SLEEP AS A PROBLEM OF LOCALIZATION

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The search for a so-called sleep center may at first sight appear a paradoxical idea. In the same manner as the waking state, so also does sleep appear as such a complex biological condition that the problem makes us at first sit up and take notice. Indeed, our entire life takes place in the alternating change of two biological conditions, the waking and sleeping state and in this way the problem might appear primarily of the same category as the problem of the center of life itself. The problem of a center of life in the nervous system has often been discussed in past centuries. But it has been put away as life is a much too complex condition as to be localized. So is sleep, too. But the change of sleep and waking state might, anyhow, have something to do with some special centers of the nervous system and that question has always been discussed over again. If we do not give to the word "center" a too narrow definition but if we agree that the expression "nervous center" signifies only such an accumulation of nervous grey matter the action of which is of direct primary importance for the production of a definite function, we might nowadays again discuss the possibility of locating sleep, regulation in some definite part of the nervous system since we know that even so complicated a biological function as the temperature of our body has got a very definite and localized regulating center in the diencephalon.

The extinction of consciousness, this most striking symptom of sleep of man and of higher animals, appeared until recently as the essential characteristic of sleep and as the only one which demanded explanation. We shall see, later on, that this view is not quite right. But for those who embraced this theory of interruption of consciousness the question of a center of sleep was merely reduced to the question where this interruption occurred. Quite a number of theories have been put out on that subject. Many investigators (Exner, Rabl-Rükhard) supposed that during sleep the ganglionic cells of the brain retract their dendrites like pseudopodia, whereby the interruption of conduction in the brain is brought about. The direct effect of this phenomenon was supposedly the ceasing of the activity of this organ, i.e., the ceasing of consciousness bringing about sleep. Others conceived the mechanism of interruption not in this delicate histological manner but somewhat more massively. Purkinje believed that by the congestion of the grey mass of the subcortical ganglia the thalamus corpus striatum, etc., pressure is excited upon the nervous fibers of the corona radiata which run through this ganglia and that due to this strangulation an interruption of conduction from and to the brain is effected thus bringing about sleep.

The Viennese ophthalmologist Mauthner assumed on the basis of Wernicke's description of encephalitis hemorrhagica superior in drinkers associated with sleep and paralysis of ocular muscles that this interruption of conduction takes place in the region of the aqueduct in the cap of the peduncular region in the interbrain. He thought, then, that a physiological recurring swelling "fatigue edema" of these parti of the brainstem blocked the conduction of the nerve fibers. In a somewhat more complicated manner the interruption was explained by Veronese and Troemner who assumed that the thalamus opticus was the point where the blockade of activity took place.

All these theories of sleep which assume an interruption or a blockade of conduction of stimuli to the cerebral cortex as the essential character of sleep, can be grouped under the name of "Theory of Lack of Stimuli." An observation of Strümpell on a patient whose body's tactile sensations had disappeared and who fell asleep immediately his eyes were closed and his ears were shut seemed to corroborate such a theory. This test case has been incorporated in all textbooks. But it was the case of a hysterical patient and these sleep phenomena might be explained nowadays by suggestive influence. All told, the theories of lack of stimuli, however important the clouding of consciousness might be, have neither in the past nor in the present, offered a satisfactory explanation for the following reasons: (1) In cases of pathological sopor, a disturbance of sensation and of tonus cannot be demonstrated, so that in these patients the interruption

of conduction to and from the brain cannot be, in itself, the cause of the change of their conscious state. (2) If the blockade of conduction were brought about by the periodic change of a congestion or an anemia of the central ganglia or by a recurrent sleep edema or by the retraction of dendrites of the cells, the very cause of this periodical daily return of these phenomena would still bave to be explained. (3) Furthermore, the change o f consciousness and unconsciousness is not the essential character of sleep but only one of its important symptoms. In fact, we know states of sleep for instance in plants which are devoid of a central nervous system and devoid of consciousness. (4) Animals without cerebrum and anencephalic monsters lacking not only the cerebrum but, to a large part also the thalamus, and lacking consciousness, show also the periodic change of sleeping and waking. (5) More recent knowledge teaches us that the sleep changes most of the organic functions in some way or other, not only by affording them rest, but also in a qualitative manner, a fact suggested by the change of the sugar and calcium content of the blood, the narrowing of the pupils, the Babinski phenomenon and other symptoms. These five reasons mentioned, are sufficient proof for the fallacy or, to use a better term, the one-sidedness of the theory of lack of stimuli.

