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Editorial remark. The following articles report, on a broad biological basis, on the real problem of sleep. We wish to thank especially M. Monnier, the well known collaborator of W.R. Hess, for preparing this interdisciplinary survey together with the other sleep specialists. We should mention that the problem of dreams (Morpheus) is beyond the scope of this survey on sleep (Hypnos) and will be the subject of a later article. H.M.

Biology of sleep. An interdisciplinary survey

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1. Introduction

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The interest in the problem of sleep arose very late in neurophysiological research. The delay can probably be accounted for by the lack of anatomical/physiological data available before the publications of Gayet (1875) and Mauthner (1890). It may also be due to the fact that the physiologists tempted by this kind of research were afraid of being confronted by the redoubtable mind-brain problem!

The viral epidemic of encephalitis in the years 1919–1920 triggered experimental research by revealing the significant correlation between inflammatory lesions of cerebral centres and the disorders of sleep characteristic of this illness. In the mesencephalic tegmentum and the posterior hypothalamus of the cat, Ranson and his co-workers located the lesions responsible for the hypersomnia, and confirmed the existence of a central structure which induced cerebral awakening. Later, Nauta was able to show in the rat the existence of a hypnogenic area in the anterior hypothalamus, where Economo had predicted it would be from his study of encephalitis cases in which severe insomnia was a dominant symptom.

Meanwhile, W.R. Hess had experimented with electrical stimulation of the cat hypothalamus and had found, amongst other things, a region in the preoptic basal area, the activation of which he called 'hypothalamic adynamia'. He then found that low frequency stimulation of a median thalamic region induced normal sleep, and he described this region as 'hypnogenic'.

These pioneering achievements gave birth to the physiology of sleep, which has developed so much since then that periodic, critical reviews are required for up-to-date surveys of the subject.

After the initial work which had been concerned essentially with localization, there followed research on the problem of how the central nervous system was involved in the process of sleep. Long before the experimental era, Purkinje had suggested that sleep might result from a sensory de-afferentation of the telencephalon. Without knowing about Purkinje's article, I carried out, in 1935–1937, transection experiments of the brainstem at different levels, which led me to the hypothesis that the immediate cause of sleep could be the reduction in the continual flow of sensory impulses below a critical amount. The summation of these impulses would maintain a 'cerebral tonus', which is the physiological condition for wakefulness. The functional state of the anterior brain, severed from the rest of the cerebrospinal system, was revealed by an electrocorticogram and an oculo-pupillary syndrome resembling those of sleep.

However, in 1949, Moruzzi and Magoun discovered that electrical stimulation of the mesencephalic tegmentum always activated the cerebral cortex. Then Magoun and his co-workers showed surgically that the ascending impulses which maintain the wakeful state do not have a direct sensory origin, but originate in the reticular formation of the brainstem. This finding concurrently demonstrated the production of activating ascending impulses from the brainstem reticular formation. A new basic notion was thus introduced, which still dominates the physiology of sleep. Like the theory of direct sensory de-afferentation – which had meanwhile been proved to be inexact – it belongs to an essentially connectionist conception of central nervous mechanisms.

The introduction of the oscillograph, which was able to record electrical potentials in animal cortexes, added the valuable criterion of the level of wakefulness to behavioral observations. And in man, electroencephalography made it possible to identify the different degrees of depth of sleep (considered until then as a unitary phenomenon), and to study the changes brought about by physiological and pathological factors. In 1953, it helped Aserinsky and Kleitman to discover phases of deep sleep paradoxically associated with cortical activity, of which dreams are the psychic manifestation. These periods are also characterized by sudden eye movements and visceral changes, which are of both physiological and medical interest. The discovery of this paradoxical sleep, known because of the rapid eye movements as REM sleep, demonstrates the extraordinary complexity of the hypnic process. This is also seen in the existence of a rebound, marked by an increase in the duration of paradoxical sleep after its suppression by artifical means. Despite the advances made by using electrocorticography, the functional significance of paradoxical sleep is still unknown.

