

Photoperiodic Regulation of Neuroendocrine-Gonadal Activity

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INTRODUCTION

Reproduction in many species is confined to a time of the year when the probability of survival for both the adults and offspring is maximum. While the ubiquity of the seasonal variation in reproductive activity has been recognized by man for thousands of years, it is only within the past 60 years that the length of the day, or photoperiod, has been recognized to be for many species the major environmental variable that synchronizes the reproductive cycle with the appropriate season of the year.

The early failure to recognize the importance of day length in the control of annual reproductive cycles is undoubtedly due to the fact that the photoperiod itself does not directly determine the most advantageous time of the year for producing offspring. Instead, such environmental variables as food supply, competition, predation pressure and climate are the "ultimate factors" that determine the most advantageous time of the year for an organism to reproduce (Baker, 1938). However, because such factors are not always reliable signals for determining the time of the year and because they often do not allow an organism to prepare in advance for the changing seasons, natural selection has resulted in the use of "proximate factors" as signals announcing the approach of a changing environment (Baker, 1938). In a wide diversity of both plant and animal species living outside of the equatorial regions of the world, the proximate factor that is used to identify the appropriate season for reproductive activity is the annual cycle in daylength. The strong reliance on daylength for the timing of the reproductive season is undoubtedly due to the noise-free nature of this variable and therefore its reliability as a marker of the phase of the seasonal environmental cycle.

Many organisms (e.g., hamsters, voles, ferrets, most temperate zone birds) require long days for the induction of reproductive activity (Gaston and Menaker, 1967; Hoffman,

1973; Grocock and Clarke, 1974; Thorpe and Herbert, 1976; Farner, 1975), while other species (e.g. sheep, deer, mink) utilize short days to signal the onset and maintenance of gonadal function (Lodge and Salisbury, 1970; Lincoln and Davidson, 1977; Mirarchi et al., 1978). In many animals, a period of sensitivity to the light cycle is followed by a period of insensitivity. For example, in many species of birds, gonadal regression follows photic-induced gonadal development even though the animals are maintained on photostimulatory long days. In order to become responsive again to long days, the birds must first be exposed to short days for a species specific period of time (Wolfson, 1952; Farner and Follett, 1966). Similarly, gonadal regression which occurs in golden (Syrian) hamsters in response to exposure to short days is followed by gonadal recrudescence after a prolonged exposure to short days (Reiter, 1972; Turek et al., 1975a). In order to become responsive again to the inhibitory effects of short days, hamsters must be exposed to long days for about 11 weeks (Stetson et al., 1977). The physiological state in which an animal is temporarily incapable of responding to a particular light cycle that had previously altered neuroendocrine-gonadal activity is referred to as the "refractory" condition (Farner and Follett, 1966).

The refractory condition observed in many species demonstrates that the neuroendocrine-gonadal axis is not simply a passive system driven by the annual cycle in daylength. Furthermore, in some photoperiodic species, annual gonadal cycles can be observed in the absence of a change in photoperiodic conditions (Berthold et al., 1971; Schwab, 1971; Ducker et al., 1973; Gwinner and Dorka, 1976). In most birds which show gonadal cycles under constant environmental conditions, the period of this cycle is usually slightly less than 1 year. This deviation of the period from exactly 1 year excludes the possibility that

uncontrolled environmental variables are regulating gonadal activity and suggests that the gonadal cycle is generated by an endogenous rhythm with a period of about 1 year (circannual). Thus, in at least some species, the photoperiod does not simply induce or terminate reproductive events, but instead synchronizes an endogenous circannual rhythm so that the reproductive events occur at the appropriate time of the year (Gwinner and Dorka, 1976; Gwinner, 1977).

In order for the photoperiod to alter the breeding condition of an animal, the following events must occur: 1) light must be perceived by the organism; 2) an assessment of the length of the day (or night) must be made, implying the existence of a time measuring system; 3) information from the time measuring system must be transferred to the hypothalamic-pituitary axis which directly regulates gonadal function and 4) an alteration in hypothalamic-hypophyseal-gonadal activity must occur. Our understanding of the neuroendocrine events associated with the above aspects of the photoperiodic response in vertebrates has been derived mainly from studies on birds and mammals. Because excellent reviews on the photoperiodic control of neuroendocrine-gonadal activity in birds have recently been published (Farner, 1975; Follett and Davies, 1975), this review will mainly emphasize the studies that have been carried out in mammals.

Perception and Transmission of Photic Information

One of the major differences in the photosexual response between mammals and the lower vertebrates is the manner by which light is perceived. Although there is some evidence to suggest that neonatal rats possess a non-ocular photoreceptor(s) that is involved in the entrainment of a circadian rhythm (Zweig et al., 1966; Wetterberg et al., 1970), it appears that in mammals the eye is solely responsible for the perception of light which is used to measure photoperiodic time. This hypothesis is supported by the observation that the photoperiodic control of reproductive function in mammals is abolished following the removal of the eyes (Thomson, 1954; Hoffman and Reiter, 1965; Dixit et al., 1977). In contrast, extraocular photoreceptors mediate the gonadal response to light in both reptiles and birds (Benoit, 1964; Menaker and Keatts, 1968;

Oishi and Lauber, 1973; Underwood, 1975). The existence of extraretinal receptors for the mediation of the photoperiodic response in birds is supported by a number of different experimental findings: 1) the reproductive condition of blind birds can still be altered by changes in the light-dark environment (Fig. 1; Benoit, 1964; Underwood and Menaker, 1970; Homma et al., 1972; McMillan et al., 1975; Yokoyama and Farner, 1976); 2) an alteration of the amount of light reaching the brain (but not the eyes) by various techniques can alter the photoperiodic gonadal response (Fig. 1; Menaker et al., 1970; Gwinner et al., 1971; Turek, 1975) and 3) directing illumination into the brain via light-conducting fibers or radioluminescent implants can induce gonadal development (Homma and Sakakibara, 1971; Oliver and Baylé, 1976; Yokoyama

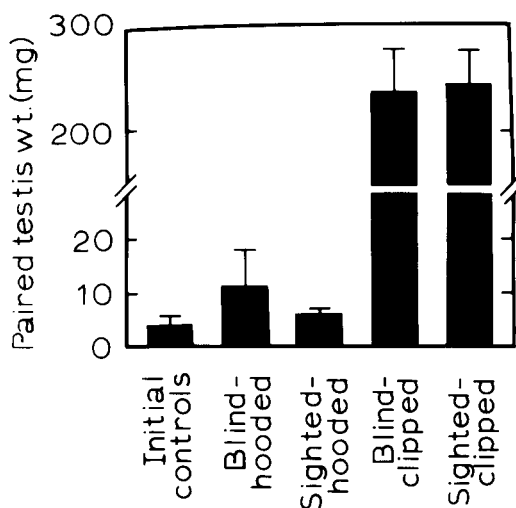


FIG. 1. Effects of low intensity red light exposure ($0.15 \text{ ergs/cm}^2/\text{second}$) of the eyes and/or brain photoreceptors on the testis weight of house sparrows. The birds were sacrificed after a 24 day exposure to an LD 16:8 red light-dark cycle. Birds were either clipped (head feathers removed) or hooded (opaque material applied beneath and above skin of skull) to alter the amount of light reaching the brain. Initial control birds (IC) sacrificed prior to the start of the experiment had regressed testes. Testicular growth occurred only in those birds with clipped head feathers, while blinding had no effect on the photoperiodic response. Red light was used because of an earlier suggestion that retinal photoreceptors were highly responsive to light in the orange-red region of the spectrum but comparable results have also been obtained using white light. (Redrawn from McMillan et al., 1975).

and Farner, 1978). Extraretinal receptors have been implicated in various stages of the avian reproductive cycle including photic-induced gonadal growth, gonadal regression and the photorefractory condition (Menaker and Keatts, 1968; Turek, 1975; Underwood, 1975). Thus, in birds, the eyes do not appear to play a major role in the perception of light involved in the photoperiodic control of reproduction, although there is some evidence to suggest that retinally perceived light does influence the reproductive system (Homma et al., 1972; Yokoyama and Farner, 1976).

Although the mammalian eye is clearly involved in the perception of light used to measure time, the identity of the photoreceptors involved in the photoperiodic response remains unknown. One should be cautious in assuming that rhodopsin-containing rods of the retina are involved in this process since albino rats with complete degeneration of the rods can still perceive light. Light which is used for light-dark and pattern discrimination, as well as for the entrainment of the plasma corticosterone rhythm, can still be perceived by albino rats following the loss of all known retinal rod photoreceptors due to exposure to constant light (Anderson and O'Steen, 1972; Bennett et al., 1972; Dunn et al., 1972). Recent evidence suggests that while exposure to constant light causes severe damage to rod photoreceptors, the cones are much less affected (Cicerone, 1976). Whether or not the perception of light which influences the photoperiodic response is also perceived by photoreceptors other than the rhodopsin-containing rods remains to be determined.

Attempts to determine the pathway by which photic information is transmitted from the eye to the system involved in photoperiodic time measurement have been carried out most extensively in the golden hamster (Rusak and Morin, 1976; Morin et al., 1977). Lesions which interrupt the primary optic tract (POT) in this species do not alter the photoperiodic control of gonadal function. In contrast, lesions of the retinohypothalamic tract (RHT), which provides a direct connection between the retina and the suprachiasmatic nuclei (SCN) of the hypothalamus (Eichler and Moore, 1974), completely block gonadal regression induced by short days in both male and female hamsters (Rusak and Morin, 1976; Stetson and Watson-Whitmyre, 1976). While these studies indicate that the RHT is responsible for the

transmission of light involved in the photoperiodic response, the data are not conclusive since the only means currently available for transecting the RHT and leaving the POT intact involve the destruction of the SCN. Numerous investigators have demonstrated that the SCN are involved in the entrainment as well as the generation of a variety of different circadian rhythms including drinking, wheel running activity, adrenal corticosterone secretion and pineal N-acetyltransferase activity (Stephan and Zucker, 1972; Moore and Klein, 1974; Moore and Eichler, 1976; Stetson and Watson-Whitmyre, 1976; Rusak, 1977). Since it is well established that circadian organization is involved in photoperiodic time measurement in the hamster (see below), lesions of the RHT-SCN complex disrupt not only visual information about the environment, but may also disrupt part of the circadian system involved in photoperiodic time measurement. Clearly lesions of the RHT-SCN complex do not simply disrupt the pathway of photic signals to the brain since gonadal function in lesioned animals is maintained regardless of the photoperiodic condition, whereas blinding leads to gonadal atrophy (Stetson and Watson-Whitmyre, 1976; Gravis, 1978).

While the existence of a direct connection between the retina and the hypothalamus has been documented for a number of different mammalian species (Hendrickson et al., 1972; Moore, 1973; Thorpe and Herbert, 1976), the importance of this projection for the transmission of light involved in the photoperiodic response in species other than the golden hamster remains to be determined.