Many other attempts of finding an explanation of sleep in one or the other of its important symptoms are afflicted with the same onesidedness, for instance the vasomotor theory of Mosso, the anemia theory and the others. They again do not first of all explain the essential character of sleep and its periodic change but only one symptom although we agree that vasomotor symptoms surely play a very important part in the production of sleep.

But even the very promoters of these theories themselves realized that they were not sufficient to explain the sleep mechanism which seemed much more complicated. Purkinje, for instance, who was the first to conceive the idea that the congestion of stem ganglia squeezing the mass of fibers of the corona radiata interrupts conduction, claims in order to explain the periodic return of that congestion that the blood has a chemical action during sleep that provokes that swelling and that it again changes and stimulates the nervous system during the waking state. Pflüger and DuBois-Raymond explain sleep as an asphyxiation of the brain due to abundance of carbon dioxide. Others have been able to prove that nerve cells after exhaustion have a changed histological appearance especially in reference to their tigroid discs and nuclei. And it is therefore very plausible to imagine that the absorption of cell substance by activity during waking state leads to a progressive decrease of the excitability of the cells and finally to sleep. These last three theories might be called the chemical theories. The best of all chemical theories is that of the French physiologist, Piéron. He made very striking experiments in reference to the chemistry of sleep. The blood serum of dogs which had overexercised for several days, and were not allowed to sleep, produced prompt sleep when injected into healthy dogs which had had sufficient sleep. That proved that fatigue produces substances in the blood which may provoke sleep. These fatigue substances are found also outside of the blood, for instance, in the cerebrospinal fluid and in the substance of the brain itself. They are nerve toxins which the author called "Hypnotoxins." Since Piéron's experiments it can be accepted as a certainty that through activity during the waking state not only carbon dioxide and lactic acid but also special fatigue substances are produced which exert a narcotic action upon the brain and may inhibit its function. The accumulation of these residues (Weichhardt calls them Kenotoxins) could very well explain the periodicity of sleep. During sleep these residues are again excreted by the organism. As compared with the previously mentioned vasomotor theory and theory of interruption this chemical theory has at least the great advantage of being partially proved. But they, however, cannot be the exclusive cause of sleep.

This fact we can deduce from many considerations of which I shall mention only the two most apparent: (1) sleep is initiated in many cases without fatigue as we may assume from the naps after meals. (2) Furthermore, the most striking characteristic of sleep, the possibility of being aroused (we call this the reversibility of sleep), shows that sleep does not represent a mere narcotic action. The reversibility of sleep means that we can at any time by stimuli which are not extreme and do not injure the organism, interrupt the sleep in such a manner that complete clearness of consciousness, recurs. During the action of narcotics, for instance during narcosis, this complete reversibility does not exist as long as the poison circulates in the central nervous system. Also the other pathological conditions of unconsciousness which may be very similar to sleep, for instance, syncope, coma, cerebral concussion, agony, etc., do not show this reversibility so characteristic only of normal sleep. Even extreme stimuli, that is, such that cause a bodily injury, can in such cases, bring about at most a very incomplete psychic reaction with a very limited return of consciousness and without disappearance of sopor. So these states are irreversible in contrast to normal sleep which is completely reversible. That shows that the chemical fatigue theory explains much but it still is insufficient to explain fully normal sleep and its periodicity.

To explain the periodicity of sleep two Italian authors, Mingazzini and Barbara assumed that this change is brought about not so much by fatigue substances as by endocrine processes and their action on the vegetative system. They claim that during the waking state the action of the excito-katabolic sympathico-tonic hormones of the thyroid, the suprarenals, the gonads and the hypophysis predominate but that during sleep the excito-anabolic stimuli influencing the tonus of the autonomic system gain control. To the periodic change of the sleeping and waking state corresponds the periodic change of distribution into the blood of hormones of the two gland groups, thereupon exerting their influence upon the brain and the other organs. While all the other theories previously referred to tend to seek the cause as well as

