

International Review of

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Edited by

CARL C. PFEIFFER

JOHN R. SMYTHIES

INTERNATIONAL REVIEW OF

Neurobiology

Edited by **CARL C. PFEIFFER**

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PREFACE

Progress in neurobiological research must maintain a delicate balance between the fascination of basic explanation of clinical and physiological phenomena by means of chemical and physical concepts on the one hand and the pressing needs for the development of new and effective treatments of disease on the other. Advances in basic biochemistry and biophysics often give rise to developments in the clinical field, but mature judgment is required to select from the vast detail of biochemistry and biophysics, those parts which are likely to apply to human disease.

The aim of this review is to enable active workers in the fields of neurobiology, neurochemistry, neuroanatomy, neuropharmacology, neurophysiology, psychopharmacology, psychology, etc., as well as those in biological psychiatry and neurology to give an account of recent progress in their fields. The review covers the whole field of neurobiology and includes work within a particular basic science as well as in neurology and psychiatry. Particular emphasis has been laid on the recent development of ideas that are of fundamental importance and general interest and also those that are likely to further our understanding of nervous and mental disease. In the past the basic neurobiological sciences have played no little part in progress toward these ends. They are most active at present and they hold great promise for the future.

These reviews and summaries ordinarily are by invitation, with a deadline for receipt of the manuscript by June 1. The editors, however, will be happy to review unsolicited manuscripts if submitted in outline form.

CARL C. PFEIFFER

JOHN R. SMYTHIES

May, 1960

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REGENERATION OF THE OPTIC NERVE IN AMPHIBIA

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I. Introduction

In this review I intend to discuss regeneration of the optic nerve with particular reference to the relationship between structure and function in the visual system. To make the story of regeneration more intelligible and to provide a background for various speculations to be made later, I shall start with a description of some aspects of visual behavior in amphibians and an outline of the known facts of visual organization in these animals; then will follow a review of the phenomena of regeneration and lastly a discussion of some of the problems brought out by the experiments and their possible significance for the understanding of normal vision.

The regenerative powers of lower vertebrates are well known; these animals have an almost proverbial ability to develop new tails and limbs after loss of the originals. This ability extends to the central nervous system as well in urodele amphibia (newts and salamanders) and anuran amphibia (frogs and toads). Whereas in mammals regeneration of cut or otherwise damaged axons within the central nervous system occurs to a very limited extent, central regeneration takes place freely in the amphibia, and particularly

well in the larval or young adult stages. The optic nerve is embryologically part of the central nervous system, and its fibers will grow again following section in these animals; and when the eye has become reconnected to the optic lobe, the animals redevelop what appears to be normal vision. It is possible therefore to follow what happens to the fibers of the nerve as they grow back, and to attempt to correlate anatomical restitution with return of function.

II. Visual Behavior in Amphibia

Most amphibia are not truly amphibious in the sense that they are equally at home in the water or on the land. In general, the larval stage of life is spent in the water, when the animals are truly aquatic, and the adult stage on land, with occasional return to water, for instance at the breeding season. Since no amphibian has more than 5 diopters of accommodation (Walls, 1942), if we consider frogs to be emmetropic in air, they will be strongly hypermetropic under water. In a similar way, the aquatic newts which are emmetropic in water will become strongly myopic on land. The eyes of frogs are relatively enormous in comparison with their body size and, as might be expected from their arrhythmic habit of life (most amphibia are nocturnal in habit) and the size of their eyes, they are largely visual animals. The urodeles are more secretive in their life habits and in keeping with this their eyes are not so well developed as those of the frogs.

