in each of the three possible positions within the sequence.

The top half of Fig. 1 provides a schematic representation of one segment of the record produced by a single rat (animal No. 3). It illustrates the sizeable changes in startle reaction to the bursts that are produced by steady and pulsed background acoustical stimulation. Pulsed noise all but eliminated the startle reaction, whereas steady noise caused a marked increase in response magnitude. The bar graph in the lower left-hand corner of Fig. 1 summarizes the data from all subjects. It shows the average magnitude of startle during the final nine blocks of ten stimuli. In this period, each treatment occurred three times. The overall effect of variation in background stimulation was sizeable. Pulsed noise suppressed the startle reflex and steady noise enhanced it. An analysis of variance yielded a significant effect of treatments ($F = 10.90$, degrees of freedom $= 3$ and 40, $p \leq .01$). The three replications, however, did not differ significantly, nor was there a significant interaction between treatments and replications. Thus, it is concluded that although the effects of the treatments were large, their effects were limited to the periods in which they occurred.

Some adaptation of the startle response was revealed when responses in the first ten trials (prior to the initiation of the treatments) were compared to the responses during the three subsequent silent periods. The average magnitude of startle reaction across all subjects during each of the four silent periods is presented in the lower right-hand graph of Fig. 1. An analysis of variance yielded a significant effect of periods ($F = 11.95$, degrees of freedom $= 3$ and 15, $p \leq .01$), but the previous nonsignificant effect of replications and an examination of Fig. 1 suggest that such adaptation as occurred was essentially complete by the end of the first period.

The finding that steady noise enhanced startle makes it clear that the suppression of startle produced by pulsed noise is not a simple masking phenomenon. Nor, for that matter, is it due to a fixed temporal relationship between the pulses and the startle stimuli. Background stimulation was initiated and terminated by hand, and for this reason the phase relationship between the background pulses and the acoustic bursts varied from one treatment condition to the next. Observation of the subject throughout testing and a subsequent examination of their records also made it clear that the pulsed noise and the steady noise never produced an overt startle reaction.

We wondered whether the effects of the background stimulus were unique to the auditory modality. In order to examine this question, several rats were run through the procedures of this experiment with the modification that the background stimulation was provided by a 100-watt light bulb. No effects on startle to the acoustic burst were observed when the background stimulus was on, off, or flashing. Thus, at present, there is no evidence that these effects extend beyond the auditory modality.

Obviously, attempts at an explanation must be speculative. It does, however, seem likely that the punctiform stimulation provided by the pulses of noise caused a partial activation of the mechanisms responsible for startle and because of the high repetition rate (one per second) they also produced a relative refractory state. If this were so, the facilitating effect of steady noise might reflect the masking of punctiform acoustic stimulation provided by the animal's movements and by random fluctuations in the ambient level. Further research which provides better acoustic isolation and which examines the effects of pulse rate, rise time, and intensity of background stimulation may help to clarify the issue. Regardless of the ultimate explanation, however, it is apparent that these results may have certain practical ramifications. There are times when a startle reaction is particularly undesirable, for example, during the performance of a precision task (*3*). If the present results are applicable to humans, the use of low-level pulsed noise may provide a convenient and effective technique for reducing the chances that a sudden intense sound will produce startle and disrupt the task (*4*).

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3 July 1963

Pulmonary Edema as a Consequence of Hypothalamic Lesions in Rats

Abstract. *Rats were observed for the incidence of pulmonary edema after the placement of hypothalamic lesions by radio frequency thermocoagulation or d-c electrolysis. In the animals with electrolytic lesions, 31 percent died with pulmonary edema and marked signs were observed in another 20 percent. Moderate transient signs appeared in only 3.7 percent of the animals with radio-frequency lesions, and there were no deaths attributable to this syndrome in this group. These results suggest that this syndrome is an irritative consequence of the electrolytic lesion process rather than a "release" phenomenon.*

One of the hazards of experimental destruction of regions in the hypothalamus by electrolytic lesions is a relatively high mortality rate. Pulmonary edema with its complications is presumably a major factor in such cases. This phenomenon has been studied experimentally in rats by Patton and his co-workers (*1, 2*). Immediately postoperatively there may be a brief period of apparent normality. This is typically followed by a phase of hyperactivity and "forced progression." Subsequent to this the animal begins to exude a froth, usually flecked with blood, from its nose and mouth. It begins to gasp and assumes a posture similar to opisthotonus, with its head thrown back and its forelimbs extended. Minimal stimulation at this stage will precipitate convulsive seizures. Death normally follows soon after. On autopsy the lungs are found to be greatly distended and deep red in color. Histological examination of the lung tissue shows severe hemorrhage and edema with distention of the alveoli and perivascular spaces with erythrocytes and fluid.

