SLEEP AND EPIDEMIC ENCEPHALITIS.

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SLEEP has been such a persistent concomitant in lethargic encephalitis that one is apt to accept the symptom as pathognomonic of this disease. The term "sleepy sickness" plainly incorporates this idea. Comparing fever and sleep, for example, however, one can rely more on a fever curve than on the occurrence of sleep. Both conditions are an expression of the organism's reaction, but fever is a more 'specific' response of the organic substratum to the noxa than sleep.

He who wishes to inquire carefully into the phenomenon of sleep in any morbid condition, cannot but notice that constitutional, habitual factors, as well as the element of age, etc., preponderate more in the sleep process than the morbid factor proper. It is a well-known fact that children and the aged, for instance, are prone to sleep through many illnesses. Changes in the blood stream (diabetic coma, eclampsia, uræmia, etc.), often produce 'comatose' sleep which by no means can be regarded as pathognomonic. Further, tumours of the brain, compression of the brain, apoplexy, etc., may cause somnolence, which should be regarded rather as an expression of the reaction of the nerve tissue in general.

We must, therefore, inquire into the phenomenon of sleep per se, i.e., its nature, purpose, mechanism, etc., in order to gain knowledge of pathological sleep.

It is timely perhaps to recapitulate briefly some of the more important theories on the nature and causation of normal sleep.

Piéron, as well as many other authors, conceived the idea that a special toxin, called hypno-toxin, is manufactured during the state of activity. The accumulation of hypno-toxin is supposed to produce fatigue of cortical cells and thus cause sleep.

Salmon thinks that sleep is a result of the derangement of the normal constituents of the cells of the cortex. When the chromophil and other substances which the cell receives from the lymph reach their normal amount, the cells of the cortex become alert to external stimulation, and we wake up; when the cells of the cortex reach normality, they are forced to spend the accumulated energy; or, as Salmon says, "We get tired to sleep."

Duval, Cajal, and others utilized the neuron doctrine for the explanation of sleep. The terminal arborizations of the afferent fibres, according to these authors, are separated during sleep from the dendrites of the cells of the cortex. This withdrawal prevents external stimuli from influencing the brain. Sleep thus results. During wakefulness the intermingling processes are again elongated, and bring the cortex back in contact with the external world.

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Tromner advanced a theory which assumes that sleep results from a sudden and complete interruption of sensory impressions on their way to the cortex ("Sinnesblockade"); the optic thalamus, which is known to have connections with all the senses as well as with all parts of the cortex, has been chosen by him as possessing the power of causing this block. He concludes, therefore, that sleep is controlled by that organ. Fundamentally, however, his theory does not differ much from that of Purkinje, who as far back as 1846 believed that sleep results from discontinuity of flow of centrifugal and centripetal impulses.

Stern, on the other hand, believes that sleep is a result of the block of rubrospinal impulses.

Hercouet thought that a sleep centre might exist in the pituitary body.

In June, 1927, von Economo of Vienna expressed his views on the subject substantially as follows. Sleep is a result of the function of two systems. One is that for cerebral sleep proper, and the other is a regulating centre in the mesencephalon. The nervous system thus plays a double rôle in sleep; one is the passive rôle, that of the telencephalon; the other, that of the mesencephalon, exercises a regulating action. Economo relies for acceptance of the double rôle which the nervous system plays in normal sleep on support derived from pharmacodynamics. It is a known fact that not all hypnotics attack the same place in the brain. There are hypnotics which attack the cortex (as for instance, bromides, alcohol, etc.), and drugs which attack the mesencephalon (veronal, luminal, etc.). The posterior wall of the third ventricle and the region of the infundibulum, as well as the aqueduct which lies immediately in front of the oculomotor nuclei, are the parts most concerned in regulating sleep.

Now, it would take too long to analyze each theory separately. One thing is, however, evident, viz., that all these theories not only fail to explain in full measure the mechanism of normal sleep, but neglect to consider the main point, viz., the biological value and significance of sleep, which is essential for its understanding. Each theory brings us face to face with the immediate causation of sleep, but leaves the biological principle of sleep aside. What, then, is, sleep? What is its significance?

