

Tris(1-Aziridinyl)Phosphine

Oxide: Caution on Use

We read with interest the report by Holmsen and Leasure (1) in which they reported the growth-inhibiting property of tris(1-aziridinyl)phosphine oxide (APO) on grasses. We feel that one of the most important biological properties of the chemical was not mentioned in the report, namely, the ability to induce mutations. Indeed APO is a powerful mutagen; APO (or triethylenephosphoramide, TEPA) produces a high frequency of mutations in *Bracon hebetor* when the latter is allowed to walk on an APO-coated surface (2×10^{-9} g per square millimeter) for five or more minutes (2). Aziridinyl compounds, of which APO is one, produce sex-linked recessive mutations in *Drosophila* (3) and sterilize male insects by inducing dominant lethal mutations (4). Furthermore, chemicals in this class efficiently break human chromosomes (5).

Our purpose is to caution against the use of APO, or any aziridinyl compound, where there is risk of the populace being exposed to it.

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Computer-Plotted Receptive Fields

Spinelli (1) reports the results of programming a computer to plot out the receptive fields of optic nerve fibers from the cat retina, but those of us who have done the same job by hand wonder if computer PDP-8 is spoofing Spinelli, or if Spinelli is spoofing his readers. The receptive fields reported certainly differ from those obtained by manual exploration and plotting, but this can possibly be explained by differences of techniques only remotely connected with the use of a computer.

Spinelli used a background intensity of 0.02 cd/m². The human increment threshold at this background would be about one tenth of this, or 0.002 cd/m², and in our experience a cat's ganglion cell would respond well to a spot only a few times brighter if it fell optimally in its receptive field. Spinelli's exploring spot was at an intensity of 200 cd/m², 10,000 times the background intensity. It is hardly surprising that he obtains unusual receptive fields, but we also wish to raise the possibility that some of his plots are not receptive fields at all, for there are two known effects of light falling far away from the receptive field as ordinarily defined. The first is the "periphery effect," described by McIlwain (2), in which light falling upon a remote retinal region can elicit a change in firing rate as a result of intraretinal interactions (3). The computer might show these effects very clearly, but as far as is known there should be no localized effects such as Spinelli reports. The other, more mundane possibility arises from light scattered or reflected outside the expected image area. Spinelli gives no details of the preservation and correction of the optics of his cats' eyes, but in our experience the optics can be truly horrifying if one does not take good care of the cornea and apply the right correction, preferably combining this with an artificial pupil.

Streaks and star-shaped images can easily result from poor optics, and this may be all that is required to account for some of Spinelli's results, but one must also remember that the inside of the eye is roughly spherical, and hence every point on the retina has an uninterrupted view of every other point. Thus, if a bright spot of light is shone on one point, all other points will be illuminated at an intensity that depends primarily upon the reflectance characteristics of the region illuminated by the spot. In the cat retina the brightly reflecting tapetum covers only part of the fundus, and the amount of intraocular scattered light would decrease dramatically if a spot of light was moved across the border. Thus, it could happen that a peripheral ganglion cell, whose own receptive field was never traversed by the scanning spot, might respond when, and only when, the scanning spot crossed the tapetal border.

There are other regions of the fundus possessing different reflectances, for instance, the optic disc and its radiating

blood vessels. When Spinelli's method is used, these discontinuities might well appear as the "receptive fields" of ganglion cells lying outside the area scanned, and it is instructive to look at his figures with these ideas in mind. Might not the "spiders" be the optic disc and blood vessels, and the "edges" the tapetal border? Naturally, verification or refutation depends upon checking the actual experimental arrangements. Do the spider-shaped "receptive fields" correspond approximately to the position of the optic disc or blind spot? Has computer PDP-8 presented the receptive fields with their horizontal axes vertical? What kind of receptive field plots are obtained if the luminance of the plotting spot is reduced to about one hundredth of its present intensity?

It is worth remembering that the 25° by 25° area scanned in Spinelli's experiments covers less than one twentieth of the visual field of the cat's eye. Accordingly, Spinelli should have found it necessary to adjust the position of his X-Y plotter in a high proportion of trials in order for it to cover the units' true receptive fields; it would be interesting to know in what proportion of trials he found this necessary.

Many years ago L. C. Thomson built himself a monochromator of unparalleled power in order to investigate color vision in the rabbit. At first he found that a light anywhere in the rabbit's visual field would excite the retinal ganglion cells, and it was only after encouragement from others, and much tedious exploration of the visual field, that he finally located regions of much greater sensitivity—the true receptive fields (4). Is it possible that Spinelli's sophisticated plotting and detecting techniques have obscured the need for performing careful controls? Is manual experimentation outmoded?