On land, frogs move by jumping, a mode of progression which involves successive periods when the visual field is stationary and when it is in violent motion. The animals appear to respond only to moving objects and the nature of the response seems to vary with the size of the stimulus. For instance a man may stand in shallow water surrounded by hundreds of frogs but unless he moves the animals pay no attention. The slightest movement on the part of the observer will lead to a sudden change in the behavior of the animals—they will cease croaking and sit still; any further movement of the observer will usually cause a sudden and general disappearance of frogs from the scene—mostly into the water. If the stimulus moving in the visual field is small, of the order of size of a fly or other small insect then the response of the animal is attack

rather than avoidance. The sequence of events during the capture of prey is of special interest since it is this reaction which is commonly used by investigators to determine the adequacy of visual function after optic nerve regeneration. In some animals, notably tree frogs, food may be captured with a single leap; Sperry (1944) reported that *Hyla cineria* frequently captured with a single jump houseflies walking at a distance of 35 cm. I have watched *Rana temporaria* and *Rana esculenta* feeding on meal worms in the laboratory, and here the sequence is rather different. If the worm is some distance away from the animal, the frog will turn to face it, jump the intervening distance, then bend its head and shoulders down, and finally flick out its tongue to grasp the food. If the worm is close to the animal, the latter first turns to face the prey, bends down to "peer" at it, then captures it. This lowering of the head just before the final capture is made has the effect of bringing the object right into the middle of the binocular field. Thus there appears to be a clear difference between the effects of a small moving stimulus in the posterior field and one in the anterior field. In the former case the stimulus sets up an orientation response, or "taxis" in Tinbergen's terminology (1951); in the anterior, binocular, field the same moving stimulus may eventually release the capturing behavior.

Thus there is ample evidence that frogs respond to gross differences in size of a visual stimulus and that they respond appropriately to variations in retinal local sign. It is doubtful, however, whether they are able to distinguish shapes and whether they have anything like color vision. Both these abilities are attributed to the frogs by Noble (1931) but more recently the evidence for color vision has been reassessed by Walls (1942) who concludes that for amphibia it is not proven. These animals are very difficult to train in any way and this may account for the difficulty in demonstrating such discriminations. It has been reported, however, that some anurans can be trained to distinguish between various shapes (Biederman, 1927). The main factors in the visual environment, then, to which frogs respond are movement and direction. The ability of many frogs to catch insects in flight argues the existence of considerable computing ability within the visual system of these animals, since to be effective a strike must be made at some estimated future position of the prey.

Another aspect of normal (experimental) visual behavior of these animals is the optokinetic response; and this is frequently used to test the return of visual function following regeneration of the optic nerve. If a normal animal is placed on a stationary platform and a striped drum is rotated round it, the animal will turn its head in the direction of the moving stripes. This is a visual response and in the absence of the eyes or if both optic nerves are destroyed the response does not occur. If one eye is removed, or one optic nerve is destroyed, then in general an animal will only respond in one direction, that is, to rotation of the drum temporonasally across the intact eye.

Summary. Little experimental work has been done on visual behavior in amphibians; what there is shows that the animals respond to gross differences in size of stimulus, to movement, and to position in the visual field.

III. Visual Organization in Amphibia

In urodeles and in anurans eye movements apart from retraction are negligible. Orientation of the eyes is controlled by movements of the head; accommodation is effected by forward movement of the lens. Reports on the accommodative state of the eye in these animals are very conflicting. According to estimates reported by Walls (1942), Duke-Elder (1958), and Rochon-Duvigneaud (1943), the frog's eye has been found to be anything from 5 diopters hypermetropic to 8 diopters myopic. Perhaps for the purpose of this review we are justified in assuming with Walls that the frog is emmetropic in air and also that the large eye, with its beautifully clear cornea (the main refracting surface) and clear media is capable of projecting a good image onto the retina. Such an assumption would certainly be borne out by the excellence of the visual behavior of these animals.

