of wide and flat blood vessels is densely intricate and multi-

layered. Its innermost vessels, the capillaries of the choriocapillaris up against Bruch's membrane have many minute gaps, or fenestrations, to allow the blood close contact with the membrane. This speeds up the diffusion of oxygen and nutrients to both the retinal pigment epithelium and the outer segments of the photoreceptor cells. When operating for vision her retinas would be even more demanding of oxygen, per mass of tissue, than her central brain; they would be the most energy-intensive tissue of her body.

As she grew by the week and month the two retinal layers continued with their maturation into her ninth month. The many villi and veils extending from each cell of the retinal pigment epithelium grew to pack the spaces between both rods and cones. One epithelium cell would wrap its extensions around many photoreceptors. These photoreceptor cells were going to face such high rates of metabolic processing during the work of vision that their internal structures would age and degrade from photo-oxidative stress. Oxygen containing molecules known as reactive oxygen species (a zoo containing superoxide anion, hydroxyl radical, singlet oxygen, hydrogen peroxide and others) would leak from the densely packed mitochondria in both rods and cones. They would damage the stacks of membranes and their photoreceptive molecules. But these rods and cones would keep growing outwards toward the epithelium. Sheathed by the villi and veils of the epithelial cells, the rods and cones would shed their degraded outermost membrane discs. Each cell of the retinal pigment epithelium would need to engulf and digest by phagocytosis up to four thousand discs every day. Another proficiency of the epithelial cells would be to function as glial cells of the brain. Such cells are supportive and protective of neurons in the brain and nerves in various ways and at this interface of the two retinal layers they would engulf and process debris from the photoreceptors. The vital retinal pigments would be recycled in a biochemical pathway that would rejuvenate their capacity to transduce the energy of photons into nerve impulses.

The boundary between the neural retina and retinal pigment epithelium was narrowly filled with a viscous fluid of complex composition. The fluid contained massive molecules of hyaluronan (a glycosaminoglycan polymer of carbohydrate). These molecules formed a stringy three dimensional network called the interphotoreceptor matrix. To this matrix were attached much smaller proteinaceous molecules (CD44 and RHAMM) that acted as hooks between the hyaluronan and certain glycoprotein molecules that were embedded across the plasma membranes of both epithelial cells and photoreceptor cells. All together the matrix created a complex glue that, together with surface tension effects, held the two retinal layers together in their crucial physiological embrace. Additionally these layers were pressed together by the stiffness of the vitreous, which now was four millilitres in volume. But no anatomical connections, no cell-to-cell junctions, no molecular nuts & bolts, ever developed between these two layers of the retina.

♦

Her parents were delighted with their new-born daughter; a sister and companion for their three year old son. The baby was healthy, she fed well, slept well and everything worked correctly. As her skull expanded and filled in its correct bone growth, her eyes came to appear less conspicuous in her face. Optically they were functional at birth, but far more than simple optics were needed for her brain to make use of objective reality as sensed through those eyes. Soon the growth of connections in her retina, between her retina and central brain, and within that brain, enabled her to follow her parent's eyes and be fascinated by their changing expressions. She smiled for the first time. To make good sense of the flood of raw information streaming through her corneas, pupils and lenses would take months and years. Central brain and eye and motor coordination centres would all need to develop in concert by formation and sensitization of myriads of neurons or nerve cells. The neurons with their axons, dendrite and synapses would form a vastly and intricately dense network.

By the time she reached her early teen years her parents noticed how close she held the books she was so often immersed in. The optometrist they consulted prescribed glasses for mild myopia. At first she hated wearing them: a nuisance and excuse for school class-mates to tease. But she learnt not to care, being too fascinated by what she could read and now understand about the natural world around her. Her curiosity and awe grew the more she looked. As she matured toward her final year at school she knew she wanted to work in chemistry, or in biology, or could she do both? It all looked exciting in the 1980s with these new fields of molecular biology and biotechnology she read about in magazines at the school library. As her chemistry teacher pointed out – soon biologists would conduct their experiments by exploiting the laws of chemistry.

Now well into her job, she researched the relationships between the genetics of enzyme cascades and the embryology of zebrafish at University of Bristol. The constant scrabbling for grant funding, the departmental politics, the lack of space in the lab, they all wore her down but she loved the work nonetheless. Much close work, manipulations at the laboratory bench and staring at mesmerizing images of computerized molecular models, was her daily lot. She preferred to wear glasses rather than contact lenses, and now one eye required a lens that corrected for slight astigmatism. She had started to see floaters shadowing her vision slightly, specially when peering through a microscope. Her optometrist had answered her question about them. The bonds between the collagen and hyaluronan molecules in her vitreous were now tending to degrade as the collagen aged and disintegrated into small fibrils. The vitreous gel became a little liquefied, a process called syneresis, and formed small pools toward the back of her eyes. The fibrils vibrated in response to saccade movements of her eyes – floaters casting vague shadows on her retina.

Too late at the end of a hectic week, she cleared her desk ready for next Monday then rushed homeward on her bicycle, across to the Clifton district above the River Avon. She diverted to a bakery for a loaf of speciality bread to go with the evening's main salad dish. Friday was one of her cooking days. She sped on, knowing her partner would be wondering why she was late already. Along through narrow winding streets, avoiding the cars on the main roads, she swerved round a sharp bend. The front wheel of her bike struck a loose drain cover. Head first she landed beside the road in a tangle of bicycle, satchel, helmet and her cyclist's sunglasses. The blow was on the left of her face, across cheekbone and brow. Although it was a grassy verge she hit, the momentum and trajectory of her body shocked her head sharply. The vitreous of her eyes jerked whilst her brain slammed against the inside of her skull. She lost consciousness.

Swimming up through the murky depths of her concussed brain she opened her right eye to people around her. She heard them talking of skull fracture, of breathing, of the blood flowing over her left eye. Someone checked her reflexes for sign of spinal injury and another had already dialled 112 for an ambulance. At their apartment her partner was wondering why she was so late without phoning to explain.