Photoperiodic Time Measurement

Since it was first discovered that the photoperiod was a primary environmental signal regulating the seasonal reproductive cycle in animals (Rowan, 1925; Bissonette, 1932), a great deal of attention has been directed toward discovering how animals measure the length of the day. Some of the early hypotheses that were advanced to answer this question were: 1) the total duration of activity, not light per se, is responsible for photic-induced gonadal development (Rowan, 1928; 1938); 2) the relative ratio of light to dark as compared to the previous ratio is the determining factor in initiating a photoperiodic response (Bissonette, 1930; 1931) and 3) the total duration

of the light or dark period is measured by some sort of hourglass timing mechanism (Jenner and Engels, 1952; Farner et al., 1953; Wolfson, 1960). In 1936, Bünning, noting that light cycles can synchronize the endogenous rhythm of plant leaf movements and that the light cycle also controls the photoperiodic response of flowering, proposed that the physiological basis of photoperiodism in plants may involve the organism's endogenous daily rhythms. This hypothesis was ignored by workers in vertebrate photoperiodism for many years and it was not until 1963 that this hypothesis was tested in birds (Hamner, 1963) and not until 1972 was it tested in mammals (Elliott et al., 1972).

What is now referred to as the "Bünning Hypothesis" is usually evoked to explain photoperiodic time measurement in vertebrates (Pittendrigh, 1967; 1972). The general concept which underlies this hypothesis is that photoperiodic time measurement somehow involves an endogenous biological clock with a period of about 24 (circadian) h. One of the most powerful methods of demonstrating that circadian rhythmicity is involved is the use of what are known as "resonance light cycles" (Nanda and Hamner, 1958). Resonance light cycles consist of a fixed photoperiod coupled to dark periods of varying duration so that the total duration of the light-dark cycle is systematically changed. (In most studies, resonance light cycles which are multiples of 12 h are employed. A typical series of resonance light cycles are depicted on the left side of Fig. 2.) Positive results from resonance experiments (i.e., photoperiodic induction rises and falls as a function of the duration of the light-dark cycle) demonstrate that neither the duration of light nor the duration of dark is the determining factor in inducing a photoperiodic response. Instead, such results indicate that time measurement involves a response to light which varies on a circadian basis. An examination of the gonadal response of golden hamsters exposed to various resonance light cycles indicates that a circadian clock is involved in measuring the length of the day in this species (Fig. 3). Exposure to light cycles of LD 6:18 or LD 6:42 induce gonadal atrophy, demonstrating that these regimes are being interpreted as short days. In contrast, gonadal function is maintained in animals exposed to either LD 6:30 or 6:54, indicating that these regimes are being interpreted as long days.

Resonance experiments have been carried out on a number of different avian species (Hamner, 1963; Follett and Sharp, 1969; Turek, 1972, 1974; Gwinner and Eriksson, 1977), but only in a few different mammals (Elliott et al., 1972; Grocock and Clarke, 1974; Stetson et al., 1976). These studies have been confined almost exclusively to males. Because the results of resonance experiments have always implicated circadian rhythmicity in vertebrate photoperiodic time measurement, it is generally assumed that such a mechanism exists in the majority of birds and mammals. However, studies involving more species, as well as females of previously examined species, are necessary in order to validate this generality.

Other experiments have demonstrated that short pulses of light at certain times of the day can induce gonadal development (Follett et al., 1974; Elliott, 1976; Farner et al., 1977). These data also indicate that photoperiodic

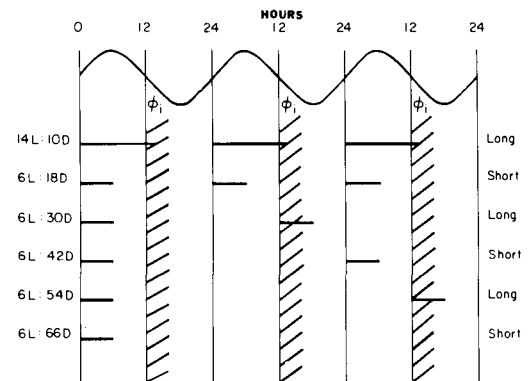


FIG. 2. Diagrammatical representation of the external-coincidence model and the way in which this model is used to explain the gonadal response to resonance light cycles. The light portion of the cycle is represented by the horizontal bars and whether or not the environmental light cycle will be interpreted as a long or a short day is shown on the right. The model predicts that there is a circadian rhythm of sensitivity to light, drawn as a sine wave at the top, which is entrained by the environmental light cycle. When light is coincident with the photoinducible phase of the sensitivity rhythm (ϕ ; crosshatched bars), drawn arbitrarily between 12 and 16 h after the onset of light, the animal will interpret the light cycle as representing a long day. In resonance light cycles consisting of a 6 h light period, the cycle will be interpreted as a short day when the cycle is 24, 48 or 72 h in duration, but will be interpreted as a long day when the cycle is 36 or 60 h in length. (From Turek, 1978a).

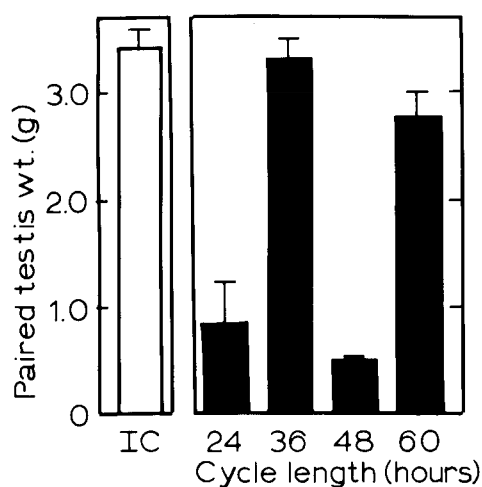


FIG. 3. Testicular weight (mean \pm SEM) of initial control animals (IC) and of groups of golden hamsters that were maintained on one of four different resonance light cycles (6 h of light/cycle) for 89 days. Photostimulation of testicular maintenance was observed in animals maintained on 36 and 60 h cycles, but not in animals exposed to cycles that were 24 or 48 h in length. These results indicate that a circadian clock is involved in measuring the length of day. (Redrawn from Elliott, 1974).

time measurement in birds and mammals involves a circadian clock, but the mechanism for such time measuring capabilities is not known. Two general hypotheses have been formulated to describe the possible role of a daily biological clock in measuring the length of the day. Pittendrigh (1972) has termed these two hypotheses the "external coincidence" and "internal coincidence" models. The external coincidence model predicts that photoperiodic induction occurs when light is coincident (or not coincident) with a certain phase of a daily biological rhythm of sensitivity to light (Fig. 2). An important feature of the external coincidence model is that light has a dual function: first, it serves to entrain a rhythm of sensitivity to light which is presumed to be an endogenous circadian rhythm and second, light induces a particular response when it is coincident (or not coincident) with a particular phase of the photosensitivity rhythm. The internal coincidence model predicts that photoperiodic induction occurs when two or more diurnal rhythms are in a particular phase relationship with respect to one another. In this model, light serves only as an entraining agent and does not play an active role in inducing a photoperiodic response. As the

length of the day changes, different phase relationships will inevitably be established between various circadian rhythms and only under certain conditions will the phase relationship between the internal oscillators be such that photoperiodic induction will occur (Danilevsky et al., 1970; Pittendrigh, 1972). Although a great deal of effort has been spent, in a number of different species, to prove or disprove either model, none of the experiments has been conclusive (Turek, 1978a).

It appears that before it will be possible to define more precisely the role of the circadian system in photoperiodic time measurement, more information must be obtained on: 1) the location of the biological clock involved in the photoperiodic response and 2) how this time measuring system is coupled to the hypothalamic-pituitary system controlling gonadal function. A great deal of attention has recently been focused on the SCN in the hypothalamus as being an important component of the circadian system involved in measuring the length of the day. As discussed in the previous section, lesions of the SCN in the golden hamster abolish the photoperiodic gonadal response and lesioned animals remain reproductively competent irrespective of photoperiodic treatment (Rusak and Morin, 1976; Stetson and Watson-Whitmyre, 1976). Thus, destruction of what is thought to be an important component of the circadian system (Morin et al., 1977; Raisman and Brown-Grant, 1977; Rusak, 1977) renders the animal incapable of differentiating between various daylengths.

Why an impairment of the circadian organization of the hamster leads to the maintenance of reproductive competence during exposure to nonstimulatory lighting conditions is not known. There is no *a priori* reason to expect that the disruption of the circadian system involved in photoperiodic time measurement would result in the maintenance of gonadal function. An explanation for this result probably lies in the determination of how the circadian system is coupled to the hypothalamic-hypophyseal axis responsible for gonadotropin release. At the present time, very little is known about the neuroendocrine events which link the time measuring system (SCN?) with the gonadotropin control center. There is evidence to suggest that the pineal gland is involved in this process and the next section will discuss the potential role of the pineal gland in the photoperiodic response.

Information Transfer from the Photoperiodic Clock to the Gonadotropin Control Center: Role of the Pineal Gland

Hundreds of papers have been published demonstrating that either the removal of the pineal gland or the administration of pineal material can influence neuroendocrine-gonadal activity in mammals (for reviews see Quay, 1975; Reiter, 1974; 1977; Minneman and Wurtman, 1975; Relkin, 1976). Nevertheless, the physiological role of this gland in the reproductive system is still not understood. A close link between the pineal gland and the photoperiodic control of the neuroendocrine-gonadal axis in mammals is suggested by the many studies demonstrating that the removal of the pineal gland alters the ability of a number of animals to respond appropriately to changes in the light-dark environment. For example, in the ferret, vole, golden and Djungarian hamster, pinealectomy blocks the inhibitory effects of short days on gonadal activity (Hoffmann and Reiter, 1965; Hoffmann, 1974; Farrar and Clarke, 1976; Thorpe and Herbert, 1976). As depicted in Fig. 4, the effect of pinealectomy in photoperiodic mammals is not a trivial one. Removal of the pineal gland in the Djungarian hamster prevents gonadal regression which normally occurs during exposure to short days (Hoffmann, 1974). The importance of this gland in the photoperiodic response of mammals is underscored by our failure to find in the literature a single demonstration that the removal of the pineal gland did not alter how an animal responded to a subsequent photoperiodic challenge. In addition to the effects observed in mammals, pinealectomy has been found to alter the photoperiodic response of fish and lizards (Levey, 1973; DeVlaming, 1975; DeVlaming and Vodicknik, 1977), although the removal of the pineal gland has minimal effects upon the avian photosexual response (Turek, 1978a).

The mammalian pineal gland is generally assumed to produce a substance, or substances, which inhibits neuroendocrine-gonadal function since pinealectomy can block the inhibitory effects of short days. However, in both the ferret and the Djungarian hamster, pinealectomy results in an inhibition of gonadal growth in animals exposed to a stimulatory light cycle (Herbert, 1969; Hoffmann and Küderling, 1975; Brackman and Hoffmann, 1977). Thus, it appears that at least in these two species,

the removal of the pineal gland can promote as well as inhibit gonadal function, depending upon the photoperiodic conditions at the time of surgery. These results are particularly interesting in view of the recent reports that a pineal product, melatonin, can either inhibit or promote gonadal function, once again depending upon the photoperiodic conditions (see below).

