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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Table 2. Bilirubin values in milligrams per 100 ml (mean ± 1 standard deviation).

Group	Age (days)						
	2	3	4	5	6	8 to 10	11 to 13
Phototherapy	13.7 ± 2.7	13.9 ± 2.2	12.0 ± 2.6*	9.0 ± 2.8*	7.9 ± 2.1	5.9 ± 1.9	5.0 ± 1.9
Control A	12.9 ± 3.0	13.6 ± 2.8	14.2 ± 3.0	13.3 ± 2.6	12.5 ± 1.7	9.9 ± 2.1	7.1 ± 2.0
Control B	12.1 ± 3.1	12.8 ± 2.5	13.8 ± 2.8	12.9 ± 2.5	11.9 ± 2.0	9.0 ± 2.2	6.8 ± 2.3

*Under phototherapy.

the serum were determined prior to, during, and for several days after phototherapy. The source of light was ten 20-watt fluorescent day lamps. Irradiance inside the incubator and at the level of the infant's head, as well as average irradiance in the middle of the nursery during the day (1 p.m.) and night (10 p.m.) are shown in Table 1.

As is usual, the eyes of the babies under phototherapy were covered with dark pads. Three control groups were also studied. Group A included 15 icteric newborns who did not receive phototherapy. Group B included six icteric newborns who did not receive phototherapy, but whose eyes were covered as were the eyes of the newborns under phototherapy. Group C included 23 nonicteric, healthy newborns. All newborns were matched for gestational age, birth weight, and postnatal age. All groups except group C were also matched for the intensity of jaundice (Table 2).

Serum LH was determined by radioimmunoassay in capillary blood drawn between 9 a.m. and 10 a.m. The standard LH used had the following characteristics: (i) biological potency: 2000 I.U./mg of the Second International Reference preparation (IPR-HMG); (ii) radioimmunological potency: 2160 ± 240 I.U./mg, 68/40 Medical Research Council, Mill Hill, or 66 ± 6 mg of LER 907 from the National Institutes of Health. The results were expressed in milliunits (international) per milliliter. The sensitivity of the assay is 0.2 mU/ml. Intra-assay and interassay variation is 8 and 12 percent, respectively. To reduce interassay variation, specimens from all testing periods in equal numbers from the phototherapy group and control group A were assayed simultaneously. Results were analyzed according to Student's *t*-test for paired and unpaired data. Preliminary data of this study were reported previously (*8*).

We observed (Fig. 1) slightly lower LH values after 24 hours, and significantly lower values after 48 to 72 hours of phototherapy in comparison to either the value prior to phototherapy ($P < .001$) or the values in the three control groups ($P < .001$). The most pronounced change in the LH levels during the entire test period was the significant transient increase that occurred after the phase of suppression ($P < .001$ for days 12 and 15). The LH concentrations did not show any change in the three control groups.

The results for control groups B and C indicate that neither darkness from closure of the eyes nor the jaundice per se accounted for the observed LH changes. It is possible, however, that products of bilirubin photodegradation caused the changes in LH concentrations.

If the LH changes were associated with the exposure of the neonates to light, then the question of how the light reached the brain (pineal, hypothalamus, other structures) should be answered, since the eyes of the light-treated babies were covered. However, it has been shown that light penetrates into the brain through the skull (*9*).

Another relevant question is why the effect of light on the human newborn is different from that on other animals; in the latter, illumination suppresses the function of the pineal gland and has a favorable effect on gonadal development and function and presumably increases the release of gonadotropins. Hence one should expect an increase rather than a reduction in LH levels. We may assume that in the human neonates the decrease in LH concentrations after prolonged, intense illumination is due to an exhaustion phenomenon of the hypothalamic-pituitary unit resulting from the lack of the inhibitory action of the pineal gland. This assumption is supported by the observations of Ortavant *et al.* (*10*) who found that in mammals, prolongation of the light photoperiod decreased production of gonadotropins.

Even more difficult to interpret is the impressive transient increase in serum LH that occurred 6 to 9 days after phototherapy had ended. Perhaps this can be attributed to a rebound phenomenon.

Not enough is known about the complex interactions of light with the pineal, hypothalamus, and pituitary, especially in the human, for us to be able to make a unified interpretation of all known data. The changes that we observed in the LH concentrations of infants receiving pho-

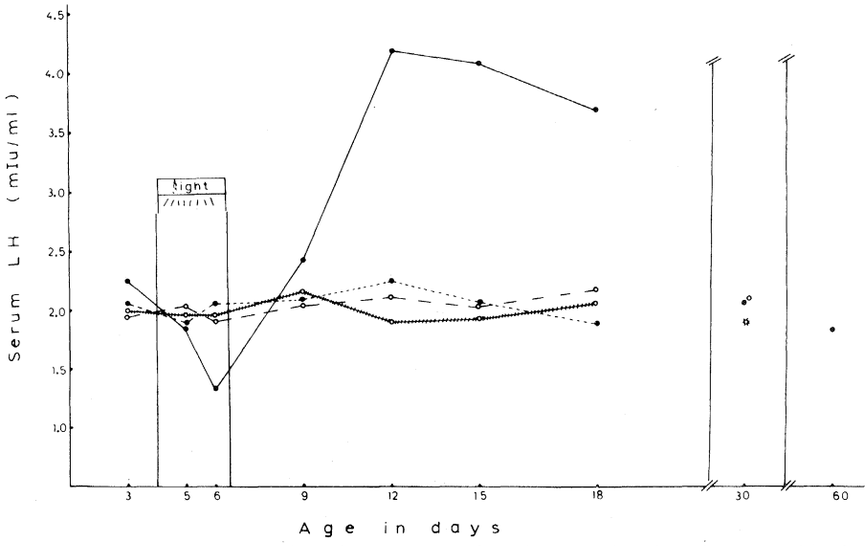

Fig. 1. Mean concentrations of LH in the serum of newborns under phototherapy and in the three control groups. Standard deviation values are indicated for jaundiced babies under phototherapy and for jaundiced babies without phototherapy. Levels in the control groups remained unchanged. In the study group there is a decrease in LH concentrations during phototherapy and a subsequent increase following interruption of phototherapy. Jaundiced babies under phototherapy (●——●); jaundiced babies without phototherapy (○— —○); jaundiced babies with covered eyes without phototherapy (● · · · · ●); healthy babies (○——○).