When she arrived at reception for accident and emergency of the Bristol Royal Infirmary one of the clinicians quickly assessed that her skull and neck vertebrae demanded his immediate attention. The laceration above her left eyebrow and the significance of the bruising developing around the orbit would also need attention after the radiology was completed. He returned to his patient an hour later with the news that the radiologist had given the all clear. Now he had time to examine what the concussion might have done to her brain and eyes. What was the state of her mental faculties? Was she confused or uncoordinated? How well could she see? Was her left eye painful? She told him about sensing flashes of light whilst waiting in the radiology department. That alerted him to some possible trauma to her eyes: retinal damage? Using a direct ophthalmoscope he saw no obvious signs of damage from a blunt blow directly onto her eyeball: the cornea was intact and no blood pooled in the anterior chamber. What he could see of the retina seemed intact. Maybe her sunglasses had protected the eyeball, although the laceration could be from a sharp edge of a broken frame. The glasses remained stuck in the grass at the accident scene.

He cleaned and stitched the wound. Then he arranged for an overnight bed so that his patient could be observed by ward nurses for any signs of developing brain damage. With that simple type of ophthalmoscope he could not view the full area of the retina and anyway specialist attention was needed to detect small wounds in the retina from a blow to the head. His last duty to this patient was to make a referral to an

ophthalmologist at the Bristol Eye Hospital to examine fully his patient's retinas as soon as possible on Saturday. His patient's report of flashes of light worried him.

Next day, approaching noon, she was released from observation and taken the short ride just over the road to the eye hospital. As the ophthalmologist set up the tools of her trade she listened to her patient's account of the accident; of how she was feeling now and how she could see. Was there any other abnormality in addition to the flashes? Then she positioned her patient on a chair in front of a slit-lamp indirect ophthalmoscope that was mounted on a table. She adjusted the head-rest to fit her patient in line with the ophthalmoscope's lens system. Next she irrigated the eye with drops of local anaesthetic. When this treatment took effect she added a viscous liquid to the cornea to ease the coupling of a special contact lens to the eye. This lens looked like a thimble but it was a Goldmann 3-mirror lens. Its intricate optical design enabled her to examine with a close view all areas of the retina, whilst adjusting the slit-lamp illumination to detect various conditions of the vitreous and retina. She sat at the other side of the table, opposite her patient and scanned the entire area of each retina through binocular lenses, with various positions of the contact lens.

In the left eye she spotted a tear in the neural retina, close to the equatorial plane of the eye, midway from lens to fovea. It was U shaped; the edges of the U were slightly open, with intact retinal pigment epithelium just visible below. She reckoned that the vitreous had partially separated from its adhesions to the inner limiting membrane of the neural retina, but had pulled at one of the places where the adhesion had become unnaturally strong. That was at an area where she could see that the superficial network of retinal blood vessels had become thinned and whitened – a lattice degeneration. Rapid deceleration during the crash would have impelled the gel part of the vitreous into sharp traction on such attachments. She saw that the end of the thin line of lattice degeneration crossed the flap. Whether or not the flap of the tear was pulled above the general retinal surface was unclear but there must be some continuing tension on the neural retina to cause the flashes of light, the photopsia, that her patient had reported. She was relieved to see no signs of any liquefied, syneretic, vitreous material penetrating beneath the edges of the tear. That would be the start a retinal detachment. Because of the position of the tear, in the upper part of the eye globe, toward the temple, any vitreous fluid that might penetrate between the two retinal layers would spread. Aided by constant saccade movements of the eyeball and the weak binding between the retinal layers, the fluid might accumulate then sink in an arc toward the area of the macula. That would threaten the functioning of her fovea. This was not yet a medical emergency but immediate preventive surgery was needed.

The ophthalmologist gave her patient a rest and reassured her that although the trauma had torn a patch of her left retina, the wound could be sealed using a laser. Other treatments, such as a freezing probe for cyropexy surgery were an option, but she

preferred the laser instrument for its precision over the size and placing of the sealing spots. Her patient wanted to know more. The laser beam would create tiny areas in which the tissues of both retinal layers weld together through the energy of the laser. These spot welds would be in the healthy retina around the entire tear, sealing it as a prophylaxis against full retinal detachment. If not repaired the tear was in serious danger of developing into a retinal detachment that could threaten central vision unless repaired using more complex surgery done invasively, within the eye. The laser repair would be non-invasive and so could be made under local anaesthesia in the out-patients department. It would be done as soon as time could be found that afternoon.

Back in front of the ophthalmoscope she again fitted the contact lens. The illumination system of this ophthalmoscope also incorporated a laser beam. The beam was created by an argon gas apparatus in a separate box and fed via a fibre optic cable into the system of lenses and mirrors of the ophthalmoscope. As any laser, this beam was highly directional or collimated, the waves of light were coherent and the energy of the photons it could deliver was intense. The beam was focussed on the retina to a spot of 500 micrometres diameter, the energy of the beam was initially applied at 150 milliwatts and adjusted against the laser pulse of 200 milliseconds to coagulate the tissues of the retina by heating to about 65^{o}C. Photocoagulation is the technical term.

The treated retina instantly turned white at the spot. Placing the spots was done through the contact lens and its mirrors with enough precision to make each spot touch the previous one in each row, with the innermost row slightly away from the outer edge of the tear where the neural retina was still healthily attached to the retinal pigment epithelium. The ophthalmologist incorporated the edges of lattice degeneration within the rows of spots. To complete the job took sixty spots in three concentric rows. The light energy of the laser's photons at each spot was absorbed mostly by the pigment of the epithelium and turned to heat. Heat energy coagulated the proteins of all cells and interphotoreceptor matrix within the spot. Everything in this lump of dead, then healing, tissue would hold together more strongly than the natural bond between these two retinal layers. The rows of spots were a palisade against forces from within the globe of the eye pulling at the torn flap of neural retina. They would prevent the tear from enlarging and allowing liquefied vitreous material to penetrate between; prevent separation of the layers from each other.

