of the central monoamine neurons in the rat. Recently the ontogenesis of these systems has been described also in man [OLSON *et al.*, 1973]. In the rat, the development of the monoamine cell and their outgrowing axons was found to be very early. Thus, the cellular identity of the 5-HT, dopamine (DA) and NA cell bodies could be established at a crown-rump length of 8, 9 and 1 mm, respectively, corresponding to a gestational age of 12–14 days.

The monoamine axons sprout into the various areas of the brain as they are being formed, which may suggest an organizing influence by these axons on the areas reached [OLSON and SEIGER, 1972]. The genesis of monoamine synapses occurs at a later stage and is mainly a post-natal event [COYLE and AXELROD, 1971; LOIZOU, 1972; OLSON *et al.*, 1972].

The early development of the NA and 5-HT cell bodies and their axons may thus have at least two functions in the fetal brain. Firstly, the outgrowth of axons into the pons and the medulla oblongata, especially the reticular formation, might be necessary for the development of PS in the prenatal brain. The stage of PS in turn may provide the proper electrical environment for the formation of the neuropil in several areas of the brain and, later on, also for the facilitation of activity in certain brain circuits involved in functions necessary for the survival of the animals [JOUVET, 1972]. Secondly, the outgrowth of the monoamine axons themselves into various areas could have a general stimulating and organizing action on the neuronal network formed [OLSON and SEIGER, 1972].

Sleep: Physiology, Biochemistry, Psychology, Pharmacology, Clinical Implications. 1st Europ. Congr. Sleep Res., Basel 1972, pp. 225–228 (Karger, Basel 1973)

Is Sleep Related to Synthetic Purpose?

I. OSWALD

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Any organism is a system in equilibrium. All systems in equilibrium are liable to oscillations and even the simplest living organisms show oscillations or *rhythms* of activity – motor activity and motor inactivity. Humans have wakefulness and sleep.

The simple, unicellular organism has both external and internal requirements. It pushes out its pseudopodia, spending energy on motor activity

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and things external. But it also spends energy on internal needs. It repairs its cell wall after damage, its structural constituents must be renewed through normal turnover, and it must spend energy on synthesis for cellular division. Here, then, are internal energy expenditures for synthesis – anabolic rather than catabolic processes.

Energy expenditure relies on enzyme systems, and Nature is economical. The biochemists tell us that the same enzyme can serve more than one function. Under one condition it will promote one process, but if the conditions are changed slightly, it will promote another. At one time, for example, it may promote a catabolic process, and at another time an anabolic process.

These basic principles of economy in enzyme systems are no less true of vertebrates, such as ourselves. We also have periods when we must expend energy chiefly to cope with the external world. It is my theme to suggest that we have other periods, namely sleep, when energy expenditure is more predominantly internally directed, for synthesis of molecules required for growth and repair.

Cell Division

I spoke of cell division as an internal energy expenditure. What of cell division in vertebrates? Peaks of mitotic activity occur in human bone marrow, and probably in human skin, soon after the usual sleep onset time [Cooper, 1939; Killman *et al.*, 1962; Mauer, 1965]. How appropriate that at this time, as the cells divide, there should be a flood of growth hormone to help the dividing cells to grow. In rats and mice, cellular division in epidermis [Halberg *et al.*, 1965], bone marrow [Clark and Korst, 1969], pineal gland [Renzoni and Quay, 1964], liver parenchyma [Halberg and Barnum, 1961], blood reticulocytes [Clark and Korst, 1969] and eosinophils [Halberg, 1960] show circadian rhythms with maxima during the hours when the animals are predominantly asleep.

Cellular and tissue synthesis are most active in the young organism that spends so much time asleep and growing, namely on internal energy demands, and less time directing energy to external demands.

Anabolism and Sleep

What further evidence can support the idea that sleep alternates with wakefulness and permits economy in metabolic systems, with catabolic pro-

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cesses predominating during wakefulness and anabolic processes during sleep?

1. Increased secretion of anabolic hormones, notably growth hormone, during sleep, especially slow-wave sleep. Growth hormone increases the rate of synthesis of protein and ribonucleic acid (RNA) [KORNER, 1965].

