scouring is less pronounced because of the lack of fracturing; (iii) the narrowness of the river allows more of the debris to be swept away; and (iv) the limestone, although resistant, appears to shed less large-size debris.

With the evidence of a consistent structural influence, we offer this generalized model for the rapid-pool-tributary sequences along the Colorado. Large faults determine zones of bedrock weakness within the Grand Canyon. Structures that run perpendicular to the river provide an advantage for side canyon drainage. The side canyon tributaries, flowing within the brecciated zones, deliver material to the main river that is too large to be carried downstream. This material forms a channel constriction, accelerated flow, and a rapid. Part of the accelerated flow at the foot of the rapids is directed downward against the bed. These high velocities, coupled with the zone of brecciation associated with the faulted bedrock, lead to deep scour below the rapids, and thus the deep pools. The hydraulic processes (autogenic) that produce regularly spaced riffles (*5*) on most streams, therefore, may dominate a few sections of the Colorado River in the Grand Canyon, but along most of its course these processes appear to be superimposed on, or modified by, local external (exogenic) controls.

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Hypophysial Responses to Continuous and Intermittent Delivery of Hypothalamic Gonadotropin-Releasing Hormone

Abstract. *In rhesus monkeys with hypothalamic lesions that abolish gonadotropic hormone release by the pituitary gland, the constant infusion of exogenous gonadotropin-releasing hormone (GnRH) fails to restore sustained gonadotropin secretion. In marked contrast, intermittent administration of the synthetic decapeptide once per hour, the physiological frequency of gonadotropin release in the monkey, reestablishes pituitary gonadotropin secretion. This phenomenon is attributable to the pattern of GnRH delivery rather than to the amounts of this hormone to which the cells of the pituitary are exposed. Moreover, the initiation of continuous GnRH administration in animals with lesions and in which gonadotropin secretion is reestablished by intermittent GnRH replacement can result in a "desensitization" or "down regulation" of the processes responsible for gonadotropin release.*

Lesions induced by radio-frequency current in the medial basal hypothalamus of rhesus monkeys (*1*) abolish the secretion of the gonadotropic hormones [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] by the pituitary gland, presumably by interfering with the release of the hypothalamic gonadotropin-releasing hormone, GnRH. Attempts to restore gonadotropin secretion in such animals by the continuous infusion of synthetic GnRH succeeded only in eliciting an evanescent release of LH and FSH despite the continued administration of the decapeptide (*1*). When, on the other hand, GnRH was administered once per hour (*2*), a rate equivalent to the physiological frequency of episodic LH release in ovariectomized monkeys (*3*), sustained increases in plasma LH and FSH concentrations were achieved for the duration of the replacement regimen (up to 7 weeks). The study described here was designed to determine whether the refractoriness of the pituitary to the continuous infusion of GnRH is attributable to the pattern of hypophysiotropic hormone stimulation per se or to the quantity of the decapeptide delivered to the pituitary.

Cardiac catheters were implanted in seven ovariectomized rhesus monkeys (4.2 to 6.8 kg of body weight) in which gonadotropin secretion had been abolished or severely curtailed by placement of radio-frequency lesions in the hypothalamus (*1*). By means of an infusion-withdrawal device that permits continuous access to the venous circulation without the animal being restrained, GnRH (*4*) was infused continuously by way of the cardiac catheter at rates of 0.001, 0.01, 0.1, and 1.0 μg per minute as described (*2*). Each infusion rate was maintained for 10 days (*5*). Blood samples were taken daily by way of the catheter, or by femoral venipuncture after the animal was sedated (30 to 40 mg of sodium thiamylal per animal, intravenously), and plasma concentrations of LH and FSH were determined by use of established radioimmunoassays (*6*). The pituitary response to GnRH administered at the rate of 1 μg per minute for 6 minutes once per hour was determined in similar fashion.

The mean circulating LH and FSH concentrations during the last 5 days of each continuous GnRH infusion, which reflected the steady-state response of the pituitary to this mode of hypophysiotropic stimulation (*7*), are shown in Fig. 1A. None of the continuous infusions of releasing hormone produced a sustained increment in plasma LH and FSH concentrations. In sharp contrast, however, long-term restoration of gonadotropin secretion was achieved in the same animals by the intermittent administration of GnRH (Fig. 1B). These observations lead to the conclusion that the failure of continuous GnRH infusion, regardless of infusion rate, to initiate sustained gonadotropin secretion in ovariectomized monkeys bearing hypothalamic lesions is the consequence of the pattern of GnRH administration rather than of the total mass of the decapeptide delivered to the gonadotrophs.