The retinal pigment epithelium, unlike any other kind of mature neural tissue, retains substantial regenerative capacity as long as it is in a healthy condition. After all, one of its main jobs is to regenerate the cones and rods at a prodigious rate. Within a few days the lasered spots in her eye began a slow process of partial repair and regeneration. The pigment epithelium was the first to reconstitute itself at each spot. Phagocytic cells ingested and removed dead cells. New epithelial cells moving in from the undamaged margins. The neural retina was without such healing capacity but nevertheless

rearranged its complex cellular architecture so that neurons spread into the wound. The ophthalmologist expected to see, during the second or third check-up, signs of the spots regressing and their grey colour turning to pink. Because of the position of the tear, far away from the fovea, the remains of the photocoagulation spots would have a scarcely perceptible effect on her patient's peripheral vision.

Her left eye felt strange from all this peering, probing, anaesthetic, and manipulation of the Goldmann lens. Nevertheless she felt confident as she listened to how she should look after herself for the next seven days resting at home before the first check-up. There was the possibility that invasive surgery would be needed to relieve any continuing tension on the tear, so she should take careful note of more flashes or newly conspicuous floaters. No problem: deeply relieved as she was to have bones and eyes working properly after that smash-up. Her partner was waiting in the reception foyer. They hailed a taxi for the trip back to their apartment, discussing what extra treats were already cooking in the oven to compensate for their missed Friday supper.

♦ ♦ ♦

In the late 1930s Valentin A. Fabrikant was a teacher of physics at the Moscow Power Engineering Institute. He also researched the behaviour of gases using spectroscopic methods at the Lebedev Physical Institute. Although busy as head of his department he registered for a doctoral degree. He had the ambition to prove by experiment a theory about the interaction of light with the electrons of an atom or molecule. The theory was known as 'stimulated emission of radiation'. Albert Einstein formulated it as one of his extraordinary thought experiments and wrote his equations and ideas in a pair of papers published in 1916 and 1917. Other workers in Europe and America had continued with such thought experiments during the 1920s, but Fabrikant was not only in a position to translate ideas into practice, he was expected to produce tangible results in an institute with a long history of optics in relation to the phenomena of fluorescence and the workings of neon and fluorescent light tubes.

Fabrikant managed to publish his thesis in 1940 and one paper on his topic in 1941 – life in Moscow then was under threat of invading armies moving eastwards. As a public servant he had more pressing duties than testing strange theories. But by 1951 he gained the support of colleagues Fatima Butayeva and Michael M. Vudyinski to assist with filing a patent based on his results on stimulated emission. The patent examiners initially rejected the application but the patent granted in 1959 bore a title that started: 'A method for the amplification of electromagnetic radiation (ultra-violet, visible, infrared and radio . . .)'.

To amplify light? Well, that sounds simple enough: just turn up the power supply to the light bulb surely. No – Einstein had predicted something far more significant. His

inspiration was that particles of electromagnetic radiation, photons, were equivalent to quanta of energy. Quanta as in quantum theory, incredibly small but entirely discrete packets, or energy-elements as Einstein called them. At the time he was toying with concepts of quanta few physicists accepted such propositions. But he had confidence in his equations. These described a situation, extremely improbable but still possible, in which an atom of a specific element with its cloud of electrons would have one electron inhabiting an orbit at an energy level higher than normal. An energy level that was at a separately more distant orbit away from the atom's nucleus would be inhabited by an electron by random chance. If a photon from an outside source were to collide with this electron then the electron would be knocked down to its next lower energy level. Another improbable event, but it was still possible. As the electron lost its energy a new photon would be emitted. Meanwhile the original photon would continue to travel along its original path, with its original frequency and phase. The new photon would accompany the original one with exactly the same characteristics. The two photons would be coherent; two for one, and there would be many more if the process was somehow to re-cycle and amplify.

For Einstein his theory of stimulated emission was a minor contribution. He wanted to return to theorizing about relativity. Other physicists saw that the key to developing this theory of stimulated emission further, and possibly to develop it into a working device, centred on those electrons in orbits higher than normal. They thought in statistical terms, following the theory of Ludwig Boltzman to describe the stochastic behaviour of populations of atoms. They thought about populations of atoms of mercury or the inert gas neon; elements already familiar from their use in lighting tubes and lamps. Rudolf W. Ladenburg at the University of Breslau, Richard C. Tolman at the California Institute of Technology, and Alfred Kastler at the Ecole Superérieure in Paris, were prominent amongst those trying to manipulate such a population. They aimed to create what they called a population inversion. That would be a state in which more electrons than by mere random chance would be in a higher level orbit than normal. The population of atoms would be excited. Ladenburg first achieved this in 1928. Fabrikant learnt of his technique, which Ladenburg had called optical pumping, and incorporated it into his application for a patent.

♦

The 1940s were as deeply troubled for physicists as other people who were lucky enough to lead a normal life. But at least some physicists enjoyed vast opportunities opened up by military demands for many new techniques and machines. Military strategists saw the need for means to detect their enemies at long distance and at night. To detect things smaller than a battle ship: maybe just the conning tower of a surfaced submarine. Physicists told the strategists that radio waves, electromagnetic radiation at wavelengths measured in many metres, were ineffective to provide the definition and

information needed. Shorter wavelengths were urgently needed, and preferably from a device small enough to fit into an aircraft. Microwaves in other words, measured in centimetres, and produced in a steady intense beam that could be directed to scan the horizon for threats.

