daily intramuscular injections of 3 μg of α-BuTx; the other eight received control injections of albumin-Ringer solution. The results showed virtually complete inhibition of sprouting in the muscles injected with α-BuTx in addition to botulinum toxin, while the other muscles exhibited a marked sprouting response (Table 2). Both procedures resulted in greatly elevated levels of extrajunctional ACh receptors. Thus, α-BuTx appears to inhibit the sprouting response without reducing the denervation changes in muscle (Fig. 2).

That this inhibitory effect of α-BuTx was not due to interference with the nerve's ability to sprout was shown by a further set of experiments. Axonal outgrowth was initiated by crushing, a procedure that directly stimulates sprouting from the proximal nerve stump. The nerve to the soleus was crushed with jewelers forceps in 12 rats at the point of entry into the muscle. One group of eight rats received six daily intramuscular injections of α-BuTx, while the control group were given injections of albumin-Ringer solution. Histological preparations after 7 days revealed abundant outgrowth of axons from the crushed nerves in both the α-BuTx–treated and control groups. This finding excludes the possibility of a general sprout-inhibiting effect of α-BuTx.

It thus seems most likely that the inhibition of nerve terminal sprouting produced by α-BuTx results from its only known action, highly specific and irreversible blockade of ACh receptors. The mechanism by which receptor blockade might inhibit sprouting is not yet certain. However, the results of our experiments and other recent reports (*7, 24*) provide suggestive evidence that the extrajunctional ACh receptors, which increase in denervated muscle, may play a role in eliciting motor nerve terminal sprouting. First, functional denervation produced by botulinum toxin or by disuse caused by TTX resulted in terminal sprouting. The experimental conditions excluded the possibility that incidental nerve or muscle damage might have been instrumental in eliciting the sprouting response. More important, the degree of sprouting was closely correlated with the level of extrajunctional ACh receptors. Second, procedures that reduce or block extrajunctional ACh receptors appear to inhibit the tendency to sprout. In one study, electrical stimulation of botulinum-treated muscle decreased both extrajunctional receptors and nerve sprouting (*24*). We now report that a specific pharmacological blocker of ACh receptors also prevents sprouting. Whether it does so by blocking the ACh recognition site itself, by sterically hindering a nearby site, or by some as yet undescribed action of α-BuTx remains a matter for future study. Although these findings do not exclude the participation of additional factors in eliciting sprouting at motor nerve terminals, they suggest an important role for ACh receptors.

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Merging of Modalities in the Optic Tectum: Infrared and Visual Integration in Rattlesnakes

Abstract. *The optic tectum of pit vipers (Crotalinae) contains a layer of infrared-sensitive neurons subjacent to the visual layer; these indirectly receive input from the facial pit organs. They respond transiently to the appearance or motion of warm objects within their 25° to 70° excitatory receptive fields (some have inhibitory regions) and presumably allow the snake to orient or strike toward prey. The infrared and visual spatiotopic tectal maps have similar but not identical axes; the infrared magnification is greater than that for vision. Bimodal neurons have receptive fields for each modality that reflect the disparity of the two maps. This finding suggests that (i) during development the infrared and visual fibers spread out independently to fill available tectal sites and (ii) bimodal neurons form local connections without regard to establishing spatial correspondence between the two modalities.*

The superior colliculus, or optic tectum, is widely recognized as a center for visual integration with primary roles in the control of eye movements (*1, 2*) and the orientation of the head or body toward a stimulus source, such as for prey capture (*2, 3*). Other sensory modalities are also represented by the responses of tectal neurons: auditory, somatic, proprioceptive, and multimodal responses are recorded in cells of the mammalian superior colliculus (*4–6*). Tectal circuitry may therefore be hypothesized to bring sources of visual and nonvisual stimulation to the same central region of the animal's visual field or zone of action. In this report, we explore the question of how similarly space is represented in the optic tectum in two distinct modalities; spatiotopic maps and the receptive fields of bimodal neurons suggest that similar principles determine the connections of each modality but that no mechanism operates to ensure that one region of space is represented at the same tectal locus or by the same tectal neurons.