Much of the search for the pineal hormone responsible for regulating neuroendocrine-gonadal activity has centered around the indoleamine N-acetyl-5-methoxytryptamine, commonly known as melatonin. However, a large body of evidence has accumulated which demonstrates that melatonin-free extract material from the pineal gland, particularly polypeptide-like molecules, can inhibit hypothalamic-hypophyseal-gonadal activity under a variety of different experimental conditions (Benson et al., 1971; Vaughan et al., 1972; Orts et al., 1974; Ebels et al., 1975; Moszkowska et al., 1976; Rosenblum et al., 1976; Reiter and Vaughan, 1977; Orts, 1977). Arginine vasotocin, a peptide with known antigonadotropin properties, has been isolated from pineal tissue, (Pavel et al., 1973; Reiter and Vaughan, 1977), but it is clearly not the only active pep-

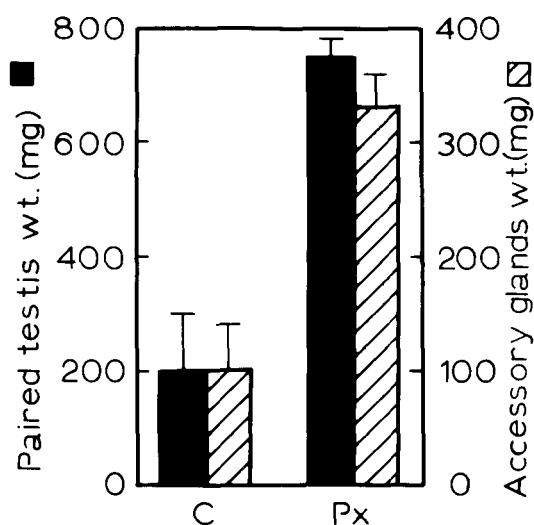


FIG. 4. Mean (\pm SEM) weight of the testes and sex accessory glands of control (C) and pinealectomized (Px) Djungarian hamsters that had been maintained on a nonstimulatory LD 8:16 light cycle for two months. At the start of the experiment all of the animals had sexually mature testes as ascertained by palpation. Pinealectomy prevented the gonadal and sex accessory gland atrophy which normally occurs during exposure to short days. (Redrawn from Hoffmann, 1974).

tide molecule in the pineal gland (Rosenblum et al., 1976).

Antigonadal or antigonadotropic effects of melatonin administration have been observed in a number of different mammalian species including ferrets, weasels, mice, monkeys, rats, gerbils, rabbits and hamsters (Rust and Meyer, 1969; Debeljuk et al., 1971; Vaughan et al., 1976; Fiske and Macdonald, 1975; Turek et al., 1976a; Lynch and Ebstein, 1976; Thorpe and Herbert, 1976). However, the magnitude of the effect of melatonin on neuroendocrine gonadal activity appears to vary widely from species to species. For example, while chronic melatonin treatment induced testicular atrophy in two photoperiodic species, the golden hamster and the grasshopper mouse, it did not alter gonadal size in two nonphotoperiodic species, the laboratory rat and the house mouse (Turek et al., 1976a). Because the effects of melatonin on neuroendocrine-gonadal activity appear to be more pronounced in species whose reproductive condition is regulated by the length of the day, it has been suggested that the pineal gland may play a more important role in regulating testicular function in animals whose reproductive activity is markedly dependent upon seasonal changes in day length, as compared to animals whose reproductive performance is relatively insensitive to photoperiodic cues (Hoffmann, 1975; Turek, et al., 1976a).

In the golden hamster, a photoperiodic species in which pinealectomy blocks short

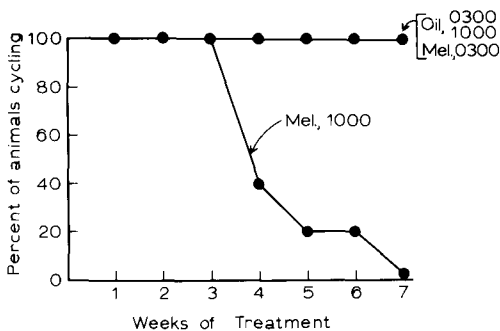


FIG. 5. Percent of female golden hamsters showing estrous cycles at the end of each weekly interval during daily administration of melatonin (25 μ g/day) or oil vehicle. Injections were performed at either 0300 or 1000 h during exposure to an LD 14:10 light cycle (lights off = 1400). Melatonin injections in the late afternoon, but not in the morning, resulted in the loss of estrous cyclicity in 100% of the animals within 7 weeks. (Redrawn from Tamarkin et al., 1976b).

day-induced gonadal regression (Hoffman and Reiter, 1965), melatonin treatment can have a severely inhibitory effect on gonadal function. Daily melatonin injections when given near the end of the light period (but not near the beginning) of an LD 14:10 light cycle both decrease serum levels of LH and FSH and induce testicular atrophy in male hamsters and block ovulation and induce acyclicity in female hamsters (Fig. 5; Tamarkin et al., 1976b, 1977a). Furthermore, the s.c. implantation of melatonin-filled Silastic capsules induces testicular atrophy in mature hamsters maintained on photostimulatory long days, and prevents photic-induced gonadal recrudescence (Fig. 6; Turek et al., 1976b). Melatonin treatment in the golden and Djungarian hamster leads to the inhibition of gonadal activity in pinealectomized, as well as intact, animals (Fig. 6), indicating that the effects of exogenous melatonin are not mediated via the pineal gland (Turek, 1977a; Tamarkin et al., 1977b; Hoffmann and Küderling, 1977).

In all species that have been studied, there is a diurnal variation in pineal melatonin

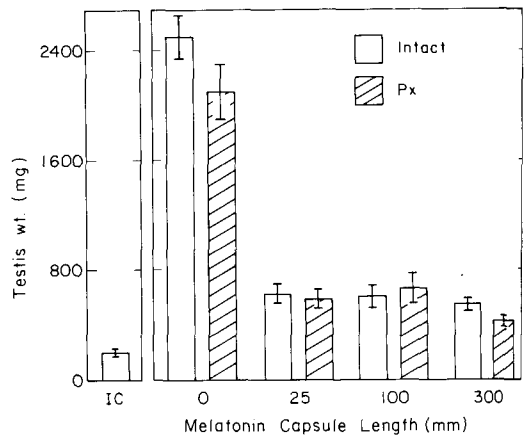


FIG. 6. Mean paired testis weight (\pm SEM) of intact and pinealectomized (Px) hamsters that were implanted with either an empty Silastic capsule (0) or melatonin-filled Silastic capsules of various sizes. Prior to implantation of the capsules, the animals were maintained on an LD 6:18 photoperiod for 65 days to induce testicular atrophy. The testis weight of initial control (IC) animals sacrificed at this time is shown in the left panel. After capsule implantation, all of the animals were transferred to an LD 14:10 photoperiod and sacrificed 45 days later. The suppression of testicular growth in pinealectomized as well as intact animals demonstrates that the antigonadal effect of melatonin is not mediated via the pineal gland. (From Turek, 1977a).

synthesis and release, with higher serum melatonin levels during the night than during the day (Ozaki et al., 1976; Rollag and Niswender, 1976; Kennaway et al., 1977). This diurnal rhythm of melatonin synthesis is thought to be due to the control of pineal N-acetyltransferase activity by the sympathetic nerves innervating the pineal gland (Kappers, 1960; Axelrod, 1975). The enzyme, N-acetyltransferase, which is responsible for converting serotonin to N-acetylserotonin, a precursor of melatonin, has a much higher level of activity during the dark than during the light (Klein and Weller, 1970; Binkley, 1976; Binkley et al., 1977). Therefore, the inhibitory effects of melatonin are consistent with the hypothesis that short day-induced gonadal atrophy in the hamster occurs in response to an increase in pineal melatonin synthesis and release during exposure to short days or constant darkness. Recent experiments with hamsters however, indicate that the effect of melatonin on neuroendocrine-gonadal activity is not always inhibitory and that the relationship between the pineal gland, melatonin and the hypothalamic-hypophyseal system regulating pituitary gonadotropin release is more complex than previously thought. Melatonin can stimulate gonadal function under certain photoperiodic conditions in the golden hamster. The administration of melatonin is able to prevent normally occurring gonadal regression in animals transferred from long to short days (Reiter et al., 1975; Turek et al., 1975b; Turek and Losee, 1978). Furthermore, if melatonin treatment is delayed until testicular regression has already occurred, testicular growth is induced in melatonin-treated animals well in advance of spontaneous testicular recrudescence (Fig. 7). This stimulatory effect of melatonin on gonadal activity during exposure to short days should be compared with the inhibitory effect of melatonin during exposure to long days (c.f. Figs. 6, 7).

While the above results demonstrate that melatonin treatment can both stimulate and inhibit gonadal activity in hamsters, under certain experimental conditions, melatonin does not appear to have any effect. For example, melatonin cannot prevent gonadal growth indefinitely in animals moved from short to long days (Turek and Losee, 1978). The time course of testicular regrowth in melatonin-treated animals transferred to long days is similar to that observed during spontaneous

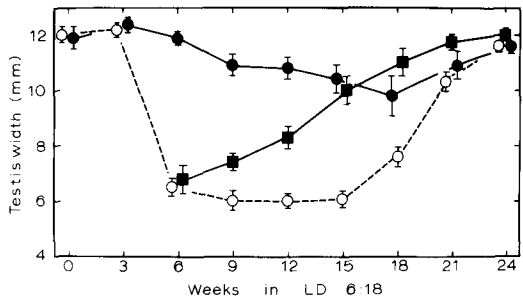


FIG. 7. Mean testis width (\pm SEM) of golden hamsters moved from a photostimulatory LD 14:10 cycle to a nonstimulatory LD 6:18 cycle for 24 weeks. Animals in one group (\circ - \circ) were implanted with empty capsules while animals in a second group (\bullet - \bullet) received 100 mm long melatonin-filled capsules at the time of transfer to LD 6:18. The implantation of 100 mm long melatonin-filled capsules into a third group (\blacksquare - \blacksquare) was delayed until they had been exposed to LD 6:18 for 6 weeks. Melatonin treatment was found to prevent testicular regression and induce testicular growth in animals maintained on short days. (Redrawn from Turek and Losee, 1978).

testicular recrudescence in untreated animals maintained on short days. If the delayed regrowth of the testes in melatonin-treated animals exposed to long days is actually due to spontaneous testicular recrudescence, this response would indicate that melatonin is able to prevent photic-induced testicular growth, but not photic independent gonadal growth in hamsters. Support for this hypothesis is found in the observation that melatonin cannot inhibit testicular growth in the golden hamster during the first 9 weeks of life (Turek, unpublished results), a photic independent event (Reiter et al., 1970).

In a second species, the Djungarian hamster, Hoffmann has also found that melatonin inhibits testicular function when the photoperiod is stimulatory and stimulates gonadal activity during exposure to inhibitory short days (Hoffmann, 1973; Hoffmann, 1974). In addition, in this species the photoperiod does influence gonadal development early in life and melatonin administration can delay this development (Brackmann, 1977).

The demonstration that immunoreactive melatonin shows a nocturnal rise in the circulation of many species (Rollag and Niswender, 1976; Kennaway et al., 1977), indicates that total melatonin secretion over a 24 h period is greater during exposure to short days than during long days. Since gonadal regression

occurs when hamsters are exposed to short days, when total pineal melatonin secretion is presumably increased, it is perplexing to observe that melatonin can act in a progonadal manner. However, recent experiments indicate that the effect of melatonin on neuroendocrine-gonadal activity in hamsters maintained on a particular photoperiod is not based solely on the total amount of melatonin administered. Daily melatonin injections during the late afternoon of an LD 14:10 light cycle induce testicular regression in males and anestrus in females (Fig. 5), while the same injections when given in the morning have no detectable effect upon reproductive function (Tamarkin et al., 1976b, 1977b). Such results caution against making assumptions about the action of melatonin on neuroendocrine-gonadal activity that are based solely on serum melatonin levels determined at limited time periods of the day or night.