The breakthrough came from the University of Birmingham in 1940 where radio researchers John T. Randall and Harry Boot built a device extraordinarily potent in its simplicity, power and future place in history. It was a magnetron, made from a saucer sized block of copper with cavities carved into it. Under conditions of great urgency and secrecy British and American diplomats made a deal for manufacture of this new microwave device by the million in exchange for its secrets. Engineers and physicists from Bell Telephone Laboratory and Raytheon Company worked at the Radiation Laboratory of the Massachusetts Institute of Technology to adapt this design for use in aircraft and warships. Aircrew and sailors proved them of crucial strategic value during the Battle of the Atlantic, lasting into 1945.

Isidor I. Rabi was one of those who worked at the Radiation Lab of MIT in those dark days. On return to his peacetime post at Columbia University in the heart of New York City he established his own laboratory. He intended to exploit the power of microwaves for studies in fundamental chemistry and physics. Already Rabi had discovered the phenomenon of nuclear magnetic resonance. This would become the basis for the invention of magnetic resonance for medical tomography by the 1970s. He had discovered NMR using a molecular beam machine. This apparatus forced a gas from a high pressure chamber, through a small nozzle and into a long chamber where the pressure was lower. The molecules (or atoms) of gas streamed together in a beam of sufficient integrity that it could be manipulated by applied magnetic fields. One possible manipulation was to separate molecules with an electron in a higher than normal energy level, excited molecules to be separated off from the rest.

Rabi found it easy to attract generous funding, the more so when awarded in 1944 the Nobel Prize for his NMR discovery. One of the researchers Rabi encouraged into his laboratory was Charles H. Townes, who wanted a return to fundamental studies after wartime duties at Bell Telephone Labs. Townes understood the ammonia molecule as an excellent subject to study in a beam machine: one nitrogen atom connected to three hydrogen atoms in the shape of a triangular pyramid. A pyramid that when energised by microwaves naturally resonates at a fixed frequency, it flips up–down as its hydrogen atoms oscillate relative to the nitrogen atom. How did that happen Townes wanted to know?

One funding agency, the Naval Office of Research, asked Townes to investigate the possibility of producing microwaves at millimetre wavelengths. Townes, however, knew the engineering difficulties would be just the start of his problems with this

project. The proposition seemed to contravene the second law of thermodynamics. Nothing does that. The engineering problem was the minute size of the oscillators needed for such short wavelengths. Townes's genius was to realize that he had small oscillators to hand. Very small ones: the ammonia molecules in his beam machine. Townes put this proposition to two research assistants: Herbert J. Zieger and James P. Gordon. The latter planned to write up the project for his doctoral thesis. Townes's hunch was that his assistants would be able to produce a population inversion amongst the ammonia molecules energised by the microwaves. The incoming photons of microwave radiation would induce stimulated emission of radiation. If the beam cavity also could act as a resonant cavity then possibly there could be an amplification of radiation. Townes hoped they could be the first to produce such a phenomenon, unknown on Earth but predicted by Einstein. He wrote down his ideas in his laboratory logbook in 1951 and had the entry witnessed by a colleague. In 1954 Gordon burst into a departmental seminar: 'It works!' They had produced microwave amplification of simulated emission of radiation, the maser. Townes applied for a patent on the device in 1955, it was granted in 1959.

Already a race was on. Research at the Lebedev Physics Institute on stimulated emission had continued with powerful contributions of Aleksandr M. Prokhorov and Nicolay G. Basov, as they published results from 1945 onwards that researchers in America would get translated to read. The topic was buzzing in the air and those with an inventive mind knew that if the maser phenomenon could be replicated with photons of light rather than microwaves, then the power to be obtained from a narrowly coherent, collimated, beam would be thousands of times greater than that of a maser of equivalent size.

Gordon Gould was a mature doctoral student in Isidor Rabi's physics department; he shared the same corridors as Charles Townes. Already he was a potential inventor with a well developed idea for a new type of contact lens, as well a varied experience of industrial and military styles of research. He enrolled at Columbia University to improve his understanding of physics the better to invent things. Soon he abandoned his set thesis topic to devote his time to a device that he described in his laboratory book as capable of: 'light amplification of radiation by stimulated emission of radiation'. A laser. Gould's ideas of how it would work were radically different from the machine that Townes had invented. In 1957 Gould went to a public notary in a nearby street store to have the nine relevant pages of his lab book witnessed. Gould listed a wide variety of potential uses of his laser, including heating and cutting using a focussed beam. He applied for a patent in 1959, but it was never granted because of technical faults and conflicts with other patents. Gould would spend the next thirty years fighting a patent war over his ideas for making lasers.

The first working laser was constructed by another inventor: Theodore H. Maiman, engineer and physicist. In 1956 he forsook fundamental studies of atomic structure using microwaves for a job with Hughes Aircraft Company, at Malibu, California. Early success with a military contract led to a grant from the company for work on his own ideas. Specifically a laser – one that would be compact, simple, with low power demand and based on a solid lasing medium. And yes, it would be the first to produce laser light. Within nine months Maiman and his assistant Irnee d'Haenens devised a machine that fitted neatly into the palm of d'Haenens hand. This polished aluminium tube contained a rod of synthetic ruby with mirrored surfaces on its perfectly flat ends forming both the lasing medium and the resonant cavity. The crystal of ruby was surrounded by a helical xenon flash bulb to pump the ruby with light energy. A small window on one mirror would let out the laser beam – if it would work. As it did, on 16 May 1960 when a pulse of intense, coherent, amplified light shot out to be recorded on their oscilloscope. Laser light for the first time, first place, unknown anywhere before. The Linde company had grown and machined the ruby crystals; the flash lamps were ordered from a catalogue. Maiman's engineering genius reduced the arcane quantum physics of Einstein to a what appeared to the casual observer as a minor gadget from the shelves of an electrical goods store.

Gordon Gould read the news ruefully, but at least he was deep in the laser business, having abandoned his thesis altogether to gain a post with a start-up company called Technical Research Group, in Nassau county, New York State. Gould enjoyed a vindication of his ideas on how to employ lasers when an ophthalmologist contacted him in 1961. Milton Zaret, working at the Bellvue Hospital of the New York University School of Medicine asked Gould for loan of one these new fangled light sources. Would they be any use to an eye surgeon, or would they be too dangerous?

