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Puberty and Menopause in the Human: Possible Relation to Gonadotropin-Releasing Hormone Pulse Frequency and the Pineal Gland

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I. INTRODUCTION

The pineal gland of mammals is potently antigonadotrophic when tested under appropriate experimental conditions [Reiter et al., 1983]. The primary regulatory influence on the pineal is the light dark cycle. For example, in the Syrian golden hamster *(Mesocricetus auratus)*, a highly photosensitive species, short days and long nights or blinding induce gonadal atrophy as a result of pineal stimulation. However, in the absence of the pineal, long periods of darkness do not produce gonadal regression [Hoffman and Reiter, 1965].

The antigonadotrophic action of the pineal has led investigators to speculate on what role the pineal might play in the onset of puberty and the fertility

of mammals in general. Of special interest are those species not as exquisitely photosensitive as the hamster, the rat and man being examples. This article will address itself to these questions. In addition, a general discussion of the mechanism of puberty and menopause will be presented.

Puberty, the transitional period between childhood and adulthood, is accompanied by the appearance of secondary sexual characteristics and the achievement of fertility. These are multiple signs of its onset. In this essay, menarche, the onset of first menses, will be taken as the onset of human female puberty. Vaginal opening will be regarded as the onset of female rodent puberty, even though in some instances this sign is not an invariant indicator of the impending onset of ovulation [Ruf, 1983].

II. FERTILITY, PUBERTY, AND THE PINEAL

In humans, the pineal may have a distinct physiologic function, comparable to that in other mammals [Vaughan et al., 1978]. Adult blind persons reportedly have less than half the 17-ketosteroid secretion rate of sighted controls, and persons with partial vision have a mean 17-ketosteroid secretion in a range between the former two groups. Moreover, cataract extraction and restoration of vision results in significant elevation of 17-ketosteroid excretion to nearly normal levels [Hollwich and Dieckhues, 1971]. In other words, the blindness may have produced the same antigonadotrophic effect in a human that it does in the hamster.

The efffect of the light dark cycle on melatonin is also similar in humans and hamsters. Melatonin, an indole probably reponsible for at least a portion of the antigonadal activity of the pineal, is produced primarily during darkness and can duplicate many of the reproductive effects of dark exposure in the hamster [Reiter, 1980]. As in the hamster, a nocturnal rise in plasma melatonin occurs in young men [Vaughan et al., 1976]. Also, melatonin secretion in humans is suppressed by light, just as it is in hamsters [Lewy et al, 1980].

Reproductive function of both hamsters and humans is affected by photoperiod. The long nights and short days, which cause gonadal atrophy in the hamster, seem to produce changes in the human reproductive tract as well. In people living near the Arctic circle, the incidence of single and especially multiple conceptions diminishes during the dark winter months [Timonen et al., 1964]. Further, in over 9,750 endometrial biopsies performed at the Helsinki University Women's Clinic from 1956 to 1960, the frequency of cystic endometrial hyperplasia or of all endometrial hyperplasia was significantly elevated; these findings are apparently the result of a greater tendency

toward anovulatory cycles during the dark months accompanied by a relative lack of the normal estrogen-progesterone balance that should exist in the second half of the menstrual cycle [Timonen and Carpen, 1968].

The long-term effects of blindness are similar in both the hamster and human. In the hamster, gonadal regression is marked after the animal has been blind for 9 weeks. But 27 weeks after blinding, the hamster's gonads and accessory reproductive organs regenerate to the normal adult condition even though the pineal gland is intact, and the animals again become normally fertile [Reiter, 1969]. Reiter has suggested that this spontaneous regeneration might be due to two phenomena: 1) the hypothalamo-hypophysial-gonadal axis becoming refractory to the pineal inhibitory substance or 2) the cessation of secretion of the pineal antigonadotrophic substance. Recent studies indicate that the former explanation is most probably correct.

As in the hamster, a woman who is blind over a long period of time will be normally fertile. Moreover, there was no significant difference in the incidence of pregnancy in blind women, most of whom had been blind since early childhood, with and without light perception [Lehrer, 1982].

The conclusions of an earlier study [Elden, 1971] that asserted that blind women are sterile are questionable. In 1969, according to Elden, only one woman blind since birth became pregnant and delivered a normal child in the state of Washington; this woman had no light perception. On the basis of the birth rate and the blind population, there should have been 120 such women. In the United States during the same year, only six pregnancies in blind women were reported, when over 1,000 should have been expected. From these data and other anecdotal evidence, Elden concluded that blindness caused infertility in women.

However, Elden did not take into account the degree of light perception of all the subjects in his study, an important consideration, since the melatonin secretion of the human pineal is suppressed by sunlight and by bright artificial light [Lewy et al., 1980]. Therefore, one would expect that only those women without light perception or with little light perception should show a pineal effect on fertility. Yet, in the blind population as a whole only about 3% of persons have no light perception [Corbett et al., 1978]. Most of the other 97% should be normally fertile. Thus, one wonders why Elden found so few fertile blind women, especially in view of the fact that about 32% of legally blind persons have 20/200 visual acuity after correction as well as normal light perception. One would expect all women in this category to be normally fertile.

One of the most puzzling neuroendocrine aspects of blindness is its relationship to the onset of puberty. A blinded immature rat shows only a

slight delay in the vaginal opening and the onset of first estrus. Not being a particularly photosensitive animal, the rat is minimally affected by simple light restriction [Reiter and Ellison, 1980]. However, blinded immature female rats that have also undergone olfactory bulbectomy show a marked delay in the onset of vaginal opening and first estrus. Why anosmia should so enhance photosensitivity is still uncertain.

In light of the pineal-mediated antigonadotrophic effect associated with blindness, it is at first difficult to understand why blindness should accelerate menarche. Zacharias and Wurtman [1964] noted this phenomenon. Though their findings were later questioned by Thomas and Pizzarello [1967], a third careful study [Magee et al., 1970] confirmed that blindness can accelerate menarche. Girls with minimal or no light perception had menarche at age 12.0 years; girls with shadow vision or guiding sight experienced menarche at age 12.8 years. Moreover, in one report rats reared in darkness had their vaginal opening significantly earlier than rats reared in an 8 hr light:16 hr dark cycle [Relkin, 1967]. Other studies show, however, that light restriction delays sexual development in rats [Reiter, 1968].

The reason for the seemingly paradoxical acceleration of puberty onset, when it occurs, is that there may be, in fact, no pineal effect at all. As was mentioned, both the rat and the human are much less photosensitive than the hamster [Johnson and Reiter, 1978]. Puberty theoretically could be accelerated in rats reared in darkness and blind girls because of an acceleration of the normal circadian rhythms [Lehrer, 1983]. The acceleration occurs when a young animal is isolated from the 24-hr light:dark cycle and its circadian rhythms free run. This point will be discussed shortly in greater detail.

