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D P L GREEN
Department of Pharmacology, University of Otago, PO Box 913, Dunedin, New Zealand

Reviews

The unique origin of rod photoreceptors in the teleost retina

Pamela A. Raymond

A population of mitotic cells that produce new neurons has recently been discovered in the layer of photoreceptors in retinas of several species of larval and adult fish. These cells generate new rods which are inserted into the photoreceptor mosaic at locations scattered across the entire expanse of the differentiated retina. Subsequently these new rods establish synaptic connections with retinal neurons already present. The continued production of rods in the fish is apparently needed to maintain visual sensitivity during postembryonic growth of the eye.

The extent of postembryonic growth and neurogenesis in the retina and brain of many species of adult teleost fish has only recently been widely appreciated[1]. This is somewhat surprising since the first thorough documentation of retinal cell addition in adult fish was provided over thirty years ago by Müller[2], who counted cells and calculated the total number of neurons in the retinas of guppies (*Lebistes reticulatus*) from hatching to adult stages. As the fish grew from 7 mm to 28 mm long he found a threefold increase in the number of ganglion cells, cones and inner nuclear layer cells, and nearly a sevenfold increase in numbers of rods. More recent studies in juvenile and adult goldfish, as well as other related species (*Carassius* spp.), have used cell counts[3,4], optic fiber counts[5] and autoradiographic techniques[6,7,8] to confirm that new neurons are added to the retina as the fish grows. Most postembryonic neuronal cell addition in the retina takes place in a narrow circumferential germinal zone that is located at the peripheral margin[2,6,8].

Neurogenesis is not restricted to the germinal zone

However, it has been discovered recently that not all neurogenesis in the teleost retina is confined to the circumferential germinal zone. Sandy and Blaxter[9] found that when [^{3}H]thymidine was injected into metamorphosing herring and sole, scattered cells in the outer nuclear layer, among the nuclei of photoreceptors, incorporated the label. Similar dividing cells were found in larval and juvenile goldfish and also in a cichlid fish (*Haplochromis burtoni*), in fish allowed to survive for a few weeks or months after the thymidine injection, labeled nuclei of rods, but no other neurons, were seen in the central retina[7,10]. Thus, whereas production of most neurons in the postembryonic teleost retina is confined to the circumferential edge, new rods continue to be produced by a dispersed population of rod precursors in central regions of the retina which have already differentiated and become functional (Fig. 1).

The demonstration that new rods are produced by mitotic division within the differentiated teleost retina provided an explanation for some puzzling observations that had been made repeatedly by several investigators but had been difficult to interpret. Principal among these was the observation that in many species of teleost fish the larval forms initially have no rods, but only cones[11]. Rods begin to appear either at metamorphosis or sometime during larval development, depending on the species, they then start to accumulate so that their proportions slowly but persistently increase during larval and/or postlarval stages of growth[2,3,7]. An especially dramatic example of this persistent addition of rods in the adult teleost retina was described by Locket[12] in a deep-sea fish, *Chauliodus sloani*. The retinas of mature fish of this species contain no cones but only rods, which are arranged in tiers, or banks, in small specimens there is one tier, but in larger animals, there are up to five tiers (Fig. 2).

Discovery of the rod precursor

It is now clear that dividing rod precursors are responsible for the delayed and prolonged production of rods in the teleost retina[7,9]. Previous attempts to explain the sudden appearance of rods in the differentiated larval retina and the persistent accumulation of new rods in the postlarval retina were unsatisfactory and, in retrospect, somewhat contrived. It was suggested, for example, that cones were transformed into rods[13] or that cells migrated out of the inner nuclear layer into the outer nuclear layer where they differentiated into rods[11], or that rods were produced in the circumferential germinal zone but were then displaced laterally into more central regions of the retina[2,6]. The possibility that mitotic division of stem cells within the differentiated retina might account for the addition of new rods did not seem to be an acceptable alternative because at that time there was little evidence for mitotic activity anywhere except at the germinal zone.