At that time, ophthalmologists routinely used intense light from a xenon arc lamp for photocoagulation surgery of the retina and other structures. This method had been invented in the 1940s by Gerhard Meyer-Schwickerath working in Germany. By the late 1950s the technique was performed with a Xenon Photocoagulator machine manufactured by the Zeiss optical company of Germany. Long before that, from the early 1920s, the concept of deliberately cauterizing tissues of the eye to prevent and even repair retinal detachments had been developed into a routine method by Jules Gonin working at the Eye Hospital in Lausanne, Switzerland. Gonin was the first to stress the importance of detecting retinal tears by routine ophthalmoscopic examination, then repairing them before they developed into detachments. He used a white hot thermocautery applied to the sclera exposed in the eye orbit, and this had to be done blind in the sense that the position of the tear, previously observed through the iris had to be translated to where it could be treated externally through the sclera. An alarming procedure, but its routine use demonstrated the imperative from patients to preserve their working vision.

Gould and his colleague Gerard Grosof had to hand a Maiman type ruby laser called *Vireo 1*. Gould himself was banned from the laboratory of the project that he led because he had no security clearance for this militarily funded research. He had been dismissed from his wartime post on the top-secret Manhattan Project for his involvement with a Marxist study group. To hell with security he thought, a medical procedure as the first application of lasers would be tremendous publicity. They smuggled *Vireo 1* over to Bellvue, where Zaret and his colleagues tested it on rabbit eyes for photocoagulation effects and possible dangers. They published their preliminary results in 1961 and within several more years other eye surgeons were using pulsed ruby lasers on human patients to repair various eye pathologies, including retinal tears. Milton Flocks and Christian Zweng reported in 1964 from California their repair of the retinas of twelve patients. The next year Charles J. Campbell in New York used the same technique on seventy one patients with retinal tears. Success was enjoyed by seventy of them, whilst of nineteen patients with detached retinas, fourteen gained restored vision.

Physicists and engineers rushed into this laser business: the stuff of science fiction. Maiman's first laser gave only a pulsed beam because the pumping light source was designed for photography not quantum physics. In 1964 at Hughes Aircraft Company W.B. Bridges invented the first laser using argon as the lasing medium. This produced a continuous beam of light in the blue to green spectrum. Ophthalmologists recognised that this quality of light would be well absorbed by the red pigment of highly vascularized tissues often needing treatment in patients with diabetic retinopathy.

Francis A. L'Esperance at the Columbia-Presbyterian Medical Center in the Washington Heights district of New York City first adapted an argon laser for eye surgery. Initially he tried an experimental laser made by the Raytheon Company under a military contract as a potential weapon. It was 3.5 metres long and so heavy that a building crane was employed to raise it to a window on the ninth floor where L'Esperance worked. The contraption looked promising in principle but something neater was obviously required for routine use by clinicians. At their factory in Waltham, Massachusetts, workers at Raytheon designed their *Model LG-13S* argon ion laser specifically for eye surgery. Still big by modern standards, about the size of a domestic refrigerator, it was coupled to an optical system of tubes, mirrors and lenses to direct the laser beam into the same light path as that of the general illumination and binocular viewing head as routinely used by ophthalmologists. L'Esperance described this in 1968, together with experimental details of his use for treating vascular disease of the retina. Soon this design was adapted for repair of retinal tears and detachments and it continued as the basis of routine equipment.

Gordon Gould suffered a retinal detachment in 1985. His ophthalmologist repaired it using an argon laser photocoagulator. Gould was then still struggling through his patent battle. Two years later Gould's lawyers won a ruling that his original ideas and subsequent patents should be recognised and moreover be backdated. Money poured in from many companies who were already making big profits from his intellectual property. Gould enjoyed his retirement as a multi-millionaire.

♦ ♦ ♦

With little force or other stimulus the neural retina will detach from its supporting epithelium of retinal pigment cells. Between the cells of this epithelium are multiple gap junctions forming a sheet with great lateral integrity. In contrast there are no such anatomical connections between the two layers of the retina. The thin space at the interface between the two layers is filled with a complex matrix in the form of a three dimensional net with small molecular hooks one function of this matrix and its associated proteins is to glue the two retinal layers together. But a molecular glue, not interlocking structural joints, has to suffice.

The unfortunate frequency of retinal tears and detachments is one more characteristic added to a list of apparent mistakes or maladaptations in the design of the vertebrate eye. Since the days when Charles Darwin struggled to explain how such a complex organ could evolve, the vertebrate eye been used as an example of the awesome power of evolution acting through the mindless power of natural selection. The eye has also been used as a cautionary tale about how natural selection throws up many examples of compromises that allow bad designs to coexist with designs that allow better survival.

The inverted retina of vertebrate eyes has obvious optical problems in comparison with the everted retina of squid and octopuses, invertebrate animals of the cephalopod group. The inverted structure in vertebrates requires light to penetrate past the retinal blood vessels then down through the dense mesh of nerve fibres, nuclei, mitochondria and Golgi apparatuses of neurons before the photoreceptors are reached and where a photon can trigger a nerve impulse. Then the impulse has to travel out to the central brain along a nerve fibre that travels over the inner surface of the retina and down into the optic nerve starting at the blind spot of the retina. Photons entering and nerve impulses departing the retina of an octopus face no such optical and anatomical barriers and contortions.