In rattlesnakes, (fam. Viperidae, sub fam. Crotalinae), the facial pits, specialized bilateral infrared sense organs, detect the appearance and motion of dis-

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tant sources of infrared (for example, an object warmer than the radiation temperature of its background), and the tectal cells respond; the facial pits thus function like infrared eyes. Tectal neurons are at least third (possibly fourth) order, since primary pit afferents innervate neurons in the lateral descending nucleus of the trigeminal (*7*).

The pit-mediated sense is important for orientation of the snake's prey-capturing strike; its exquisite sensitivity can detect and localize a rat at the distance of 1 m (*8*). Perhaps it is for this reason that the infrared sense, as well as vision, is prominently represented in the tectum, providing us with an opportunity to study the details of visual and nonvisual integration and those of spatial representation of a nonvisual modality.

Hartline (*9*) reported a spatiotopic organization of snake tectal infrared neurons similar to that found in the visual system in other vertebrates (*10, 11*). This sort of spatiotopic mapping, found also in auditory and somatic (*5, 10*) representation in the mammalian superior colliculus, has not been studied in sufficient detail to allow precise comparison of visual and nonvisual maps, although in mammals (*5, 10*) and snakes (*9, 12*), rough correspondence of maps of different modalities appears to be the rule. In the mammalian superior colliculus, multimodal neurons have receptive fields, in their several modalities, whose locations approximately coincide. This lends credence to the hypothesis of similarity of visual and nonvisual functions of the tectum.

Our findings confirm earlier reports that, in pit vipers, visual and infrared spatiotopic tectal organizations are similar; this resemblance suggests a similarity of the processes that govern the formation of tectal connections by neurons of each modality. However, we found greater magnification in the infrared map and differences in axis alignment between infrared and visual maps; these differences suggest that the two maps do not determine each other to achieve spatial congruence. Bimodal neurons do not appear to correct for the disparity of the maps. Rather than coincidence of infrared and visual receptive field centers, we found systematic, locus-specific displacements of infrared receptive fields relative to visual fields of bimodal neurons. That the maps account well for the displacements suggests that bimodal cell inputs are spatially similar to those of nearby unimodal visual and infrared neurons.

We have recorded from neurons of the superficial and deep layers of the optic tectum of the pit viper, *Crotalus viridis*. Snakes were deeply anesthetized with methoxyflurane for surgery and were allowed to recover pupillary and tail-pinch reflexes before recordings were made. We used KCl- or NaCl-filled micropipette electrodes (25 to 80 megohms) for unit isolation, stainless steel electrodes for histological (Prussian blue) localization of the tectal layers in which infrared or visual units are found, and either one for multi-unit mapping experiments.

Visual units were found in layers 7b and 8 to 13 of Ramon, the superficial 450 μm of the tectum (*13*). They responded to motion of thermoneutral targets such as a black cardboard wand at room temperature. Their responses disappeared if the room lights were extinguished or if the contralateral eye was occluded (few