The finding that mitotically active cells give rise to new neurons within fully differentiated regions of retina was totally unanticipated. It contradicted all previous conceptions of how retinal histogenesis might be organized. To date most studies have observed that in the developing retina cytogenesis and differentiation take

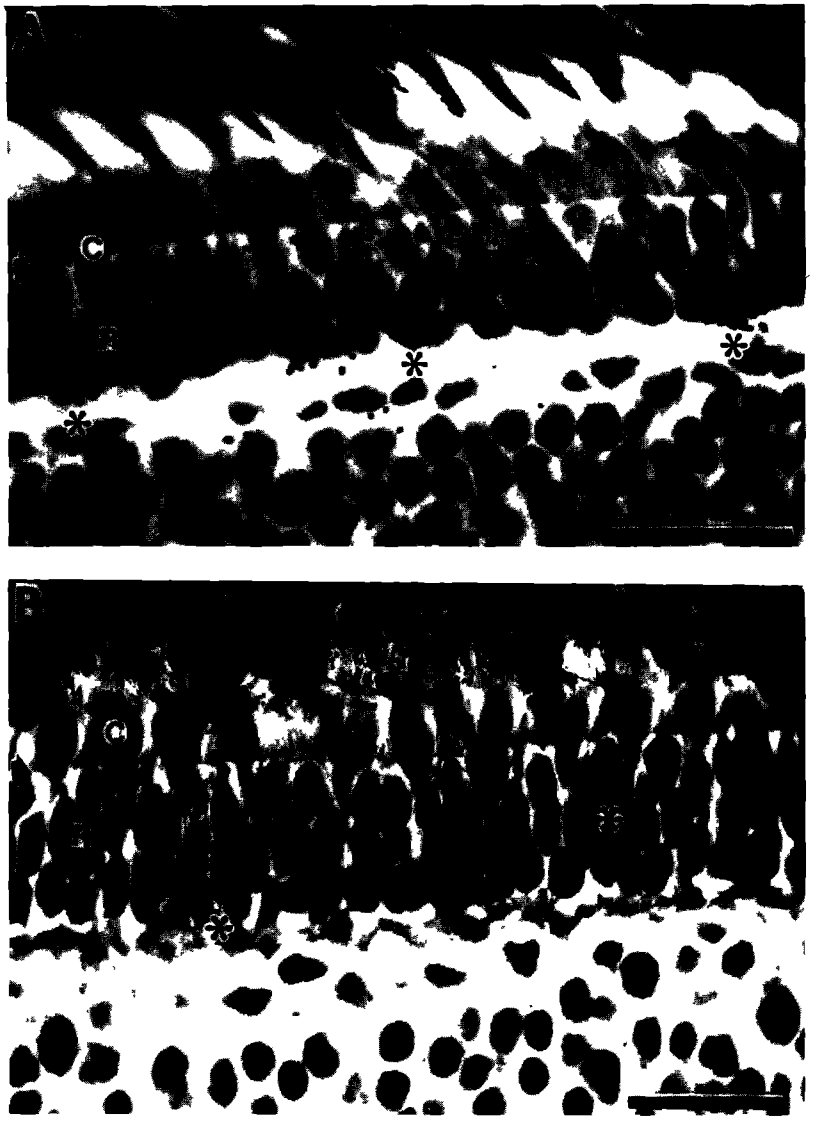

Fig. 1. A. *Dividing rod precursors in the retina of a juvenile goldfish [³H]Thymidine was injected 4 h before the animal was sacrified and the retina was prepared for autoradiography Three heavily labeled nuclei (asterisked) are at the base of the outer nuclear layer among the spindle-shaped nuclei of differentiated rods (R), cone nuclei (C) are lighter and peanut-shaped and lie in a single stratum above the rod nuclei, at the level of the external limiting membrane (arrow) Calibration bar is 20 μm* **B.** *Labeled rod nuclei in the retina of a juvenile goldfish This fish was injected with [³H]thymidine 20 days prior to sacrifice Rod precursors incorporated the label, then divided and their progeny (still labeled) differentiated into rods (asterisked) Note that labeled rod nuclei are dispersed through all levels of the outer nuclear layer from the base to the external limiting membrane (arrow) Cone nuclei (C) were never labeled except in association with the circumferential germinal zone Calibration bar is 20 μm*
(Reprinted with permission from Johns, 1982)