The effects on gonadotropin secretion of a shift in GnRH administration from the intermittent to the continuous mode, without a change in the infusion rate, were investigated in four similarly prepared monkeys in which gonadotropin secretion had been reestablished by pulsatile hypophysiotropic stimulation. The institution of continuous GnRH administration was followed by a brief increase in plasma LH and FSH lasting approximately 5 hours. Thereafter, however, circulating gonadotropin declined, reaching a nadir within 7 to 10 days where they remained for the duration of the continuous infusion period. This inhibition was reversed when pulsatile GnRH administration was reinstituted (Fig. 2).

These influences of pattern of hypophysiotropic stimulation may be related to the phenomenon of "desensitization" or "down regulation" (*8*), whereby pro-

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longed exposure to a high circulating concentration of hormone or drug results in a decrease in the response of the target tissue. Continuous infusions of GnRH, albeit of relatively short duration, have also been reported to result in the development of pituitary refractoriness in rats and sheep (*9*). The phenomenon of "down regulation," which has been described for insulin, LH, and catecholamines, may result, in part, from a reduction in available receptors for the agonist (*10*). A decline in the number of growth hormone receptors on lymphocytes, and of thyrotropin-releasing factor receptors on a clonal strain of pituitary cells has also been reported after long-term exposure to the homologous hormone (*11*). In relating the association between receptor loss and "down regulation" to the present findings, it is tempting to speculate that an intermittent supply of GnRH permits the regeneration of its receptors, whereas the continuous mode of hypophysiotropic stimulation does not. Whatever the underlying cellular mechanism responsible for our findings may be, it appears that the intermittent mode of GnRH stimulation is optimal in eliciting gonadotropin secretion, thereby underlining the physiologic significance of the pulsatile nature of endogenous GnRH release by the hypothalamus (*3*, *12*).

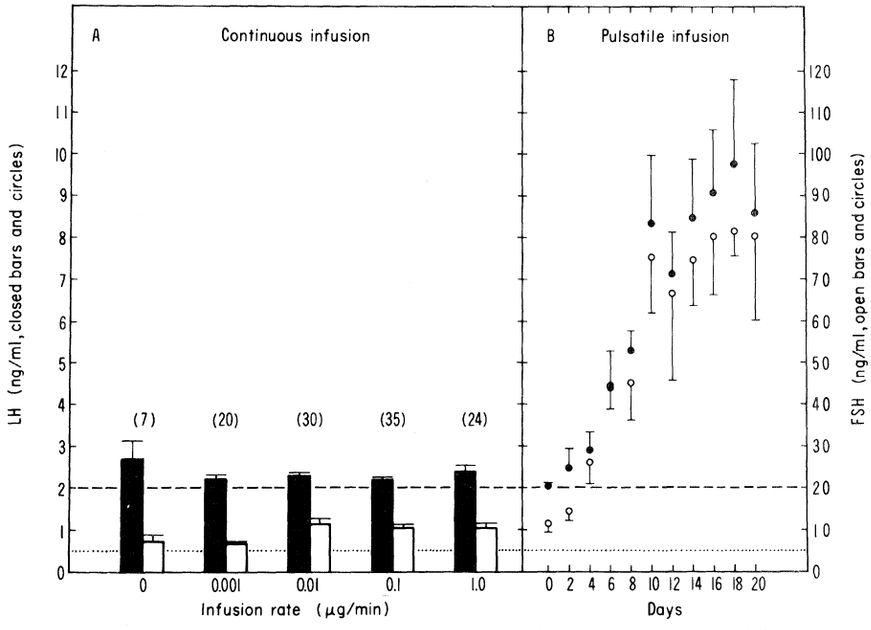

Fig. 1. (A) Failure of four continuous intravenous GnRH infusion rates to reestablish gonadotropin secretion in ovariectomized rhesus monkeys bearing hypothalamic lesions. Each bar represents the mean ± standard error (S.E.) of the number of observations in parentheses obtained during the last 5 days of the infusion period. Plasma gonadotropin concentrations during the control period were obtained just before the initiation of the GnRH infusions. (B) Effect of an intermittent GnRH infusion (1 μg/min for 6 minutes once per hour) on gonadotropin secretion in the same animals shown in (A). Each point is the mean ± S.E. of three to five observations. The horizontal dots and dashes show the sensitivity limits of the FSH and LH assays, respectively.