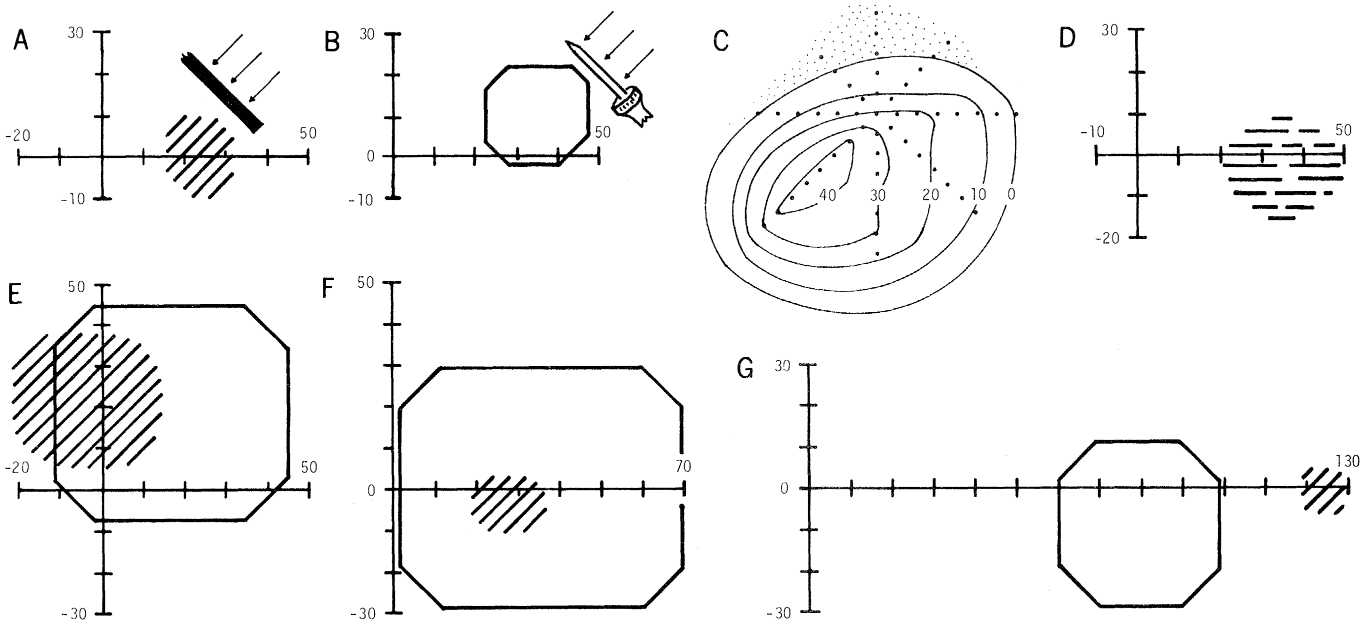

Fig. 1 (A). A visual neuron's (V3J1) receptive field mapped by introducing a dark cardboard thermoneutral wand against a tangent screen. The vertical axis is given in degrees above the horizontal plane through the snake's head (latitude); the horizontal axis in degrees from the midline on the side of the head contralateral to the tectal recording site (longitude), as in a cyclindrical projection of the earth. Negative values are ipsilateral. The origin is directly ahead of the snake's nose. The contralateral eye's optical axis is at about 0° latitude, 75° longitude. (B) An infrared neuron's (V2C2) receptive field, mapped by introducing a hot soldering iron along each of eight directions toward the approximate field center. The iron's entry into the enclosed area evoked a crisp burst of impulses. (C) Equal-response contour plot of infrared neuron (V1OM) based on the response to a stimulus presented at different points in the receptive field. The stimulus was positioned at points separated by 5° along a circular track centered on the pit organ (solid points). The track was oriented at different angles about an axis through the point 10° latitude, 50° longitude. Note that this is a polar azimuthal projection. A computer counted spikes during three iterations of a 1-second stimulus at each point [the glowing filament of a tungsten-iodide bulb modulated by a gold-leaf shutter (Vincent)], and the mean spontaneous rate was subtracted. The mean spontaneous rate, which fluctuates slowly with time, was obtained separately at each point by counting the mean firing rate in the three final seconds of the 10-second stimulus epoch. Equal response contour lines (at 0, 10, 20, 30, or 40 spikes per stimulus above the spontaneous rate) are smooth approximations of linear interpolation or extrapolation from data points shown. The stippled area indicates depression below the spontaneous rate, which, in turn, indicates an inhibitory area. (D) The nebulously defined receptive field of bimodal AND neuron (V5.2A1) responded only to movement of a warm object (hand or soldering iron) across the field in the presence of illumination. (E-G) The infrared (solid boundaries) and visual (hatched area) receptive fields of bimodal OR neurons [V24C1 (E), V24J1 (F), and V23MM (G)]. Infrared fields were mapped with a hot soldering iron as in (B); visual fields were mapped with a thermoneutral black wand as in (A).

ipsilaterally driven visual units were found). To characterize the spatial receptive field properties of visual units, the black wand was moved toward the approximate center of the field. Superficial units responded transiently to the advance of the black wand's border into a region about 5° to 20° in diameter (Fig. 1A). Thus, they were similar to tectal visual units in other cold-blooded vertebrates and in mammals. In deeper visual units, directional selectivity and complicated receptive field properties (such as the requirement for restricted spatial extent of the stimulus) and larger receptive fields were found. Within the first 300 μm of the tectal surface (layers 8 to 13), visually responsive units were not sensitive to infrared stimulation in the dark.