2. If tissue reserves are burnt up severely then more slow-wave sleep is taken afterwards, as if in some way to help compensate and promote restoration of tissues. (a) BAEKLANDE and LASKY [1966] reported that exercise taken during the early or middle part of the day by *athletes* was associated with increased slow-wave sleep at night. (b) HOBSON [1968] reported increase of slow-wave sleep caused by exercise in cats. We have lately found that exercise in the early part of the day, and in an amount appropriate to the general level of fitness in the individual concerned, is associated with a rise in growth hormone secretion during sleep [OGUNREMI *et al.*, 1973]. (c) Whereas in hypothyroidism there is a loss of slow-wave sleep [KALES *et al.*, 1967], in hyperthyroidism there is a great excess of stages 3 and 4 sleep [OSWALD *et al.*, 1972]. We also found increased growth hormone secretion during sleep in hyperthyroidism. (d) One may also burn up one's tissue reserves rapidly by starvation and, in recent studies, we have found that starvation accompanied by potassium supplements was associated with a significant rise in stages 3 and 4 sleep amounts, especially after 3–4 days of starvation [MACFAYDEN *et al.*, 1973]. In such persons there is a higher peak of nocturnal growth hormone, as noted by PARKER *et al.* [1972], in whose data one may also observe that there was an increase of stages 3 and 4 sleep. (e) Similarly where there is weight loss in association with the amphetamine derivative, fenfluramine, there can be excess of stages 3 and 4 sleep [LEWIS *et al.*, 1971]. We also found a higher level of nocturnal growth hormone in those studies.

The above evidence seems to point to the presence of restorative mechanisms being brought into play during sleep, as if an effort were being made to restore tissue losses, particularly through slow-wave sleep stages 3 and 4.

Paradoxical Sleep

I shall, for reasons of economy, here only point out again that considerable evidence links paradoxical sleep with brain synthetic processes for early growth or later repair [OSWALD, 1969; OSWALD, 1970].

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Summary

It is argued that it is more economical for enzyme systems to promote at some times catabolic processes and at others anabolic processes, and evidence is adduced to suggest that the latter processes are enhanced during sleep, and that at this time energy demands are related especially to internal needs.

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Discussion of Dr. OSWALD*'s Paper*

PARMEGGIANI: I should like to ask you what happens with desynchronized sleep in those particular cases presenting an increase in synchronized sleep.

OSWALD: Are you referring to starvation?

PARMEGGIANI: Yes, I am. Starvation, exercise, etc.

OSWALD: I do not know about exercise. In starvation desynchronized sleep went down. In the hypothyroid patient, as well, desynchronized sleep was a bit low.

PARMEGGIANI: Would you agree that somehow there may be an inverse relationship between the durations of desynchronized and synchronized sleep? I found some indications for this on studying the effects of environmental temperature on sleep phases [PARMEGGIANI, RABINI and CATTALANI, 1969].

OSWALD: I would not like to say that there is an inverse relationship. They vary fairly independently.

VALATX: In rats chronically exposed to heat there is hypothyroidism. The animals show an increase of both desynchronized and synchronized sleep over a 24-hour period. How do you explain that?

OSWALD: I think this indicates not only that there are differences between species but also between the ways we study species. Our study as well as that of KALES et al. [1967] was made on hypothyroid human subjects who slept at night, while you have an animal which sleeps, wakes and sleeps throughout the day.

General Discussion

ROSSI: If you permit me, I think that the general discussion might be preceded by a very short attempt to synthetize not the findings, of course, but the interpretative hypotheses which were based on the findings.

If I am not wrong, it appears that two main ways of considering the physiological rôle of sleep have been indicated by our speakers.

The first one – which seems to be shared by the large majority of you – is that the main functional rôle of sleep is that of ' restoring ' some brain loss occurring during wakefulness. In particular, this is the view of KOELLA and OSWALD. Quite close to this position is that of VALATX and FUXE, who suggest that – in addition to facilitating 'restoration ' – sleep, in the newborn organism, might as well facilitate ' maturation '. It appears that there is also some agreement on the view that brain ' restoration ' and ' maturation ' take place particularly during paradoxical sleep. What happens during slow-wave sleep would be – in a way – preparatory to the paradoxical sleep events. Actually, this way of considering the physiological role of sleep seems to be the most popular not only here, but also in the sleep literature. It might perhaps interest you to know the various terms used to describe this role of sleep. Going through the literature, I could find the following terms: sleep ' restores ', ' restitutes ', ' repairs ', ' reorganizes ', ' renews ', ' recovers ', ' protects ' and, finally, ' detires '.

The second way of considering the physiological role of sleep is that indicated by PARMEGGIANI: sleep, he says, might be regarded as a sequence of processes leading to a consummatory act, identified with the desynchronized sleep episode. The possible utility of approaching the problem of the functional rôle of sleep from an ethological point of view – i.e., to regard sleep as an instinctive behavior – was stressed by MORUZZI a few years ago [1969]. MORUZZI suggested that ' sleep may be regarded as a chain of consummatory acts, represented by the alternation of synchronized and desynchronized episodes; it is preceded by an appetitive phase, whose subjective correlate is drowsiness ' [MORUZZI, 1969, p. 212]. PARMEGGIANI's hypothesis is somewhat different. In fact, for him the consummatory act is not sleep *per se*, but only its desynchronized phase.