Some speculation about the role of the pineal in normal puberty has been engendered by the precocious puberty known to result from a pineal tumor. But tumors of the pineal occur in both boys and girls, whereas sexual precocity has been limited almost exclusively to affected boys. New evidence suggests that the precocity may not result from activation of the hypothalamic-pituitary axis and true puberty. It may be due instead to the secretion of human chorionic gonadotropin (hCG) by some pineal tumors. Girls with these tumors may not undergo puberty because ovarian follicular development is dependent on stimulation by both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [Sklar et al., 1981]. But hCG is not secreted by all pineal tumors; the mechanism of precocious puberty in cases of tumors not elaborating hCG is still not well understood.

Because of the antigonadotrophic action of melatonin, efforts have been made to determine whether some change in melatonin secretion might be associated with the onset of puberty. One study showed a high daytime

melatonin level in boys at early puberty (Tanner stage I), with a dramatic fall in melatonin during the latter phases of puberty [Silman et al., 1979]. A second study [Lissoni et al., 1983] showed diminished average melatonin levels in pubertal boys in comparison with prepubertal boys. A third study [Gupta et al., 1983] did not reveal any change of plasma melatonin in children during the daytime with progressive pubertal development but did demonstrate a decline in net increments (dark phase value—daytime value) from pubertal stage I to pubertal stage II. Other studies found no significant fluctuation in daytime melatonin levels during puberty [Ehrenkranz et al., 1982; Lenko et al., 1982; Sizonenko et al., 1982].

Currently, therefore, one can state that the data are as yet inconclusive as to the involvement of the pineal gland and melatonin in human puberty. But a great deal of physiologic evidence now suggests that the onset of both puberty and menopause are a direct result of a reduction in the frequency of gonadotropin-releasing hormone (GnRH) pulses due to hypothalamic aging. In the discussion to follow, the relation of the pulse frequency reduction to puberty will be described first; the relationship to menopause will be dealt with thereafter.

III. PUBERTY AND GnRH PULSATION

Puberty now seems to be the result of the reduction in frequency of the GnRH pulses that occurs at birth and continues throughout life [Lehrer, 1983]. In humans, monkeys, and rats, the reproductive cycles and puberty are a direct result of the pulsatile release of GnRH from the arcuate nucleus of the hypothalamus. The GnRH stimulates the anterior pituitary to release the gonadotropins, also in a pulsatile fashion. In the Rhesus monkey, the normal GnRH pulse frequency is one pulse per hour. In the human, the normal frequency, though not as precisely documented, is probably a bit lower: one pulse every hour and one half (0.67 hr^{-1}). Most importantly, these pulses are the only neuroendocrine signal required to produce the 28-day menstrual cycle of the Rhesus monkey. Puberty can be induced in an infant monkey when the pulses are administered intravenously by means of a pump [Knobil, 1981].

Puberty occurs when the arcuate nucleus intrinsic frequency has slowed from its high rate at birth to 0.67 hr^{-1}. The GnRH-releasing cells of the arcuate nucleus are an inependently functioning oscillator with their own intrinsic or free running frequency. But in a normal, intact animal the arcuate nucleus interacts with a second oscillator, an ultradian pacemaker (frequency higher than one cycle in 24 hr—in this case 0.67 hr^{-1}) and resonance occurs

(Fig. 1). Resonance is well documented in animals [Veerman and Vaz Nunes, 1980].

GnRH and the resulting gonadotropin surges increase in intensity at this time, causing puberty and the reproductive cycles, because when two oscillators interact the oscillations surge to a maximum amplitude at resonance. This can be likened to the motion of a swing being pushed periodically. When the pushes occur with a frequency other than the intrinsic one of the swing, the displacement of the swing is rather small. But as the frequency of the pushes approaches the intrinsic frequency of the swing, the displacement of the swing becomes larger and larger. Resonance is said to occur when an oscillator, be it swing or arcuate nucleus, is acted on by a periodic series of impulses (from the ultradian pacemaker in the case of puberty) having a frequency equal or nearly equal to its intrinsic frequency.

The ultradian pacemaker, which would be called a *frequency multiplier* in an electronic circuit, is coupled to a circadian pacemaker, a third oscillator, with a 24-hr cycle. Because of the coupling the frequency of the ultradian pacemaker is an integral multiple or harmonic of the frequency of the circadian pacemaker [$0.67 = 16 \times (1/24)$].

In mammals and other vertebrates, the circadian pacemaker generates the normal 24-hr circadian rhythms. In rats and hamsters this pacemaker may be situated within a hypothalamic structure, the suprachiasmatic nucleus (SCN) [Zucker, 1980]. In birds, the circadian pacemaker is found within the pineal gland. In humans, the exact location of the circadian pacemaker is still uncertain.

The circadian pacemaker rhythms are exactly synchronized with the external light-dark cycle, a so-called *Zeitgeber* or time giver, by impulses received from the eyes through a retinohypothalamic projection. In a blind animal or an animal kept in constant darkness or constant dim illumination, the circadian pacemaker rhythm is free running, that is, somewhat greater or less in

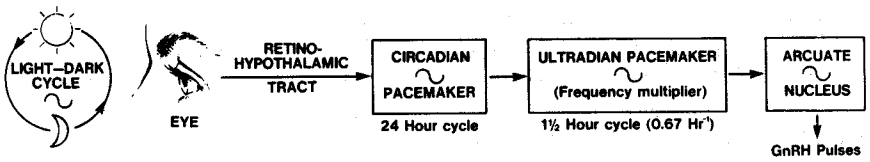

Fig. 1. Oscillator system regulating reproductive function. Circadian (24-hr) body rhythms are controlled by a circadian pacemaker with a 24-hr cycle. The circadian pacemaker is normally coupled to the 24-hr light:dark cycle by a retinohypothalamic tract. An ultradian pacemaker is coupled to the circadian pacemaker and serves as a frequency multiplier. The arcuate nucleus of the hypothalamus interacts, perhaps electrically, with the ultradian pacemaker. The GnRH pulses are produced by the arcuate nucleus.

frequency than one cycle in 24 hr. The circadian pacemaker is believed to be a master clock, probably driving other physiologic rhythms, including plasma corticosterone levels and pineal N-acetyltransferase levels in rats [Pohl and Gibbs, 1978]. In blind rats these rhythms are also free running, though synchronized with each other.

An aberration in circadian pacemaker frequency appears to be responsible for the reported early menarche in blind girls. Blind adult humans and sighted humans deprived of a Zeitgeber have a free running frequency of about one cycle in 25 hr [Miles et al., 1977], but the free running frequency of children is probably higher—perhaps one cycle in 21 hr—and slows with age. Such slowing with age has been demonstrated in hamsters [Davis and Menaker, 1980]. In blind girls, the circadian and ultradian pacemaker frequencies may be higher than normal; thus the intrinsic frequency of the arcuate nucleus does not have to diminish as much for resonance to occur, and puberty can take place at an earlier age (Fig. 2). Experimental confirmation of the effect of abnormally high circadian pacemaker frequency on puberty has been obtained by showing that rats reared on a 21-hr light:dark cycle have vaginal opening significantly earlier than rats reared on a 24-hr light:dark cycle [Lehrer, 1983] (Fig. 3).