Infrared units were identified by their responses to the movement of a warm object (hand or soldering iron), which persisted in the dark. The responses disappeared when the contralateral pit was occluded. Such neurons were encountered between 300 μm and 1.2 mm in depth, layers 7a and 7b (in 60-cm snakes). To map the receptive field of a known infrared neuron, a soldering iron was advanced toward the center of the field, and the iron's position at the time the response began was noted (as distinguished on the audio monitor). This procedure was repeated for each of four or eight equally spaced directions; from it was derived the square or octagonal receptive field map (Fig. 1B), which contained the approximately elliptical receptive field. Fields were 25° to 70° across their largest dimension. A more laborious method of determining the receptive field that obtained similar borders to within 5° was used for several neurons. A computer stepped the infrared source (a shutter-modulated glowing tungsten-iodide lamp operated at a fraction of its normal wattage) across great-circle arcs of the hemisphere surrounding the pit contralateral to the tectal recording site. At each position, a poststimulus-time histogram was calculated for three to ten iterations of the stimulus: a 1-second exposure to the glowing blub repeated every 10 to 20 seconds. Histograms were obtained for a set of arcs covering the receptive field. A graph was constructed relating spatial position to the number of impulses above background elicited by the stimulus. From these, constant-response-magnitude contour plots were made (Fig. 1C).

Figure 1C shows the excitatory receptive field of an infrared unit, mapped by the computer method. It shows, as well, a partially mapped inhibitory region in which onset of the infrared stimulus depressed spontaneous activity. Antagonistic regions were not easily demonstrable in all units; they may be sensitive to anesthetic level. In these and in all infrared units characterized in adult snakes, we observed phasic responses (which adapted to the spontaneous rate within about 1 second even for intense stimulation). Motion of an infrared source was always a good stimulus, even at rates of 5° per second. We have occasionally observed a form of directional selectivity: a response to motion of an infrared source across the entire field in one but not the other direction along the same axis.

About 10 percent of the units encountered below 300 μm (layers 7a and 7b) were bimodal cells. Some responded to visual and to infrared stimulation (Fig. 1, E–G); these are designated OR units. The OR units are identified by (i) responsiveness to cardboard thermoneutral wand stimulation that is abolished by occlusion of the contralateral eye and (ii) responsiveness to a soldering iron presented in the dark that is abolished by occlusion of the contralateral pit. The OR units were often stimulated more vigorously by combined submaximal visual and infrared stimulation than by either one alone, which indicates some intermodality summation. Some OR neurons exhibited directional selectivity. They responded maximally to motion of a large infrared or visual stimulus in one direction (which we could establish to within ±20°). Motion of the same stimulus in the opposite direction gave no response; motion along other axes gave suboptimal responses. In a few neurons for which we could establish the optimal directions of motion for both infrared and visual modalities, the directions were the same within the limits of our measurement.

Some bimodal neurons responded only to combined stimulation in infrared and visual modalities; these are designated AND neurons. They could only be stimulated by presenting a warm stimulus (hand or soldering iron) in the presence of illumination. Their receptive fields were difficult to establish, since the neurons usually responded to only the first few iterations of a stimulus and often required rapid stimulus motion (Fig. 1D).

We constructed the infrared and visual spatiotopic maps of the tectum with greater resolution than that of maps presented in earlier studies (*9*, *12*). We used multi-unit recordings to establish aver-