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The remarks of Barlow *et al.* on my report (1) can be usefully divided into two segments: a technical one and a theoretical one. I will try to answer the technical first (2).

The gradient between spot and background is 4 log units; this is small compared with the range over which the retina normally operates, namely, 9 log units. It is, therefore, well within the range of stimuli that the cat, or the experimenter, faces in ordinary life. For example, gradients of 5 or more log units are present in an ordinarily lighted room. I agree with Barlow that the Mollwain effect should produce no localized responses; it should therefore not appear in the maps. The most serious technical comments deal with the cat's optics and with the possibility that light reflected from the tapetum, vessels, or the optic disc might contaminate the results. The cat's optics were taken care of according to principles set forth by Bishop and his co-workers (3).

Contact lenses were used and the eye was refracted; perfect refraction was not attempted as there seems to be general agreement in the literature that this is not necessary (3, 4). An artificial pupil was also used most of the time even though it does not seem to be indispensable. A quote from a report of Barlow *et al.* (4) on this subject may help: "Fields have been plotted before and after refracting. The main features appear to be unchanged even by large refractive errors. We have occasionally used . . . artificial pupils. Evidence of improved definition was obtained, but the main features of the fields were unchanged." In other words, it is sufficient for the spot on the retina to be very small compared with the receptive field size. The reflectance of the tapetum is more of a problem. After a search of the literature (the tapetum is there for everybody), it seemed to me that the best way of eliminating or detecting the influence of the tapetum was to map receptive fields that were located in approximately the same retinal region. The center of the display system was therefore aligned with the area centralis [as defined by Bishop *et al.* (3)], and all units with fields outside the region thus scanned were rejected. The receptive field position was

first determined by moving a small bulb, very dimly lit, attached to a black stick, in front of the cat's eye, and only afterward was the receptive field mapped with the X-Y plotter. Light scattered by the tapetum or other retinal structures cannot explain the findings of diverse receptive field shapes in the same retinal region. The "spiders"—it is a good name, by the way—are more suggestive of a cell body and its dendritic tree projection; it makes good sense to assume that the shape of the ganglion cell determines the shape of its receptive field.

The second segment of the remarks of Barlow *et al.* has to do with a sense of wonder about the data. Were these findings really so much outside the expectations of the researchers in this field? I think that this question can best be answered by quoting, respectively, Kuffler, Levick, and Barlow.

Kuffler (5): "Not in all units was the field laid out in a regular concentric manner as in Figure 6. The areas were frequently irregular. In some instances there appeared 'gaps' between regions; *i.e.*, isolated spots in the periphery seemed to be functionally connected to a ganglion cell. . . . There seems to exist a very great variability between individual receptive fields and, therefore, a detailed classification cannot be made at present."

Levick (6): "One may be inclined to hold that the frog is a rather primitive vertebrate and results should not be carried over to mammals. . . . In the cat, for instance, nothing as sophisticated has been found for the retinal ganglion cells. . . . However, this idea is back in the melting pot because Barlow and Hill, and Barlow, Hill and I, have recently described retinal ganglion cells in the rabbit which abstract complex aspects of the retinal image. . . . namely, the direction in which an image is moving and also the speed with which images move. More recently still, Barlow and I have found cells which detect the orientation of contrasting borders in the retinal image. . . . There is abundant evidence that the above behavior is not caused by cylindrical refractive errors; thus *vertically- and horizontally-sensitive cells could be found in the same regions of the retina*" (italics mine).

Barlow and Levick (7): "We think there are two aspects of recent work on the visual pathway that are interesting in this respect. The first is the specificity of the features that are effective in triggering the activity of sensory neurones. Examples of this are provided by the 'fly detectors' (Barlow, 1953) and 'convexity detectors' (Lettvin *et al.*, 1959) of the frog's retina, . . . the 'horizontal edge detectors' of the pigeon retina (Maturana and Frenk, 1963), and the directionally selective elements found in all these preparations as well as in the rabbit's retina. . . . Presumably the trigger features of the visual system . . . enable the input states to be classified in an effective way without requiring a googolian number of separate representations."

Barlow *et al.* (4): "This survey of ganglion cells in the rabbit's retina confirms the fact that complex analysis of sensory information occurs in the periphery before the neural activity is projected to the higher nervous centres. Each class of cell has its own 'trigger feature' to which it is most sensitive, in the same way that different classes of cutaneous neurones are selectively sensitive to mechanical deformation, temperature change, tissue damage, and so on."

Barlow's and Levick's work deals with the rabbit's retina. It is not surprising that the cat's retina should be as complex or more so. As to the question "Is manual experimentation outmoded?" my answer would be that the above-quoted works show this is not the case; it is a fact, though, that automation allows a tremendous amount of effortless precision and speed.

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