Other scientists have disparaged the design of the vertebrate eye in comparison with cameras. However, this comparison relies on false logic. Humans (living things) invent, design and construct tools and machines (dead things) to enhance the limited biological capabilities they have inherited. Glasses enhance the optical performance of eyes of those humans born with optical defects in their light refracting system or who

acquire optical defects as they age. Glasses have no meaning or function without a human's eyes both to focus photons into an image on the retina, and crucially then to process that image as something the human brain can use. A camera of powerful design mounted on a robot that lands on a comet in order to beam radio signals back to Earth to be displayed on television screens for astronomers to view is without meaning or function unless information reflected from the comet's surface is brought to life and meaning in the retinas and central brains of those ecstatic astronomers. Forget about cameras and other machines; comparing them with humans and their eyes is a category error. Stick to comparisons within the relevant category: humans compared with squid in their undersea gloom, or with hawks spotting mice darting amongst bright grass.

Eyes only work when they are alive. Living things need nutrients and multicellular organisms also need oxygen. The human retina consumes more oxygen per mass of tissue than even the same mass of tissue of our highly energetic central brain. The photoreceptors are densely packed with mitochondria, as are the cells of the retinal pigment epithelium. The metabolism and physiology of photoreception, support of the photoreceptors by the pigment epithelium, and pre-processing of information in the neural retina require massive traffic of oxygen, glucose and other nutrients into the tissues. Then out must go carbon dioxide, waste metabolites and dangerous reactive oxygen species. The specific adaptation for this is the design of the blood supply to the epithelium and photoreceptors: the choroid. In addition the neural retina is deeply penetrated by its separate blood capillaries. If your optometrist shows you the electronic image she has made of your retina you will be struck by its uniformly bright red colour; the hue of red blood cells illuminated through the iris by the camera's flash. The inverted retina of vertebrates has allowed the evolutionary opportunity for the choroid to develop around the outside of the retina. It could not work effectively for an everted retina because incoming light would have to penetrate this thick mat of choroidal blood vessels.

In comparison, the inner retinal circulation, supplying the neuron layers and vitreous is a minor barrier to good reception of photons. The crucial part of the vertebrate retina, the fovea, is clear of these retinal blood vessels. It is also clear of the mass of neuronal connections of the rest of the neural retina and is densely packed with cones. This special combination of features is a specific adaptation for the highly acute vision of vertebrates because the fovea works in concert with the automatic saccade mechanism of the eye's lens and muscles. The system provides your ability to read the few sharply focussed words of this sentence that you need to concentrate on to understand my message, whilst rapidly scanning along the line of the sentence as it is vaguely perceived by your peripheral vision.

The zebra fish that swim around the aquaria of some biologists have been a good source of knowledge about embryonic development. The eyes of fish fry are

disproportionately large and are crucial to survival of these plankton feeding fish within the five days after the eggs being fertilized and the fry hatching out. Seeing underwater requires a strongly refractive lens, almost spherical. In these smallest of vertebrate eyes the space between the lens and the neural retina, where the vitreous would be expected, is filled with retinal cells. This saves valuable space in such small animals. If these eyes were not of the inverted design characteristic of all vertebrates, but of the everted design of cephalopods such space saving would be impossible. The cephalopod eye packs its neural processing into the large optic lobes of the brain, posterior to the globe of the eye. This requires more space and allows more signal noise to intrude between photoreceptors and processing neurons.

The mystery of how the inverted retina of vertebrates started out in evolutionary history remains unsolved. But once our small and ancient marine ancestors started out on an embryological pathway that formed an inverted eye that worked well enough there was no going back. Natural selection can only work on the differential reproductive rates of new mutant forms of an organism: forwards only. But far from maladaptive design, this happenstance of evolution gave rise to opportunities for selection of the best adapted eyes in the animal kingdom, opportunities for the evolution of many groups of animals in which vision is the foremost sense system for their survival. For the evolution of primates swinging through trees in search of colourful fruit, for vultures searching carcasses from a kilometre or two above the plains. Evolution throws up many make-do compromises, roundabout kluges, as solutions to the problems of survival, reproduction, and passing on genes. Our eyes certainly reveal one example of compromise. The retina detaches too easily because the dynamic and complex relationship between the photoreceptors and the cell of the pigment epithelium seems to be impossible without a loose interface that allows heavy and constant traffic of cell to cell interactions.

Sources and notes

Development of the vertebrate eye

Barischek, Y. R., 2001. *Embryology of the Eye and its Adnexae*. Karger, Basel.

Bozanic, D., *et al*., 2003. Role of apoptosis and mitosis during human eye development. *European Journal of Cell Biology*, **82**: 421-429.

England, S.J., *et al*., 2006. A dynamic fate map of the forebrain shows how vertebrate eyes form and explains two causes of cyclopia. *Development*, **133**: 4613-4617. [Contains links to videos of motile cells in embryonic fish eyes.]

Forrester, J. *et al*., 1996. *The Eye: Basic Science in Practice*. W.B. Saunders Ltd., London.

Mann, I.C., 1969. *The Development of the Human Eye*. British Medical Association, London. [Also published in 1964 by Grune and Stratton, New York. Although dating from studies done in the 1920s this remains a solid basis for understanding the embryology of the human eye; well illustrated by the author's drawings and photographs.]

Oyster, C.W., 2000. *The Human Eye*. Sinauer Associates Inc., Sunderland, Massachusetts.

Reh, T.A., 2012. The development of the retina. In: *Retina*, chapter 13, pgs 330-341. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Spooner, J.D., 1983. *Ocular Anatomy: the Anatomy, Histology, Embryology, Ontogeny and Phylogeny of the Human Eye and its Related Structures*. London, The Association of Dispensing Opticians.

Evolution of eyes

Anonymous, 2014. *Evolution of the eye*. Wikipedia: http://en.wikipedia.org/wiki/Evolution_of_the_eye [See the image*:* *"*Vertebrates and octopuses developed the camera eye independently.*"*]

Dawkins, R., 1997. *Climbing Mount Improbable*. London, Penguin. [Chapter 5 is devoted to the evolution of vertebrate eyes.]

