core protein are visible in the gel pattern of the isolate, because of the method of lysate preparation used, during which most of the core protein is lost by centrifugation. Under these conditions the E_3 structural protein is not sufficiently labeled to appear in the gel.

Two serum specimens were obtained from the patient, the first taken on 13 June, the second on 20 June, the day of death. They were tested in a micro neutralization test against the isolate and the Osterrieth strain of SFV. A significant increase in antibody titer could be observed with both antigens (Table 1). For control purposes, the two serum samples from the patient were tested in a micro neutralization test against herpes simplex virus: both samples were negative (1: <8).

Hemagglutination inhibition tests were also performed, with antigen preparations of the isolated strain, the Osterrieth strain, and the Smithburn and Haddow prototype strain (*5*). The patient's serum, our rabbit antiserum to SFV (Osterrieth), and ascitic fluid of mice infected with the Smithburn and Haddow prototype strain (*5*) were examined for the presence of cross-reacting hemagglutination-inhibiting antibodies. The results (Table 2) show an increase in antibody titer from the first to the second sample of the patient's serum as well as cross-reactions between the antigens, as would only be expected between related strains of one and the same virus.

It is noteworthy that the Osterrieth strain of SFV used here for comparative identification of the isolate was obtained in 1969 by one of us (G.K.) from the same institute in which the patient was later employed. It has recently been unambiguously characterized in this institute as a strain of SFV by "fingerprinting" (oligonucleotide mapping) of the viral ribonucleic acids (RNA's) (*6*). In that work, the RNA's of the Osterrieth strain were found to be almost identical to those of the Smithburn and Haddow prototype strain. The RNA fingerprints of three other alphaviruses (Sindbis, O'nyong-nyong, and Chikungunya) examined, however, were completely different not only from those of the SFV strains but also from each other.

When the patient's brain and spinal cord were examined neuropathologically, a meningoencephalomyelitis was found. The histopathologic picture consisted essentially of gliomesenchymal nodules scattered throughout all parts of the central nervous system (Fig. 3) and foci of spongy necrosis, corresponding

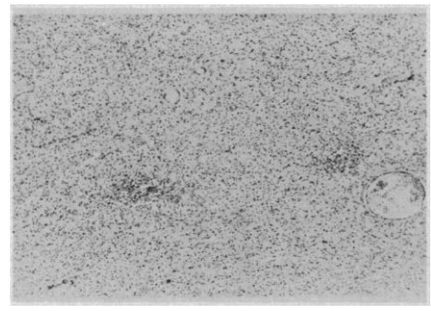

Fig. 3. Histopathological picture of the patient's cerebral white matter, stained by cresyl violet. Two gliomesenchymal nodules can be seen.

to the cellular nodules. The meninges and the perivascular spaces showed mild to moderate infiltration by lymphocytes and histiocytes. These features correspond to those described for panencephalitides caused by arboviruses (*7*).

To summarize the above findings, we conclude that SFV played an important role in the etiology of this fatal encephalitis. To our knowledge this is the first case of disease caused by SFV infection of a human being, although antibodies against this virus can be demonstrated in the serum of many laboratory personnel working with it (*8*).

We consider three possible explanations for the extraordinary course of this infection. First, host-specific factors may have been influential, for example, the preexisting bronchitis. Second, the patient may have been infected via an unusual route or by an unusually high viral dosage. Neither of these possibilities can be verified. The third possibility is the evolution of a mutated strain of SFV, either before or after infection of the patient took place. This question is being investigated.