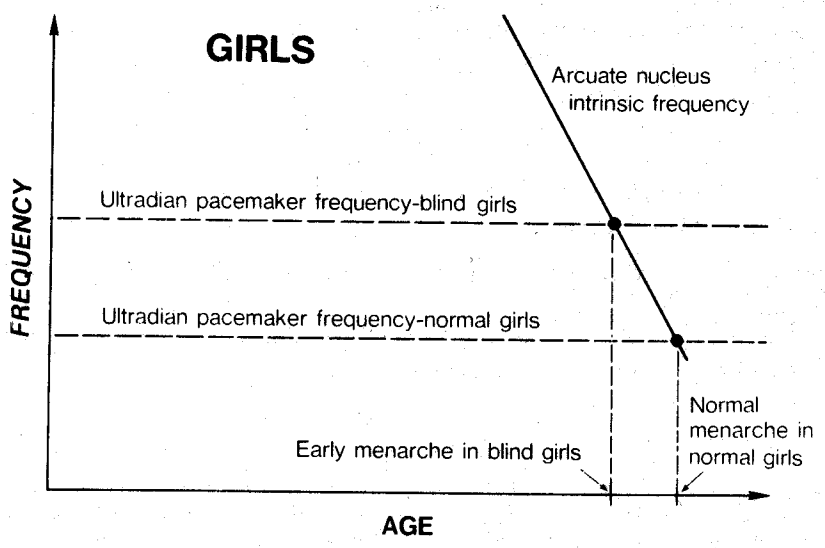

Fig. 2. Blind girls appear to have circadian and ultradian pacemaker rhythms of abnormally high frequency. As a result, the intrinsic frequency of the arcuate nucleus does not have to diminish as much for resonance to occur and menarche can occur at an earlier age.

The resonance mechanism and reduction in GnRH pulsation rate over time provide an explanation for the elevated gonadotropins at birth. Luteinizing hormone (LH), for example, is high at birth, falls between the ages of 2 and 4 years, then rises again at puberty (Fig. 4) [Grumbach, 1980]. This fluctuation, corresponding with the period of infant sexuality and subsequent latent period posited by Freud [1905], is especially prominent in agonadal children. The elevation at birth may occur because the frequency of the arcuate nucleus of an infant is very much higher than that of an adult, specifically 1.33 cycles per hr. Resonance of the ultradian pacemaker with the arcuate nucleus will occur, because 1.33 cycles per hr (1.33 hr^{-1}) is an integral multiple (harmonic) of 0.67 cycle per hr (that is, almost 2×0.67). As the frequency of the arcuate nucleus diminishes between 4 and 8 years of age, resonance is lost and LH levels drop. But when the frequency of the arcuate nucleus has slowed to 0.67 cycle per hr, resonance again occurs, resulting in the gonadotropin surge necessary for secondary sexual development.

The LH pulses that occur only during sleep in puberty [Boyar et al., 1972] can be explained with the resonance mechanism. During puberty, the arcuate nucleus frequency is very close to the frequency of the ultradian pacemaker. When two oscillators of very nearly the same frequency interact, the beat phenomenon will occur (Fig. 5). The rhythms combine to give a rhythm whose amplitude varies periodically with time. Such a mechanism is familiar in mammals, having already been invoked to explain the hormone level variations in the rat estrous cycle [Yochim and Shirer, 1981]. During puberty, the beats correspond with the LH pulses during sleep.

IV. PULSE FREQUENCY REDUCTION DURING THE REPRODUCTIVE YEARS

During the reproductive years, the arcuate nucleus intrinsic frequency* and GnRH pulsation rate continue to diminish, though at a reduced pace. In fact, the rate of diminution seems to slow logarithmically. Referring to Fig. 4, one can see that the peak LH level in infancy occurs at about age 1.6, the

*There is an LH pulse frequency reduction during the menstrual cycle, from one pulse every 1½ hours in the follicular phase to one pulse every four hours in the luteal phase (Yen et al, 1972), presumably the result of ovarian steroid feedback. However, the arcuate nucleus intrinsic frequency, referred to here, is that of the follicular phase of the menstrual cycle, i.e., one pulse every 1½ hours; it is this basic frequency, which must be present for at least part of the cycle, that is needed to maintain normal cycling.

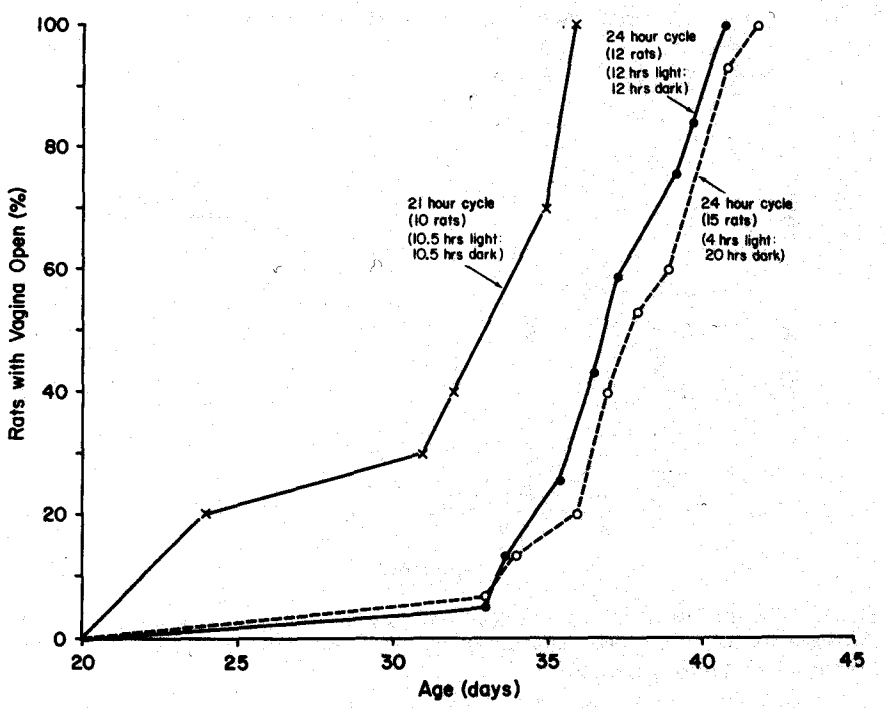

Fig. 3. Rats reared on a 21-hr light:dark cycle (10.5:10.5) had vaginal opening significantly ($P < 0.01$) earlier than rats reared on two variants of a 24-hr light:dark cycle (12:12 or 4:20).

minimum at age 5, and the peak pubertal level at age 16. The logarithms for each of these ages are as follows:

age	1.6	5	16
log age	0.2	0.7	1.2.