Electrocorticography also led not only to the discovery in the cat, by Moruzzi and his co-workers in 1959, of a bulbar hypnogenic area in a reticular region near the nucleus of the solitary bundle, but also to the confirmation in 1962, by Sterman and Clemente, Hernandez-Péon and his co-workers of the anterior hypnogenic region, to which Economo had alluded. The probable presence of this area in the basal preoptic region had already been suggested in the works of Hess and Nauta (mentioned previously).

This duality, at first surprising, of the hypnogenic system in mammals may be explained by the hypothesis that each of the two 'centres' in primitive mammals had only a phasic or circumstantial activity, which promoted the circulatory and thermic homeostases. During the course of phylogenetic evolution they could have acquired a tonic function, which is regulated in higher mammals by a very precise system of positive and negative feed-backs.

The localization of the preoptic centre in the diencephalon facilitated its study. This showed that its function is to induce the direct post-synaptic inhibition of the ascending reticular formation, and that a reciprocal inhibitory interaction exists between the reticular formation and the hypnogenic system. Moruzzi and myself then suggested that it was possible to explain, thanks to this reciprocal interaction, the process of falling and remaining asleep by a chain of inhibitions and de-inhibitions of the components of sleep and wakefulness, resulting finally in the deactivation of the ascending reticular system.

However, a strictly connectionist interpretation could not pretend to account for all the aspects of a theory of sleep. In fact, there is evidence that humoral mechanisms, the agents of which are not identical to the chemical mediators of nerve transmissions, play an important part in the sleep phenomenon. The research of Monnier and his co-workers – which shows the importance of interdisciplinary team work – demonstrated the release of a nonapeptide with a significant hypnogenic effect after intraventricular cerebral injection (cf present survey). This nonapeptide was obtained from the venous cerebral blood of sleeping rabbits, which had been subjected to electrical stimulation of the centro-median intralaminar thalamus.

The question arises whether the powerful hypnogenic action exerted by the anterior nuclei of the pontine raphe by the release of serotonin in the anterior brain is a neurohumoral process, or whether this effect is the expression of synaptic transmissions, mediated by 5-hydroxytryptamin. Jouvet and his co-workers have shown, in a series of very convincing experiments, the part played by this serotonergic nuclear structure in the physiology of sleep. But it now seems established that these raphe nuclei are not indispensable for the process of falling asleep. Their no less important role would be to participate in the control of the depth of slow-wave sleep. Hypnotonic rather than hypnogenic, these nuclei might represent a very ancient phylogenetic structure of the brainstem, subserving secondarily the regulation of sleep. The significance of this primitive function is still uncertain.

The old problem of the function of sleep, considered only in mammals, and in the case of slow-wave sleep, has been re-assessed on the basis of recent electrophysiological, biochemical and neuro-endocrinological data. It may be adequate to state here that without the discovery of hypnogenic centres, the notion of a function of the phenomenon of sleep could not have firm experimental support. Indeed, the variety and perfection of adaptive behavior preceding sleep could not be considered as a decisive argument in favour of a function of sleep. But, as soon as one knows that the mammalian brain creates its own sleep, the notion of a function of the hypnic phenomenon cannot be doubted. One must acknowledge however that the exact nature of this function is still very mysterious. The hypothesis that a process of restoration is necessary after a period of prolonged vigilant activity is still of current interest. But what kind of restoration could it be? That of brain or that of body? The study in man of day-night fluctuations in the secretion of growth hormone, which is known to control the anabolic processes of an organism, has led J.H. Horne (in this survey) to decide on a restoration of the brain. But we still do not know the nature of the alteration of the physiological neuronal processes which require correction by means of sleep. The discovery of this alteration, which may not be far off, would no doubt represent a fundamental progress in the understanding of the higher nervous activities.