In the frog the ratio of the number of rods per unit area to the number of cones is approximately 2:1 and this ratio is much the same over almost the entire extent of the retina (Rochon-Duvigneaud, 1943). The frog retina has no fovea or macula acuta but it does have a very poorly defined area centralis; otherwise the entire extent of the retina is fairly uniform. It has been stated (Walls,

1942) that the slight excess of ganglion cells in the region of the area centralis has the effect of making this an area of acute vision; and while the first maps of the retinal projection to the optic lobe in the frog failed to show any significant difference in resolving power between the various parts of the retina (Gaze, 1958a), more recently it has been found that there is actually a difference of about 2:1 in "magnification factor" between peripheral retina and area centralis (Jacobson, personal communication). One would expect the posterior region of the retina to be more specialized than the anterior, since it is onto posterior retina that the anterior, binocular, field projects. So far there is nothing to support this, except perhaps the observations of Barlow (1953a) that off units are more common in the posterior retina than elsewhere. Four types of visual element are commonly found in the retinae of frogs: red and green rods and single and double cones. Essentially the same types are to be seen in the urodele retina, only here the individual elements are both larger and sparser. There is also a higher visual-to-ganglion cell ratio than in frogs.

The optic nerve arises from the layer of retinal ganglion cells and passes backward from the eye across the optic chiasma to reach the optic lobe on the other side. Some fibers are also apparently given off before the lobe is reached, to the geniculate region and various other parts of the midbrain. All authors who have described the optic chiasma of the frog and salamander state that it is totally crossed—fibers from the one eye all go to the other side of the brain. Breusch and Arey (1942) made counts of the optic nerve fibers in various animals including some amphibia; they found that in *Bufo americanus* the optic nerve contained 5300 unmyelinated fibers and 10,200 myelinated ones, while the nerve of *Rana pipiens* showed 13,700 unmyelinated fibers to 15,300 myelinated ones. More recently, work with the electron microscope has shown that these figures for the unmyelinated fibers in anurans are far too small; Maturana (1959) has reported finding some 470,000 of these in the optic nerve of the frog and about 320,000 in the toad. In urodeles the count is considerably smaller; Herrick (1941) estimated that the optic nerve of adult *Amblystoma tigrinum* contained a total of about 8000 fibers. Bishop, in 1933, found evidence of three distinct groups of fibers in the optic nerve of the bullfrog. The fastest conducting group showed velocities of 8–16 meters per

second (mps) while the second group conducted at 2-5 mps. On the analogy of somatic sensory nerves one is tempted to look for differential functions in the different groups of optic nerve fibers, but so far there is no evidence about the physiological significance of the different conduction velocities. The suggestion made by Herrick in 1941 that the faster conducting fibers (*Amblystoma*) might be a form of activating mechanism for the visual brain while the slower conducting fibers might be a localized projection from the retina is interesting, but remains speculation only.¹ Most of the fibers in the optic nerve are, of course, afferent, but there are also some efferent fibers running from the optic lobes to the retina, the function of which is uncertain. The efferent fibers play a part in the control of retinal pigment migration in fishes (Arey, 1916), but this is more doubtful in amphibia. Nor has it yet been shown that these fibers exercise control over the retinal response to light, as appears to be the case in cats (Granit, 1955).

The main visual centers in amphibia are the optic lobes. These are paired, ovoid structures situated between the diencephalon and the cerebellum; the optic lobes are the most conspicuous parts of the brain in the frog, being enveloped in pigmented membranes. The roof of the optic lobe shows marked lamination, especially so in the anura. If we adopt the terminology used by Larsell (1931) and Kollros (1953) there are nine layers, numbered outward from the ventricle to the surface; this layered structure is complex to a degree that allows comparison with the mammalian cerebral cortex. The outermost or ninth layer is called the stratum opticum or opticus layer and it is here that most of the optic tract fibers run. According to Wlassak (1893) some of the optic fibers also run in the seventh or deep medullary layer, and some, the basal bundle, run more ventrally still to end in Herrick's nucleus opticus tegmenti, near the nucleus of the third nerve.

Those optic fibers which ramify in the roof of the tectum, however, do so mostly in the superficial or opticus layer. The optic fibers turn ventrally to terminate in or around layers 8 and 7 (Kollros, 1953). Apart from the axons of the optic tract, the opticus layer contains axons and dendrites from cells in the deeper layers; there are also cells in the opticus layer whose processes run for some distance within this layer (Larsell, 1931).

¹ But see Lettvin *et al.* (1959).