The logarithmic slowing is suggested by the equal logarithmic difference, 0.5, between the three age points. In other words, there is much more frequency reduction between age 1 and age 2 than there is between age 50 and age 51.

The constant reduction in GnRH pulsation rate during the reproductive years is suggested by the reduction in length of the menstrual cycle, from about 31 days at age 16 to about 27 days at age 40 (Fig. 6) [Treloar et al., 1967]. Experimental evidence already indicates that the 4–5-day estrous cycle of the rat is regulated in length by an ultradian pacemaker [Yochim and

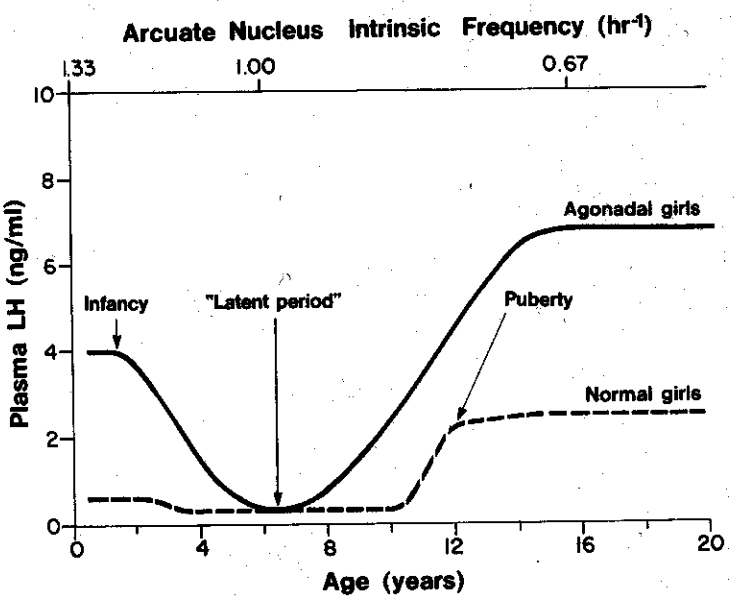

Fig. 4. The high LH levels at birth and puberty, in both normal and agonadal girls, can be accounted for by a continually diminishing arcuate nucleus intrinsic frequency after birth [modified from Grumbach, 1980].

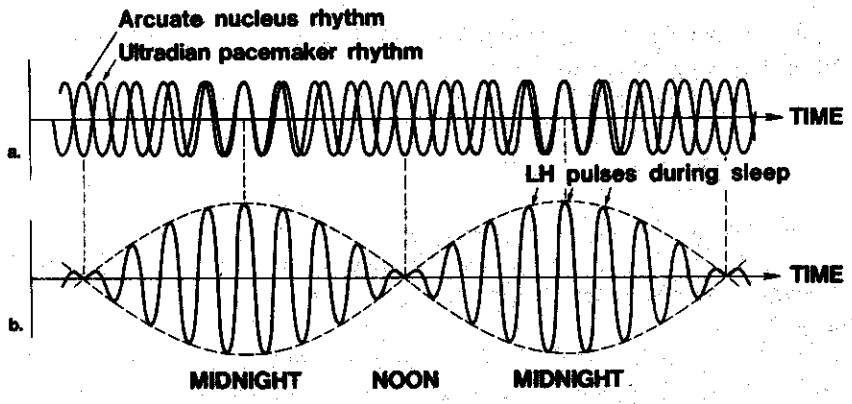

Fig. 5. The beat phenomenon. Two rhythms of slightly different frequencies, shown in a, combine in b to produce a rhythm whose amplitude (broken line) varies periodically with time. This variation might account for the LH pulses that occur only during sleep at puberty.

Shirer, 1981]. If the menstrual cycle is regulated in the same manner, and if its ultradian pacemaker is identical to that in Figure 1, the reduction in pulse frequency would be responsible for the change in menstrual cyle length as well as for the onset of puberty and menopause.

The continued reduction in arcuate nucleus pulse frequency between the ages of 40 and 50 appears to result in menopause. There are at least three pieces of evidence to support this idea: 1) Experimental data confirms that loss of fertility in the aging rat is definitely a hypothalamic phenomenon [Cooper and Walker, 1979]; 2) there is a known sensitivity of the ovary to gonadotropin pulse frequency [Pohl et al., 1983]; and 3) body weight affects the time of onset of menarche and menopause [Frisch, 1980; Flint, 1976]. A fourth phenomenon, the increase in the FSH:LH ratio in the years just preceding menopause, may or may not indicate a pulse frequency reduction. These points will now be discussed in more detail.

V. LOSS OF FERTILITY IN THE AGING RAT

In the female rat, the loss of fertility with advancing age is a hypothalamic phenomenon. Between the ages of 10 and 12 months, the regular 4- or 5-day estrous cycle and associated changes in the vaginal epithelium are replaced by prolonged anovulatory periods of constant vaginal cornification (CVC) or predominantly leukocytic smears, termed *repetitive pseudopregnancies* (RP) [Cooper and Walker, 1979]. Ovulation occurs less frequently, and fewer ova are shed per ovulation. Yet, if the ovary of an old rat is transplanted beneath the kidney capsule of an ovariectomized young female rat, vaginal cyclic activity will resume in the recipient animal, along with corpora lutea formation in the old transplanted ovary [Peng and Huang, 1972]. In addition, placement of L-DOPA, a catecholamine precursor, into the medial preoptic area of the hypothalamus results in a reinitiation of vaginal cycles in an old rat [Cooper et al., 1979].

VI. PULSE FREQUENCY AND OVARIAN FUNCTION

GnRH pulse frequency is extremely critical for normal ovarian function and ovulation. As was mentioned, GnRH pulses administered by pump at 1-hr intervals result in corresponding hourly gonadotropin pulses and a normal menstrual cycle in an infant rhesus monkey [Knobil, 1981]. However, if the pump delivery of GnRH is reduced to one pulse in 90 min, cyclic follicular development is disturbed [Pohl et al., 1983]. For example, of six rhesus monkeys receiving pulses of this frequency, one was completely anovulatory,

four had only one ovulatory cycle before the ovary ceased to ovulate, and only one had even a second ovulatory cycle. In addition, estradiol levels were below normal. These changes correspond with the ovulatory irregularities and diminished estradiol of perimenopausal women and suggest that reduced pulse frequency of GnRH could be responsible. The failure of the ovary and its diminished estradiol production would be responsible for the gonadotropin rise at menopause (Fig. 6) due to absence of ovarian steroid feedback on the pituitary-hypothalamic axis.