the essential character of sleep in the elimination of the activity of the nervous system-which is not right as we can see by the fact that sleep is occurring also in plants which lack any nervous system-Mingazzini's quite original thought of explaining the periodicity by a balancing change of activity of two groups of endocrine glands, represents really the first attempt of showing sleep to be a state not solely concerning the central nervous system. Indeed we are familiar in the lower species as well as in higher species, with many periodic functions not related in their process to the central nervous system. Let me remind you, for instance, of the periodicity of genital functions, namely, ovulation, mating and menstruation. Almost in the same manner as in relapsing fever, the parasite produces by its development in the body of the host a reaction repeating itself in phases of three days, so does the development of the ovum produce the genital periodicity in the female sex. Genetically, this periodicity is entirely independent of the central nervous system, though it stands in intimate relation to it. In a very similar manner, it would be plausible that some periodical recurring process running in diurnal phases, might be the more intrinsic and primary cause of the periodicity of sleep. Mingazzini's endocrine theory has, therefore, brought us much closer to the essence of the problem than the other attempts at explanation.

We must acknowledge that the chemical theories mentioned, especially that of Weichhardt, Piéron and the hormonal theory of Mingazzini are able to satisfy our desire for seeing cause and effect more than all the others mentioned. And in fact, most of the scientists, physiologists as well as pathologists, were thoroughly contented with these explanations of sleep. The former attempts to locate sleep function were looked at as obvious. Though some curious pathologic facts were known, for instance, the occurrence of sleep as a frequent symptom in cases of tumor of the infundibulum and were especially mentioned by Claude and Lherniitte, this Lhermitte himself stated in 1910, during the discussion of narcolepsy, "We absolutely object to the thought of the existence of a nerve center attributed to the function of sleep." Veronese expressed his doubt in the sentence, "The conception of a center for sleep is erroneous, as it disavows the most simple principles of physiology." And Dejerine said in 1914: "Sleep cannot be localized."

So stood the facts when two years later the appearance of lethargic encephalitis, which I first described in 1916 -17, refuted all these statements however well founded they appeared. The lethargic epidemic encephalitis shows in its most ordinary somnolent-ophthalmoplegic form, outside of disturbances of the eye muscles, as the most striking symptom, a sopor of different degree varying from simple somnolence to the deepest sopor in which the patients may sleep for weeks and months but from which in the majority of cases, it is possible to arouse them. The disease is produced by an inflammation of the central grey matter localized in the main in the cap of the interbrain at its junction with the thalamus. The inflammation may spread frontally and caudally to other parts of the nervous system and produce other symptoms. So it could be shown later that those cases of encephalitis which began with choreatic unrest presented at the beginning a striking and tormenting insomnia. The combinations chorea and insomnia on the one hand, eye muscle disturbances and sleep on the other hand, and our knowledge that many choreiform diseases originate in the region of the stem ganglia, leads to the assumption that the inflammation in cases associated with insomnia, is localized anteriorly in the lateral wall of the third ventricle, near the corpus striatum while it is localized in cases showing disturbances of ocular muscles with sopor in the posterior wall of the third ventricle near the nuclei of the oculomotorius in the cap of the interbrain.

The lethargic encephalitis produces, furthermore, outside of insomnia and sopor, a number of other disturbances of sleep, for instance, the inversion of sleep, i.e., the reversal of the periodicity of sleeping and waking, patients sleeping in the day time and being awake at night. Another very frequent sleep disturbance in encephalitis it what I call the dissociation of cerebral and body sleep and observed in a series of akinetic cases, patients being in day time mentally wideawake while their bodies were akinetic and drowsy as in sleep; at night these patients are again mentally asleep while their bodies are restless, which circumstance produces states of somnambulism. It was supposed by many investigators that it might be the toxic effect of lethargic encephalitis being an infectious disease, that was the reason for the sleep symptoms. But I called attention to the fact that quite a number of other diseases affecting the same region of the nervous system, as lethargic encephalitis does, namely, Wernicke's disease, Gayet's disease, then tumors of the infundibular region present outside of disturbances of the eye muscles, also sopor. Some recent findings in cases of softening (in hemorrhages) of this region have shown the sanie syniptomatology. The consideration that diseases of such different nature can always be productive of sleep if they occur in this region of the nervous system, proves the correctness of the statement that not the individuality of the disease as such, but its localization at this very definite area of the nervous system is decisive for the occurrence of sleep. Inasmuch as furthermore in lethargic encephalitis sleep is disturbed in such various ways as sopor, insomnia, inversion of sleep, dissociation of sleep, etc., we have additional proof that we must consider this region of grey matter as the site from which sleep can be primarily and directly influenced. This area is therefore selective for the function of sleep and as in more than 85 per cent of the cases of encephalitis there occur some troubles of the sleep function, we must suppose that the virus of encephalitis has a special affinity to these accumulations of grey matter which are of special importance for the sleep and which I designate as the "center for regulation of sleep."