In early embryonic life the optic lobe consists of a mass of undifferentiated cells. With the arrival of the first retinal axons, cells become detached from the periventricular gray and migrate outward to form the beginnings of the various layers (Kollros, 1953). This differentiation of the layered structure of the lobe begins at the anterior pole, where the optic fibers first arrive, and spreads gradually posteriorly. In the absence of optic nerve fibers, as for instance when the opposite eye is removed in an early stage, the lobe fails to develop properly. The hypoplasia is most marked in the outer layers (56% in layers 7-9) but still appreciable in the inner layers (38% in layers 1-6; Kollros, 1953). This diminution in the size of a deprived lobe is due to absence of optic fibers, reduction in the number of cells in the affected layers, and poor development of some of the remaining cells.

The optic nerve fibers from the retinal ganglion cells are not distributed to the opticus layer in a random manner. There is an orderly topographical projection from retina to optic lobe, such that each area of retina is specifically connected to a corresponding region of lobe surface. In *Triturus* this orderly projection has been found by Stroer (1940) using anatomical techniques; and Sperry (1944), by ablating parts of the lobe, has shown in the frog that anterior, posterior, and inferior parts of the retina each project to separate areas of lobe surface. The representation of the retina on the lobe of the frog has also been investigated electrophysiologically by Gaze (1958a), who showed, by stimulating the intact eye with a small light and recording the arrival of action potentials at the optic lobe, that there is a point to point (or rather area to area) connection between retina and lobe. All these investigations point to the same conclusion, which is that the posterior retina (anterior visual field) projects to the anterior pole of the lobe, the anterior retina (posterior visual field) to the posterior pole, with inferior retina (superior field) near the mid-line and superior retina (inferior field) tucked round the lateral edge of the lobe.

Frogs have a considerable degree of overlap of the visual fields anteriorly, and by means of the evoked potential technique it has been shown (Gaze, 1958b) that, within the binocular field, a point in space is represented binocularly on each optic lobe. Since the chiasma is reported as being completely crossed in the amphibia, it was to be expected that each eye would project only to the con-

tralateral lobe; however, that part of the retina which receives stimuli from the binocular field sends impulses to both optic lobes. It is not known so far what paths these impulses take.

The electrical activity of the optic lobe in response to stimulation of the eye by light has been investigated by various workers. Buser (1949a) recorded from the frog lobe a series of potential changes after a flash of light to the eye: the fast initial deflections (with a latency of 60 msec and lasting 80–100 msec) he attributed to activity in the optic fibers themselves, and the following slow waves (latency 250 msec or more; duration 200 msec) he thought due to the activity of the postsynaptic neurons of the tectum. These two components, fast and slow, could be dissociated to some extent experimentally; application of pentobarbital to the surface of the lobe rapidly abolished the slow waves while the fast spikes were more resistant to this treatment. Somewhat similar fast and slow components have been recorded from the tectum of fish following electrical stimulation of the optic nerve; in this case (Buser, 1949b) the latency of the responses was, of course, very much shorter, and high-frequency stimulation caused the slow waves to decrease markedly while the rapid spikes were unaffected. As the recording electrode was moved from tectal surface to the incoming optic tract the slow wave disappeared leaving only the fast component (Buser, 1950). Responses from the optic lobe to stimulation of the eye by light have also been recorded by Gaze (1958a, 1959); in these experiments a small light (subtending less than 1° at the eye) was mainly used, and the recording system had a time constant of less than 10 msec; the responses obtained consisted in most cases of bursts of action potentials from groups of units rather than slow wave potentials. The latency of the responses was enormous—of the order of 100–200 msec—and this is at present difficult to account for. The conduction distances involved, assuming that the impulses travel by the shortest route from eye to lobe, amount to only about a centimeter. The fastest fibers in the frog's optic nerve conduct at approximately 8–16 mps (Bishop, 1933) which would give a minimum conduction time from retina to lobe of less than a millisecond. Even assuming (what may well be true) that the majority of the optic fibers conduct at less than 2 mps, this would still only account for a delay of 10 msec or so. A considerable amount of the latency of the responses to small light flash must