However, the frequency reduction necessary to produce menopause is apparently much less than that needed to create a complete loss of resonance and gonadotropin fall comparable to that at age 5 or 6. When such a large frequency reduction has taken place in an extremely old woman the gonadotropins do finally fall, but at least 40 or 50 years after menopause (Fig. 6).

The ovary will apparently function normally only within a very narrow gonadotropin pulse frequency band (Fig. 6). As has been mentioned, the rate of fall in arcuate nucleus pulse frequency diminishes approximately logarithmically with time. Thus, the frequency diminution from age 45 to age 50, though sufficient to cause the GnRH pulse frequency to fall below that needed for normal ovarian function, is not great enough to cause loss of arcuate nucleus resonance. In contrast, the much greater rate of fall in frequency from birth to age 5 is sufficient to result in loss of resonance as well as the fall in gonadotropins so prominent in agonadal girls.

Because the elevation of the gonadotropins at birth is attributed to an arcuate nucleus intrinsic frequency (1.33 hr^{-1}), which is double that at puberty (0.67 hr^{-1}), one might wonder whether the observed gonadotropin pulse frequency at birth would be double that at puberty. In fact, at least in the Rhesus monkey, the LH pulses appear at the same rate at birth and during the reproductive years, about once per hr [Plant, 1982]. The reason is as follows: Although the arcuate nucleus may be pulsing at a frequency of 1.33 hr^{-1}, or one pulse per 45 min, only one-half of these pulses are appearing as gonadotropin pulses—that is, one sees only one gonadotropin pulse every 1½ hours (0.67 hr^{-1}). One-half of the arcuate nucleus pulsations are being lost at one of two sites.

One site of loss might be at the anterior pituitary gland. Preliminary studies have already shown that when pulsatile gonadotropin-releasing hormone is administered to adults to induce puberty, not every pulse of GnRH produces a gonadotropin pulse. If the GnRH pulses are given rapidly, two GnRH pulses often provoke only a single pituitary gonadotropin pulse [Crowley, 1983; Hoffman and Crowley, 1982].

A second site of pulse loss might be within the arcuate nucleus itself. Studies of multiunit electrical activity in the region of the arcuate nucleus

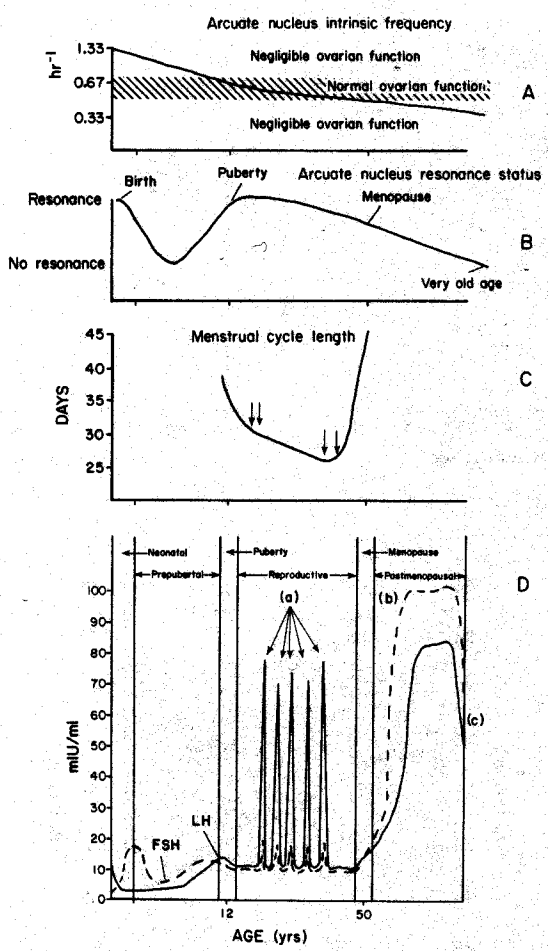

Fig. 6. A, as a female develops and ages, arcuate nucleus frequency constantly diminishes. The rate of diminution is roughly logarithmic. Between puberty and menopause, arcuate nucleus frequency falls into a range that permits normal ovarian function. B, resonance of the arcuate nucleus with the ultradian pacemaker occurs at birth and at puberty. Loss of resonance occurs at age 5 and in very old age. C, menstrual cycle length shortens during the reproductive years (between double arrows) probably because arcuate nucleus intrinsic frequency diminishes (data from Treloar, [1967]). D, menopause occurs when arcuate nucleus intrinsic frequency has dropped enough to fall below range that permits normal ovarian function (hatched region in A) and ovaries fail. Gonadotropins rise (b) because of lack of ovarian steroid feedback. In a very old woman, arcuate nucleus resonance is finally completely lost and gonadotropins fall (c). Pulses (a) are preovulatory gonadotropin surges (data from Yen [1980]).