place in a strictly centrifugal fashion[2,14]. In the early presumptive retina, neuroepithelial germinal cells across the entire retinal epithelium are actively dividing; cell differentiation commences in the central region, near the origin of the optic nerve. As differentiation progresses, more and more cells differentiate, and the postmitotic region enlarges centrifugally toward the front of the eye In birds and mammals, once the circular wave of differentiation reaches the perimeter of the retina, at the junction with iris epithelium, the population of germinal cells is exhausted and neurogenesis ceases. The retina then contains its full complement of neurons. In fish and amphibians, in contrast, a residuum of dividing cells persists and becomes the circumferential germinal zone of the postembryonic retina[7]. This scheme not only provides an inherently consistent and simple explanation for the observed pattern of concentric cell addition at the perimeter of the growing retinas in these animals, but it also fosters a strong bias against the idea that mitosis might occur elsewhere, such as in the central regions of the retina Furthermore, the central retina appears to be made up of differentiated neurons arranged in well organized laminae, whereas the cells in the circumferential germinal zone look very much like the neuroepithelial cells of the embryonic retina Both of these considerations tended to support the belief that postembryonic neurogenesis must be restricted to the germinal zone

The nature of the rod precursor probably also accounts, in part, for the failure to recognize these cells until recently The dividing rod precursors are not very different in overall nuclear size or in light microscopic staining characteristics from the mature rod nuclei that surround them (They can be distinguished with electron microscopy, however; this is discussed later) They are diffusely scattered across the retina, and in juvenile goldfish, for example, they comprise only about 0.5% of the total rod population[7]. Because of their scattered distribution and scarcity, their discovery required that somehow they be marked or labeled to set them apart from the differentiated rod nuclei around them. [³H]Thymidine, which is incorporated into the nuclei of mitotically active cells, provided an ideal marker. Though occasional reports of mitotic activity in the outer nuclear layer had appeared in the literature before 1980 (cited in Ref 9), these were largely ignored.

Dividing rod precursors have recently been identified in the larval goldfish retina using thymidine autoradiography at the electron microscopic level, and several labeled precursors have also been reconstructed from serial thin sections[15] The nucleus of the rod precursor usually, though not always, lies at the base of the outer nuclear layer, adjacent to the outer plexiform layer, a neuropil region where synaptic contacts are made between mature photoreceptors (both rods and cones) and second-order neurons Rod nuclei are located in the same stratum as the precursors, whereas nuclei of cones are more apically positioned, at the level of the external limiting membrane (Fig. 1) Rod pre-

cursors are typically pear-shaped, with a thin apically-directed process that approaches but does not reach the external limiting membrane (Fig. 3). This is an important observation because it shows that rod precursors are not equivalent to neuroepithelial cells in the germinal zone (see below). The rod precursors are sometimes grouped in clusters of five to 10 cells, entwined in a tight spiral[15] At other times, they are found singly or in pairs An interesting feature of the shape of these cells is the presence of lateral fins or ridges which extend about 1 μm from the somata, their function is unknown

What are rod precursors?

Rod precursors do not fit into the classic scheme of retinal histogenesis Retinal histogenesis is essentially similar in all vertebrates and can be simply but quite accurately thought of as an orderly and sequential partitioning of the primitive neuroepithelium into three cellular layers[14,16]. Primitive neuroepithelial cells are spindle-shaped and maintain an attachment to the apical (ventricular) surface (In the retina, the external limiting membrane is homologous to the ventricular surface) The basal process of the cell is withdrawn during mitosis as the nucleus migrates to the apical surface to divide[17] (Fig. 4A and B) This to and fro movement of the nucleus is called 'interkinetic nuclear migration' When a neuroepithelial cell completes its terminal mitotic division, it loses its cytoplasmic attachment to the apical surface and, now a young neuron, it migrates basally to settle in its appropriate laminar position (Fig 4B) The innermost, or most basal layer, is always the first to form, it becomes the ganglion cell layer of the mature retina The photoreceptors in the outermost layer, the outer nuclear layer, are typically the last neurons to be born, that is, to cease dividing (Fig 4C). According to this scheme all retinal neurons are derived from neuroepithelial cells As pointed out above, however, the rod precursors are not part of this primitive layer, which has dispersed by the time that production of rods commences (Fig 4C, D) Moreover, rod precursors do