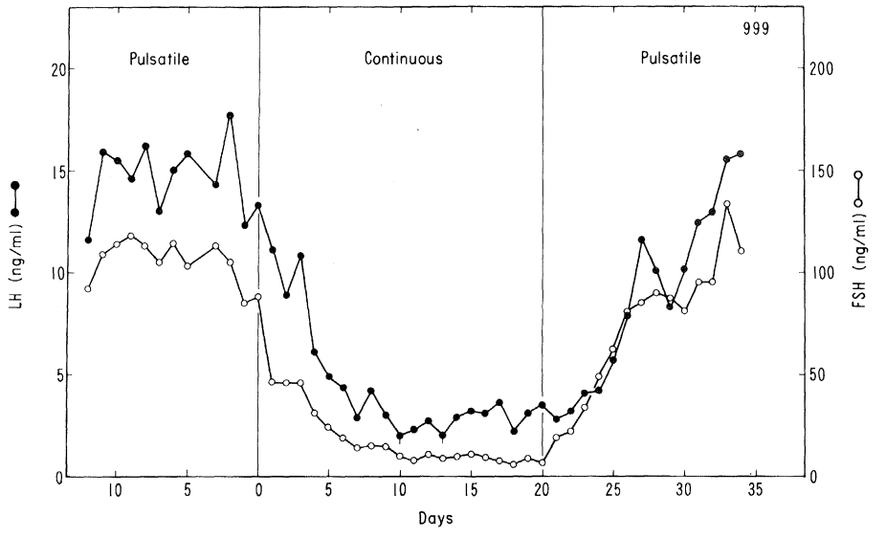

Fig. 2. Suppression of plasma LH and FSH concentrations after initiation, on day 0, of a continuous GnRH infusion (1 μg/min) in an ovariectomized rhesus monkey with a radio-frequency lesion in the hypothalamus; gonadotropin secretion had been reestablished by the intermittent (pulsatile) administration of the decapeptide (1 μg/min for 6 minutes once per hour). The inhibition of gonadotropin secretion was reversed after reinstitution of the intermittent mode of GnRH stimulation on day 20. The vertical lines beneath the LH data points on days 10 and 13 of the continuous infusion regimen indicate values below the sensitivity of the radioimmunoassay.

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4. Stock solutions of synthetic GnRH, provided by R. Guillemin (LRF, 14-200-500 and 14-136-06), Abbott Laboratories (lot-34-414AL), and the National Institutes of Health (lot 26-306AL), were prepared in 0.01*M* acetic acid in 0.9 percent NaCl and stored in small portions at −85°C. Prior to use, portions were thawed and diluted with sterile saline for infusion.
5. The GnRH was infused in both ascending (four animals) and descending (three animals) rate sequences with the same results.
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7. The transient discharge of gonadotropin described previously during the initiation of continuous GnRH administration (*1*) was also observed in this study at the highest GnRH infusion rate (1 μg/min). This sudden release of gonadotropin, which resulted in a marked increase in circulating LH and FSH concentrations 7 to 10 hours after initiation of continuous infusion followed by a decline to control levels within 2 days was only observed, however, in the three animals which received the highest GnRH infusion rate first.
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Slow Axonal Transport of Neurofilament Proteins: Impairment by β,β′-Iminodipropionitrile Administration

Abstract. *β,β′-Iminodipropionitrile (IDPN) administration prevented normal slow axonal transport of [^{35}S]methionine- or [^{3}H]leucine-labeled proteins in rat sciatic motor axons. Ultrastructural and electrophoretic studies showed that the neurofilament triplet proteins in particular were retained within the initial 5 millimeters of the axons, resulting in neurofilament-filled axonal swellings. Fast anterograde and retrograde axonal transport were not affected. The IDPN thus selectively impaired slow axonal transport. The neurofibrillary pathology in this model is the result of the defective slow transport of neurofilaments.*

The axon utilizes special systems of cytoplasmic motility to convey materials along its length. These axonal transport systems are generally distinguished, on the basis of direction and rate of movement, into fast, slow, and intermediate anterograde transport (conveying materials away from the cell body) and retrograde transport (carrying materials toward the cell body) (*1*). Neither the mechanisms of transport nor the relationships between these systems are fully defined. A unitary mechanism for all types of transport has been proposed in which the differences in rate are related to the proportion of time that various transported materials are associated with the transport mechanism (*2*). Alternatively, a mechanism for slow transport distinct from that for bidirectional rapid transport has been suggested (*3*).