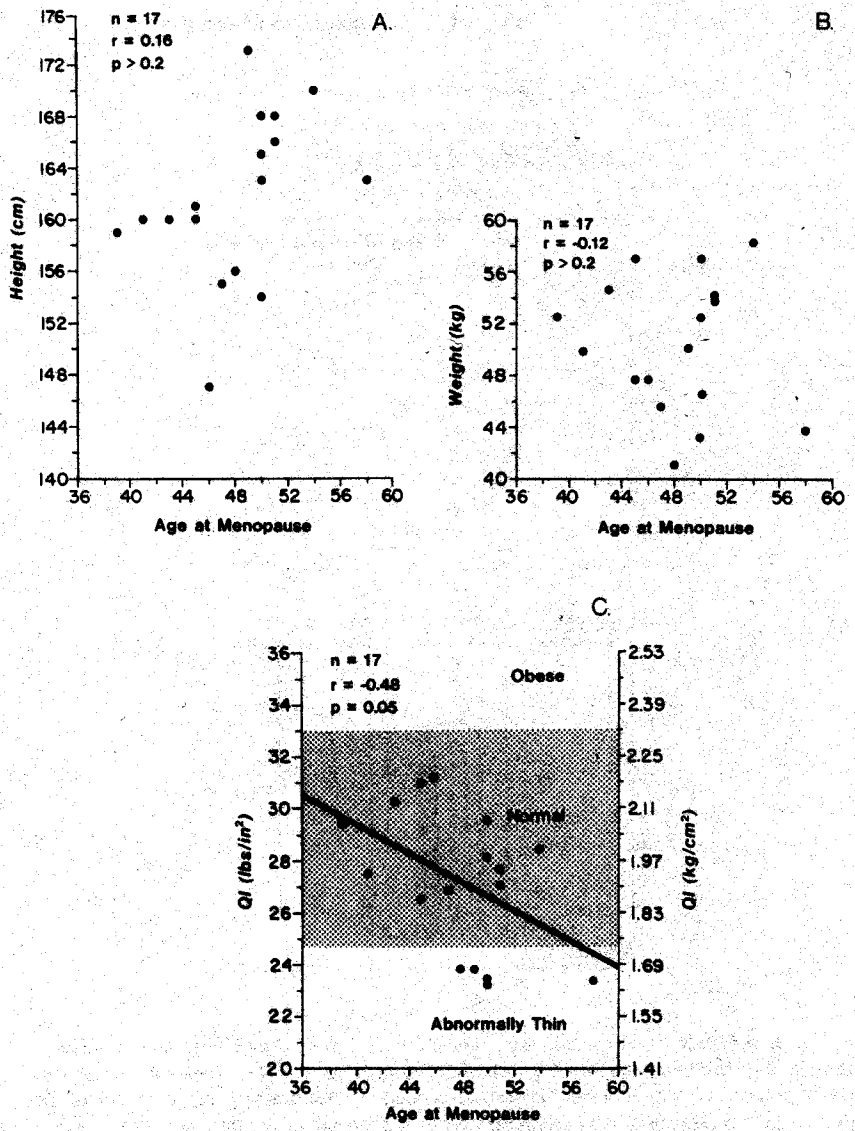

Fig. 7. Relationship of height (A), weight (B), and Quetelet index (weight/height^2) (QI, C) to age at menopause. The QI is a widely used index of fatness and thinness. Note that only QI and age at menopause had a statistically significant relationship, indicating that the thinner a woman is the later she will have menopause. Note also that the majority of the subjects were normally or abnormally thin, normal and abnormal being here determined by the Metropolitan Life tables of desirable weights for women, according to height and frame. The question arises as to why this data contradicts that of Sherman et al, 1981. The answer is that Sherman used subjects who were almost all obese or at the upper limit of normal weight. Above the menopausal age of 45, the QI's of Sherman's women were between 32 and 35 (lbs/in^2), the

reveal that an electrical pulse is coincident with the initiation of each LH pulse [Knobil, 1981]. Perhaps when they are occurring rapidly, two electrical pulses may result in only one GnRH pulse.

VII. BODY WEIGHT, BLINDNESS, MENARCHE, AND MENOPAUSE

Body weight is known to influence the onset of menarche and menopause. Obese females typically have their menarche earlier than normal-weight girls; conversely, extremely thin girls, ballerinas, for example, have their menarche later than usual [Frisch, 1980].

The effect of body weight on menopause is somewhat less distinct. An early study indicated that obese women might have an early menopause [Flint, 1976]. In three later studies, there was not a clear, statistically significant relationship between menopause and body weight [Daniell, 1978; MacMahon and Worcester, 1966; Sherman et al., 1981]. However, these studies employed obese women or women at the upper limits of normal weight, because most women gain weight after menopause. But a preliminary study on thin, postmenopausal women suggests that among thin women menopause occurs latest in the thinnest (Fig. 7).

One can explain these deviations by postulating that body weight causes a frequency shift in the arcuate nucleus oscillator. Extreme thinness causes an upward shift, whereas relative fatness results in a downward shift (see Fig. 8). This mechanism would predict that a very thin woman might have menopause later than usual and furnishes a satisfactory explanation for the other effects of thinness and obesity noted above.

Further confirmation of the frequency shift mechanism comes from the effect of rapid weight loss in an otherwise normal young postpubertal woman. As has been mentioned, the LH pulses occurring only during sleep in puberty can be attributed to beats caused by the slight frequency difference between

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majority lying at the high end of this range. In contrast, the QI's of the above subjects vary from 23 to slightly above 31 (lbs/in^2). Furthermore, most would be considered normally or abnormally thin if ranked with the Metropolitan Life Tables. Therefore, the effect of increasing QI on age at menopause would seem to be analogous to the blackening effect of light on photographic film. Proportionate increases in the amount of light result in proportionate increases in the blackening of the film, but only to a certain point. Thereafter, the film will not become blacker, no matter how much additional light it is exposed to. Likewise, a very thin woman will have a change in the age of menopause proportionate to QI, but beyond a certain point, increasing QI will have no further effect on age at menopause. At this point, other factors affecting age at menopause (e.g., smoking, parity) predominate, and the statistical relationship between age and QI disappears. This phenomenon was apparent in the above data: When the QI's and ages at menopause of obese women were combined with it, the significant negative correlation was obliterated.

the arcuate nucleus and the ultradian pacemaker. The weight loss in a young postpubertal woman causes a return to the pubertal LH secretory pattern [Kapen, 1981]; the return is expected in view of the above mechanism, because the thinness would produce an upward frequency shift in the arcuate nucleus oscillator causing slight desynchronization with the ultradian pacemaker and restoring "LH beats" during sleep.

An interesting sidelight to the effect of thinness on menarche in ballerinas should be mentioned. In dancers and other thin, athletic women, there may be two factors delaying menarche: 1) the above-mentioned frequency shift of thinness and 2) the athleticism. The stress of exercise, which causes increased catecholamines, may stimulate the pineal to produce antigonadotrophic melatonin. Indeed, exercise is associated with increased melatonin levels [Carr et al., 1981].

Since blindness reportedly causes an early menarche, one might wonder whether blindness also would affect the age at menopause. In fact, blind women with and without light perception seem to have their menopause at the same age, about 49 [Lehrer, 1982]. This apparent lack of influence of blindness on the age at menopause can be understood in terms of the mechanism just presented.

As was mentioned previously, blind adult human beings have free running circadian rhythms about 25 hr in length. The effect of this rhythm on the arcuate nucleus would be that its intrinsic frequency would have to diminish more than the normal amount for resonance to be lost; therefore, at any given time around menopause, its pulse amplitudes would be increased in a blind woman but its pulse frequency would be unaffected. Since menopause is due to a change in pulse frequency, not pulse amplitude, the age at menopause would be totally unaffected by blindness.

VIII. FSH:LH RATIO CHANGE AROUND MENOPAUSE

In regularly menstruating perimenopausal women, there is striking elevation of FSH concentrations during the early follicular phase of the cycle and persistent elevation during the remainder of the cycle compared with younger women [Sherman and Korenman, 1975; Korenman, 1982]. Estradiol levels are consistently lower in the older group, whereas LH concentrations are indistinguishable from those observed in younger women.

After menopause and the complete cessation of ovulation, average LH and FSH concentrations in blood increase and remain elevated until very old age, FSH increasing to a greater extent than LH. In a postmenopausal woman the ratio of FSH:LH is greater than 1; in an ovulating woman it is less than 1.