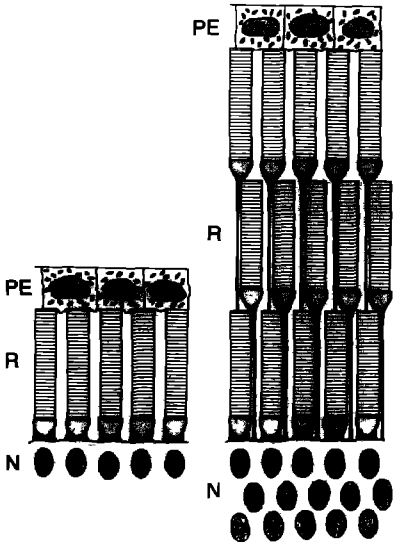

Fig. 2. *Diagram to show the addition of new tiers of rods during postembryonic growth of the fish,* Chauliodus sloani *Small specimens (29 to 36 mm standard body length exclusive of tail) have one row or tier of rods (R), as shown on the left Rods consist of a cylindrical outer segment (striped) containing visual pigment on top of a spheroidal inner segment (gray) containing mostly mitochondria The long slender attachment of the inner segments to the rod nuclei (N) is difficult to resolve in the light microscope and is omitted from the diagram The pigmented epithelium (PE) is at the top of the figure Larger specimens (120 to 192 mm standard body length) have three tiers of rods and three rows of rod nuclei, as shown on the right Even larger specimens have four or five tiers*
(Adapted from Locket, 1980)

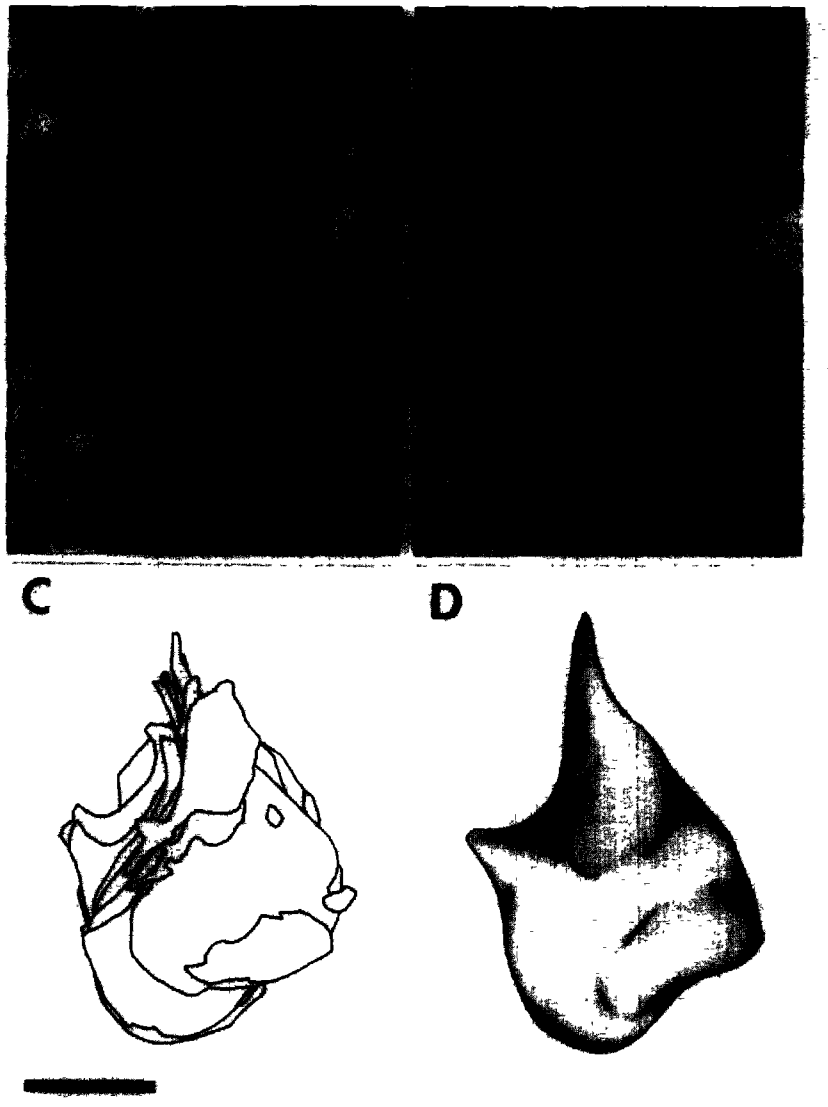

Fig. 3. *Morphology of rod precursors Dividing rod precursors were labeled by injecting a 26-day-old goldfish with 1 μCi of [³H]thymidine Serial thin sections were prepared and every 20th section in the series was processed for both autoradiography and electron microscopy*
A. *a labeled rod precursor (arrow) Calibration bar, 2 μm* **B.** *the same cell in another section from the serial set, not processed for autoradiography* **C.** *a three-dimensional reconstruction of this cell generated by a computer graphics program from digitized tracings of every fifth section Calibration bar, 2 μm* **D.** *an artist's rendition of the cell* (A , B and C reprinted with permission from Raymond and Rivlin 1984)