Gehring, W.J., 2005. New perspectives on eye development and the evolution of eyes and photoreceptors. *Journal of Heredity*, **96**: 171-184. [Mostly on genetics and deep history of eyes.]

Lamb, T.D., Collin, S.P. & Pugh, E.N., 2007. Evolution of the vertebrate eye: opsins, photoreceptors, retina and eye cup. *Nature Reviews Neuroscience*, **8**: 960-976.

Land, M. F. & Nilsson, D.-E., 2002. *Animal Eyes*. Oxford University Press, Oxford.

Weiss, K., 2002. How the eye got its brain. *Evolutionary Anthropology*, **11**: 215-219. [A quirky but informative article about evolution using the eye as an example. See pg. 219: 'My title? Light by itself is useful, but its pattern can be more So. Single celled organisms already possessed basic photoreception Very Long Ago. But though they could detect light, complex organisms had to evolve a brain so they could see. Now that is a pretty good Story!']

Structure and function of retina

Anonymous, 2014. *Retina*. Wikipedia: http://en.wikipedia.org/wiki/Retina [See the highly informative image: 'Illustration of image as "seen" by the retina independent of optic nerve and striate cortex processing.' This manufactured image emphasizes the role of the fovea, peripheral vision, and saccade mechanism. Also see the section 'Vertebrate and cephalopod retina differences' for an argument about possible adaptive advantages of the inverted retina of vertebrates.]

Chen, J. & Sampath A.P., 2012. Structure and function of rod and cone photoreceptors. In: *Retina*, chapter 14, pgs 343-359. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Grant, M. B. & Lutty, G.A., 2012. Retinal and choroidal vasculature: retinal oxygenation. In: *Retina*, chapter 18, pgs 433-466. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Gregg, R.G., *et al*., 2012. Function and anatomy of the mammalian retina. In: *Retina*, chapter 15, pgs 361-400. (Edited by W.C. Ryan,) S.J. Mosby, St Louis.

Gregory, R.L., 1998. *Eye and Brain: the Psychology of Seeing*. Oxford University Press.

Hageman, G.S., *et al*., 1995. The interphotoreceptor matrix mediates primate retinal adhesion. *Archives of Ophthalmology*, **113**: 655-660.

Hollyfield, J.G., 1999. Hyaluronan and the functional organization of the interphotoreceptor matrix. *Investigative Ophthalmology & Visual Science*, **40**: 2766-2769.

Hudspeth, A.J. & Yee A.G., 1973. The intercellular junctional complexes of retinal pigment epithelium. *Investigative Ophthalmology*, **12**: 354-365.

Katamay, R. & Nussenblatt, R.B., 2012. Blood-retinal barrier, immune privilege and autoimmunity. In: *Retina*, chapter 27, pgs 580-589. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Kolb, H., *et al*., (editors) 2014. *Webvision: The Neural Organization of the Vertebrate Retina.* John Moran Eye Center, University of Utah, Salt Lake City, Utah. http://webvision.med.utah.edu/ [Packed with free information, from numerous authors, at medical textbook level, on the biology of human vision.]

Lamb, T.D., Pugh, E.N. & Collin, S., 2008. The origin of the vertebrate eye. *Evolution Education Outreach*, **1:** 415-426.
http://www.ntskeptics.org/creationism/evolution/TheOriginOfTheVertebrateEye.pdf

Lamb, T.D., 2013. Evolution of phototransduction, vertebrate photoreceptors and retina. *Progress in Retinal and Eye Research* **36**: 52-119.

Marmor, M.F., 2010. Retinal pigment epithelium.
http://medtextfree.wordpress.com/2010/12/29/chapter-100-retinal-pigment-epithelium/

Rizzolo, L.J., 2007. Development and role of tight junctions in the retinal pigment epithelium. *International Review of Cytology*, **258**: 195-232.

Steinberg, R.H., 1985. Interactions between the retinal pigment epithelium and the neural retina. *Documenta Ophthalmologica***, 60**: 327-346.

Strauss, O., 2005. The retinal pigment epithelium in visual function. *Physiological Reviews*, **85**: 845-881.

Thumann, G., *et al*., 2012. Cell biology of the retinal pigment epithelium. In: *Retina*, chapter 16, pgs 401-414. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Factors leading to retinal tears and detachments

Brantley, M.A. & Sternberg P., 2012. Mechanisms of oxidative stress in retinal injury. In: *Retina*, chapter 22, pgs 517-528. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Ghazi, N.G. & Green, W.R., 2002. Pathology and pathogenesis of retinal detachment. *Eye*, **16**: 411-421.

Haimann, M.H., *et al*., 1982. Epidemiology of retinal detachment. *Archives of Ophthalmology*, **100**: 289-292.

Kirchhof, B., *et al*., 2012. Pathogenetic mechanisms of retinal detachment. In: *Retina*, chapter 95, pgs 1616-1621. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Liang, F.-Q. & Godley B.F., 2003. Oxidative stress-induced mitochondrial DNA damage in human retinal pigment epithelial cells: a possible mechanism for RPE aging and age-related macular degeneration. *Experimental Eye Research*, **76**: 397-403.

Marmor, M. F. (2012). Mechanisms of normal retinal adhesion. In: *Retina*, chapter 19, pgs 448-463. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Mitry, D., *et al*., 2011. The predisposing pathology and clinical characteristics in the Scottish Retinal Detachment Study. *Ophthalmology*, **118**: 1429-1434.

Sebag, J. & Green W.R., 2012. Vitreous and vitreoretinal interface. In: *Retina*, chapter 21, pgs 482-515. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Soubrane, G. & Coscas, G., 2012. Pathogenesis of serous detachment of the retina and pigment epithelium. In: *Retina*, chapter 30, pgs 618-623. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Photocoagulation technique for retinal tears

Aylward, G.W. 2012. Optimal procedures for retinal detachment repair. In: *Retina*, chapter 105, pgs 1784-1792. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Campbell, C.J., *et al*., 1965. Clinical studies in laser photocoagulation. *Archives of Ophthalmology*, **74**: 57-65.