We should constantly keep in mind the fact that sleep, primarily, is imperative in the great scheme of preservation 'urge'; and that, in the second place, through the ages it has developed into a habit. Biologically, sleep or rest is peculiar to every living cell, including those of plants. The organization of cells into cell-groups and into organisms, with their complicated activities, only increases this necessity for rest and sleep, and it reaches its height in the higher animals and in man.

The necessity for sleep developed into a will to sleep; this will existed long before the development of any nervous system arrived. In the course of countless years it acquired a condition of automatism. Thus sleep can be

regarded as an automatic manifestation of the will, in the same sense as that employed by Wundt, who looks upon all instincts as mechanical will forces.

There are some strong factors in the causation of sleep. These factors are instinct and habit. The tendency to sleep is a result of the workings of both an instinct and a habit. Just as the climbing of certain plants became habitual for the sake of preservation, so sleep also became a habit, notwithstanding the development of the nervous system and the cortex, with its influence upon higher animals and man. It is characteristic of every habit that it has a tendency to repeat, especially if it is of vital importance and is of a pleasurable nature. One must therefore regard sleep as one of the chief principles of the preservation instinct. The brain's participation in the process of sleep is fundamentally equivalent to the participation of any organ of the body, with the exception that in the course of evolution the nerve tissues became the barometer of the organism's activities. *There are therefore no centres for sleep, properly speaking.*

A conscious form of life arrived with the development of the cortex. We shall later see that this fact became the main point of departure in the sleep of the higher animals and of man.

Our conscious activities are largely enacted by means of conditioned reflexes, which are cerebral units and whose seat is in the cortex. Conditioned reflexes are firmly attached to and are built round an instinct. Events which, under ordinary circumstances, may have little or nothing to do with the function of the organism, as soon as they coincide several times with the workings of an instinct or unconditioned reflex, gain in importance and acquire the ability of causing the same reaction as the instinct itself. Thus these temporary factors act as signals and actually may substitute for or aid the work of the instinct. Conditioned reflexes, appended to the organism, become a strong biological lever; they enrich the organism with a keener and more sensitive equipment, rendering the relation of the animal to the external world more acute. Conditioned reflexes can also be formed within the organism, that is, from internal organs, as for instance, from heart, lungs, stomach, intestines, etc. Their activities are identical with the working of conditioned reflexes formed from the skin and other sense organs, that is, external. The interest and demands of the organism are thus constantly guarded by these two systems of conditioned reflexes.

The two systems work in strong co-ordination, and very often one stimulates the other. In the matter of sleep, conditioned reflexes play the same important rôle as in any other function of the organism.

That conditioned reflexes actually signal sleep to the cortex is seen from the practice of every-day life. Thus when there is no strong desire to sleep, at any time sleep can be induced by means of conditioned reflexes (a process of inhibition). Very often monotony alone or lack of occupation will cause

us to fall asleep ; conversely, when there is a necessity for sleep we can keep awake for a considerable time by stimulating various zones of the cortex through conditioned reflexes.

Pavlov, experimenting on dogs, found that each more or less continuous stimulus which falls upon a definite point in the cerebral hemisphere, will sooner or later lead to sleep. The stimulus does not require to be of vital importance to the organism ; stimuli without any vital importance and regardless of how powerful they may be, if they are not accompanied by stimulation in other points, or if the stimulus itself is not changed, will sooner or later, as already mentioned, lead to sleepiness and sleep. The instrument in this phenomenon in inhibition, which Pavlov identifies with sleep. He says that *inhibition and sleep are the same thing*. The process of inhibition has a tendency to spread all over the cortex and sometimes also reaches the midbrain. In other words, sleep in the course of activities of conditioned reflexes, on certain occasions, can be artificially provoked and this without any necessity for it as urged by the sleep instinct. In fact sleep is 'sensed' in the cortex a long time before there is real demand for it in the organs of the body.

One of the chief principles in the work of conditioned reflexes is that of facilitating free adaptation of the individual to external surroundings. This mechanism is evidently to ensure existence. The tendency is manifest in the entire living kingdom and is fundamental to all forms of life. In lower species it finds its expression in the form of a simple reflex.