Melatonin treatment has been shown to alter neuroendocrine-gonadal activity at the level of the hypothalamus and pituitary gland, as well as the ovary and testis (Kamberi et al., 1971; Peat and Kinson, 1970; Trentini et al., 1976; Martin and Klein, 1976; Kano and Miyachi, 1976; Kao and Weisz, 1977). However, a definite site of action of endogenous melatonin has not been conclusively demonstrated. The observation that melatonin can stimulate, inhibit, or have no effect on neuroendocrine-gonadal activity, depending upon the photoperiodic conditions at the time of treatment, suggests that melatonin may alter neuroendocrine-gonadal activity by an interaction with the circadian system involved in photoperiodic time measurement. A link between melatonin and at least part of the circadian system, the SCN, has been established by Moore and Klein (1974). They observed that ablation of the SCN abolishes the diurnal rhythm of pineal N-acetyltransferase activity. In addition, melatonin has been localized immunohistologically in the SCN (Bubenik et al., 1976) suggesting a possible effect of melatonin on SCN activity. Melatonin has also been found in the retina of rats and chickens (Bubenik et al., 1976; Pang et al., 1977) and the intriguing possibility that the photoperiodic control of neuroendocrine-gonadal activity may involve melatonin found in the retina and the SCN, as well as the pineal gland, remains to be investigated.

In this brief review of the role of the pineal

gland in the photoperiodic gonadal response, we have chosen to emphasize the possible physiological role of melatonin, rather than the polypeptides for the following reasons: 1) melatonin administration to a variety of different photoperiodic species alters the gonadal response of the animals to photic information (Rust and Meyer, 1969; Hoffmann, 1974; Reiter et al., 1975; Turek et al., 1975b, 1976a; Thorpe and Herbert, 1976; Lynch and Epstein, 1976); 2) the antagonistic action of melatonin is observed in pinealectomized animals indicating that the response to exogenous melatonin is not mediated via other pineal products (Turek, 1977a; Tamarkin et al., 1977b; Hoffmann and Küderling, 1977); 3) the pineal gland appears to be the principal source of circulating melatonin (Pang et al., 1974; Ozaki and Lynch, 1976; Kennaway et al., 1977) and 4) the synthesis and release of pineal melatonin is regulated by the photoperiod, as would be expected of a substance involved in the photoperiodic control of reproduction (Ozaki et al., 1976; Rollag and Niswender, 1976; Kennaway et al., 1977). While these observations suggest that melatonin is a pineal hormone involved in the photoperiodic control of reproduction, more information is necessary in order to establish that melatonin is indeed the major pineal product to influence the hypothalamic-pituitary-gonadal axis.

Photic-induced Changes in the Hypothalamic-Pituitary-Gonadal Axis

Testicular atrophy, induced in many species by an exposure to a nonstimulatory photoperiod, is accompanied by a cessation of spermatogenesis and a decline in serum androgen levels (Lodge and Salisbury, 1970; Desjardins et al., 1971; Berndtson and Desjardins, 1974; Grocock and Clarke, 1975; Lincoln et al., 1977). In many female mammals, an exposure to a nonstimulatory light cycle induces acyclicity which is accompanied by a cessation of ovulation and marked changes in serum estrogen and progesterone levels (Seegal and Goldman, 1975; Sharp and Ginther, 1975; Van Horn, 1975; Van Horn and Resko, 1977; Legan et al., 1977; Oxender et al., 1977). Photic-induced inhibition of reproductive physiology is also associated with a reduction in sexual behavior (Sachs, 1969; Adkins, 1973; Crews, 1975; Morin et al., 1977; Campbell et al., 1978). While this de-

cline in reproductive behavior is probably due, at least in part, to a decline in circulating steroid levels (Beach and Pauker, 1949; Tiefer, 1970), it appears that an exposure to a non-stimulating photoperiod can also decrease the behavioral responsiveness of seasonally breeding animals to the stimulating effects of gonadal hormones (Lincoln et al., 1972; Steel and Hinde, 1976; Morin and Zucker, 1978; Campbell et al., 1978). For example, significantly higher incidences of intromission and ejaculation are observed in testosterone-treated, castrated hamsters maintained on stimulatory long days than in similarly treated animals exposed to nonstimulatory short days (Fig. 8).

In addition to changes in the reproductive system and sexual behavior, there are a number of other behavioral and metabolic changes which accompany alterations in the photoperiod. For example, many male animals become highly aggressive toward conspecifics and establish territories in response to long day stimulation (Lincoln et al., 1972; Crews, 1974; McKeever, 1963). In some species (Crews, 1974), the onset of aggression is very rapid in response to long day exposure and precedes mating, suggesting that this behavioral change is a steroid independent one. Further-

more, seasonal changes in body weight occur in Djungarian hamsters (Heldmaier and Hoffmann, 1974), ground squirrels (McKeever, 1963), dairy cattle (Peters et al., 1978), lemmings (Hasler et al., 1976) and golden hamsters (Campbell, unpublished observations). In at least some species, there is no concomitant change in food intake, which suggests that there is an alteration in metabolic processes due to the alteration in daylength (Peters et al., 1978). Much more work is required to ascertain whether seasonal changes in both body weight and aggression are steroid dependent or steroid independent responses to photoperiodic stimulation.

While the length of the day appears to have only a minimal effect upon the reproductive system of the laboratory rat, constant bright light leads to a rapid and quite severe disruption of the estrous cycle. Even within the first two cycles in this lighting condition, the gonadotropin surge is either absent or delayed (Campbell and Schwartz, 1978) and ovulation often fails to occur (McCormack and Sridaran, 1978; Campbell and Schwartz, 1978). Eventually a state of persistent vaginal estrus occurs, characterized by continuous vaginal cornification, constant behavioral receptivity, cystic follicles and anovulation (Lawton and Schwartz, 1967). This constant light syndrome also occurs in a small proportion of female mice (Campbell et al., 1976) and after a very prolonged period of time in female hamsters (Kent et al., 1968). In rats, the condition of persistent estrus only occurs if the intensity of illumination is sufficiently great; exposure to dim continuous light simply results in a free running rhythm of LH release and ovulation (McCormack and Sridaran, 1978). As valuable as these experimental paradigms have been in characterizing the interdependence of the various rhythms of the estrous cycle and the critical role that light cues play in synchronizing these rhythms, the changes induced do not appear to be similar to those observed in seasonally breeding animals exposed to different light cycles. In fact, seasonally breeding animals respond quite differently to constant light than they do to long day photoperiods (Kent et al., 1968). For these reasons, we feel it is inappropriate to attempt to reconcile the effects of constant light on the reproductive system within the context of the adaptive physiological changes in neuroendocrine gonadal activity that

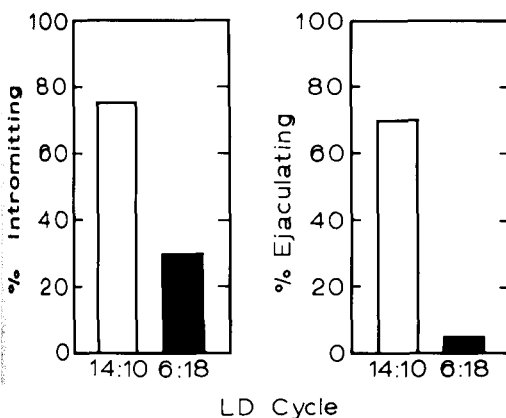


FIG. 8. Percent of castrate male golden hamsters intromitting and ejaculating 40 days after implantation with a testosterone-filled Silastic capsule that maintained serum testosterone levels found in intact, sexually mature males (≈ 3.0 ng/ml). The animals were castrated and maintained under either LD 14:10 or 6:18 for 10 weeks prior to the start of testosterone treatment and they remained under these respective light cycles for the duration of the study. Significantly higher incidences of both intromission and ejaculation were observed in long day as compared to short day animals. (Redrawn from Campbell et al., 1978).

(Turek et al., 1977), suggesting that the photoperiod does not directly alter the responsiveness of the pituitary gland to LHRH. Furthermore, Pickard (1977) has recently reported that hypothalamic LHRH content is increased by about 25% in male hamsters exposed to short days for 13 weeks when compared to control animals maintained on photostimulatory long days. Since this increase in hypothalamic LHRH was correlated with a decrease in serum and pituitary LH concentration, it was hypothesized that an exposure to short days inhibits hypothalamic LHRH release, which would, in turn, result in a decrease in the synthesis and release of LH from the pituitary gland (Pickard, 1977).

The mechanism by which the photoperiod regulates hypothalamic LHRH activity is not known. A number of recent reports indicate that at least part of the photic-induced change in pituitary gonadotropin release may be due to an alteration in the sensitivity to steroid feedback of the gonadotropin control center, as suggested by Hoffmann (1973). Gonadal hormones inhibit gonadotropin release (Gay and Midgley, 1969; Campbell and Schwartz, 1977) and in both sheep and hamsters, an exposure to a nonstimulatory photoperiod renders the hypothalamic-hypophyseal axis extremely sensitive to the negative feedback effect of steroid hormones (Pelletier and Ortavant, 1975a; Tamarkin et al., 1976a; Legan et al., 1977; Turek, 1977b; Ellis and Turek, 1978a). The pineal gland may mediate photic-induced changes in steroid feedback sensitivity in the male hamster, since pinealectomy blocks the short day-induced increase in responsiveness to testosterone feedback (Fig. 10).

While the above studies indicate that an alteration in steroid feedback sensitivity is involved in the photoperiodic control of neuroendocrine-gonadal activity, other studies suggest that the photoperiod can alter hypothalamic-pituitary gonadal activity independent of steroid hormones. In animals as diverse as grouse, quail, sparrows, pony mares and rams, photic-induced changes in circulating gonadotropin levels are observed in castrated as well as intact animals (Wilson and Follett, 1974; Pelletier and Ortavant, 1975b; Gibson et al., 1975; Garcia and Ginther, 1976; Mattocks et al., 1976; Sharp and Moss, 1977). Interestingly, while the photoperiod can alter

serum levels of LH in castrated rams (Pelletier and Ortavant, 1975b), no effect of day length is observed in ovariectomized ewes (Legan et al., 1977). A second line of evidence which suggests that the photoperiod can alter hypothalamic-hypophyseal activity independently of steroid hormones is the observation that castration of birds, hamsters and hares exposed to nonstimulatory short days does not result in as marked an increase in serum gonadotropin levels as it does following castration of animals maintained on a stimulatory photoperiod (Davis and Meyer, 1973; Gibson et al., 1975; Turek et al., 1975c; Tamarkin et al., 1976a). Adrenal steroids are apparently not involved in this response since castrated-adrenalectomized hamsters exposed to short days also show an attenuated castration response (Ellis and Turek, 1978b).

