were positive. Since in this series no such agent was found until the young reached 20 days of age (Table I), it would appear that they were not affected by the presence of the active agent in their mothers during pregnancy, either as a result of artificial, intracerebral inoculation, or, as already mentioned, of their harboring it naturally in their intestines.

Absence of Agent in Brains of Normal Mice. The brains of 32 normal mice, the intestinal contents of which yielded the active agent, failed to exhibit any specific effect on intracerebral passage to 52 normal mice. In other words, while the encephalomyelitis-producing agent can be found invariably in the intestinal tract of normal mice of a certain age, their brains remain free from it.

Conclusions. Certain additional characteristics have been described of the active agent which is present in the intestines of normal mice and which can induce encephalomyelitis indistinguishable from that of the spontaneous Theiler's disease. Among other findings, it was ascertained that, irrespective of whether mothers harbor virus (by means of artificial, cerebral inoculation or naturally in their intestinal contents), the incitant is not detectable in the intestines of their young from the fetal stage to 12 days of age, but it is demonstrable at the age of 20 days or older. Moreover, at 30 days of age, practically every mouse that has come under observation has yielded specifically active intestinal contents. By some mechanism not as yet understood, old mice harbor less of the agent than do young adults. Finally, in the latter age-group, while the mice carry regularly the active substance in their intestines, it is not at all recoverable from their brains.

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Sleep Induced by Subthalamic Lesions with the Hypothalamus Intact.

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The sleep-producing effect of hypothalamic lesions has been convincingly demonstrated (Ranson[1]). There are, however, still many unsolved problems which bear upon the central mechanism of the

1 Ranson, S. W., *Arch. Neur. and Psych.*, 1936, **35**, 1175; 1939, **41**, 1.

sleep-waking process. Supporting the view, notably that of Kleitman,[2] that sleep primarily depends upon a reduction of afferent impulses, Bremer[3] demonstrated that a transection of the brain stem behind the 3rd nuclei produces in the electrocorticogram and in the behavior of the eyeballs signs characteristic of sleep. Extensive bilateral thalamic lesions which destroyed the chief endings of the centripetal pathways from the spinal cord and rhombencephalon (Ranson) failed, however, to abolish the normal waking state. This indicates that centripetal systems outside the dorsal thalamus play an important part in maintaining the waking state. Thalamic lesions extending more ventrally than those of Ranson, reaching beyond the dorsal thalamus, but remaining outside the hypothalamus, were produced by Spiegel and Inaba,[4] who observed prolonged sleep following such lesions. The region ventrally adjacent to the thalamus, the so-called subthalamus, contains important fiber connections with the hypothalamus (Woollard,[5] and Papez[6]). It therefore seemed pertinent to investigate whether lesions of the subthalamus, sparing the hypothalamus, would interfere with the normal sleep-waking rhythm.

By means of the Horsley-Clarke stereotaxic apparatus the thalamus was pierced on both sides and bilateral circumscribed lesions were placed in the subthalamus. In control experiments lesions were confined to the thalamus or the hypothalamus. Experiments in all were made on 25 cats. Regardless of the anesthetic used (ether or nembutal), the cats with subthalamic lesions exhibited sleep (average duration 4 days). There was usually first deep sleep from which the animals could not be awakened and then somnolence associated with catatonia. In some animals the period of sleep was followed for about an equal length of time by a catatonic state without somnolence, the whole disturbance lasting up to 7-9 days. In other animals catatonia was the only disturbance. The histological examination of the sleep-producing punctures revealed that they passed through the posterior part of the thalamus, at the level of the ganglion habenulae and of the corpora mammillaria and immediately in front of these ganglia, traversed the medial part of the subthalamus, remaining lateral to the Vicq d'Azyr bundle, and ending dorsal to the inner end of the cerebral peduncle. The hypothalamus was histologically intact. Lesions limited to the thalamus proper failed to disturb the

2 Kleitman, N., *Physiol. Rev.*, 1929, **9**, 624.

3 Bremer, F., *C. R. Soc. de biol.*, 1935, **118**, 1235; *Bull. Acad. de Med. de Belgique*, 1937, p. 68.

4 Spiegel, E. A., and Inaba, C., *Z. f. d. ges. exp. Med.*, 1927, **55**, 164.

5 Woollard, H. H., *Proc. Roy. Soc. Med.*, London, 1932, p. 1579.

6 Papez, J. W., *Arch. Neurol. and Psych.*, 1937, **38**, 725.

waking state. This was true also for punctures of the subthalamus at more rostral levels.

Interference with the blood supply of the hypothalamus can play at most only a minor rôle since punctures with a dorsal entry, lateral to the hypothalamus and terminating at a considerable distance above the base of the brain, would hardly be expected to pierce blood vessels which go to the hypothalamus from the circle of Willis. Shock upon the hypothalamus may be partly responsible for the experimentally induced sleep, but it seems not sufficient cause to explain a disturbance lasting one week or longer (sleep plus catatonia in this series up to 9 days, sleep of 3 weeks' duration in Spiegel and Inaba's experiments on dogs). Besides it should be borne in mind that destruction of the hypothalamus itself also produces in cats disturbances of the waking state which are transitory only. The fact that unilateral hypothalamic punctures and even bilateral hypothalamic lesions when not extensive enough, fail to produce sleep, also speaks against the assumption that the symptoms observed after the subthalamic lesions are merely the consequence of shock upon the hypothalamus. It must, therefore, be concluded that damage of pathways passing through or synapsing in the subthalamus contributes to the genesis of the symptoms induced by the lesions. Ascending tracts conducting impulses from sensory spinal and cranial nerves as well as descending systems, particularly pallidofugal systems, must be considered. In this connection it is relevant to remark that sleep is produced by section of the midbrain and not by section behind the rhombencephalon (Bremer). In the former procedure ascending tracts from the cord and the rhombencephalon are severed as well as descending tracts from the higher centers. In the latter instance only the pathways ascending from and descending to the cord are interrupted. Since the majority of the descending hypothalamic tracts carries impulses to the vegetative centers in the cord and sleep does not follow a disruption of all descending systems entering the cord but is produced by a section interrupting the centripetal systems from the cord and rhombencephalon, it would seem that in the production of sleep by subthalamic injuries damage of ascending tracts plays an important part. The possibility, however, that lesion of the pallidofugal fibers may contribute to the production of the symptoms observed, particularly as regards the catatonic symptoms, cannot be denied.