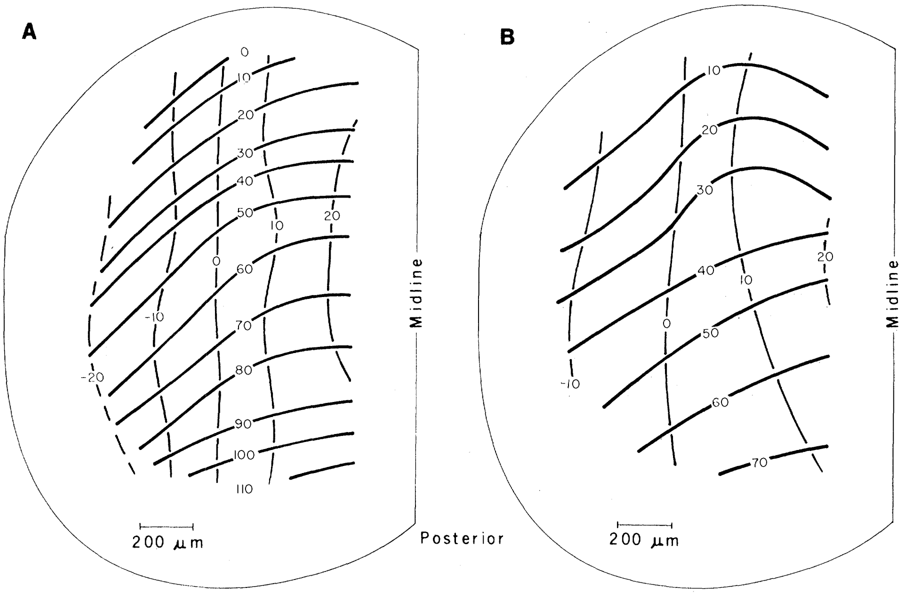

Fig. 2. Spatiotopic maps of visual and infrared organization of the tectum. Visual and infrared receptive field centers were localized for a grid of points separated by 200 μm. Each field's center was specified by spherical coordinates. Positive latitude gives elevation above the horizontal plane; positive longitude gives the contralateral displacement of the vertical meridian through the field center (0° is directly in front of the snake's nose). The blank areas on these maps were not exposed during the recording. In other animals, we could record visual responses over the entire tectum and infrared responses to within 200 to 300 μm of the edge of the tectum, presumably because of downward curvature of the infrared layer. (A) Visual-field centers were used to calculate tectal position for latitudinal (interrupted) and longitudinal lines (continuous) at 10° spacing by linear interpolation. Smooth curves were hand-drawn to fit linear interpolation maps. (B) Infrared spatiotopic map. The procedure for constructing the map was the same as for (A) except that infrared receptive field centers were used for the interpolation process. The solid outline indicates approximate edges of the tectum. The entire region of tectal exposure was mapped, but the mapping did not cover the entire tectal surface.

age receptive field centers corresponding to points on an imaginary grid (200-μm spacing) covering much of the tectal surface. At each grid point, the visual multi-unit field center and then the infrared field center were determined. For visual fields, the electrode depth was superficial and the stimulus was specific for vision because of its thermoneutrality. For infrared fields, the electrode was deep enough that no thermoneutral wand response was obtained. Thus the determination of neither visual nor infrared field was contaminated by the other modality. From the spherical coordinates of the field centers, projection maps of the visual (Fig. 2A) and infrared (Fig. 2B) "worlds" onto the tectal surface were constructed by linear interpolation and smoothing. The lateral hemisphere surrounding the pit and eye on the side contralateral to the recording electrode served as the basis of the coordinate system.

In Fig. 2, the tectal locations corresponding to latitudinal lines are represented by thin interrupted lines. Along these, which traverse the tectum in an anterior-posterior direction, elevation is constant. Adjacent lines are separated by 10° of elevation. The tectal locations corresponding to longitudinal lines are represented by heavy continuous lines. Along these, which traverse the tectum medio-laterally, the anterior-posterior angle is constant. Adjacent lines are separated by 10°.

Important systematic differences between visual and infrared maps are evident. The magnification factors (distance separating tectal loci whose receptive field centers are separated by 1°) for both anterior-posterior and medio-lateral tectal axes are greater for the infrared system than for the visual system. The area of tectal surface devoted to each particular region of space is larger in the infrared system than in the visual system. A systematic deviation in the opposite direction would be expected if the curvature of the tectal surface and the relative depth of the infrared and visual units were the cause of this discrepancy.