Identification of selective effects of pharmacologic agents on the various transport systems provides one approach to further studies of the mechanisms and the interrelationships of the axonal transport systems. In this study, we have examined the effects on axonal transport of β,β′-iminodipropionitrile (IDPN). Previous studies (*4*, *5*) have shown that IDPN administration produces large neurofilament-filled swellings in the most proximal portion of the axon. Since neurofilaments are known to be carried by slow transport (*1*, *3*), this pathology suggested that IDPN might have an effect on slow transport. Our results show that IDPN selectively impairs slow axonal transport, without direct effects on fast or retrograde transport. This model is of special interest, since it represents the first disorder in which the pathogenesis of neurofibrillary pathology can be reconstructed.

Slow axonal transport was studied by injecting [^{3}H]leucine or [^{35}S]methionine into the lumbar ventral horns of Sprague-Dawley or Wistar rats (*6*). The animals were returned to their cages, and 1 to 8 weeks later they were killed. The sciatic nerves were rapidly removed and divided into 5-mm segments. These nerve segments were each homogenized manually in a mixture of sodium dodecyl sulfate, urea, and β-mercaptoethanol (*3*) and heated to 100°C for 4 minutes. After centrifugation, only a minute residuum remained undissolved, and essentially all the radioactivity in the segments was solubilized (*3*). To construct curves of the distribution of radioactivity along the nerve, an aliquot of each sample was counted by liquid scintillation techniques, and counts per minute for each segment were plotted against the position of the segment along the nerve (*3*, *6*).

In addition, to determine the pattern of migration of individual slowly transported proteins, portions of the samples were subjected to electrophoresis on polyacrylamide slab gels (*7*); the gels were then impregnated with 2,5-phenyloxazole and dried, and fluorograms were prepared by exposure of Kodak type RP x-ray film to the gels for 2 weeks to 4 months (*7*). [The x-ray film was preexposed to a measured light flash (*8*).] The resulting fluorograms revealed the relative amounts of individual labeled proteins in each segment of nerve.

The IDPN (Eastman Kodak, Rochester, N.Y.) was administered in one of two ways: by intraperitoneal injection of 1 or 2 g/kg, or by sustained exposure to 0.05 percent IDPN in the drinking water only (*9*). Because of the different means of administration, transport studies were performed on animals ranging from 3 to 12 months of age. Age-matched controls, purchased at the same time as experimental animals, were used in all studies.

In 14 normal animals the curves of slow transport were similar to those previously reported (*1*, *3*), with the major slow component peak moving down the nerve at 1.5 to 2 mm/day (in 200-g animals) (Fig. 1a). The fluorograms from these control animals (Fig. 2a) showed the three major groups of labeled proteins described by Hoffman and Lasek (*3*): actin (molecular weight, 46,000); proteins presumptively identified as tubulin (molecular weights, 53,000 and 57,000); and the neurofilament triplet proteins with estimated molecular weights of 68,000, 145,000, and 200,000 (*3*, *10*). In each of 11 normal rats, the rate of actin and tubulin migration ranged from 0.5 to 5 mm/day, with the density of label greatest in segments corresponding to rates of 1.0 to 3.5 mm/day (Fig. 2a). The neurofilament triplet proteins moved together at a more restricted range of rates of 1 to 2.5 mm/day, coinciding with the major slow component peak (Fig. 2a).

Similar studies were performed with rats injected with IDPN. In these studies IDPN was given either 1 to 2 days before or 1 to 2 days after microinjection of the labeled precursor into the spinal cord. Groups of animals were then killed 7, 14, or 21 days after labeling. At all times after labeling, the major slow transport peak failed to migrate beyond the initial 5 to 10 mm of the ventral roots (Fig. 1b). Gel fluorography (21 days after labeling) showed that movement of all the major slow component proteins was abnormal, with the neurofilament triplet proteins being the most strikingly affected (Fig. 2b). Most of the labeled neurofilament triplet proteins were retained in the initial 5 to 10 mm of the roots; only a small proportion were transported beyond this level. Following injection of IDPN, tubu-

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