B eing selected a Cannon lecturer by the American Physiological Society is a singular honor under any circumstances, but a particularly poignant one for me because of my origins in Cannon's old Department at the Harvard Medical School. In fact, when I began my career there as an instructor 45 years ago I was assigned a small room that was to serve as a laboratory. It was totally bare except for an ancient fume hood in one corner and an old rolltop desk in another that, I soon discovered to my delight, had belonged to Professor Cannon. It still had a button attached to it that was marked "Fellows." Needless to say, it was not connected to anything. When I arrived on the scene some years after Professor Cannon left it, his scientific legacy was still very much in evidence and, indeed, remains so to this day. The concept of homeostasis and its elegant experimental underpinnings are the very essence of integrative biology. They have underlined the beauty of the complex control systems that permit organisms to function and survive in the most hostile environments. But in contemplating the wisdom of the body, as he named one of his most famous books, Cannon failed to address another fundamental attribute of nearly all living things: they all die! It has been stated by one astute observer that the corrected death rate of humans is 100%. The physiological mechanisms that have evolved to deal with this inevitable fact of life and thus ensure the survival of the species are no less impressive than those that ensure the survival of the individual and, in many ways, more so.

From a physiological standpoint the basic instrument for the propagation of most species is remarkably simple. The union of two gametes and the fusion of their genomes initiate the creation of a new individual. This basic device that ensures societal homeostasis, as Cannon called it, differs from the more familiar kind in that it involves two individuals rather than just one.

The evolutionary history of the gametes themselves is equally uncomplicated. It begins with two cells, morphologically indistinguishable from one another, that meet and exchange genetic material. This is followed by the appearance of two cells, one larger and relatively sessile, the other smaller and more motile, and finally the advent of two highly differentiated cells, the ovum and the flagellated spermatozoon. The utility of this system is underlined by the fact that this most advanced stage of gamete development is already achieved in the Protista and that there is no further evolution in the basic design of these reproductive cells throughout the entire range of multicellular organisms.

This remarkably simple evolutionary history stands in sharp contrast to the staggering variety of systems that have evolved to deliver these gametes, to ensure that they encounter each other and go on to produce viable young. Among the vertebrates alone one need only reflect momentarily on their mating rituals, their sexually dimorphic pelages and plumages, and their myriad ways of delivering and rearing their offspring to be awed by the staggering diversity of reproductive strategies and of their regulation.

In all the vertebrates, from the lamprey eel to our own species, this vast and varied infrastructure for reproduction is sustained by the sex hormones whose production is governed by a relatively simple and surprisingly well-conserved control system that, in addition, subserves the primary function of the gonads, the production of the gametes. The components of this control system are illustrated in Fig. 1 from the classic monograph by Geoffrey Harris published in 1955 (4). While all the components of this control system were known at that time, the dynamics of their interactions were poorly understood and, in fact, are debated to this day. The production of the gonadal hormones is controlled by two peptide hormones secreted by the pituitary gland, the luteinizing (LH) and follicle-stimulating (FSH) hormones, the so-called gonadotropic hormones, and the secretion of these in turn is modulated by...
feedback interactions between the pituitary and the circulating gonadal steroids. In addition, in all vertebrates studied to date, the secretion of these gonadotropic hormones by the pituitary is totally dependent on the production of a hypothalamic neurohormone that, in the higher vertebrates, reaches the pituitary gland by way of the hypophysial portal circulation. This neurohormone turns out to be a decapeptide that has evolved with but trivial modification from cyclostomes to man. This peptide, first characterized and synthesized by Roger Guillemin, an earlier Cannon lecturer, and Andrew Schally, who both received the Nobel Prize for this labor, has been called the luteinizing hormone-releasing hormone (LHRH) or, because it can stimulate the secretion of both LH and FSH, the gonadotropic hormone-releasing hormone (GnRH).

Unknown to Harris when he wrote his monograph was the episodic nature of the interaction between the hypothalamus and the pituitary. This was demonstrated in my own laboratory nearly 30 years ago with the finding that LH, when measured in the peripheral circulation using a then newly developed radioimmunoassay, described totally unanticipated rhythmic oscillations (Fig. 2).