Taken together, the results obtained in

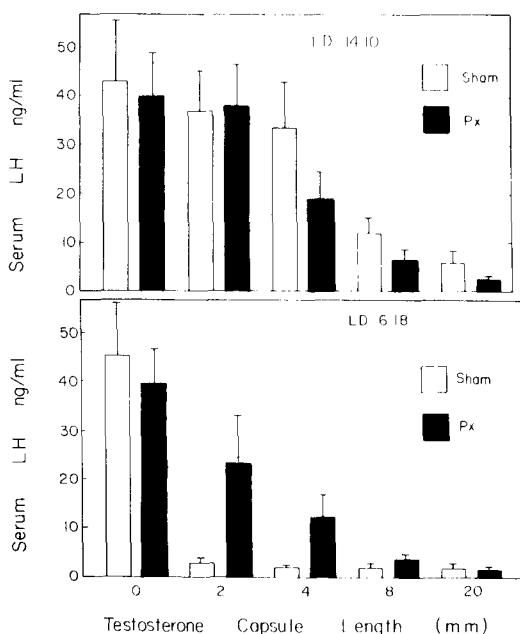


FIG. 10. Mean (\pm SEM) serum levels of LH in castrated hamsters 21 days after the implantation of either empty or various size testosterone-filled capsules. Prior to testosterone treatment, the animals had been either sham pinealectomized (Sham) or pinealectomized (Px) and maintained on either LD 14:10 (top) or LD 6:18 (bottom) for 8 weeks. The inhibitory effects of testosterone were more pronounced in sham operated LD 14:10 animals or PX animals exposed to either photoperiod. The results indicate that the pineal gland mediates, at least in part, the short day-induced increase in steroid feedback sensitivity. (From Turek, 1978b).

castrated and testosterone treated animals belonging to a number of different species suggest that two mechanisms, one steroid dependent, the other steroid independent, are involved in the photoperiodic control of neuroendocrine-gonadal activity. Whether or not these two mechanisms for the photoperiodic control of reproduction share a common neuroendocrine pathway from the light receptors, to the clock involved in time measurement, to the pineal gland and to the gonadotropin control center, remains to be determined.

SUMMARY

The annual reproductive season in numerous species is regulated by the seasonal change in the length of the day. Control of the breeding season by photoperiod implies that an organism can perceive light, differentiate between subtle changes in the proportion of light to dark per day, and transduce this information into changes in the hypothalamic-pituitary-gonadal axis. In lower vertebrates, it is well established that light which is involved in the photoperiodic control of reproduction is perceived primarily by nonocular photoreceptors, presumably located in the brain. In contrast, the eyes appear to be the principal photoreceptor for this response in mammals. An endogenous circadian clock is involved in the process of measuring the length of the day, although neither the physiological nor the cellular basis of this process is known. The neuroendocrine events associated with the transfer of information from the photoperiodic time measuring system to the hypothalamic-pituitary system responsible for gonadotropin regulation remain an enigma, although there is evidence to suggest that the pineal gland and its product, melatonin, are involved in this process. Both steroid dependent and steroid independent mechanisms are apparently involved in the photoperiodic alteration of hypothalamic-pituitary activity. Photoc-induced changes in circulating gonadotropin levels then lead to an alteration in germ cell activity and steroid hormone production by the gonads, which in turn lead to a number of behavioral and metabolic changes. Thus, the modification of environmental lighting, either under natural or artificial conditions, can trigger a sequence of neuroendocrine changes which can ultimately alter a broad range of physiological and behavioral systems in the organism.

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REFERENCES

- Adkins, E. K. (1973). Functional castration of the female Japanese quail. *Physiol. Behav.* 10, 619-621.
- Alleva, J. J., Waleski, M. V. and Alleva, F. R. (1970). The zeitgeber for ovulation in rats: non-participation of the pineal gland. *Life Sci.* 9, 241-246.
- Anderson, K. V. and O'Steen, W. K. (1972). Black-white and pattern discrimination in rats without photoreceptors. *Exp. Neurol.* 34, 446-454.
- Axelrod, J. (1975). The pineal gland: a model to study the regulation of the β -adrenergic receptor. In: *The Nervous System*. (D. B. Tower, ed.). Raven Press, New York. pp. 395-400.
- Baker, J. R. (1938). The evolution of breeding season. In: *Evolution*. (Essays presented to E. S. Goodrich). pp. 161-177.
- Bartke, A., Croft, B. T. and Dalterio, S. (1975). Prolactin restores plasma testosterone levels and stimulates testicular growth in hamsters exposed to short day-length. *Endocrinology* 97, 1601-1604.
- Bartke, A., Hafiez, A. A., Bex, F. J. and Dalterio, S. (1978). Hormonal interactions in regulation of androgen secretion. *Biol. Reprod.* 18, 44-54.
- Bast, J. D. and Greenwald, G. S. (1974). Serum profiles of follicle-stimulating hormone, luteinizing hormone and prolactin during the estrous cycle of the hamster. *Endocrinology* 94, 1295-1299.
- Beach, F. A. and Pauker, R. S. (1949). Effects of castration and subsequent androgen administration upon mating behavior in the male hamster. *Endocrinology* 45, 211-221.
- Bennett, M. H., Dyer, R. F. and Dunn, J. D. (1972). Light induced retinal degeneration: effect upon light-dark discrimination. *Exp. Neurol.* 34, 434-445.
- Benoit, J. (1964). The role of the eye and of the hypothalamus in the photostimulation of gonads in the duck. *Ann. N.Y. Acad. Sci.* 117, 204-215.
- Benson, B., Matthews, M. J. and Rodin, A. E. (1971). A melatonin-free extract of bovine pineal with antigonadotropic activity. *Life Sci.* 10, 607-612.
- Berndtson, W. E. and Desjardins, C. (1974). Circulating LH and FSH levels and testicular function in hamsters during light deprivation and subsequent photoperiodic stimulation. *Endocrinology* 95, 195-205.
- Berthold, P., Gwinner, E. and Klein, H. (1971). Circannuale Periodik bei Grasmücken (*Sylvia*). *Experientia* 27, 399.
- Bex, F. J. and Bartke, A. (1977). Testicular LH binding in the hamster: Modification by photoperiod and prolactin. *Endocrinology* 100, 1223-1226.

- Binkley, S. (1976). Pineal gland biorhythms: N-acetyltransferase in chickens and rats. *Fed. Proc.* 35, 2347–2352.
- Binkley, S., Stephens, J. L., Riebmán, B. and Reilly, K. B. (1977). Regulation of pineal rhythms in chickens: photoperiod and dark-time sensitivity. *Gen. Comp. Endocrinol.* 32, 411–416.
- Bissonnette, T. H. (1930). Studies on the sexual cycle in birds. I. Sexual maturity, its modification and possible control in the European starling (*Sturnus vulgaris*). *Amer. J. Anat.* 45, 289–305.
- Bissonnette, T. H. (1931). Studies on the sexual cycle in birds. II. Experimental modification of the sexual cycle in males of the European starling, *Sturnus vulgaris*, by changes in daily period of illumination and by muscular work. *J. Exp. Zool.* 58, 281–320.
- Bissonnette, T. H. (1932). Modification of mammalian sexual cycles. Reactions of ferret (*Putorius vulgaris*) of both sexes to electric light added in November and December. *Proc. Roy. Soc. London Ser. B* 110, 332.
- Brackmann, M. (1977). Melatonin delays puberty in the Djungarian Hamster. *Naturwissenschaften* 64, 642–643.
- Brackmann, M. and Hoffmann, K. (1977). Pinealectomy and photoperiod influence testicular development in the Djungarian hamster. *Naturwissenschaften* 64, 341–342.
- Breton, B. and Billard, R. (1977). Effects of photoperiod and temperature on plasma gonadotropin and spermatogenesis in the rainbow trout salmon *Gairdnerii richardson*. *Ann. Biol. Anim. Bioch. Biophys.* 17, 331–340.
- Bridges, R. and Goldman, B. (1975). Diurnal rhythms in gonadotropins and progesterone in lactating and photoperiod induced acyclic hamsters. *Biol. Reprod.* 13, 617–622.
- Bubenik, G. A., Brown, G. M. and Grota, L. J. (1976). Differential localization of N-acetylated indolealkylamines in CNS and the harderian gland using immunohistology. *Brain. Res.* 118, 417–427.
- Bünning, E. (1936). Die endogene Tagesrhythmik als Grundlage der Photoperischen Reaktion. *Ber. Dtsch. Bot. Ges.* 54, 590–607.
- Campbell, C. S., Ryan, K. D. and Schwartz, N. B. (1976). Estrous cycles in the mouse: relative influence of continuous light and the presence of a male. *Biol. Reprod.* 14, 292–299.
- Campbell, C. S. and Schwartz, N. B. (1977). Steroid feedback regulation of luteinizing hormone and follicle-stimulating hormone secretion rates in male and female rats. *J. Toxicol. Environ. Health* 3, 61–95.
- Campbell, C. S. and Schwartz, N. B. (1978). The impact of constant light on the estrous cycle of the rat. *The Physiologist* 21, 16 Abstr.
- Campbell, C. S., Finkelstein, J. S. and Turek, F. W. (1978). The interaction of photoperiod and testosterone on the development of copulatory behavior in castrated male hamsters. *Physiol. Behav.* 21, 409–415.
- Cicerone, C. M. (1976). Cones survive rods in the light-damaged eye of the albino rat. *Science* 194, 1183–1185.
- Crews, D. (1974). Effects of group stability, male-male aggression, and male courtship behaviour on environmentally-induced ovarian recrudescence in the lizard, *Anolis carolinensis*. *J. Zool. Lond.* 172, 419–441.
- Crews, D. (1975). Psychobiology of reptilian reproduction. *Science* 189, 1059–1065.
- Danilevskii, A. S., Goryshin, N. I. and Tyschenko, V. P. (1970). Biological rhythms in terrestrial arthropods. In: *Annual Review of Entomology*. Vol. 15. (R. F. Smith and T. E. Mittler, eds.). Annual Reviews, Inc. Palo Alto, California. pp. 201–244.
- Davis, G. J. and Meyer, R. K. (1972). The effect of daylength on pituitary FSH and LH and gonadal development of snowshoe hares. *Biol. Reprod.* 6, 264–269.
- Davis, G. J. and Meyer, R. K. (1973). Seasonal variation in LH and FSH of bilaterally castrated snowshoe hares. *Gen. Comp. Endocrinol.* 20, 61–68.
- Debeljuk, L., Vilchez, J. A., Schnitman, M. A., Paulucci, O. A. and Feder, V. M. (1971). Further evidence for a peripheral action of melatonin. *Endocrinology* 89, 1117–1119.
- Desjardins, C. D., Ewing, L. L. and Johnson, B. H. (1971). Effects of light deprivation upon the spermatogenic and steroidogenic elements of hamster testes. *Endocrinology* 89, 791–800.
- Dixit, V. P., Sharma, O. P. and Agrawal, M. (1977). The effects of light deprivation/blindness on testicular function of Gerbil (*Meiones Hurrianæ Jerdon*). *Endokrinologie* 70, 13–18.
- Ducker, M. J., Bowman, J. C. and Temple, A. (1973). The effect of constant photoperiod on the expression of oestrus in the ewe. *J. Reprod. Fert. (Suppl.)* 19, 143–150.
- Dunn, J., Dyer, R. and Benett, M. (1972). Diurnal variation in plasma corticosterone following long-term exposure to continuous illumination. *Endocrinology* 90, 1660–1663.
- Dzuik, P. (1973). Ovulation in pigs, sheep and cows. In: *Handbook of Physiology* (R. O. Greep and E. B. Astwood, eds.). Section VII, Vol. 2. Part 1. American Physiological Society, Washington, D. C. pp. 143–152.
- Ebels, I., Citharel, A. and Moszkowska, A. (1975). Separation of pineal extracts by gel filtration. III. Sheep pineal factors acting either on the hypothalamus, or on the anterior hypophysis of mice and rats in *in vitro* experiments. *J. Neural Trans.* 36, 281–302.
- Eichler, V. B. and Moore, R. Y. (1974). The primary and accessory optic systems in the golden hamster, *Mesocricetus auratus*. *Acta Anat.* 89, 359–371.
- Elliott, J. (1974). Photoperiodic regulation of testis function in the golden hamster: Relation to the circadian system. Ph.D. Dissertation, University of Texas, Austin, Texas.
- Elliott, J. (1976). Circadian rhythms and photoperiodic time measurement in mammals. *Fed. Proc.* 35, 2339–2346.
- Elliott, J. A., Stetson, M. H. and Menaker, M. (1972). Regulation of testis function in golden hamsters: A circadian clock measures photoperiodic time. *Science* 178, 771–773.
- Ellis, G. B. and Turek, F. W. (1978a). Time course of