We must insist on the anatomical fact that the center for regulation of sleep is in the immediate vicinity of the other important vegetative centers located in

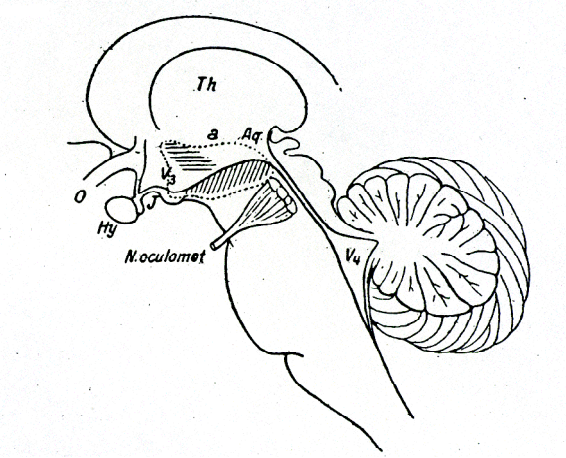
the infundibular region and we can suppose that it forms with them a larger physiological entity but that it is, anyhow, to be distinctly separated from the other vegetative centers by its localization as well as by its chemical a ffinity as its affinity to the virus of encephalitis proves, because in the acute stage of that disease we generally do not find other disturbances of the vegetative nervous system.

The action of that sleep-regulating center probably consists in a coordination of the different changes which occur in sleep in our vegetative animal and psychic system. As to the psychic system, the center for regulation of sleep has the rôle of initiating the cerebral sleep which, as we know, is characterized by partial extinction of consciousness and by the difficulty of conduction in the brain. How does this mechanism act physiologically? I think that Pawlow's experiments give us a precious hint to answer this question. We know by these experiments on conditional reflexes that a repeated interruption of these reflexes have a local inhibitory action on the cerebral cortex which can with a certain experimental arrangement, spread over the entire cerebral cortex. If that inhibition spreads over the whole cortex, it suddenly produces sleep. This experimental fact suggests that normal cerebral sleep might be considered as an inhibitory action brought about by the center of sleep regulation upon the cerebrum and thalamus. We are acquainted with different similar inhibitory processes in the nervous system in other conditions, for instance the inhibition of antagonists during stimulation of motor centers or the inhibitory fibers of the heart, etc. This way of acting by a nervous inhibition explains also the possibility of being aroused from sleep and many other particularities of normal sleep much better than the theories of anemia or the chemical theories can do because in chemical and vasomotor states we can't admit such sudden changes.

Outside of the effects of cerebral functions, the center of sleep regulation certainly exerts a regulating influence as previously mentioned, on the other vegetative and animal components of sleep which we might call "body sleep" for instance the change of respiration, perspiration, metabolism, etc. That influence is effected directly on the neighboring vegetative centers as for instance the centers of temperature, for sugar and calcium content of the blood, for regulation of the water metabolism, etc., which all change during sleep and the centers of which are located in the subthalamic region and in the wall of the third ventricle.

To fall asleep is therefore to be regarded as a very complex function. Its coordination and release is effected by the center of sleep regulation although the character of sleep and its periodicity is as previously mentioned, much more deeply and more generally anchored in the vegetative organism, somewhat similar to the hormonal explanation.