These “pulses” of LH occurred with a frequency of approximately one per hour and led to the coining of the adjective “circhoral,” to describe events with a mode of approximately one hour (2). Each pulse of LH appeared to be the result of a brief injection of the peptide hormone into the circulation followed by an exponential decay in its concentration. We reasoned, at the outset, that this phenomenon must be the consequence of pulsatile secretion of GnRH by the hypothalamus into the pituitary portal circulation. That this is indeed the case was demonstrated most beautifully a number of years later by Fred Karsch and his colleagues working in the ewe (Fig. 3). The pulsatile nature of GnRH secretion has been shown in all vertebrates studied in this regard, another remarkably well-preserved phenomenon. Such observations inevitably gave rise to the notion of an oscillator or signal generator in the central nervous system responsible for the rhythmic release of the neuropeptide. This signal generator has been named the GnRH pulse generator and was eventually localized, at least in the rhesus monkey, to the arcuate nucleus of the mediobasal hypothalamus as evidenced by the finding that placement of a radio frequency lesion in this area results in an abrupt fall in the production of the gonadotropic hormones (22). Large hypothalamic lesions that spare the arcuate nucleus have no significant effect.

For the longest time we had no inkling of the physiological significance of the striking pulsatile nature of this secretory system. The first insight into the profound functional importance of episodic GnRH release was provided by experiments such as the one illustrated in Fig. 4. When giving exogenous GnRH by constant infusion to verify that the pituitary or portal vessels had not been infarcted by the radio frequency lesions, an immediate increment in circulating LH was observed, but this was not sustained no matter what the dose or duration of GnRH administration. We then remembered with considerable embarrassment that we ourselves had first suggested nearly a decade earlier that, under physiological circumstances, GnRH was delivered to the pituitary in pulsatile fashion (2). When we switched from continuous infusion to the pulsatile administration of the neuropeptide at the physiological frequency of one pulse per hour, normal gonadotropin secretion was quickly reestablished. Thus the control of gonadotropin secretion by GnRH is a frequency-dependent system rather than solely a concentration-dependent one, a new notion in endocrinology at the time. I should add, in passing, that pulsatile administration of GnRH at frequencies that deviate from the physiological by ± 30 min or so also fails to reestablish normal gonadotropin secretion.

We could thus add the GnRH pulse generator to Harris’ basic scheme. It engenders the LH and FSH pulses in the peripheral circulation, and these, in turn, control gonadal function. In the
case of the female, the gender that we shall consider for the remainder of this talk, this stimulus subserves the maturation of the graafian follicle and the production of estradiol.

The central event of the cycle, its business end if you will, is the rupture of the mature graafian follicle and ovulation. To my knowledge, in all vertebrates studied in this regard, ovulation is initiated by a bolus of LH secreted by the pituitary gland, the so-called preovulatory gonadotropin surge. This surge is superimposed upon, or temporarily replaces, the pulsatile pattern of LH secretion.

The initiation of this signal is easily explained in a group of animals known as reflex or induced ovulators, in which the sensory inputs associated with the act of copulation impinge on the hypothalamus and there cause the release of a bolus of GnRH that, in turn, occasions the secretion of the preovulatory LH surge. The rabbit is a case in point. In fact, it was the study of the induction of ovulation in this species that led Harris to formalize the concept of the neurohumoral control of pituitary function. This is a devilishly efficient system for ensuring fertilization of the ovum and the procreation of the species. But what about the rest of us, the so-called spontaneous ovulators, where the timing of ovulation is unrelated to sexual activity?

After much controversy, it is now generally accepted that the zeitgeber for this phenomenon is not the hypothalamus but the ovary itself. I am compelled to tell you how this conclusion was arrived at.

Figure 5 shows the time courses of the gonadal and gonadotropic hormones in the rhesus monkey menstrual cycle (7). This is essentially identical to that in our own species. In the human and the macaque, ovulation is initiated, as in all others, by the preovulatory gonadotropin surge, which occurs once every 28 days on the average. On the basis of experiments in rodents it was believed by many, and is still held by some, that
the preovulatory LH surge in women and in monkeys is initiated by a rise in circulating progesterone. The very first descriptions of the time course of progesterone in the human menstrual cycle made this notion difficult to accept because progesterone is largely undetectable until after the surge has already been initiated (15). But if, on the other hand, one examines the time course of estradiol during the follicular phase of the cycle, wherein levels of the steroid rise gradually at first and then more exuberantly in response to the growth and maturation of the Graafian follicle, this steroid may be regarded as a plausible candidate for an initiator of the LH surge. This hypothesis seemed easy to test simply by injecting estradiol early in the follicular phase of the cycle to see whether this maneuver would elicit a premature LH surge. But the results of our early experiments were disappointing indeed because even when huge doses of the steroid were injected intravenously, causing a brief spike in circulating estradiol, only the inhibition of LH secretion, the classic negative feedback effect of the hormone, was observed. When, however, the normal time course of plasma estradiol during the follicular phase of the cycle was replicated by the repetitive administration of small doses of the steroid, unambiguous LH surges were invariably induced both in intact and ovariectomized monkeys, providing clear evidence that estradiol alone can account for the initiation of the preovulatory LH surge, the so-called positive feedback action of the steroid.