not exhibit at least two of the most characteristic features of neuroepithelial germinal cells (i) they are not attached to the apical surface, and (ii) their nuclei do not show interkinetic migration It seems, then, that rods in the teleost retina derive from a uniquely specialized precursor cell, not previously described in other developing vertebrate retinas

Although not part of the accepted pattern of neurogenesis in the retina, there is a precedent for neuronal production by cell division outside the ventricular zone (as the primitive neuroepithelium is sometimes called[17]) in other parts of the vertebrate CNS In some regions of the developing brain, notably in the cerebellum and the hippocampal formation, a secondary zone of neurogenesis called the subventricular zone forms when some of the cells in the ventricular zone migrate away from the ventricular surface[17] Subventricular cells, like rod precursors, divide *in situ* and are responsible for the formation of certain late-generated neurons, such as the granule cells of the dentate gyrus and the cerebellar cortex The evidence is consistent with the notion that rod precursors constitute a kind of subventricular zone within the retina, but the retinal subventricular zone differs from other such zones as it is not a separate and distinct layer but instead a scattered collection of cells dispersed among mature neurons

The origin of the rod precursors is ultimately the neuroepithelium of the presumptive embryonic retina or the circumferential germinal zone of the growing postembryonic retina (Fig 5). The steps involved in the production of new retina at the growing margin of the postembryonic eye recapitulate the stages of histogenesis in the embryonic and larval retina[2,7]. Here we consider only the formation of the photoreceptor layer. The outer nuclear layer is initially composed of a single layer of postmitotic but immature cone nuclei[7,9,18] and the rod precursors are nowhere to be found Only after the cones begin to differentiate, do the rod precursors appear at the base of the outer nuclear layer (Fig 4C); until that time they are sequestered in the inner nuclear layer, and they must migrate across the developing outer plexiform layer to reach their final position[7] Migration of cells from inner to outer nuclear layers in the developing teleost retina had been suggested previously as a mechanism to explain the delayed appearance of rods[11], though at that time it was not realized that the migrating cells were dividing rod precursors A better known example of migration of immature cells from one retinal lamina to another has been described by Hinds and Hinds[19], who suggested that at least some amacrine cells in the developing mouse retina are transiently located in the ganglion cell layer and then migrate across the inner plexiform layer to reach their definitive location in the inner nuclear layer where they complete their differentiation In this case, however, the migrating cells are postmitotic

The rod precursor appears to be dedicated to the production of one and only one class of neuron, rods This conclusion derives from examination of retinas after long term thymidine labeling, in which the only labeled cells in the central retina are rods[7]. The apparent specificity of rod precursors is a unique ontogenetic character It is generally believed that germinal cells of the CNS are homogeneous and pluripotent and give rise sequentially to several different types of neurons and eventually even to glia[17], but recent evidence, presented by Rakic and colleagues[20,21], has cast doubt on this interpretation With immunocytochemical techniques they probed the nature of the neuroepithelium at the molecular level and found that there is more than one population of germinal cells: some cells stained positively for antibodies to a glial-specific marker, glial fibrillary acidic protein (GFAP) but others were unstained. They interpreted this as evidence that separate glial and neuronal lineages coexist in the ventricular zone (see Ref 22 for a different view) If we extend this idea to the rod precursor in the teleost retina, we might postulate that it represents a further specialization of the