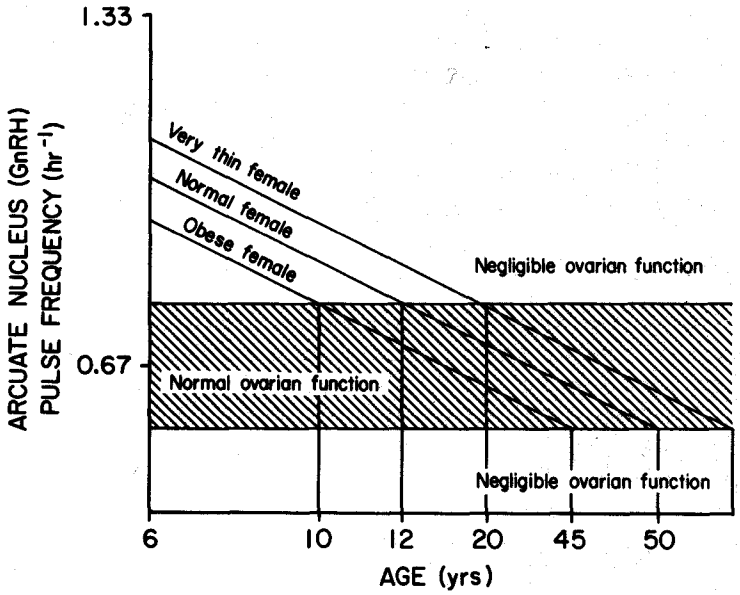

Fig. 8. Body weight, age at menarche, and menopause. A fat girl has her menarche earlier (age 10) than a normal girl (age 12). An extremely thin girl, a ballerina, for example, will have her menarche later than usual, sometimes as late as age 20. A fatter woman will have her menopause earlier (age 45) than a very thin woman (age 50). One may explain these deviations by postulating that body weight causes a frequency shift of the arcuate nucleus oscillator. This frequency shift causes the arcuate nucleus pulse frequency to fall within the frequency band of normal ovarian function (hatched region) at an earlier or later time than normal. The numbers on the abscissa of this figure were chosen arbitrarily for illustrative purposes; those on the ordinate are generated by the hypothesis presented in this article.

These changes can be compared to those in a castrated monkey, after arcuate nucleus destruction, receiving GnRH pulses intravenously from a pump [Wildt et al., 1981]. Reducing the GnRH pulse frequency from the normal one pulse per hr to one pulse per 3 hr causes a 65% rise in the serum FSH concentration, which is analogous to the rise around menopause.

However, the changes in the monkey and human gonadotropins are not exactly comparable, because with one pulse of GnRH per 3 hr mean monkey plasma LH declines by about 50%. In contrast, both FSH and LH rise at menopause.

A final word is now in order about pulse frequency and menopause. The pulsation of gonadotopins has been documented in the neonate [Plant, 1982];

in children [Jakacki et al., 1982]; and in adolescents, adults, and postmenopausal subjects [Yen et al., 1982]. Though pulse amplitude of gonadotropins is markedly increased after menopause, assay and sampling techniques have been insufficiently precise to identify pulse frequency changes with certainty. At the present time, it is impossible to say whether gonadotropin pulse frequency after menopause is increased, decreased, or unchanged. Consequently, direct confirmation of the mechanism for menopause presented in this article must await increasingly sophisticated studies of pulse frequency.

IX. SUMMARY

Under special experimental circumstances, a pineal effect on the timing of puberty can be demonstrated in rats. However, in humans the data are as yet inconclusive as to the involvement of the pineal gland and melatonin in puberty. The timing of both puberty and menopause may be due to a reduction in the gonadotropin-releasing hormone pulse frequency occurring continually throughout life.

X. REFERENCES

Boyar RM, Finkelstein JW, Roffwarg H, Kapen S, Weitzman ED, Hellman L (1972): Synchronization of augmented luteinizing hormone secretion with sleep during puberty. N Engl J Med 287:582–586.

Carr DB, Reppert SM, Bullen B, Skrinar G, Beitins I, Arnold M, Rosenblatt M, Martin JB, McArthur JW (1981): Plasma melatonin increases during exercise in women. J Clin Endocrinol Metab 53:224–225.

Cooper RL, Brandt S, Linnoila M, Walker R (1979): Induced ovulation in aged female rats by L-Dopa implant into the medial preoptic area. Neuroendocrinology 28:234–240.

Cooper RL, Walker RF (1979): Potential therapeutic consequences of age dependent changes in brain physiology. Interdisc Top Geront 15:54–76.

Corbett DA, Harrigan B, Verderame M (1978): "Massachusetts Commission for the Blind, 1977 Report of the Register." Boston: Masachusetts Commission for the Blind.

Crowley W: Personal communication. November 16, 1983.

Daniell HW (1978): Smoking, obesity, and the menopause. Lancet 2:373.

Davis, FC, Menaker M (1980): Hamster through time's window: Temporal structure of hamster locomotor rhythmicity. Am J Physiol 239:R149–155.

Ehrenkranz JRL, Tamarkin L, Comite F, Johnsonbaugh RE, Bybee DE, Loriaux DL, Cutler GB (1982): Daily rhythm of plasma melatonin in normal and precocious puberty. J Clin Endocrinol Metab 55:307–310.

Elden CA (1971): Sterility of blind women. Jpn J Fertil Steril 16:48–50.

Flint M (1976): Cross-cultural factors that affect age at menopause. In van Keep PA, Greenblat RB, Albeau-Fernet M (eds): "Consensus on Menopause Research." Lancaster, England: MTP, pp 73–83.

Freud S (1905): "Drei Abhandlungen zur Sexualtheorie." Frankfurt am Main: S. Fischer Verlag, pp 47–77.

Frisch RE (1980): Pubertal adipose tissue: Is it necessary for normal sexual maturation? Evidence from the rat and the human female. Fed Proc 39:2395–2400.

Grumbach M (1980): The neuroendocrinology of puberty. In Krieger DT, Hughes JC (eds): "Neuroendocrinology." Sunderland, Massachusetts: Sinauer Associates, pp 249–258.

Gupta D, Riedel L, Frick HJ (1983): Circulating melatonin in children: In relation to puberty, endocrine disorders, functional tests and racial origin. Neuroendocrinol Lett 5:63–78.

Hoffman AR, Crowley WF (1982): Induction of puberty in men by long term pulsatile administration of low dose gonadotropin releasing hormone. N Engl J Med 307:1237–1241.

Hoffman RA, Reiter RJ (1965): Pineal gland: Influence on the gonads of male hamsters. Science 148:1609–1611.

Hollwich F, Dieckhues B (1971): Endokrines System und Erblindung. Deutsch Med Wochenschr 96:363–368.

Jakacki RI, Kelch RP, Sauder SE, Lloyd J, Hopwood NJ, Marshall JC (1982): Pulsatile secretion of luteinizing hormone in children. J Clin Endocrinol Metab 55:453–458.

Johnson LY, Reiter RJ (1978): The pineal gland and its effect on mammalian reproduction. Prog Reprod Biol 4:116–156.