Further studies demonstrated that this action of estradiol has both threshold- and time-dependent attributes. Plasma estradiol concentrations had to exceed ~150 pg/ml for 36 h or longer for the positive feedback effect of the steroid to be demonstrable (6). Shorter exposures only inhibit gonadotropin secretion, regardless of the dose administered. This positive feedback action of estradiol can also be elicited by a single subcutaneous injection of estradiol benzoate, an ester of the steroid that retards absorption, or by the subcutaneous implantation of a Silastic capsule containing crystalline estradiol, both methods resulting in elevations in plasma estradiol levels for more than 36 h, assuring that threshold concentrations are exceeded for the requisite length of time. These findings, in the aggregate, led to the conclusion that it is indeed the preovulatory rise in estradiol that acts on the hypothalamic-pituitary apparatus to initiate the LH surge.

But what, then, is the site of action of this steroid? Does it act at the level of the hypothalamus to release a bolus of GnRH that initiates the surge? A most reasonable supposition in the light of a large and compelling literature in rodents. Or does it act directly at the level of the pituitary, there causing the sudden increase in the secretion of LH? Or both? To address this question we devised what we like to refer to as the "hypophysiotropic clamp" preparation. This consisted of monkeys with lesions in the mediobasal hypothalamus that abolished endogenous GnRH secretion and, thereby, the production of the gonadotropic hormones. Normal gonadotropic hormone secretion was then reestablished and maintained by the pulsatile administration of exogenous GnRH, a classical ablation-replace-
This was accomplished by the use of reservoirs containing GnRH solutions connected to the animals via chronic indwelling atrial catheters by way of peristaltic pumps that were programmed to deliver 1 µg GnRH/min for 6 min once every hour. These devices were, in effect, hypothalamic prostheses whose performance could be rigidly controlled or "clamped." We reasoned that if estradiol exerted its positive feedback action at the level of the hypothalamus, it would have no effect in this preparation because the relevant portion of the nervous system had been ablated. Conversely, if estradiol effected its positive feedback action at the level of the pituitary gland, an LH surge should be initiated. A representative experiment using this preparation is shown in Figure 6. Ovariectomized monkeys were studied initially because their higher gonadotropin levels facilitate assessment of the lesion's efficacy. Following postoperative control periods to ensure that regeneration of hypothalamic function had not occurred, gonadotropin secretion was reestablished using the standard regimen of hourly pulses of GnRH as just described. When circulating levels of gonadotropins reached control levels, Silastic capsules containing estradiol were inserted subcutaneously, raising circulating levels of this steroid from 0 to far above threshold. This step increase in estradiol concentration caused a prompt fall in plasma LH and FSH levels (the negative feedback effect of the steroid), but this inhibition of gonadotropin secretion was abruptly reversed and a surge in both gonadotropins was initiated despite an unchanging GnRH and steroidal environment. These findings lead to the inescapable conclusion that both the negative and positive feedback actions of estradiol are at the level of the pituitary gland and not at the hypothalamus (14). GnRH, while essential, plays but a permissive role in this response. This is in striking contrast to all other nonprimate species studied in this context, wherein an increment in GnRH is causal in the initiation of the preovulatory gonadotropin surge. How estradiol acts on the gonadotropin-producing cells of the pituitary gland to both inhibit and stimulate gonadotropic hormone secretion (the biphasic action of the steroid) remains a mystery and, in my view, a major challenge to cell biologists.