It should be remembered that so-called inhibition is not the same as fatigue or exhaustion, which comes after prolonged work by the organism and is a sort of auto-intoxication. Inhibition is a definite physiological process peculiar to all reflexes. From the work of Kabanevitch it follows that fatigue, as seen normally, i.e., within physiological limits, is a result of the function of conditioned reflexes, i.e., is a process of internal inhibition. The physiological mechanism of internal inhibition is connected with various combinations of ion groups, which form a fundamental factor in the process of nerve stimulation. The character and degree of fatigue in each organ, at a given moment, depend on the quantitative concentration of stimulating and inhibiting ionic groups. This type of fatigue should be therefore regarded as a kind of protective valve, which prevents the threatening intoxication by waste products formed in the process of metabolism.

Just as Pavlov is able, by means of a sound, to stimulate the hunger instinct in a dog, when the dog is not even hungry, so in the same manner sleep can be brought about through conditioned reflexes without there being any real necessity for sleep.

The action of conditioned reflexes in producing sleep would be unthinkable were it not for the existence of an instinct of sleep ; from the study of conditioned reflexes we have already noted the fact that conditioned reflexes can only be established round an instinct.

Theoretically we must differentiate between real sleep, as necessitated by the instinct (real fatigue in the same sense as hunger instinct), and conditioned sleep as produced by means of conditioned reflexes. In practice, however, under normal physiological conditions, such a separation is impossible because of the close co-operation of the two. In the pathological state, however, this co-ordination ceases and various alternations in the degree and periodicity of sleep ensue.

If we analyze sleep in epidemic encephalitis, we observe that the type of sleep varies. It is either deep sleep from which the patient cannot be aroused, or else it is light sleep, i.e., the patient can be aroused, answers questions, takes in food, etc. (partial or light sleep). As to the rhythm of sleep, some patients cannot sleep at night, but sleep in the daytime; others seem not to be able to fall asleep at all, while still others sleep continuously with the degree which we may call light or partial sleep. The more usual type of sleep in acute and chronic lethargic encephalitis is light sleep, i.e., one from which the patient can be readily aroused.

There is enough evidence for the assumption that the instinct of sleep is actually regulated by conditioned reflexes. It is known that sleep and sleep disturbances in epidemic encephalitis begin before there are any marked changes traceable in the midbrain. The acceptance of a centre in the midbrain cannot, therefore, explain the pathological sleep. *We believe that the toxic effect upon the organism is instrumental in changing the ion-concentration in the nerve cell, which in turn changes the inhibition mechanism of conditioned reflexes and results in disturbances of sleep.* Reversibility in the rhythm of sleep can be similarly explained. Continuous inhibition in the realm of conditioned reflexes leads to alternation in the relationship of conditioned reflexes to the sleep instinct. It may also lead to absolute sleeplessness when a number of conditioned reflexes at different points are stimulated at once, usually at the onset of encephalitis lethargica. In deep forms of sleep, similar to coma, the sleep instinct becomes quasi-free. Toxicity of the cortical cells is the cause of absolute inactivity of conditioned reflexes and their respective influence upon the sleep instinct.

We must keep in mind that conditioned reflexes, being capable of inducing sleep, may at the same time act inhibitably towards the instinct for sleep. With the development of the cortex and consciousness, however, the instinct for sleep became modified by conditioned reflexes.

SUMMARY.

(1) There is not sufficient evidence for the acceptance of a regulating sleep centre anywhere in the midbrain.

(2) Properly speaking there are no centres for sleep; sleep is the expression of the work of an instinct strengthened by habit and regulated by conditioned reflexes.

(3) The cortex, the place of activity of the conditioned reflexes, being the centre of consciousness and wakefulness, assumes the leading rôle in sleep.

(4) In pathological states where the cortex is directly or indirectly involved, the signalling of conditioned reflexes for sleep becomes irregular and inadequate ; thus states of sleepiness, sleeplessness or irregularity in rhythm are the result.

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