- the photoperiod-induced changes in hypothalamic-hypophyseal sensitivity to steroid feedback. *Fed. Proc.* 37, 96 Abstr.
- Ellis, G. B. and Turek, F. W. (1978b). Response of the hypothalamic-pituitary axis to removal of gonadal and adrenal steroid feedback in male hamsters exposed to nonstimulatory lighting. *Biol. Reprod.* 18 (Suppl. 1), 15A Abstr.
- Farner, D. S. (1975). Photoperiodic controls in the secretion of gonadotropins in birds. *Amer. Zool.* 15 (Suppl. 1), 117–135.
- Farner, D. S., Mewaldt, L. R. and Irving, S. D. (1953). The roles of darkness and light in the activation of avian gonads. *Science* 118, 351–352.
- Farner, D. S. and Follett, B. K. (1966). Light and other environmental factors affecting avian reproduction. *J. An. Sci.* 25, 90–118.
- Farner, D. S., Donham, R. S., Lewis, R. A., Mattocks, P. W., Jr., Darden, T. R. and Smith, J. P. (1977). The circadian component in the photoperiodic mechanism of the house sparrow, *Passer domesticus*. *Physiol. Zool.* 50, 247–268.
- Farrar, G. M. and Clarke, J. R. (1976). Effect of chemical sympathectomy and pinealectomy upon gonads of voles (*Microtus agrestis*) exposed to short photoperiod. *Neuroendocrinology* 22, 134–143.
- Fiske, V. M. and Macdonald, G. J. (1975). Estrogen secretion and its relation to corpus luteum formation in monkeys (*Macaca fascicularis*) given melatonin. *Fertil. Steril.* 26, 609–612.
- Follett, B. K. and Sharp, P. J. (1969). Circadian rhythmicity in photoperiodically induced gonadotrophin release and gonadal growth in the quail. *Nature (Lond.)* 223, 968–971.
- Follett, B. K., Mattocks, P. W., Jr. and Farner, D. S. (1974). Circadian function in the photoperiodic induction of gonadotropin secretion in the white-crowned sparrow. *Zonotrichia leucophrys gambelii*. *Proc. Nat. Acad. Sci. U.S.A.* 71, 1666–1669.
- Follett, B. K. and Davies, D. T. (1975). Photoperiodicity and the neuroendocrine control of reproduction in birds. *Symp. Zool. Soc. Lond.* 35, 199–224.
- Garcia, M. and Ginther, O. (1976). Effects of ovariectomy and season on plasma luteinizing hormone in mares. *Endocrinology* 98, 958–962.
- Gaston, S. and Menaker, M. (1967). Photoperiodic control of hamster testis. *Science* 167, 925–928.
- Gay, V. L. and Midgley, A. R., Jr. (1969). Response of the adult rat to orchidectomy and ovariectomy as determined by LH radioimmunoassay. *Endocrinology* 84, 1359–1364.
- Gibson, W. R., Follett, B. K. and Gledhill, B. (1975). Plasma levels of luteinizing hormone in gonadectomized Japanese quail exposed to short or to long days. *J. Endocrinol.* 64, 87–101.
- Gordon, K. (1977). The effect of photoperiod on reproductive function in the albino rat. M. S. Thesis, Northwestern University, Evanston, Illinois.
- Gravis, C. J. (1978). Testicular involution after optic enucleation: ultrastructure and alkaline phosphatase cytochemistry of the peritubular tissue. *Am. J. Anat.* 151, 213–226.
- Hoffman, R. A. and Reiter, R. (1965). Pineal gland: influence on gonads of male hamsters. *Science* 148, 1609–1611.
- Hoffmann, J. (1968). Effect of photoperiod on estrous cycle length in the rat. *Endocrinology* 83, 1355–1356.
- Hoffmann, J. (1973). The influence of photoperiods on reproductive function in female mammals. In: *Handbook of Physiology*. (R. O. Greep and E. B. Astwood, eds.). Section VII, Vol. 2, Part 1. American Physiological Society, Washington, D. C. pp. 57–77.
- Hoffmann, K. (1973). The influence of photoperiod and melatonin on testis size, body weight and pelage colour in the Djungarian hamster (*Phodopus sungorus*). *J. Comp. Physiol.* 85, 267–282.
- Hoffmann, K. (1974). Testicular involution in short photoperiods inhibited by melatonin. *Naturwissenschaften* 61, 364–365.
- Hoffmann, K. (1975). On the function of the pineal in photoperiodic mammals. *Acta. Endocr. (Kbh.) Suppl.* 193, 16.
- Hoffmann, K. and Küderling, I. (1975). Pinealectomy inhibits stimulation of testicular development by long photoperiods in a hamster (*Phodopus sungorus*). *Experientia* 31, 122–123.
- Hoffman, K. and Kuderling, I. (1977). Antigonadal effects of melatonin in pinealectomized Djungarian hamsters. *Naturwissenschaften* 64, 339–340.
- Homma, K. and Sakakibara, Y. (1971). Encephalic photoreceptors and their significance in photoperiodic control of sexual activity in Japanese quail. In: *Biochronometry*. (M. Menaker, ed). *Nat. Acad. Sci., Washington, D. C.* pp. 333–341.
- Homma, K., Wilson, W. O. and Siopes, T. D. (1972). Eyes have a role in photoperiodic control of sexual activity of coturnix. *Science* 178, 421–423.
- Grocock, C. and Clarke, J. (1974). Photoperiodic control of testis activity in the vole, *Microtus agrestis*. *J. Reprod. Fert.* 39, 337–347.
- Grocock, C. A. and Clarke, J. R. (1975). Spermatogenesis in mature and regressed testes of the vole (*Microtus agrestis*). *J. Reprod. Fert.* 43, 461–470.
- Gwinner, E. (1977). Photoperiodic synchronization of circannual rhythms in the European starling (*Sturnus vulgaris*). *Naturwissenschaften* 64, 44–45.
- Gwinner, E. G., Turek, F. W. and Smith, S. D. (1971). Extraocular light perception in photoperiodic responses of the white-crowned (*Zonotrichia leucophrys*) and of the golden-crowned sparrow (*Z. atricapilla*). *Z. Vergl. Physiologie* 75, 323–331.
- Gwinner, E. and Dorka, V. (1976). Endogenous control of annual reproductive rhythms in birds. In: *Proceedings of the 16th International Ornithological Congress*. Australian Academy of Science, Canberra. pp. 223–234.
- Gwinner, E. G. and Eriksson, L. (1977). Circadian Rhythmik und Photoperiodische Zeitmessung beim Star (*Sturnus vulgaris*). *J. für Ornithol.* 118, 60–67.
- Hamner, W. M. (1963). Diurnal rhythm and photoperiodism in testicular recrudescence of the