2. Electrophysiological semeiology of sleep

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Summary. The main characteristics of electroencephalograms, electro-oculograms and electromyograms in human sleep are described. This electrophysiological semeiology permits the identification of the different stages in normal sleep. In animals, sleep is generally less differentiated; the possibility of recording subcortical structures allows the observation of additional phenomena such as hippocampal theta activity and PGO spikes. Evoked brain electrical activity is less well known than the spontaneous activity in sleep. Recent technological developments offer many interesting possibilities in the processing of the EEG and other physiological signals.

Soon after the development of the electroencephalogram (EEG) by Berger[1] it was recognized that brain electrical activity shows typical patterns depending on the level of alertness. Loomis et al.[2] recorded the brain activity of sleeping subjects and described 5 different stages, from wakefulness to deep sleep, termed stages A to E, respectively. In these early days, the usefulness of recording other physiological parameters together with the EEG was not obvious. It was shown later that during sleep there are periods, reccurring at regular intervals, during which the eyes display rapid movements, whereas they are unactive the rest of the time.[3] This discovery permitted the identification of a stage of sleep previously missed, paradoxical sleep, and clearly indicated the necessity of recording several physiological parameters in order to monitor the changes in alertness.

Based on these techniques a new classification was developed and is still mostly used to-day[4,5]. This classification distinguishes 2 main parts in sleep: NREM sleep also called slow sleep after the French terminology, and REM sleep or paradoxical sleep. REM stands for rapid eye movements, and REM sleep designates the stage during which rapid eye movements occur, whereas NREM sleep represents the remaining stages, normally lacking rapid eye movements. After a slight modification of the classification of Loomis, NREM sleep was subdivided into 4 stages, numbered 1-4, corresponding roughly to stages B-E of Loomis.

A polygraph recording consists of the simultaneous monitoring of several physiological parameters by means of convenient amplifiers and display devices. With the great variety of transducers now available, a large number of organs or physiological modifications in the body can be recorded. Only 3 basic parameters are necessary for defining the stages of sleep: EEG, eye movements or electro-oculogram (EOG), and muscle activity or electromyogram (EMG). Depending on the purpose, many other variables can be taken into consideration; to mention just a few: electrocardiogram, respiration movements, air flow through the nostrils, composition of expired air, and penile tumes-

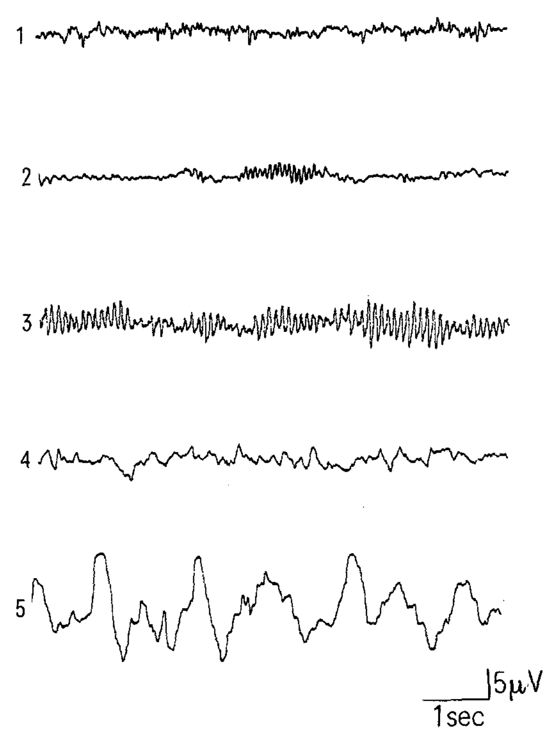

Fig. 1. Samples of the main EEG frequencies of interest in the different states of alertness. *1* beta activity; *2* spindle; *3* alpha rhythm; *4* theta activity; *5* delta activity.