Kapen S, Sternthal E, Braverman L (1981): A pubertal 24 hour luteinizing hormone (LH) secretory pattern following weight loss in the absence of anorexia nervosa. Psychosomatic Med 43:177–182.

Knobil E (1981): Patterns of hypophysiotropic signals and gonadotropin secretion in the Rhesus monkey. Biol Reprod 24:44–49.

Korenman SG (1982): Menopausal endocrinology and management. Arch Intern Med 142:1131–1136.

Lehrer S (1981): Twenty-one hour light:dark cycle accelerates vaginal opening in the rat. Bull NY Acad Med 57:705–708.

Lehrer S (1982): Fertility of blind women. Fertil Steril 38:751–752.

Lehrer S (1983): Puberty and resonance: a hypothesis. Mt Sinai J Med 50:39–43.

Lenko HL, Lang U, Aubert ML, Paunier L, Sizonenko PC (1982): Hormonal changes in puberty: VII. Lack of variation of daytime plasma melatonin. J Clin Endocrinol Metab 54:1056–1058.

Lewy AJ, Wehr RA, Goodwin FK, Newsome DA, Markey SP (1980): Light suppresses melatonin secretion in humans. Science 20:1267–1269.

Lissoni P, Resentini M, Mauri R (1983): A study of the melatonin rhythm in normal subjects and cases of delayed puberty. J Endocrinol Invest 6[Suppl 1]:25.

MacMahon B, Worcester J (1966): "Age at Menopause." (US Health and Vital Statistics, Series 11, No. 19.) Washington, D.C.: U.S. Government Printing Office.

Magee K, Basinska J, Quarrington B, Stancer HC (1970): Blindness and menarche. Life Sci 9:7–12.

Miles LE, Raynal M, Wilson MA (1977): Blind man living in normal society has circadian rhythms of 24.9 hours. Science 198:421–423.

Peng MT, Huang HH (1972): Aging of hypothalamic-pituitary-ovarian function in the rat. Fertil Steril 23:535–542.

Plant TM (1982): Pulsatile luteinizing hormone secretion in the neonatal male Rhesus monkey (Macaca mulatta). J Endocrinol 93:71–74.

Pohl CR, Gibbs FP (1978): Circadian rhythms in blinded rats: Correlation between pineal and activity cycles. Am J Physiol 234:R110–114.

Pohl CR, Richardson DW, Hutchison JS, Germak JA, Knobil E (1983): Hypophysiotropic signal frequency and the functioning of the pituitary-ovarian system in the Rhesus monkey. Endocrinology 112:2076–2080.

Reiter RJ (1968): The pineal gland and gonadal development in male rats and hamsters. Fertil Steril 19:1009–1017.

Reiter RJ (1969): Pineal function in long term blinded male and female golden hamsters. Gen Comp Endocrinol 12:460–468.

Reiter RJ (1980): The pineal and its hormones in the control of reproduction of mammals. Endocrine Rev 1:109.

Reiter RJ, Ellison NM (1970): Delayed puberty in blinded anosmic female rats: role of the pineal gland. Biol Reprod 2:216–222.

Reiter RJ, Richardson BA, Vaughan MK, Johnson LY (1983): Pineal actions and mechanisms in reproductive physiology. Jikeikai Med J 28[Suppl 1]:35–46.

Relkin R (1967): Pineal function relation to absolute darkness and sexual maturation. Am J Physiol 213:999–1002.

Ruf KB (1983): On the significance of 5-alpha-androstane-3-alpha,17-beta-diol in the peripubertal female rat. J Steroid Biochem 19:887–890.

Sherman BM, Korenman SG (1975): Hormonal characteristics of the human menstrual cycle throughout reproductive life. J Clin Invest 55:699–706.

Sherman B, Wallace R, Bean J, Schlabaugh L (1981): Relationship of body weight to menarcheal and menopausal age: Implications for breast cancer risk. J Clin Endocrinol Metab 52:488–493.

Silman RE, Leone RM, Hooper RFL, Preece MA (1979): Melatonin, the pineal gland and human puberty. Nature 282:301–303.

Sizonenko PC, Lang U, Aubert ML (1982): Neuro-endocrinologie de la puberte. Role de la melatonine chez l'homme. Ann Endocrinol 43:453–464.

Sklar CA, Conte FA, Kaplan SL, Grumbach MM (1981): Human chorionic gonadotropin-secreting pineal tumor: Relation to pathogenesis and sex limitation of sexual precocity. J Clin Endocrinol Metab 53:656–660.

Thomas J, Pizzarello D (1967): Blindness, biologic rhythms and menarche. Obstet Gynecol 30:507–509.

Timonen S, Carpen E (1969): Multiple pregnancies and photoperiodicity. Ann Chir Gynaecol Fenn 57:135–138.

Timonen S, Franzas B, Wichmann K (1964): Photosensibility of the human pituitary. Ann Chir Gynaecol Fenn 53:165–172.

Treloar AE, Boynton R, Behn BG (1967): Variation of the human menstrual cycle through reproductive life. Int J Fertil 12:77–126.

Vaughan GM, Meyer GG, Reiter RJ (1978): Evidence for a pineal-gonad relationship in the human. Prog Reprod Biol 4:191–223.

Vaughan GM, Pelham RW, Pang SF, Loughlin LL, Wilson KM, Sandock KJ, Vaughan MK, Koslow SH, Reiter RJ (1976): Nocturnal elevation of plasma melatonin and urinary 5-hydroxyindoleacetic acid in young men: Attempts at modification by brief changes in environmental lighting and sleep and by autonomic drugs. J Clin Endocrinol Metab 42:752–764.

Veerman A, Vaz Nunes M (1980): Circadian rhythmicity participates in the photoperiodic determination of diapause in spider mites. Nature 287:140–141.

Wildt L, Häusler A, Marshall G, Hutchison JS, Plant TM, Belchetz PE, Knobil E (1981): Frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the Rhesus monkey. Endocrinology 109:376–385.

Yen SSC (1980): Neuroendocrine regulation of the menstrual cycle. In Krieger DT, Hughes JC (eds): "Neuroendocrinology." Sunderland, Massachusetts: Sinauer Associates, pp 259–274.

Yen SSC, Tsai CC, Naftolin F, Vandenberg G, Ajabor L (1972): Pulsatile patterns of gonadotropin release in subjects with and without ovarian function. J Clin Endocrinol 34:671–675.

Yochim JM, Shirer HW (1981): Evidence for a photoperiod-sensitive pacemaker for estrous cycle of the rat. Am J Physiol 241:E261–267.

Zacharias L, Wurtman R (1964): Blindness: Its relation to age of menarche. Obstet Gynecol 30:507–509.

Zucker I (1980): Light, behavior, and biologic rhythms. In Krieger DT, Hughes JC (eds): "Neuroendocrinology." Sunderland, Massachusetts: Sinauer Associates, pp 93–101.