- house finch. *Science* 142, 1294–1295.
- Asler, J. F., Buhl, A. E. and Banks, E. M. (1976). The influence of photoperiod on growth and sexual function in male and female collared lemmings (*Dicrostonyx groenlandicus*). *J. Reprod. Fert.* 46, 323–329.
- eldmaier, G. and Hoffmann, K. (1974). Melatonin stimulates growth of brown adipose tissue. *Nature* 247, 224–225.
- endrickson, A. E., Wagoner, N. and Cowan, W. M. (1972). An autoradiographic and electron microscopic study of retino-hypothalamic connections. *Z. Zellforsch.* 135, 1–26.
- enner, C. E. and Engels, W. L. (1952). The significance of the dark period in the photoperiodic response of male juncos and white-throated sparrows. *Biol. Bull.* 103, 345–355.
- amberi, I. A., Mical, R. S. and Porter, J. C. (1971). Effects of melatonin and serotonin on the release of FSH and prolactin. *Endocrinology* 88, 1288–1293.
- ano, T. and Migachi, Y. (1976). Direct action of melatonin on testosterone and cyclic GMP production using rat testis tissue *in vitro*. *Biochem. Biophys. Res. Comm.* 72, 969–975.
- ao, L.W.L. and Weisz, J. (1977). Release of gonadotrophin-releasing hormone (Gn-RH) from isolated, perfused medial-basal hypothalamus by melatonin. *Endocrinology* 100, 1723–1726.
- appers, J. A. (1960). The development, topographical relations and innervation of the epiphysis cerebri in the albino rat. *Z. Zellforsch. Mikrosk. Anat.* 52, 163–215.
- ennaway, D. J., Frith, R. G., Phillipov, G., Matthews, C. D. and Seamark, R. F. (1977). A specific radioimmunoassay for melatonin in biological tissue and fluids and its validation by gas chromatography-mass spectrometry. *Endocrinology* 101, 119–127.
- Kent, G. C., Ridgway, P. M. and Strobel, E. F. (1968). Continual light and constant estrus in hamsters. *Endocrinology* 82, 699–703.
- Klein, D. C. and Weller, J. (1970). Indole metabolism in the pineal gland: a circadian rhythm in N-acetyltransferase. *Science* 169, 1093–1095.
- Lawton, I. E. and Schwartz, N. B. (1967). Pituitary ovarian function in rats exposed to constant light: a chronological study. *Endocrinology* 81, 497–508.
- Legan, S. J., Karsch, F. J. and Foster, D. L. (1977). The endocrine control of seasonal reproductive function in the ewe: a marked change in response to the negative feedback action of estradiol on luteinizing hormone secretion. *Endocrinology* 101, 818–824.
- Levey, I. L. (1973). Effects of pinealectomy and melatonin injections at different seasons on ovarian activity in the lizard *Anolis carolinensis*. *J. Exp. Zool.* 185, 169–174.
- Lincoln, G. A., Guinness, F. and Short, R. V. (1972). The way in which testosterone controls the social and sexual behavior of the red deer stag (*Cervus elaphus*). *Horm. and Behav.* 3, 375–396.
- Lincoln, G. A. and Davidson, W. (1977). The relationship between sexual and aggressive behaviour and pituitary and testicular activity during the seasonal sexual cycle of rams and the influence of photoperiod. *J. Reprod. Fert.* 49, 267–276.
- Lincoln, G. A., Peet, M. J. and Cunningham, R. A. (1977). Seasonal and circadian changes in the episodic release of follicle-stimulating hormone, luteinizing hormone and testosterone in rams exposed to artificial photoperiods. *J. Endocrinol.* 72, 337–349.
- Lincoln, G. A., McNeilly, A. S. and Cameron, C. L. (1978). The effects of a sudden decrease in daylength on prolactin secretion in the ram. *J. Reprod. Fert.* 52, 305–311.
- Lodge, J. and Salisbury, G. (1970). Seasonal variation and male reproductive efficiency. In: *The Testis*. Vol. 3. (A. D. Johnson, W. R. Gomes and N. L. Van Demark, eds.). Academic Press, New York. pp. 139–167.
- Lynch, G. R. and Epstein, A. L. (1976). Melatonin induced changes in gonads, pelage and thermogenic characters in the white-footed mouse, *Peromyscus leucopus*. *Comp. Biochem. Physiol.* 53C, 67–68.
- Martin, J. and Klein, D. (1976). Melatonin inhibition of the neonatal pituitary response to luteinizing hormone-releasing factor. *Science* 191, 301–302.
- Mattocks, P. W., Jr., Farner, D. S. and Follett, B. K. (1976). The annual cycle in luteinizing hormone in the plasma of intact and castrated white-crowned sparrows, *Zonotrichia leucophrys gambelii*. *Gen. Comp. Endocrinol.* 30, 156–161.
- McCormack, C. E. and Sridaran, R. (1978). Timing of ovulation in rats during exposure to continuous light: evidence for a circadian rhythm of luteinizing hormone secretion. *J. Endocrinol.* 76, 135–144.
- McKeever, S. (1963). Seasonal changes in body weight, reproductive organs, pituitary, adrenal glands, thyroid gland and spleen of the Belding Ground Squirrel (*Citellus beldingi*). *Am. J. Anat.* 113, 153–167.
- McMillan, J. P., Underwood, H. A., Elliott, J. A., Stetson, M. H. and Menaker, M. (1975). Extraretinal light perception in the sparrow. IV. Further evidence that the eyes do not participate in photoperiodic photoreception. *J. Comp. Physiol.* 97, 205–213.
- Menaker, M. and Keats, H. (1968). Extraretinal light perception in the sparrow. II. Photoperiodic stimulation of testis growth. *Proc. Nat. Acad. Sci. U.S.A.* 60, 146–151.
- Menaker, M., Roberts, R., Elliott, J. and Underwood, H. (1970). Extraretinal light perception in the sparrow. III. The eyes do not participate in photoperiodic photoreception. *Proc. Nat. Acad. Sci. U.S.A.* 67, 320–325.
- Minneman, K. P. and Wurtman, R. J. (1975). Effects of pineal compounds on mammals. *Life. Sci.* 17, 1189–1200.
- Mirarchi, R. E., Howland, B. E., Scanlon, P. F., Kirkpatrick, R. L. and Sanford, L. M. (1978). Seasonal variation in plasma LH, FSH, prolactin and testosterone concentrations in adult male white-tailed deer. *Canad. J. Zool.* 56, 121–127.
- Moore, R. Y. (1973). Retinohypothalamic projection in mammals: a comparative study. *Brain Res.* 49, 403–409.
- Moore, R. Y. and Klein, D. C. (1974). Visual pathways and the central neural control of a circadian

- rhythm in pineal serotonin N-acetyltransferase activity. *Brain Res.* 71, 17–33.
- Moore, R. Y. and Eichler, V. B. (1976). Central neural mechanisms in diurnal rhythm regulation and neuroendocrine responses to light. *Psychoneuroendo.* 1, 265–279.
- Morin, L. P., Fitzgerald, K. M., Rusak, B. and Zucker, I. (1977). Circadian organization and neural mediation of hamster reproductive rhythms. *Psychoneuroendo.* 2, 73–98.
- Morin, L. P. and Zucker, I. (1978). Photoperiodic regulation of copulatory behavior in the male hamster. *J. Endocrinol.* 77, 249–258.
- Moszkowska, A., Hus-Citharel, A., L'Héritier, A., Zurburg, W. and Ebels, I. (1976). Separation of pineal extracts by gel filtration. V. Location by paper chromatography of a sheep pineal principle inhibiting hypophyseal gonadotropic activity. *J. Neural Trans.* 38, 239–247.
- Nanda, K. R. and Hamner, K. C. (1958). Studies on the nature of the endogenous rhythm affecting photoperiodic responses of Biloxi soybean. *Bot. Gaz.* 120, 14–25.
- Oishi, T. and Lauber, J. K. (1973). Photoreception in the photosexual response of quail. I. Site of photoreceptor. *Am. J. Physiol.* 225, 155–158.
- Oliver, J., Herbuté, S. and Baylé, J. D. (1977). Testicular response to photostimulation by radioluminous implants in the deafferented hypothalamus of quail. *J. Physiol., Paris* 73, 685–691.
- Orts, R. J. (1977). Reduction of serum LH and testosterone in male rats by a partially purified bovine pineal extract. *Biol. Reprod.* 16, 249–254.
- Orts, R. J., Benson, B. and Cook, B. E. (1974). Some antagonodotrophic effects of melatonin-free bovine pineal extracts in rats. *Acta. Endocrinol.* 76, 438–448.
- Oxender, W. D., Noden, P. A. and Hafs, H. D. (1977). Estrus, ovulation and serum progesterone, estradiol, and LH concentrations in mares after an increased photoperiod during winter. *Am. J. Vet. Res.* 38, 203–207.
- Ozaki, Y. and Lynch, H. J. (1976). Presence of melatonin in plasma and urine of pinealectomized rats. *Endocrinology* 99, 641–644.
- Ozaki, Y., Lynch, H. J. and Wurtman, R. J. (1976). Melatonin in rat pineal, plasma, and urine: 24-hour rhythmicity and effect of chlorpromazine. *Endocrinology* 98, 1418–1424.
- Pang, S. F., Ralph, C. L. and Reilly, D. P. (1974). Melatonin in the chicken brain: Its origin, diurnal variation, and regional distribution. *Gen. Comp. Endocrinol.* 22, 499–506.
- Pang, S. F., Brown, G. M., Grota, L. J., Chambers, J. W. and Rodman, R. L. (1977). Determination of N-acetylserotonin and melatonin activities in the pineal gland, retina, hardierian gland, brain and serum of rats and chickens. *Neuroendocrinology* 23, 1–13.
- Pavel, S., Dumitru, I., Klepsh, I. and Dorcescu, M. (1973). A gonadotropin inhibiting principle in the pineal of human fetuses. *Neuroendocrinology* 13, 41–46.
- Peat, F. and Kinson, G. A. (1971). Testicular steroidogenesis *in vitro* in the rat in response to blinding, pinealectomy and to the addition of melatonin. *Steroids* 17, 251–264.
- Pelletier, J. (1973). Evidence for photoperiodic control of prolactin release in rams. *J. Reprod. Fert.* 35, 143–147.
- Pelletier, J. and Ortavant, R. (1975a). Photoperiodic control of LH release in the ram. II. Light-androgens interaction. *Acta Endocrinol.* 78, 442–450.
- Pelletier, J. and Ortavant, R. (1975b). Photoperiodic control of LH release in the ram. I. Influence of increasing and decreasing light photoperiods. *Acta. Endocrinol.* 78, 435–441.
- Peters, R. R., Chapin, L. T., Leining, K. B. and Tucker, H. A. (1978). Supplemental lighting stimulates growth and lactation in cattle. *Science* 199, 911–912.
- Pickard, G. (1977). Changes in hypothalamic luteinizing hormone-releasing hormone (LH-RH) in the male golden hamster in response to shortened photoperiods. *Soc. For Neuroscience III.* 354. Abstr.
- Pittendrigh, C. S. (1966). The circadian oscillation in *Drosophila pseudoobscura* pupae: a model for the photoperiodic clock. *Z. Pflanzenphysiol.* 54, 275–307.
- Pittendrigh, C. S. (1972). Circadian surfaces and the diversity of possible roles of circadian organization in photoperiodic induction. *Proc. Nat. Acad. Sci. U.S.A.* 69, 2734–2737.
- Przekop, F., Skubiszewski, B. and Domanski, E. (1975). The effects of indoleamines (serotonin and melatonin) on induction of ovulation in rabbits. *Acta. Physiol. Pol.* XXVI, 395–398.
- Quay, W. B. (1974). *Pineal Biochemistry*, C. C. Thomas, Springfield, Illinois.
- Raisman, G. and Brown-Grant, K. (1977). The "suprachiasmatic syndrome": endocrine and behavioural abnormalities following lesions of the suprachiasmatic nuclei in the female rat. *Proc. R. Soc. Lond. B.* 198, 297–314.
- Reiter, R. J. (1972). Evidence for refractoriness of the pituitary gonadal axis to the pineal gland in golden hamsters and its possible implications in annual reproductive rhythms. *Anat. Rec.* 173, 365–371.
- Reiter, R. J. (1974). Circannual reproductive rhythms in mammals related to photoperiod and pineal function. *Chronobiologia* 1, 365–395.
- Reiter, R. J. (1977). *The Pineal*. Eden Press, Montreal. pp. 1–184.
- Reiter, R. J., Sorrentino, S., Jr. and Hoffman, R. A. (1970). Early photoperiodic conditions and pineal antagonodal function in male hamsters. *Int. J. Fert.* 15, 163–170.
- Reiter, R. J. and Johnson, L. Y. (1974). Depressant action of the pineal gland on pituitary luteinizing hormone and prolactin in male hamsters. *Hormone Res.* 5, 311–320.
- Reiter, R. J., Vaughan, M., Blask, D. and Johnson, L. (1975). Pineal methoxyindoles: New evidence concerning their function in the control of pineal-mediated changes in the reproductive physiology of male golden hamsters. *Endocrinology* 96, 206–213.
- Reiter, R. J. and Vaughan, M. K. (1977). Pineal antagonodotrophic substances: polypeptides and indoles. *Life Sciences* 21, 159–172.
- Relkin, R. (1976). *The Pineal*. Eden Press, Montreal. pp. 1–187.