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18 September 1978; revised 1 December 1978

Opioid Peptides Modulate Luteinizing Hormone Secretion During Sexual Maturation

Abstract. *Subcutaneous injections of naloxone, an opiate antagonist, lead to an increase in serum luteinizing hormone concentrations in female but not in male rats before they reach puberty. In addition, estradiol benzoate specifically blocks the luteinizing hormone response to naloxone in prepubertal female rats, suggesting that the opioid peptides have a physiological role in the endocrine events leading to sexual maturation.*

Several recent studies have implicated the endogenous opioid peptides in the regulation of growth hormone, prolactin (PRL), and luteinizing hormone (LH) secretion. Both morphine and opioid peptides induce rapid changes in the concentrations of circulating anterior pituitary hormones (*1*), whereas the antagonists naloxone or naltrexone reverse these effects. Moreover, the administration of antagonists such as naloxone alone leads to an increase in serum LH and a decrease in serum PRL levels (*1*, *2*). These last findings constitute the most direct evidence that the endogenous morphine-like peptides are involved in the control of LH and PRL secretion. The effect of opiate antagonists has been examined in

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29-day-old female rats (*2*) as well as in adult male rats (*1*), but no systematic study of the effect of age and sex on the response of pituitary hormone secretion to naloxone has been conducted. In the present study we report that, at certain discrete periods before rats reach puberty, naloxone administration leads to a striking increase in serum LH in females, while at all times in the prepubertal male no change in serum LH occurs in response to naloxone. In the female at puberty, when estrogen secretion increases, the increase in serum LH after naloxone administration is diminished and in the adult female is absent. Moreover, exogenous estrogens completely abolish the naloxone-induced serum LH increase in the prepubertal female. However, in the male, an increase in serum LH after naloxone administration is detectable for the first time at puberty. These results suggest that opioid peptides may mediate the changing secretory patterns of LH during development and hence opioids may be an important link in the chain of events that leads to puberty.

In female rats (*3*) injected with naloxone, serum LH increased four to nine times above saline-injected controls in 10- or 15-day-old animals, but at 18 or 20 days of age LH did not increase significantly after naloxone injection (Fig. 1, upper panel) (*4*). At 22 days, naloxone induced at least a fivefold increase in serum LH above control values which were undetectable (< 12.5 ng/ml). Furthermore, naloxone engendered a fourfold and sevenfold increase in serum LH at 24 and 26 days, respectively. Thereafter, LH was not altered by naloxone until 35 days of age [the mean day of vaginal opening was 36.4 × 1.7 (standard deviation), $N = 23$]. Cycling female rats failed to respond to naloxone with a significant increase in serum LH, and twice-daily injections of naloxone (2.5 mg/kg) did not alter the pattern of vaginal smears.

The male rat (Fig. 1, lower panel) responded quite differently to naloxone. A significant increase in serum LH after naloxone administration occurred only at days 40 and 45 and in the adult. The response of the male rat to naloxone was comparable to that observed in the peripubertal female rat. Thus, the data indicate that the pituitary secretion of LH after naloxone administration varies in the prepubertal period in female rats, while in the male serum LH does not increase until near puberty.

Female rats treated with estradiol benzoate show none of the characteristic increase in serum LH when they are subsequently injected with naloxone at 24 days (Fig. 2), whereas the well-known naloxone-induced decrease in serum PRL is unaltered.

The failure of naloxone and opiate peptides to affect the secretion of hormones by cultured pituitaries (*2*) suggests that naloxone acts on the hypothalamus to influence pituitary hormone secretion. Naloxone competes with endogenous opioid peptides for specific binding sites in the brain (*5*), and therefore it is likely that naloxone either interrupts a direct opioid inhibition of LH or blocks opioid peptide control over brain amine turnover [for example, dopamine (*6*)], indirectly affecting LH secretion. Regardless of the ultimate mechanism of action of naloxone on the release of LH, it probably involves luteinizing hormone releasing hormone (LHRH), the final effector of LH release. By examining changing patterns of LHRH in the hypothalamus and the response to exogenous LHRH in developing female rats, we can perhaps explain, in part, the age-dependent variations in naloxone sensitivity. During the early period of LH responsiveness to naloxone (10 or 15 days), hypothalamic LHRH concentrations are increased and sensitivity to exogenous LHRH is enhanced (*7*). Although the LH response to LHRH declines after 15 days