In a previous study (*3*), I showed that the signs of hypothalamic hyperphagia usually associated with electrolytic lesions in the ventromedial region of the hypothalamus failed to appear when the lesions were produced by radio-frequency thermocoagulation. I suggested that the effects of the electrolytic lesions were due to irritation rather than simple tissue removal. Because the number of animals involved in that study was relatively small, a subsequent investigation was

carried out in which hypothalamic lesions were placed stereotaxically under Nembutal anesthesia in 128 adult male albino rats of the Sprague-Dawley strain. The animals were carefully observed during the first 72 hours postoperatively to detect signs of pulmonary edema. Postmortem examination included gross and microscopic examination of lung tissue. In 74 of the rats the lesions were produced by anodal direct current. In the other 54 rats the lesions were produced with a radio-frequency sine-wave current at 2 Mcy/sec at an intensity sufficient to produce lesions of comparable size to the electrolytic lesions. In all cases a stainless-steel monopolar electrode, insulated except at the tip, was used. The stereotaxic coordinates were those appropriate for the ventromedial hypothalamic nuclei in 55 of the animals with electrolytic and 40 of the animals with radio-frequency lesions. In 19 animals with electrolytic lesions and 14 with radio-frequency lesions, coordinates for the ventrolateral hypothalamus were used. In both ventromedial groups, current parameters were varied in order to produce lesions varying in size from very discrete to complete destruction of the region bounded rostrally by the optic chasm, caudally by the mammillary bodies, laterally and dorsally by the trapezoid formed by the fornices and mammillothalamic tracts, and ventrally by the base of the brain. Lesions were examined histologically in all animals. This examination showed the distribution of lesions with respect to size and locus to be comparable in both groups.

Of the 74 animals with electrolytic lesions, 23, or 31 percent, died with pulmonary edema. Lung tissue from these animals was found on gross and microscopic examination to have the characteristics typically found in pulmonary edema (Fig. 1). An additional 15, or 20 percent, showed severe signs, including effusion of pink froth from the nose and mouth, and convulsions, but managed to survive. Marked signs of pulmonary edema, therefore, appeared in 51 percent of the animals with electrolytic lesions. In the 54 animals with radio-frequency lesions, there were only three deaths, and none of these were attributable to pulmonary edema. Two animals showed transient, very moderate signs. Aside from a transient emotionality in a few and the development of diabetes insipidus in several, and the development of aphagia in animals with ventrolateral lesions, the other 49 animals (91 percent) appeared completely normal postoperatively, even though many of them had sustained massive destruction of hypothalamic tissue.