- Rollag, M. D. and Niswender, G. D. (1976). Radioimmunoassay of serum concentrations of melatonin in sheep exposed to different lighting regimens. *Endocrinology* 98, 482–489.
- Rosenblum, L. Y., Benson, B. and Hruby, V. J. (1976). Chemical differences between bovine pineal antigonadotropin and arginine vasotocin. *Life Sci.* 18, 1367–1374.
- Rowan, W. (1925). Relation of light to bird migration and development changes. *Nature, Lond.* 115, 494–495.
- Rowan, W. (1928). Reproductive rhythms in birds. *Nature, Lond.* 122, 11–12.
- Rowan, W. (1938). Light and seasonal reproduction in animals. *Biol. Rev.* 13, 374–401.
- Rusak, B. (1977). The role of the suprachiasmatic nuclei in the generation of circadian rhythms in the golden hamster, *Mesocricetus auratus*. *J. Comp. Physiol.* 118, 145–164.
- Rusak, B. and Morin, L. P. (1976). Testicular responses to photoperiod are blocked by lesions of the suprachiasmatic nuclei in golden hamsters. *Biol. Reprod.* 15, 366–374.
- Rust, C. C. and Meyer, R. K. (1969). Hair color, molt and testes size in male, short-tailed weasels treated with melatonin. *Science* 165, 921–922.
- Sachs, S. (1969). Photoperiodic control of reproductive behavior and physiology of the male Japanese quail (*Coturnix coturnix japonica*). *Horm. and Behav.* 1, 7–24.
- Schanbacher, B. D. and Ford, J. J. (1976). Seasonal profiles of plasma luteinizing hormone, testosterone and estradiol in the ram. *Endocrinology* 99, 752–757.
- Schwab, R. G. (1971). Circannian testicular periodicity in the European starling in the absence of photoperiodic change. In: *Biochronometry* (M. Menaker, ed.). U. S. Nat. Acad. Sci., Washington, D. C. pp. 428–447.
- Schwartz, N. B. (1973). Mechanisms controlling ovulation in small mammals. In: *Handbook of Physiology*. (R. O. Greep and E. B. Astwood, eds.). Sect. VII, Vol. 2, Part 1. American Physiological Society, Washington, D. C. pp. 125–141.
- Seegal, R. F. and Goldman, B. D. (1975). Effects of photoperiod on cyclicity and serum gonadotropins in the Syrian hamster. *Biol. Reprod.* 12, 223–231.
- Sharp, D. C., III, and Ginther, O. J. (1975). Stimulation of follicular activity and estrous behavior in anestrus mares with light and temperature. *J. An. Sci.* 41, 1368–1372.
- Sharp, P. J. and Moss, R. (1977). The effects of castration on concentrations of luteinizing hormone in the plasma of photorefractory red Grouse (*Lagopus lagopus scoticus*). *Gen. Comp. Endocrinol.* 32, 289–293.
- Siville, P. C., McNeilly, A. S. and Collins, P. M. (1978). A comparison of the effectiveness of FSH, LH and prolactin in the reinitiation of testicular function of hypophysectomized and estrogen-treated rats. *Biol. Reprod.* 18, 878–885.
- Steel, E. and Hinde, R. A. (1976). Effect of a skeleton photoperiod on the daylength-dependent response to oestrogen in canaries (*Serinus canarius*). *J. Endocrinol.* 70, 247–254.
- Stetson, M. H., Matt, K. S. and Watson-Whitmyre, M. (1976). Photoperiodism and reproduction in golden hamsters: circadian organization and the termination of photorefractoriness. *Biol. Reprod.* 14, 531–537.
- Stetson, M. H. and Watson-Whitmyre, M. (1976). Nucleus suprachiasmaticus: The biological clock in hamsters? *Science* 191, 197–199.
- Stetson, M. H., Watson-Whitmyre, M. and Matt, K. S. (1977). Termination of photorefractoriness in golden hamsters—photoperiodic requirements. *J. Exp. Zool.* 202, 81–88.
- Stephan, F. K. and Zucker, I. (1972). Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proc. Nat. Acad. Sci. U.S.A.* 69, 1583–1586.
- Tamarkin, L., Hutchison, J. S. and Goldman, B. D. (1976a). Regulation of serum gonadotropins by photoperiod and testicular hormone in the Syrian Hamster. *Endocrinology* 99, 1528–1533.
- Tamarkin, L., Westrom, W., Hamill, A. and Goldman, B. (1976b). Effect of melatonin on the reproductive systems of male and female Syrian hamsters: a diurnal rhythm in sensitivity to melatonin. *Endocrinology* 99, 1534–1541.
- Tamarkin, L., Lefebvre, N. G., Hollister, C. W. and Goldman, B. D. (1977a). Effect of melatonin administered during the night on reproductive function in the Syrian hamster. *Endocrinology* 101, 631–634.
- Tamarkin, L., Hollister, C. W., Lefebvre, N. G. and Goldman, B. D. (1977b). Melatonin induction of gonadal quiescence in pinealectomized Syrian hamsters. *Science* 198, 953–955.
- Thomson, A.P.D. (1954). The onset of oestrus in normal and blinded ferrets. *Proc. Roy. Soc. B.* 142, 126–135.
- Thorpe, P. and Herbert, J. (1976). Studies on the duration of the breeding season and photorefractoriness in female ferrets pinealectomized or treated with melatonin. *J. Endocrinol.* 70, 255–262.
- Thorpe, P. A. and Herbert, J. (1976). The accessory optic system of the ferret. *J. Comp. Neurol.* 170, 295–310.
- Tiefer, L. (1970). Gonadal hormones and mating behavior in the adult golden hamster. *Horm. and Behav.* 1, 189–202.
- Trentini, G. P., Botticelli, A. R., Botticelli, C. S. and Silva, C. B. (1976). Decreased ovarian LH incorporation after melatonin treatment. *Horm. Metab. Res.* 8, 234–236.
- Turek, F. W. (1972). Circadian involvement in termination of the refractory period in two sparrows. *Science* 178, 1112–1113.
- Turek, F. W. (1974). Circadian rhythmicity and the initiation of gonadal growth in sparrows. *J. Comp. Physiol.* 92, 59–64.
- Turek, F. W. (1975). Extraretinal photoreception during the gonadal refractory period in the golden-crowned sparrow. *J. Comp. Physiol.* 96, 27–36.
- Turek, F. W. (1977a). Antigonadal effect of melatonin in pinealectomized and intact male hamsters. *Proc. Soc. Exp. Biol. Med.* 155, 31–34.
- Turek, F. W. (1977b). The interaction of the photoperiod and testosterone in regulating serum

- gonadotropin levels in castrated male hamsters. *Endocrinology* 101, 1210–1215.
- Turek, F. W. (1978a). Diurnal rhythms and the seasonal reproductive cycle in birds. In: *Environmental Endocrinology*. (I. Assenmacher and D. S. Farner, eds.). Springer-Verlag, New York. pp. 144–152.
- Turek, F. W. (1978b). Role of the pineal gland in photoperiod-induced changes in hypothalamic-hypophyseal sensitivity to steroid feedback. *Fed. Proc.* 37, 438. Abstr.
- Turek, F. W., Elliott, J., Alvis, J. and Menaker, M. (1975a). Effect of prolonged exposure to non-stimulatory photoperiods on the activity of the neuroendocrine-testicular axis of golden hamsters. *Biol. Reprod.* 13, 475–481.
- Turek, F. W., Desjardins, C. and Menaker, M. (1975b). Melatonin: antagonadal and progonadal effects in male golden hamsters. *Science* 190, 280–282.
- Turek, F. W., Elliott, J., Alvis, J. and Menaker, M. (1975c). The interaction of castration and photoperiod in the regulation of hypophyseal and serum gonadotropin levels in male golden hamsters. *Endocrinology* 96, 854–860.
- Turek, F. W., Desjardins, C. and Menaker, M. (1976a). Differential effects of melatonin on the testes of photoperiodic and nonphotoperiodic rodents. *Biol. Reprod.* 15, 94–97.
- Turek, F. W., Desjardins, C. and Menaker, M. (1976b). Melatonin-induced inhibition of testicular function in adult golden hamsters. *Proc. Soc. Exp. Biol. Med.* 151, 502–506.
- Turek, F. W., Alvis, J., Elliott, J. and Menaker, M. (1976c). Temporal distribution of serum levels of LH and FSH in adult male golden hamsters exposed to long or short days. *Biol. Reprod.* 14, 630–631.
- Turek, F. W., Alvis, J. D. and Menaker, M. (1977). Pituitary responsiveness to LRF in castrated male hamsters exposed to different photoperiodic conditions. *Neuroendocrinology* 24, 140–146.
- Turek, F. W. and Losee, S. H. (1978). Melatonin-induced testicular growth in golden hamsters maintained on short days. *Biol. Reprod.* 18, 299–305.
- Underwood, H. (1975). Extraretinal light receptors can mediate photoperiodic photoreception in the male lizard *Anolis carolinensis*. *J. Comp. Physiol.* 99, 71–78.
- Underwood, H. and Menaker, M. (1970). Photoperiodically significant photoreception in sparrows: Is the retina involved? *Science* 167, 298–301.
- Vaughan, G. M., Bigelow, L. and Altschule, M. D. (1972). Inhibition of compensatory ovarian hypertrophy in the mouse and vole: a comparison of Altschule's pineal extract, pineal indoles, vasopressin, and oxytocin. *Gen. Comp. Endocrinol.* 18, 372–377.
- Vaughan, M. K., Vaughan, G. M., Blask, D. E. and Reiter, R. J. (1976). Influence of melatonin, constant light, or blinding on reproductive system of gerbils (*Meriones unguiculatus*). *Experientia* 32, 1341–1342.
- Van Horn, R. N. (1975). Primate breeding season: photoperiodic regulation in captive *Lemur catta*. *Folia Primatol.* 24, 203–220.
- Van Horn, R. N. and Resko, J. A. (1977). The reproductive cycle of the ring-tailed lemur (*Lemur catta*): Sex steroid levels and sexual receptivity under controlled photoperiods. *Endocrinology* 101, 1579–1586.
- Vlaming, V. L. (1975). Effects of pinealectomy on gonadal activity in the cyprinid teleost, *Notemigonus crysoleucas*. *Gen. Comp. Endocrinol.* 26, 36–49.
- Vlaming, V. L. and Vodcink, M. J. (1977). Effects of pinealectomy on pituitary gonadotrophs, pituitary gonadotropin potency and hypothalamic gonadotropin releasing activity in *Notemigonus crysoleucas*. *J. Fish Biol.* 10, 73–86.
- Wetterberg, L., Geller, E. and Yuwiler, A. (1970). Harderian gland: an extraretinal photoreceptor influencing the pineal gland in neonatal rats. *Science* 167, 884–885.
- Wilson, F. E. and Follett, B. K. (1974). Plasma and pituitary luteinizing hormone in intact and castrated tree sparrows (*Spizella arborea*) during a photoinduced gonadal cycle. *Gen. Comp. Endocrinol.* 23, 82–93.
- Wolfson, A. (1952). The occurrence and regulation of the refractory period in the gonadal fat cycles of the junco. *J. Exp. Zool.* 121, 311–326.
- Wolfson, A. (1960). Regulation of annual periodicity in the migration and reproduction of birds. *Cold Spring Harbor Symp. Quant. Biol.* 25, 507–514.
- Yokoyama, K. and Farner, D. S. (1976). Photoperiodic responses in bilaterally enucleated female white-crowned sparrows, *Zonotrichia leucophrys gambelii*. *Gen. Comp. Endocrinol.* 30, 528–533.
- Yokoyama, K. and Farner, D. S. (1978). Induction of Zugunruhe by photostimulation of encephalic receptors in white-crowned sparrows. *Science* 201, 76–79.
- Yuthasastrakosol, P., Palmer, W. M. and Howland, B. E. (1975). Luteinizing hormone, oestrogen and progesterone levels in peripheral serum of anoestrous and cyclic ewes as determined by radioimmunoassay. *J. Reprod. Fert.* 43, 57–65.
- Zweig, M., Snyder, S. H. and Axelrod, J. (1966). Evidence for a nonretinal pathway of light to the pineal gland of newborn rats. *Proc. Nat. Acad. Sci. U.S.A.* 56, 515–520.