In anesthetized and paralyzed snakes, the equatorial latitudinal lines of visual and infrared maps approximately coincide. Because of the greater infrared magnification factors, the medial border of the mapped part of the tectum (the tectal exposure was incomplete) represents greater elevation (by 5° to 10°) in visual than in infrared systems. At the lateral border of the map, visual field centers are of lesser elevation (by 5° to 10°) than infrared field centers. Similar statements can be made for the longitudinal lines, which approximately coincide in the two modalities at between 10° and 30° contralateral. In the posterior tectal region, visual fields are centered 20° to 40° posteriorly to infrared fields.

The two maps also show that the latitudinal and longitudinal lines of the two modalities are not perfectly aligned with each other. The tectal region where this is most conspicuous is the anterior third, where the longitudinal lines dip toward the anterior pole, especially on the equatorial line. The dip (amounting to 200 to 300 μm) is not seen in the visual map. It contributes to a 20° posterior displacement of the infrared receptive field center relative to the visual map in this region. These are consistent features of the maps of all four animals for which adequate data have been obtained.

What is the relationship between the visual receptive field and the infrared receptive field of a bimodal OR unit? Alternative possibilities are (i) connections of bimodal cells are formed such that spatial coincidence of field centers occurs despite the disparity of maps of the two modalities; (ii) bimodal cells receive input from nearby infrared and visual cells, yielding disparate field centers; and (iii) bimodal cells receive input from the same afferent fiber populations that innervate nearby unimodal cells, also yielding disparate field centers. The OR neurons with anterior infrared fields have visual fields that are even more anterior (Fig. 1E); those with infrared fields at 20° to 40° have nearly concentric visual fields (Fig. 1F); those with posterior infrared fields have visual fields that are even more posterior (Fig. 1G). These results would be expected only under hypotheses (ii) or (iii). Further evidence for these hypotheses comes from penetrations in which visual units or infrared units were encountered before or after receptive fields were mapped for an OR unit. In these, visual unit field centers were within about 5° of the bimodal unit's visual field center, and infrared field centers were within 5° of the bimodal unit's infrared field center.

The biological significance of dual-modality spatial organization of the tectum or superior colliculus may result from recognition or orientation functions of this structure. Its role in orientation is demonstrated by (i) stimulation of deep tectal layers, which causes orientation of the eyes, head, or body toward the region of space corresponding to the stimulated locus (*1-3*) and (ii) studies that demonstrate deficits in orienting behavior caused by tectal ablation (*14*). If natural stimuli in each of several modalities are to produce orientation responses, the spatiotopic relationships of each should be similar. If so, neural circuitry for initiating and directing movement could be shared. Recognition functions would also be enhanced by similarity of spatiotopic arrangement. One way to recognize an object might be to look for spatial coincidence of stimulation originating from that object in several modalities. This could easily be done by bringing information from a particular region of space to the same tectal locus regardless of modality.

In each of these cases, the more exact the correspondence between the spatial organization of tectal modalities, the better it would seem that the biological function of the tectum would be served. The advantage of spatial correspondence would be reduced if there were poor spatial localization in the nonvisual modality or an absence of a fixed spatial relationship between the sensory organs involved, such as that caused by eye, head, or ear movements. In these cases, nonvisual maps might be poorly defined and might correspond only crudely to visual maps. This explanation has been invoked for the diffuse auditory and somatic tectal maps in cats and mice (*6*).

The discrepancy between visual and infrared maps and between receptive fields of bimodal cells in the two modalities is not due only to the large size of most infrared fields (which we may presume precludes accurate localization of a stimulus by such neurons). Size alone could not account for the systematic deviation of visual and infrared coordinates evident in our maps—up to 40° at the extreme margins of the tectum. This sort of discrepancy would have been less dramatic in earlier studies of other animals because in those studies nonvisual receptive fields are localized with about one-fifth the precision we could obtain for infrared fields (*5, 10*). Eye movements also, although present in rattlesnakes, would not account for systematic map discrepancies. We must look elsewhere to discover why infrared and visual maps do not correspond closely.