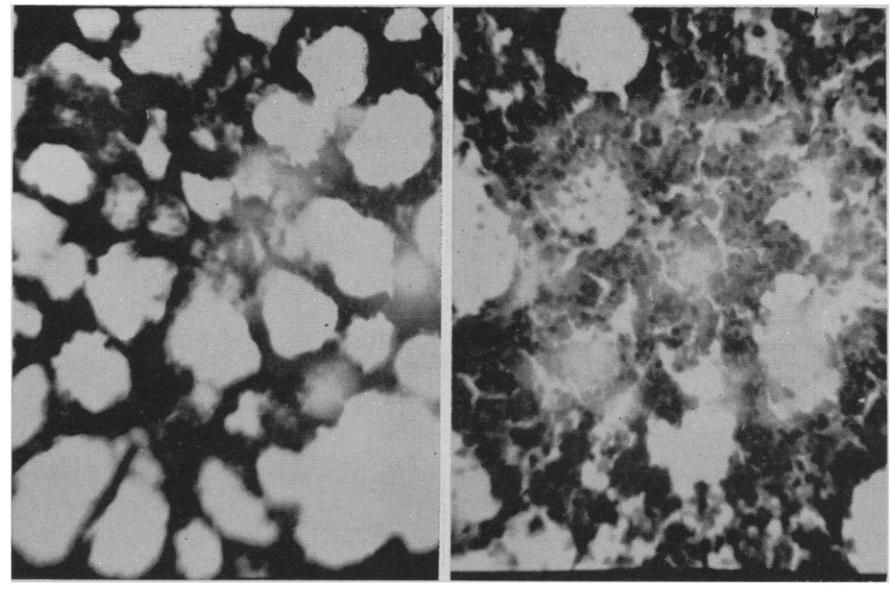

Fig. 1. Photomicrographs of lung tissue from normal rat (left) and rat that died with pulmonary edema (right).

There was no consistent relationship between size or locus of lesion and the incidence of pulmonary edema in the electrolytic group. In view of the fact that this syndrome did not develop in the animals with radio-frequency lesions, it cannot, in any case, be attributed to the removal of tissue. It should be noted that the effective lesions in the studies by Gamble and Patton and Maire and Patton (*1*, *2*) were located either laterally or medially in the preoptic region. Indeed, in one investigation (*2*) lesions in the ventromedial hypothalamic region were reported as affording protection against the production of pulmonary edema by subsequent preoptic lesions. This is directly contradicted by the present data, since electrolytic lesions in the ventromedial hypothalamus by themselves clearly produced pulmonary edema (Fig. 2). Although Maire and Patton concluded that pulmonary

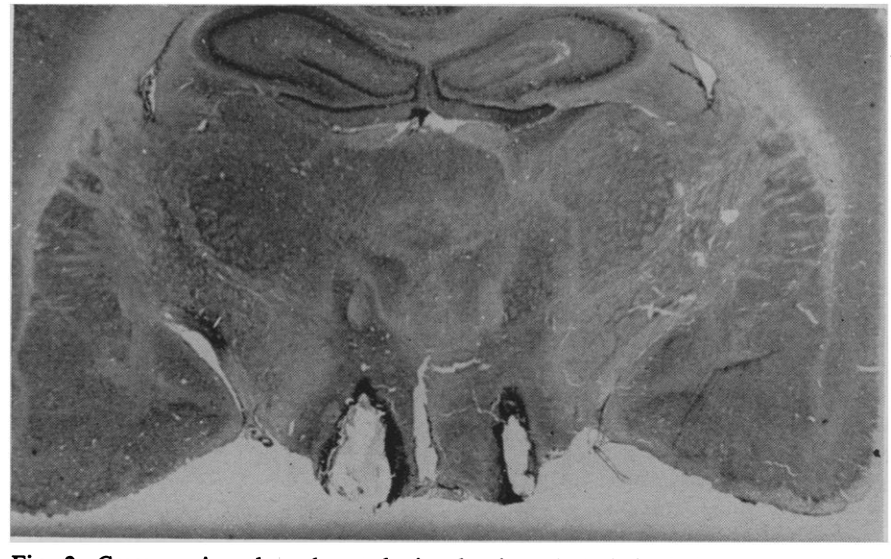

Fig. 2. Cross section through rat brain showing electrolytic lesions in region of ventromedial hypothalamic nuclei. This rat died with pulmonary edema. Its lung tissue is shown in Fig. 1.

edema is a release phenomenon resulting from the removal of centers which were presumed normally to inhibit activity in a postulated hypothalamic edemagenic center, the present data indicate that this phenomenon, like hyperphagia, may be the result of tissue irritation. The failure of the syndrome to appear after radiofrequency lesions may be attributable to the fact that such lesions are relatively clean, leaving little foreign debris in the tissue and cauterizing blood vessels in the vicinity. Electrolytic lesions, on the other hand, characteristically leave large metallic deposits and frequent small hemorrhages in the tissue surrounding the lesion. These can serve as foci for the chronic irritation of the surrounding tissue. Pulmonary edema, therefore, is quite likely the result of irritation of fibers in sympathetic pathways descending through the hypothalamus rather than the release of an edemagenous center from inhibition. These data in turn lend support to the hypothesis (*3*) that those effects of electrolytic lesions which have been described as "release" phenomena are actually the result of irritation of surrounding tissue by the lesion (*4*).