The foregoing findings, most controversial at the time, led to formulation of the hypothesis that the timing of ovulation in the menstrual cycle can be accounted for entirely by the rising tide of estrogens in the circulation consequent to the

---

*FIGURE 4.* Time courses of serum LH, follicle-stimulating hormone (FSH), and prolactin in an ovariectomized monkey before and after bilateral placement of radio frequency lesions in the arcuate region of the hypothalamus. Reconstruction of the lesions from serial coronal sections of the brain is superimposed in black on a diagrammatic parasagittal section of the hypothalamus. These lesions caused a cessation of gonadotropin secretion without altering prolactin secretion, and estradiol benzoate treatment (EB) was unable to elicit an LH surge. An infusion of GnRH, also known as luteinizing hormone-releasing hormone (LHRH; open bar) resulted in a prompt discharge of LH and FSH, but this release was not sustained. OCH, optic chiasm; LT, lamina terminalis; VMN, ventromedial nucleus; AC, anterior commissure; SC, suprachiasmatic nucleus; MM, mammillary body. Redrawn from Ref. 22.

*FIGURE 5.* Time courses of LH, FSH, estradiol (E2), and progesterone (Prog) in plasma samples taken daily throughout the menstrual cycle of rhesus monkeys. The data are normalized to the peak of the LH surge (day 0), and ovulation occurs 20–44 h later. Redrawn from Ref. 7.

"...both the negative and positive feedback actions of estradiol are at the level of the pituitary gland...."
maturation of the graafian follicle, acting directly at the pituitary level under the permissive influence of GnRH. This hypothesis predicts that normal 28-day ovulatory menstrual cycles would be produced in monkeys with hypothalamic lesions by the invariant pulsatile administration of exogenous GnRH at the physiological frequency of one pulse per hour. A representative experiment performed to test this hypothesis is shown in Fig. 7. Hypothalamic lesions were followed by cessation of gonadotropic hormone secretion. Pulsatile GnRH administration resulted in the restitution of pituitary gonadotropin production and consequent follicular development, as evidenced by rising plasma levels of estradiol. When these exceeded the threshold concentration for more than 36 h, an LH surge was initiated. This was followed by ovulation and normal luteal function as shown by the normal time course of progesterone in the circulation. Cessation of pulsatile GnRH administration led to reversion to the control state. The hypothesis, totally anti-intuitive at first, was thus confirmed (9). Similar findings have subsequently been obtained in women with hypothalamic amenorrhea (Kallmann syndrome), a genetic defect wherein GnRH cells are absent from the mediobasal hypothalamus. These women, who functionally resemble monkeys with hypothalamic lesions, ovulated and became pregnant when given invariant pulsatile GnRH infusions (3, 11).

It must be reemphasized that neither an increment of GnRH delivery nor a change in its frequency is needed to induce the preovulatory LH surge, but this neuropeptide is essential for the proper hypophysial response to estradiol.

While normal 28-day ovulatory menstrual cycles could be subserved in females bereft of hypothalamic GnRH pulse generator activity by replacement with an unvarying pulsatile GnRH replacement regimen, questions remained regarding the control of ovulation during the normal menstrual cycle. For example, it was believed by some that the GnRH pulse generator, as evidenced by LH pulses in the peripheral circulation, accelerated prior to the preovulatory gonadotropin surge and that this alleged phenomenon was somehow responsible for its initiation. For this and other reasons, it became more important than before to study the operation of the GnRH pulse generator in normal animals. One approach is to monitor the frequency of LH pulses in plasma. This would involve the sampling of blood at 10- to 20-min intervals around the clock for prolonged periods, a most difficult
technical feat. Alternatively, GnRH pulses can be measured in hypothalamic extracellular fluid sampled by implanting “push-pull” cannulae in the mediobasal hypothalamus or in the third ventricle, an approach utilized by several groups (10, 24, 25).

We decided to approach the study of the GnRH pulse generator more directly using electrophysiological techniques, reasoning that if neurosecretory events are initiated by action potentials and if all GnRH cells in the hypothalamus must fire synchronously to produce boluses of GnRH, we should be able to detect changes in hypothalamic electrical activity associated with the initiation of each LH pulse. To this end we stereotaxically implanted bilateral arrays of recording electrodes in the area of the arcuate nucleus using bony landmarks obtained roentgenographically (17).