Flocks, M. & Zweng, H.C., 1964. Laser coagulation of ocular tissue. *Archives of Ophthalmology*, **72**: 604.

Gonin, J.J., 1930. The treatment of detached retina by searing the retinal tears. *Archives of Ophthalmology*, **4**: 621-625.

Hamilton, A.M.P., *et al*., 1998. *Text Atlas of the Retina*. Martin Dunitz Ltd., London,

Kanski, J.J. & Gregor Z.J., 1994. *Retinal Detachment, a Colour Manual of Diagnosis and Treatment*. Butterworth-Heinemann Ltd., Oxford

Karlin, D.B., 1995. *Lasers in Ophthalmic Surgery*. Blackwell Science, Cambridge, Massachusetts, and Oxford, England.

Kreissig, I., (Editor) 2005. *Primary Retinal Detachment: Options for Repair*. Springer-Verlag, Berlin.

L'Esperance, F.A., 1968. An ophthalmic argon laser photocoagulation system: design, construction, and laboratory investigations. *Transactions of the American Ophthalmological Society*, **66**: 827-904.

Meyer-Schwickerath, G., 1960. *Light Coagulation*. C.V. Mosby Co., St. Louis

Packer, A.J., 1989. *Manual of retinal surgery*. Churchill Livingstone, New York & Edinburgh.

Palanker, D. & Blumenhranz, M.S., 2012. Retinal laser therapy: biophysics and applications. In: *Retina*, chapter 39, pgs 746-760. (Edited by W.C. Ryan.) S.J. Mosby, St Louis.

Yanoff, M. & Duker, J.S., 2013. *Ophthalmology*. Elsevier Health Sciences, London.

Zaret, M.M., Ripps, H., *et al*., 1963. Laser photocoagulation of the eye, *Archives of Ophthalmology*, **69**: 97-104.

Invention of the laser

Basov, N.G. & Prokhorov, A.M., 1954. 3-level gas oscillator. *Zhurnal Eksperimentalnoi i Teoreticheskoi Fiziki*, **27**: 431.

Bertolotti, M., 2005. *The history of the laser*. Institute of Physics Publishing, Bristol, England

Einstein, A., 1916. Radiation emission and absorption according to quantum theory. *Verhandlungen der Deutschen Physikalischen Gesellschaft*, **18**: 318-323.

Bridges, W.B., 1964. Laser oscillation in singly ionised argon in the visible spectrum. *Applied Physics Letters*, **4**: 128-130.

Fabrikant, V.A., Vudynskii., M.M. & Butayeva, F., 1959. A method for the amplification of electromagnetic radiation (ultraviolet, visible, infrared and radio waves), distinguished by the fact that the amplified radiation is passed through a medium which, by means of auxiliary radiation or other means, generates excess concentration, in comparison with the equilibrium concentration of atoms, other particles, or systems at upper energy levels corresponding to excited states. USSR Patent 132209. [The first patent on the idea of a laser, but not a description of a device that could work.]

Gordon, J.P., Zeiger, H.J. & Townes, C.H., 1954. Molecular microwave oscillator and new hyperfine structure in the microwave spectrum of NH3. *Physical Review*, **95**: 282-284.

Gould, G. 1987. Light amplifiers employing collisions to produce a population inversion US Patent 4,704,583 [This is the patent that was granted when Gould won his 30 year battle over patent rights.]

Hecht, J., 2005. *Beam: the Race to Make the Laser*. Oxford University Press. [An accessible and comprehensive account of history of laser invention.]

Maiman, T.H., 1960. Stimulated optical radiation in ruby. *Nature***, 187**: 493-494. [The first description of a working laser.]

Maiman, T.H., 1967. Ruby laser systems. US Patent 3,353,115. Assigned to Hughes Aircraft Company. [The first patent for a working laser device.]

Maiman, T.H., 2000. *The laser odyssey*. Laser Press. [Maiman's account of the invention of the first working laser.]

Taylor, N., 2000. *Laser: the Inventor, the Nobel Laureate and the Thirty Year Patent War*. New York, Kensington Publishing Corp. [A lively and informative account of the race to the first working laser.]

Townes, C.H., 1999. *How the Laser Happened: Adventures of a Scientist*. Oxford University Press, New York. [Townes's personal account of invention of the laser.]

Advantages and disadvantages of an inverted retina

Goldsmith, T.H., 1990. Optimization, constraint, and history in the evolution of eyes. *The Quarterly Review of Biology*, **65**: 281-322. [An academic and theoretical account of eye evolution.]

Gurney, P.W.V., 1999. Is our 'inverted' retina really 'bad design'?, *Creation Ex Nihilo Technical Journal*, **13:** issue 1. http://www.neuroanatomy.wisc.edu/selflearn/invertedretina.htm [An argument by an ophthalmologist for intelligent design of the human eye.]

Kröger, R.H. & Biehlmaier, O., 2009. Space-saving advantage of an inverted retina. *Vision Research***, 49**: 2318-2321.

Lamb, T.D., 2011. Evolution of the eye. *Scientific American,* (July issue): 65-69. http://www.grochbiology.org/EyeEvolution.pdf [An argument by an evolutionary biologist for evolution by natural selection producing the design of the vertebrate eye.]

Lane, N., 2009. *Life Ascending: the Ten Great Inventions of Evolution.* Profile Books, London. [See Chapter 7, *'Sight'*.]

Sleggs, G.F., 1926. The functional significance of the inversion of the vertebrate retina. *American Naturalist***, 60**: 560-573. [An early argument for an adaptive advantage of the inverted retina of the vertebrate eye.]

Wirth, A., Cavallacci, G., & Genovesi-Ebert, F., 1984. The advantages of an inverted retina. A physiological approach to a teleological question. *Developments in Ophthalmology*, **9**: 20-28.