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Sleep: Cortical and Subcortical Recordings in the Chimpanzee

Abstract. *Electroencephalographic sleep patterns of chimpanzees reveal greater similarities to human records than those of lower mammals. Flash-evoked responses in the midbrain reticular formation remain during "paradoxical" sleep, which does not appear to necessarily involve deep unconsciousness. Characteristic spindling occurs in the amygdala during a "paradoxical" type sleep while other areas were desynchronized. Telencephalic sleep-control mechanisms in higher primates are considered.*

Although a phase of sleep characterized by rapid electrical records has been recognized for many years (*1*), it has been the formulation of the term "activated sleep" by Dement (*2*) and later "paradoxical" or rhombencephalic sleep by Jouvet (*3*) in studies with cats that has elicited such interest in this phenomenon. Their studies provoked interest not only in the general mechanisms of sleep, but also as to whether this rapid electrical phase related to deep or light sleep. The latter question was a prime motivation for the present study on three chimpanzees. Fifteen all-night records were obtained, and there was good consistency in electroencephalographic (EEG) records and sleep states on different nights in the same animal and some minor differences between animals.

Electrodes were stereotaxically implanted in the following subcortical areas: left and right amygdala, left anterior and right posterior hippocampus, left rostral midbrain reticular formation, and left entorhinal (posterior pyriform) cortex. Screw electrodes were placed over the (left) frontal, parietal, and occipital cortex. Recordings were made with a Grass EEG (eight channels) and also recorded on magnetic tape. Stimuli, signal markers, and timing were controlled with Tektronix wave form, and pulse generators and flashes were delivered by a Grass stroboscope unit.

The animals were placed in a sound-attenuated box (6 by 6 by 8 ft) and were lightly restrained in a comfortable form-fitting chair in a slightly reclining position. A strobe light source was adjusted to flash in the face, regardless of the position of the animal (the restraint prevented a complete turn), and the general position and movement were monitored by television. A dim light was left on (for television monitoring and to reduce fear) and the air-conditioning noise presented a constant background sound. Flashes were presented once every 5 seconds in series of 40 or continuously through the night. Visual evaluation of the EEG was used to determine the consistency of the electrical activity during stimulation. Evoked responses were averaged either by a Mnemotron C.A.T. computer or a Control Data Corporation 160-A general-purpose digital computer.

Sleep patterns, based primarily on surface cortical recordings, showed essentially the same phases as described in man (*1*). With the onset of sleep, cortical leads always showed an initial alpha fragmentation, followed by spindling and K complexes, and then slow waves at 1 to 3 cy/sec. Subcortical leads showed dissociated patterns in the initial descent to the phase of large slow waves. Rostral midbrain reticular activity showed a slight increase in fast components until cortical slow waves predominated, but then followed the pattern of cortical slow activity. It is of considerable interest that in these phases of spindle and slow-wave sleep the hippocampal leads failed to show the reciprocity of rhythm patterns said to characterize relations between the hippocampal system and neocortex in the cat, guinea pig, and rat (*4*). Initially, the hippocampal activity was intermittently rhythmic, with sharp-wave or spike-like configurations, followed by a spindling phase, coincident with the phase of cortical spindles. Records from adjacent entorhinal cortex exhibited close similarities to occipital cortical rhythms.

The "paradoxical" phase of sleep appeared only after 3 to 5 hours of spindle and slow-wave patterns, and was characterized by eyelid and eyeball movements, fleeting jaw movements, and head turning, all clearly visible on the television monitor, but with characteristic EEG patterns, fulfilling the criteria of this sleep phase (Fig. 1). Neocortical, hippocampal, and reticular leads showed fast, essentially irregular activity, but the most dramatic manifestation was consistently in amygdaloid leads, which have not been shown to exhibit such graded characteristics from consciousness to deep sleep in lower mammals. The typical rapid irregular amygdaloid records in the waking state showed a slowing during cortical spindling, with spindle bursts at 4 to 5 cy/sec coincident in frequency and duration with those in cortical records. With the progression to delta waves in cortical records, the amygdala continued to show short irregular spindle bursts.

In the "paradoxical" phase, long trains of rhythmic waves at 6 to 8 cy/sec were noted in the amygdaloid