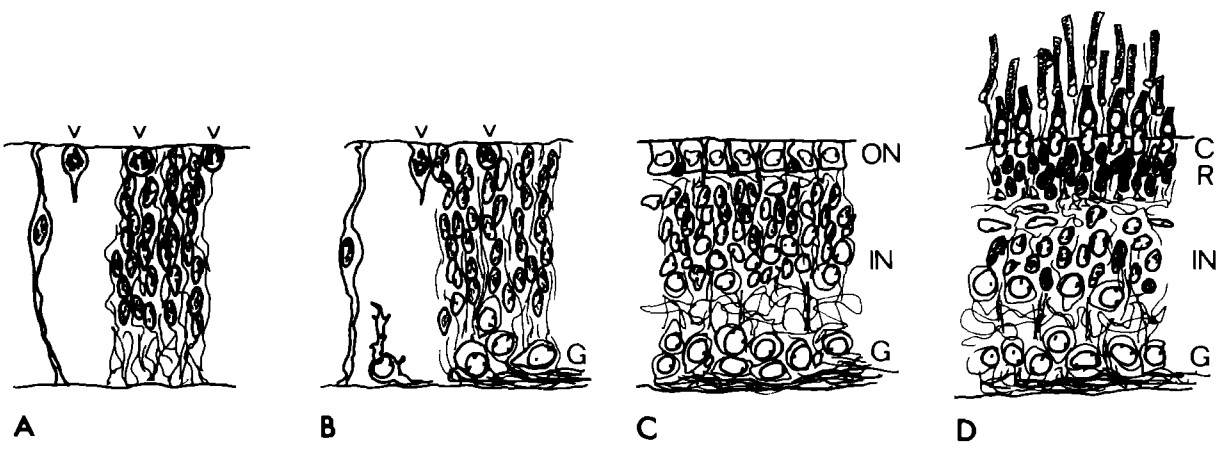

Fig. 4. *Retinal histogenesis* **A.** *The primitive retinal epithelium is a homogeneous sheet of dividing neuroepithelial cells These are spindle-shaped cells which typically span the width of the epithelium, as shown by the isolated cell on the left During mitosis the basal process is withdrawn, the nucleus moves to the apical surface and the cell rounds up to divide (arrowheads)* **B.** *The first neurons to differentiate are invariably ganglion cells (G) As a young neuron leaves the mitotic cycle it detaches from the apical surface and the nucleus moves down the basal process until it reaches the appropriate level, which for the ganglion cells is next to the inner (basal) surface While the nucleus is still migrating an axon begins to grow out, as can be seen in the isolated cell at center left* **C.** *With further development the cells of the neuroepithelium are partitioned into the three definitive strata of the differentiated retina, the ganglion cell layer (G), the inner nuclear layer (IN), and the outer nuclear layer (ON) In teleost fish and also in primates, rods are at first under-represented in the layer of photoreceptor nuclei (the outer nuclear layer) At this early stage, the outer nuclear layer consists of a single row of immature cone nuclei, a few small dark nuclei at the base of the cones are presumed to be rods (in the primate retina) or are known to be rods and rod precursors (in the fish retina) This drawing equally well depicts the fetal primate retina[14,24] or the larval teleost retina[7,9,18]* **D** *In the mature teleost retina there is a single row of cone nuclei (C) and multiple rows of rod nuclei (R) in the outer nuclear layer (The species of fish depicted in Fig 2 is an exception) A similar situation holds in non-foveal regions of the mature primate retina*

neuroepithelial cell, and if so, the teleost retina might offer a convenient model in which to study questions related to cell lineage and cell determination in the developing nervous system.

The role of rod precursors

Just how unique are the rod precursors and what is the purpose of persistent generation of rods in the postembryonic teleost retina? The fact that rods in the teleost retina are the last neurons to be born is not unusual Carter-Dawson and LaVail[23] have shown that in the developing mouse retina production of rods begins later and lasts longer than production of cones Thus the sequence and timing of photoreceptor production is qualitatively similar in fish and mammals and may reflect a general, though perhaps not universal, pattern of retinal histogenesis.

An even more intriguing comparison can be made between developing rods and cones in primate and teleost retinas In primates, as in fish, the outer nuclear layer can first be recognized as a single row of postmitotic nuclei that differentiate into cones[14,24] The row of cones is separated from the incipient inner nuclear layer, which still contains undifferentiated neuroepithelial cells, by a narrow fibrous zone, the presumptive outer plexiform layer Rod nuclei later accumulate beneath the developing cone nuclei, and it is implicitly assumed that the immature rods migrate across the outer plexiform layer from the inner nuclear layer where they are temporarily sequestered Thymidine studies have yet to be done, so it is not known when rod production by mitosis ceases nor whether the rod progenitors continue dividing after they cross the outer plexiform layer and enter the outer nuclear layer It is entirely possible that a rod precursor like the one described here might also exist at least temporarily in the developing primate retina