totherapy could be peculiar to a developing neuroendocrine system and might have little similarity to results that would be derived from adult organisms.

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Opiate Receptors for Behavioral Analgesia Resemble Those Related to the Depression of Spinal Nociceptive Neurons

Abstract. *With naloxone as antagonist, a dose-ratio analysis of the depression by morphine of nociceptive neurons in the spinal cord reveals that this opiate depression of single unit activity has the same pharmacological properties as observed with morphine analgesia. This suggests that the opiate receptor, mediating the observed cellular depression, and those mediating analgesia are presumably the same.*

Lamina 5 neurons in the dorsal horn of the spinal cord are discharged by the administration of noxious stimuli to their receptive fields and by Aδ and C fiber activation, while the application of narcotics in doses sufficient to produce analgesia will depress this discharge (*1, 2*). If these cells are in fact part of the pathway through which behaviorally defined changes in the pain threshold are mediated, then the pharmacology of the opiate effect measured on the cellular response should be identical to the pharmacology of the analgesia resulting from these drugs. Both the neuronal activity of these cells and the behavioral relief from pain produced by opiates are stereospecific and antagonized by naloxone (*1–3*). However, the simple observation of naloxone antagonism is not a sufficient premise to assume the pharmacological identity of the receptor systems mediating either effect. The dose ratio analysis (*4, 5*) in the behaving animal has demonstrated that different values for the pA_2, a parameter reflecting the interaction between a competitive antagonist and agonist in a given receptor system, may be obtained for morphine and naloxone when different opiate effects, such as respiratory depression, temperature, and analgesia, are measured (*6*). Such results suggest that different forms of the opiate receptor may be related to brain structures mediating these various functions. If the depressive effects of systemically administered opiates on the response of lamina 5 neurons to noxious stimuli are related to the substrate mediating the observed behavioral analgesia, then the dose ratio analysis carried out with the discharge of the cell rather than the behavioral response as an end point should yield the same results, as has been reported for the interaction of morphine and naloxone on analgetic tasks in the behaving animal.

These studies were conducted as follows. Microelectrode penetrations (*7*) were made into the dorsal horn of the unanesthetized, decerebrate spinal cat which had been paralyzed with flaxedil and artificially respirated. During penetration, the sural nerve, mounted on silver hooks and cut distally, was stimulated at an intensity which produced an Aδ and C volley as monitored on adjacent recording hooks. Cells were selected for study only if they showed a relatively low level of background activity (2 to 10 Hz) and if they responded to sural nerve stimulation with a stable discharge pattern having an identifiable fast and slow component corresponding to the large and small fiber input. The amplified response of the cell went into a spike trigger, and this output went both into a rate meter (spikes per second) and into an averager to give a post-stimulus histogram (PST). Throughout the experiments, the shape of the spike was continuously monitored by a delay line to verify that the recorded activity was derived from a single isolated cell and that the same spike was present during the entire experimental sequence. One of two drug paradigms was used. In the first, morphine was given in two doses; the second dose was ten times larger and was delivered after the first dose had produced its maximum effect. In this manner, a dose response function was obtained for each unit. Three different morphine dose ranges were used to give a dose response curve ranging from 0.3 to 10.0 mg/kg (that is, 0.3 and 3.0, 0.5 and 5.0, and 1.0 and 10.0 mg/kg). As the dose separation was always a factor of 10, the effect of the first dose on the effect produced by the second dose was considered negligible. At the time that the effect of the

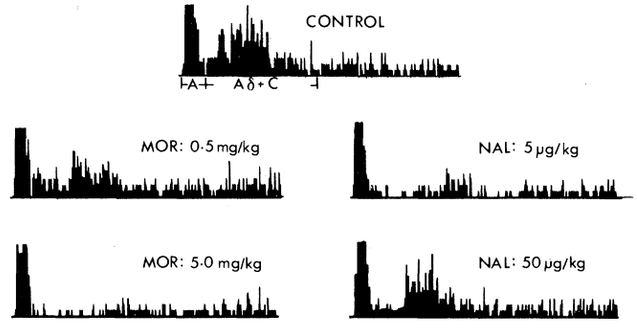

Fig. 1. Post-stimulus histograms each indicating the average of 32 sweeps and derived from a single cell before (*CONTROL*) and after the injection of morphine sulfate (*MOR*) and naloxone hydrochloride (*NAL*). The sequence of injections was morphine (0.5 mg/kg) followed by morphine (5.0 mg/kg). At this time, naloxone was given at 5 μg/kg and then 50 μg/kg. Ten minutes elapsed after each injection of morphine and 5 minutes after each naloxone injection. The evoked discharge related to large (*A*) and small (*Aδ and C*) fibers is indicated in the control PST. The axis bars are 100 msec and 20 spikes. As the settings required to examine Aδ and C fiber evoked activity, the response to A fibers exceeded the capacity of the averager, resulting in the sharp cut off seen in these records.

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