Now we must put forward the question "what sets the regulation center into action?" It seems most plausible to admit that this center is ordinarily and normally set into action by fatigue substances while circulating in the blood in an amount yet insufficient to bring about intoxication but acting already in small quantities specifically on that center of sleep. The latter then inhibits by an active nervous inhibition, the action of brain and thalamus which produce cerebral sleep and directs, in the meantime, the coordination of the different subthalamic centers concerned with body sleep. In this sense, the statemerit of Claparède that we sleep not because we are intoxicated by hypnotoxins but in order not to get intoxicated by them, is probably quite correct. This also differentiates the normal sleep from other abnormal sleep-like states. We might say the normal sleep is an active nervous inhibition, whilé syncope, narcosis, and other similar states are conditions which differ from it by their being passive intoxicatory and mechanical interruptions of nervous function. In consequence the latter are not immediately reversible as normal sleep is, which ends in the very moment the nervous inhibition by the sleep regulating center is set off.



Schema of the median section of the inter - brain; the dotted line is the boundary of the field, in which the center for brain regulation is lying.

We may, then, assume that the localized mechanism we postulate. for the supervision of sleep is really existing and we must look out how best we can localize it. Our experience with cases of lethargic encephalitis and other infundibular processes shows that sopor may occur in these diseases as an isolated symptom but that it appears principally associated with paralysis of eye muscles, especially with ptosis. That corresponds to the most frontal part of the nucleus oculomotorius, so we must place the posterior border of the center for sleep regulation immediately in front of the nuclei of the eye muscles in the grey junction of interbrain and thalamus where the aqueduct of Sylvius opens into the third ventricle.

The anterior part of that center may be located further frontally in the grey walls of the third ventricle near the caput of the corpus caudatum, as we find the symptom of insomnia combined with choreatic disturbances. Pathological-anatomical examination of encephalitis material has not resulted in a more exact localization but I am under the impression that we have to do not so much with a narrowly circumscribed grey nucleus but with a mass of grey substance spreading

over the posterior and lateral walls of the third ventricle and reaching laterally also into the hypothalamus. The different parts of that grey matter act in a sort of balancing way. I arrive at this conclusion on account of the multiplicity of sleep disturbances observed in the course of encephalitis.

To return then once again to the previously discussed definition of the words "nervous center," the center of sleep regulation cannot be classified within a narrow definition of this term. It is not considered a narrowly circumscribed seat of sleep function but as a center in a wider sense, i.e., as an accumulation of grey matter the function of which is of primary importance for the normal course of sleep.

The problem of more exact localization could only be solved in a conclusive way by physiological experiments. Different attempts in this direction have been made by Spiegel, Inaba, Demole, Marinesco. But all these attempts are surpassed by the very recent experiments of Hess in Zurich. He succeeded in making cats fall asleep normally with all symptoms of fatigue, of yawning and position of rest, by electrical stimulations with very fine electrodes introduced into the brain and by very weak currents which acted upon the anterior region of the aqueduct and the posterior wall of the third ventricle. If these results are verified in the future, irrefutable proof is furnished for the correctness of our conception of a center for the supervision of sleep situated at the junction of the thalamus and the interbrain from which sleep is actively initiated. It is therefore manifest by all these recent studies, that there is an apparatus which controls the general periodic alternation of sleeping and the constellation of our organism similar to high and low tide and similar to other vegetative function centers of the central nervous system.

As we have seen not only lethargic encephalitis but also other diseases of that region in the diencephalon may produce sleep disturbances. It is very probable though not yet proved, that the narcolepsy of Gélineau, Westphal and Redlich has its primary cause in a yet unknown disease of that region.

Now you may think the statement of the existence of such a regulating center for sleep is a very interesting physiological fact but you will ask for the practical consequence of such a statement. I will first point out to you that all knowledge of localization has a practical effect inasmuch as it helps us to localize different diseases, for instance, tumors, and helps us to get at them practically in a curative way. On the other hand, you know we are ardently seeking to find methods to excite externally either by electricity or rays or diathermy through the skull,4he centers of our nervous system in the intention of producing a therapeutic effect. Some initial results have already been obtained in that direction by diathermy. Imagine we once had an effective method of influencing deep lying centers, in this case the exact knowledge of the localization of the center for sleep regulation which I have attempted to give you, would make it possible to treat insomnia and other sleep disturbances in a better and more active way than by drugs or by the roundabout way of hydrotherapy and psychotherapy. Let us express the hope that we shall soon be able to have such results.