However, fish are clearly different from mammals as their retina continues to grow and add new cells throughout life Easiest to understand is the cell proliferation which occurs at the circumferential germinal zone, where production of new neurons is least likely to interfere with ongoing neural function[2] More difficult to comprehend is the insertion of new rods into the mosaic of differentiated photoreceptors in central regions

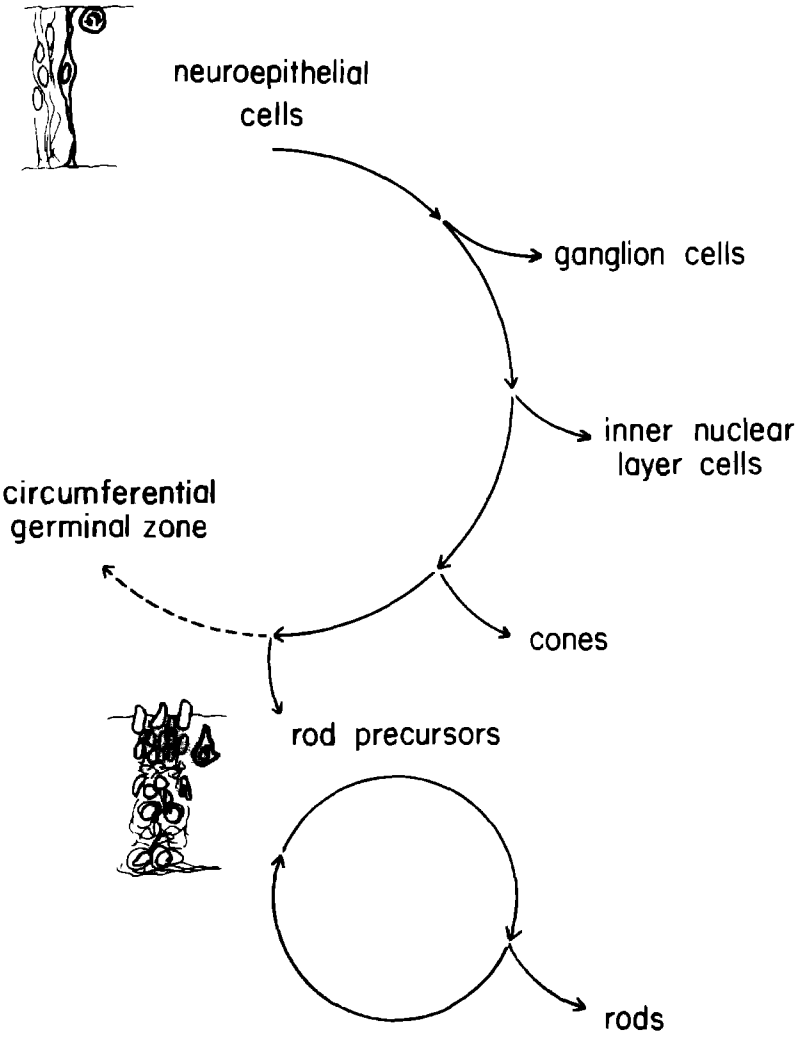

Fig. 5. *Diagram to show the ontogenetic history of teleost retinal neurons From the primitive neuroepithelial cells are produced ganglion cells, inner nuclear layer cells, cones and rod precursors. The remnants of the neuroepithelial population persist in the circumferential germinal zone, which continues to produce retinal neurons in the adult fish. The rod precursors constitute an independent proliferating population that gives rise exclusively to rods*

Why is such an apparently disruptive activity necessary? Part of the growth of the teleost retina is due to expansion or stretching of the retinal surface with an accompanying decrease in the density of cells per unit area[2,3]. The rods are the only exception: density of rods increases during postembryonic growth (Fig. 6) For example, by the time a goldfish is about a year old the rod precursors have built up the rod population to a density of about 200 000 rods mm^{-2} of retinal surface From then on production of new rods continues at a rate only sufficient to maintain this density, as the forces of expansion pull the rods apart[3,7] Thus the goal of rod proliferation appears to be related to the generation and maintenance of a high density of rods as the retina expands The motive force underlying postembryonic expansion of the retinal surface is unknown, but may be related to the intraocular pressure. Whatever the mechanism, it is a universal property of the vertebrate eye, which enlarges postembryonically in all species[14], though by varying amounts.