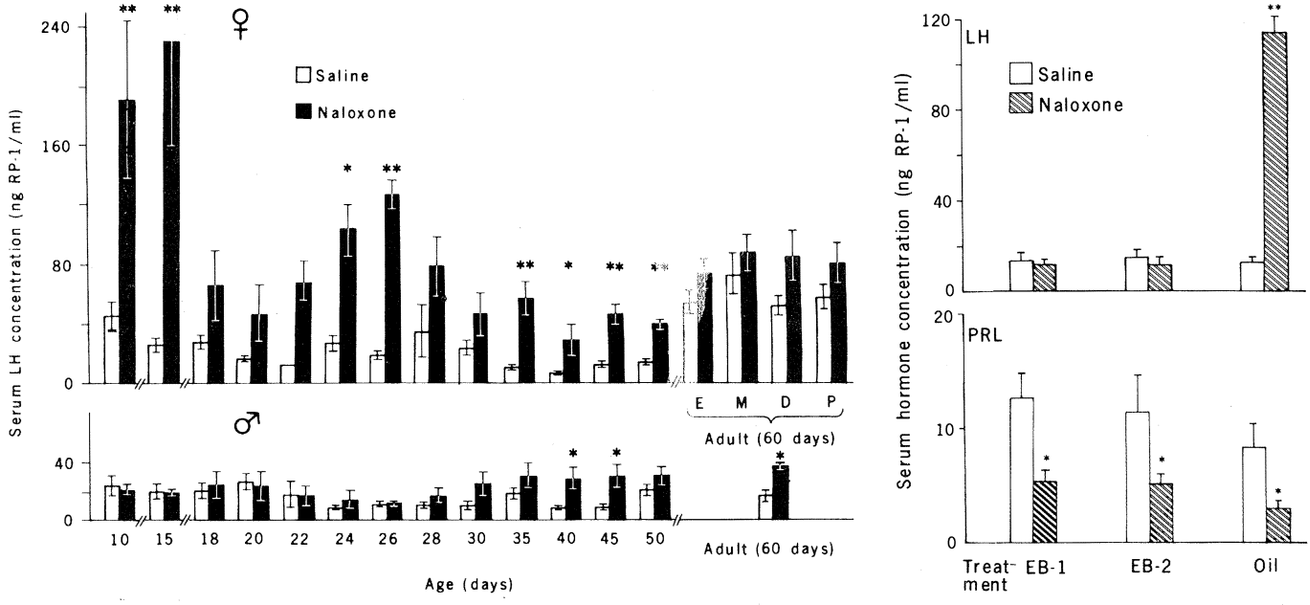

Fig. 1 (left). Serum LH concentrations in female (top panel) and male (bottom panel) rats 15 minutes after they received a subcutaneous injection of either saline (0.1 ml) or naloxone (2.5 mg per kilogram of body weight) at various ages between birth and maturity. The rats were bled by decapitation between 1230 and 1330 hours. Each bar represents the mean hormone concentration ± 1 standard error (vertical lines) in four to eight rats. Probability levels are indicated by * <.05 and ** <.01, compared to saline controls at the same age. Serum LH concentrations in female saline controls at 22 days of age were below assay sensitivity. Fig. 2 (right). Effect of estradiol benzoate on the response of serum LH (top panel) and serum PRL (lower panel) in female rats injected with naloxone at 24 days of age. Rats received an injection of estradiol benzoate (1 μg/day) for 1 day (on day 23, *EB-1*), 2 days (on days 22 and 23, *EB-2*), or oil vehicle alone (on days 22 and 23). On day 24, six animals in each group were injected with naloxone (2.5 mg/kg) and the six remaining rats with saline. Each bar represents the mean hormone concentration ± 1 standard error (vertical lines) in six rats. Probability levels are indicated by * <.05, and ** <.01, compared to saline controls. There were no significant differences among the saline- or naloxone-treated groups in terms of serum PRL.

of age, hypothalamic LHRH again peaks between days 22 and 28 (*7*). In addition, pituitary LH concentration increases toward puberty (*7*). Perhaps increased hypothalamic LHRH and pituitary LH account for the return of a response to naloxone on days 22 to 26 and during the peripubertal period. On the other hand, the male's increased sensitivity to exogenous LHRH toward puberty (*7*) might explain the heightened sensitivity to naloxone at this time.