We therefore hypothesize that the spatial organization of the visual and infrared modalities in the tectum does not follow a rule simply requiring spatial superposition to the greatest degree possible. Rather, connectivity appears to be governed by (i) a rough alignment of axes and (ii) a rule dictating that all available infrared and visual input fibers should spread out to fill all available tectal sites in their respective laminae across the tectal surface. We attribute the difference in infrared and visual magnification factors to the smaller size of the total field of the infrared pit organ compared to the total visual field of the eye. The regional differences in magnification and axis alignment of tectal visual and infrared maps could be a consequence of the innervation pattern of the pit, of the distribution of target sites in the tectum, or of other mapping mechanisms. An untested alternative to our hypothesis is that visual and infrared maps influence each other to achieve the observed disparity. Among many possible explanations for these data, our hypothesis is attractive because of its simplicity.

That all available input fibers should spread out to occupy all available target sites appears to be an important rule governing development of neural connections. If one removes half of the retina of *Xenopus*, the ganglion cell fibers develop to invade all available tectal sites, not just the ones they would have occupied had no cells in the retina been removed (*15*). The spatial distribution of two sets of afferent fibers (visual and infrared) in the tectum is economically explained if the connections of one modality do not affect those of the other. The approximate similarity of the axes of orientation of the tectal maps could result from shared developmental mechanisms or from similarity of independent ones. The differences of the maps invite generalization of the rule. "Spread out to occupy all available tectal sites," and suggest that it may be applied to systems in which a single brain structure is innervated by two distinct fiber populations.

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Effect of Prolonged Illumination (Phototherapy) on Concentrations of Luteinizing Hormone in Human Infants

Abstract. *Concentrations of luteinizing hormone in the serums of human neonates were altered when the neonates were exposed to prolonged, intense illumination (phototherapy) with their eyes covered. Concentrations decreased after 48 to 72 hours of exposure, increased 6 to 9 days after phototherapy, and subsequently returned to levels similar to those of controls. These data suggest that light may affect pituitary-gonadal function in the human neonate.*

In birds and mammals, light has a stimulatory effect on gonadal development and function, whereas darkness has the opposite effect (*1*). This stimulatory effect seems to be mediated through the pineal gland, whose secretory activity is controlled by light (*1, 2*).

In humans, the effect of light on the neuroendocrine system and, more specifically, on sexual maturation is not known. The available clinical and biochemical data point to a possible relationship between environmental light and pineal-gonadal development in humans. Delayed or precocious puberty has been reported in association with pineal tumors (*3*); parenchymatous pinealomas are usually associated with depressed gonadal function, whereas nonparenchymatous lesions, such as gliomas and teratomas that destroy the pineal gland, are more apt to be associated with precocious puberty. Hence pineal hyperfunction seems to be associated with delayed puberty, and hypofunction with advanced puberty. The dark period of the Arctic winter probably is associated with suppression of ovulation in Eskimo women (*4*). Zacharias and Wurtman (*5*) found that in girls who were blind at birth or became blind shortly thereafter, menarche was earlier than in controls. Melatonin concentrations in the blood of humans were found to be higher at night than during the day; however, when the light periods were prolonged, the effect on melatonin levels was equivocal (*6*). A peak of blood melatonin was found at the time of menstruation while a nadir coincided with the luteinizing hormone (LH) peak (*7*).

Neonated jaundice is currently treated by exposing the affected infant to prolonged, intense illumination. Such treatment provides an appropriate situation for studying the effect of light on humans undergoing a critical period of development of the neuroendocrine system. In our studies of human neonates receiving phototherapy we found that the concentrations of pituitary LH were altered by prolonged, intense illumination.

In 17 icteric but otherwise healthy newborns who received phototherapy continuously for 3 days (third to sixth day of life), the concentrations of LH in

Table 1. Irradiance measurements at the level of the infant inside the incubator and in the nursery.

Site of measurement	Wave band (nm)	Irradiance (μW/cm^2)
Inside the incubator during phototherapy	420 to 460	250 ± 40
Inside the incubator during phototherapy	460 to 650	700 ± 60
Middle nursery (1 p.m.)	400 to 500	25 ± 10
Middle nursery (10 p.m.)	400 to 500	5 ± 4

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