After thorough acclimatization of the monkeys to restraint in primate chairs, multiunit electrical activity (MUA) was recorded while blood sam-

FIGURE 7. Induction of ovulatory menstrual cycles in a monkey with hypothalamic lesions by an unvarying hourly GnRH infusion (open bar). Note the reappearance of normal follicular phase gonadotropin levels after the initiation of GnRH replacement (day 82), followed by follicular development as shown by the rise in circulating estradiol levels (middle panel) culminating in ovulation and a normal luteal phase illustrated by the rise and fall of serum progesterone levels (bottom panel). A second cycle was nearly complete when GnRH replacement was terminated (day 155) Estradiol benzoate (EB) elicited an LH surge (day 115) before the lesions. Neither EB treatment after the lesion (day 7 or day 190) nor opening the negative feedback loop by ovariec-
tomy (Ovex) after the termination of GnRH treatment elicited a rise in serum gonadotropin levels, attesting to the effectiveness of the hypothalamic lesions in abolishing endogenous GnRH production. The lines below the data points indicate that the values lie below the sensitivity of the assay methods. Reproduced with permission from Ref. 9. Copyright 1980 American Association for the Advancement of Science.
samples were taken at 10-min intervals through the distal end of a cardiac catheter by way of an access port placed under the skin for the measurement of LH. We first chose ovariectomized animals for this exercise, simply because of their large LH pulses, our marker for anticipated changes in electrical activity.

After many false starts and a multitude of technical modifications we were able to obtain the recordings illustrated in Fig. 8, which show that each pulse of LH in the circulation is preceded by an abrupt and striking rise in MUA. The correspondence between MUA bursts and LH pulses was unambiguous and absolute, leading to the conclusion that these volleys of electrical activity were indeed a measure of GnRH pulse generator activity. Because of the size of the electrodes (50 µm), we cannot be sure whether we were recording from GnRH cells, GnRH fibers, or other neuronal elements associated with the GnRH pulse generator (23).

A host of experiments utilizing this preparation has shown that the functioning of the pulse generator can be perturbed by many pharmacological and other interventions, but these, unfortunately, have provided little insight into the physiology of the system. In summary, suffice it to say that pulse generator frequency is inhibited by stress, anesthesia, dopaminergic and α (but not β)-adrenergic blocking agents, morphine, and, more significantly from a physiological standpoint, progesterone, testosterone, and estradiol. The actions of these steroids can be blocked by naloxone, suggesting that these are mediated by endogenous opioid peptides (see, for review, Ref. 5).

Up to this time our electrophysiological investigations of the GnRH pulse generator were conducted in ovariectomized animals restrained in primate chairs, because for reasons that were not initially apparent, we could never see LH pulses in restrained intact animals. We belatedly discovered that although they had normally functioning GnRH pulse generators as judged by the fact that they had normal, regular menstrual cycles, the generator simply stopped on the day of the experiment when the animals were removed from their cages and placed in the restraining device. While the pulse generator is remarkably robust in the absence of the ovaries (as demonstrated in the experiments in ovariectomized monkeys), it appears to be exquisitely sensitive to the perturbations of handling and chair restraint in the presence of the ovaries, an effect of estrogens the mechanism of which remains unexplained. In any case, we decided to circumvent the impediments of chair restraint by substituting telemetry for the hard-wired recording system just described. A small radio transmitter was connected to the distal ends of the recording electrodes and the hypothalamic signals relayed by receiving antennas placed above the cage to FM receivers, thus permitting the telemetry of pulse generator activity throughout the menstrual cycle in freely behaving animals. On occasion, they were fitted with blood sampling devices to verify the correspondence between the electrical signals and demonstration of concomitant LH pulses (19).
Figure 9 shows a composite of 11 menstrual cycles studied in this manner. Note that GnRH pulse generator frequency increases during the first few days of the follicular phase of the cycle and then achieves a plateau of approximately one pulse per hour. It is slower at night than during the day, a phenomenon attributable to an intrinsic diurnal rhythm but on which an effect of light, independent of the time of day, is superimposed (18). Unexpectedly, just after the initiation of the preovulatory LH surge, we saw an abrupt decline and a virtual arrest of the pulse generator lasting for a day or two. It turned out that the same estrogenic stimulus that triggers the surge also inhibits the hypothalamic pulse generator, but only after the product of the mature Graafian follicle has done its job and the LH surge has been initiated. This phenomenon has also been observed in the rat and the goat (16) but does not seem to obtain in women (1). Thereafter, pulse generator activity accelerates, but only to the low frequency characteristic of the luteal phase of the cycle, attributable to the inhibitory effect of progesterone. It should be emphasized at this juncture that the physiological significance of these major shifts of GnRH pulse generator frequency is obscure because, as has been shown in monkeys and in women, perfectly normal ovulatory cycles can be sustained by exogenous GnRH pulses of unchanging frequency and amplitude.