Since LH release is modulated by estrogen and since we found that estradiol benzoate selectively blocked the naloxone-induced LH surge, patterns of serum estradiol and estradiol receptor concentrations during prepubertal life might also explain the variable LH response to naloxone in the female (*8*). Alternatively, the major effect of endogenous estrogens in modulating opioid-regulated LH secretion might be through a neurotransmitter system involving dopamine (*9*). We could reasonably assume that testosterone exerts a similar modifying influence in the male.

Although a different latency for the effects of estradiol benzoate on PRL and LH cannot be excluded, the failure of estradiol benzoate to alter the naloxone-induced decrease in serum PRL (at least within 48 hours of estrogen exposure) indicates that the opioids probably exert their control over LH and PRL secretion through different mechanisms.

Although it is well known that the opioids and their antagonists alter basal levels of circulating anterior pituitary hormones, we have presented evidence that implicates the opioids in a physiologically important context: the regulation of LH secretion during development and therefore in the onset of puberty itself. Furthermore, the data indicate an interaction between two widely divergent systems in the control of LH secretion: gonadal steroids and morphinelike brain peptides.

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27 July 1978; revised 30 October 1978

A Test of Some Models of Hemispheric Speech Organization in the Left- and Right-Handed

Abstract. *A new method generates specific predictions concerning the expected frequencies of aphasia after unilateral injury to the brain in the left- and right-handed. These predictions are then compared with the observed data for all known studies between 1935 and 1973 to derive the best-fitting model of hemispheric speech lateralization in the left- and right-handed.*

Clinicians have long reported a higher incidence of aphasia in the left-handed (LH) than the right-handed (RH) after unilateral injury to the adult brain (*1*). These reports, many anecdotal, have led some investigators to hypothesize an incomplete functional lateralization of speech in the majority of the LH, which results in greater sensitivity to acute brain lesions (*2–4*). At the other extreme, some investigators have dismissed reports of a higher incidence of aphasia, hypothesizing left-sided dominance for speech in the vast majority of both LH and RH adults (*5*). These two polar views are contrasted with other reports of a more variable pattern of cortical speech representation in the LH. According to one of these positions, the cortical speech mechanisms in the LH are unilateral, though variable, with the majority being dominant on the left side (*6–8*). The other position proposes a more complex pattern involving different types of cortical speech organization; some of the LH are hypothesized to have variable unilateral hemispheric speech (left- or right-sided) and some bilateral speech (*9–11*).

If the incidence of aphasia after unilateral brain injury were demonstrated to be higher in the LH, it would at least suggest the presence of a different pattern of hemispheric speech; it would provide no information, however, on the type of organization (unilateral, bilateral, or both). I now present an approach designed to address both of these issues.

Table 1 presents a review of (to my knowledge) all twelve studies (1935 to 1973) that have reported the incidence of aphasia following unilateral brain injury (left- and right-sided) in LH adults. Five of the studies also reported frequency data for RH adults. The data have been recalculated to show the frequency of aphasia separately for left- and right-sided brain injury in each study and a composite frequency (proportion) of aphasia for combined lesions in each study (final column). The incidence of aphasia after brain injury on the left and right side in the LH, ranged from a low of 0.3 (study 9) to a high of more than 0.9 (study 2). The overall mean frequency across studies was 60 percent (187 of 313). Comparative frequencies for the RH ranged from a low of 33 percent (study 8) to a high of 38 percent (study 11) with an overall mean frequency of 35 percent (714 of 2070). This frequency difference (proportions) is significant and points to an almost twofold increase in the incidence of aphasia in the LH after unilateral brain injury. Moreover, the incidence of left-handedness approximates closely the estimates of left-handedness in the general population (313 of 2383 = 13 percent).

As they stand, however, the results merely suggest that the cortical representation of speech is different among

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