Recently Stell and Kock[25] have provided a direct demonstration that new rods added in the adult goldfish are integrated into the retinal circuitry They showed by serial sectioning of identified, Golgi-impregnated cells that the number of rods connected to each *b1* bipolar cell (a particular type of second-order neuron which contacts

every rod that falls within its dendritic domain) increased by 50% as goldfish grew from about six months to five years of age. Synaptogenesis continues at higher-order levels of processing, too. In the inner plexiform layer, where bipolar and amacrine cells synapse onto ganglion cells, the density of synapses mm^{-2} of retinal surface increases by about 30% during growth of adult goldfish from about one to four years of age[26]

There is little reason to doubt, then, that the new rods are functional, but what is the effect of continued addition of rods on the visual behavior of the fish? Powers and Bassi[27] have attempted to answer this question by measuring the absolute visual threshold in goldfish of various sizes. (The absolute visual threshold is defined as the minimum intensity of light needed for detection by a fully dark adapted eye.) The larger fish required only slightly more photons incident at the retina to detect a light; the small increase was directly proportional to the calculated increase in neural noise due to the extra rods. Thus, nearly constant visual sensitivity is maintained during growth of the adult goldfish eye while millions of new rods are added. Though a causal relation has not been proven, the inference that rod addition is required to maintain sensitivity seems plausible

It is interesting that the cones do not follow the same strategy as the rods. New cones are added with retinal growth, but only at the marginal germinal zone, and thus the density of cones, measured in number mm^{-2}, in central regions of retina decreases[2,3,13] When measured as density of cones visual degree^{-2}, however, the density increases as the eye enlarges This is a consequence of the fact that the lens grows in direct proportion to the retina, therefore the retinal magnification factor (μm retinal surface subtended-degree visual angle^{-1}) also increases, in other words, the image formed on the retina by a given stimulus is larger, more magnified, in large goldfish eyes compared to smaller ones[28] Intuitively, then, the 'grain' of the cone mosaic can be allowed to become coarser in larger retinas, i e the cone density (in number mm^{-2}) can decrease, without sacrificing resolving power Visual acuity has been measured behaviorally as a function of size in a few teleost species[29,30,31] and the results consistently show an increase in acuity with growth just as predicted

The prolonged period of rod genesis in the teleost retina and the formation of a special precursor population of dividing cells within the retina therefore appears to be necessitated by the conditions imposed by the process of postembryonic growth, especially the stretching or expansion of the retinal surface The continued insertion of new rods into the photoreceptor mosaic and the formation of new synaptic connections as the new rods become incorporated into the retinal circuitry is another example[1] of the remarkable degree of plasticity that is part of the normal growth process in these animals

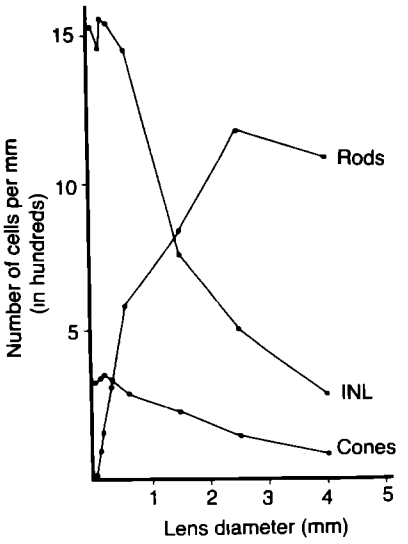

Fig. 6. *The linear density of cells in the retina of postembryonic goldfish The number of cells mm^{-1} of retinal length is plotted as a function of the diameter of the lens in mm In eyes from small fish, one sample was taken from the center of the retina in each of three meridional sections, in larger eyes, four to six samples equally spaced across the retina were counted in one meridional section The data plotted are means of counts from two to five eyes in each of eight successive, non-overlapping ranges of lens diameter from less than 0 1 to 4 0 mm The fish ranged in age from newly hatched larvae to 4- and 5-year-old adults INL, cells in the inner nuclear layer* (Reprinted with permission from Johns, 1982)

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Pamela A Raymond is Assistant Professor at the Department of Anatomy and Cell Biology, University of Michigan Medical School, Ann Arbor, MI 48109-0010, USA