It is common knowledge that in women, ovarian function is inhibited during lactation, a phenomenon replicated in the rhesus monkey wherein it is particularly striking in intensity and duration. To determine the role of the GnRH pulse generator in this physiological circumstance, normal cycling monkeys were instrumented as before and, after a suitable control period, were given newborn infants recently delivered by other animals. If these foster mothers ever had young of their own, they accepted and adopted these infants with alacrity. As seen

---

**FIGURE 9.** Frequency of GnRH pulse generator activity (MUA volleys/h) monitored by radiotelemetry during the menstrual cycle of rhesus monkeys in relation to the time courses of serum LH, estradiol (E2), and progesterone (P4). The data are normalized to the day of the LH peak (day 0). The recording rooms were supplied with artificial illumination on a 12L(day):12D(night) schedule. Reproduced with permission from Ref. 19. Copyright The Endocrine Society.
in Fig. 10, suckling promptly initiated prolactin secretion and full lactation and induced an anovulatory period lasting more than 10 months in this case. GnRH pulse generator activity spontaneously recovered from its long-term inhibition when the baby was about 350 days old, a time when it was still suckling intermittently but had long since begun to eat solid food. Note that prolactin levels remain elevated as long as the young suckles. The relative roles of elevated serum prolactin and the direct neural inputs associated with suckling in the inhibition of the GnRH pulse generator activity and consequent cessation of ovarian activity remain to be determined, although it has been established that this phenomenon can occur when prolactin secretion is blocked pharmacologically (20). It should be mentioned in passing that GnRH pulse generator activity is totally inhibited during gestation.

What exactly is the GnRH pulse generator? What is its neuronal basis? Compelling evidence has been adduced that GnRH cells themselves, studied in vitro, have intrinsic rhythmic activity (12). If this is indeed so, how are the activities of the GnRH cells, relatively low in number and scattered throughout the area of the mediobasal hypothalamus, synchronized so that they all fire at the same time? Is there a zeitgeber of some sort that accomplishes this function? What determines the frequency of the GnRH pulse generator, a mode of approximately one hour, rather rare in neuronal systems except for REM sleep and the basic rest-activity cycle (BRAC) as well as the rhythm of the enteric nervous system. How is this frequency modulated by inputs from higher centers, by the steroid hormones and a variety of neurotransmitters? Major questions without compelling answers.

Lastly, a cardinal problem in human physiology remains to be successfully addressed: the advent of puberty. In our own species and in the rhesus monkey, the GnRH pulse generator, surprisingly, is fully operational at birth (see, for review, Ref. 21). But several weeks later its frequency gradually declines, and the pulse generator becomes essentially dormant for the long duration of infancy and childhood. Then, after a decade (in the human) of virtual inactivity, the GnRH pulse generator emerges from its somnolence, gradually achieves a frequency compatible with the activation of the pituitary-gonadal axis, and puberty is initiated. What causes the pulse generator to turn off in early infancy, and what causes it to reawaken to initiate the pubertal process, remains a mystery.

The GnRH pulse generator, the small hourly clock in the hypothalamus, while absolutely limiting in the procreation of all higher vertebrates, not a trivial function, remains an enigma. I trust that new generations of physiologists will rise to

---

**FIGURE 10.** GnRH pulse generator activity and plasma levels of prolactin (PRL), LH, estradiol (E₂) and progesterone (P₄) in a normally cycling animal before and after adopting and nursing an infant (open horizontal bar). At the time of adoption the infant was 44 days old. Note the immediate and sustained increase in PRL in response to suckling. After 10 mo, but before weaning, GnRH pulse generator activity was reinitiated. Normal cycles resumed thereafter. Reproduced from Ref. 20.
the challenge and unravel its secrets thus adding a new and resplendent chapter to the wisdom of the body.

The studies from the author’s laboratory were generously supported by grants from the National Institute of Child Health and Human Development (National Institutes of Health), the Ford Foundation, the Clayton Foundation, and the Ellwood Foundation.

References