If you accept this schematic attempt of synthesis we might now discuss the two main hypotheses: sleep has the function of allowing restoration and maturation, and sleep is an instinctive behavior.

Both hypotheses are open to discussion. I would appreciate that the discussion be started by two well-known experts of sleep who are present here: Prof. MONNIER and Prof. JUNG.

MONNIER: I would like to emphasize the concept of sleep as ' protector ' of waking functions. Wakefulness is a function to be considered as primary, sleep as a control organization with inhibitory mechanisms. I think it is impossible to speak of sleep without considering wakefulness, just as it is impossible to speak of heat loss without considering heat production. I was always very impressed during my research on neural as well as on humoral organization of sleep, by the duality of both states. This duality, for instance, seems apparent at thalamic level. The so-called intralaminary hypnogenic area is concerned mainly with modulation of cortical activity, modulation of attention, modulation of perceptions. This area can exert both an activating and an inhibiting action on the cortex. In other waking areas – viz., the hippocampus and hypothalamus – we have control systems antagonizing chiefly the emotional aspects of wakefulness and the instinctive aspects of wakefulness. In the original work of the school of Pisa, it was proposed that there are modulators which are concerned partly with body sleep and so on.

Now the problem which puzzles me most is ' What are the requirements for the phase reversal; what happens in the moment of phase reversal from sleep to wakefulness? '

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This is a very important question. The neural and humoral organization of the brain must allow a rapid shift from sleep to wakefulness. This is a very important biochemical and pharmacological problem to solve. When we started our experiments on serotonin (around 1957), we were for the first time confronted with the two aspects of serotonin and we described the pattern of arousal, mixed arousal and relaxation: serotonin was found to have an ambivalent function. As we well know, thalamic stimulation with high frequency produces cortical activation; thalamic stimulation with low frequency induces synchronized sleep. When we studied some of the properties of the factor extracted from the blood while stimulating the thalamus, and thus inducing synchronized sleep, we found it most difficult to produce this synchronized sleep factor without contamination by the waking factor; we had to establish conditions which did not allow contamination of the substance to be extracted by the waking factor. This synchronized sleep factor was found to be labile and very sensitive; it is sensitive to all kinds of physicochemical factors and must be purified very well in order to get reliable stability, but even this stability may fade after some weeks. This substance probably has something to do, or some properties in common, with those of the releasing factors of the hypothalamus. In my opinion, this sleep factor may allow a shifting from deep sleep state to arousal. But serotonin is not like that. Serotonin acts for a long time, it is a long-acting substance; serotonin, in my opinion, has some effectory function, it is closer to the effector level than this factor produced by stimulating the thalamic region. We may call it a modulator of sleep activity.

JUNG: I am afraid I have not much to say but to give some comments to the interesting things we have heard this morning. I think that in spite of the many publications on sleep in these last 10 years, we still need basic concepts. As Prof. ROSSI has said, we know very little about the restoration processes; everybody agrees that we are restored in sleep, but how we are restored we don't know. One interesting aspect is mitosis in slow-wave sleep, but probably it has nothing to do with the brain: the brain has no mitosis. So slow-wave sleep may be more for the body, as I understood from OSWALD. But what happens to the brain? Is only paradoxical sleep necessary for the brain? PARMEGGIANI suggested this for the instinct. I think that only 20 % of sleep for brain restoration would be too little, and I suspected that the other 80 % should have also some importance for the brain. We do not know very much about this. I think that it was from biochemistry that the main advances came in the last years. For instance, the stimulating work of JOUVET on the monoamines, which is an important key for understanding some of the things which happen in the brain stem and the brain stem–cortical relations. When we look back, I think that the concepts of HESS still stand. Although, of course, we know today many more details, the general concepts are still sound and I was very happy to hear the comment on this made by Prof. KOELLA. It appears that some people do not know very much about HESS' work; as we heard in the discussion, it was thought that stimulation of the hypothalamus causes sleep; HESS stressed the midline thalamus.

Well, I hope that the biochemist joins forces with the physiologist, and the clinician. I think one of the main intriguing problems is emotion and sleep. This was stressed by HARTMANN in his work on long sleepers and short sleepers. I would not be surprised if most of these short sleepers were more asthenic and the long sleepers more athletic. I don't know if Dr. HARTMANN has looked for these constitutional correlations. This brings me to psychiatry. I think that the manic-depressive syndrome is still the key for this con-

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nection between emotion and sleep, and if we could know more about the biochemical changes in the manic-depressive phases, perhaps we might find answers to this problem.

ROSSI: I think that most, if not all of us, agree that biochemistry or – to our purposes – neurochemistry appears one of the most promising tools to approach the problem of sleep. Now, if we want to continue to discuss that sleep facilitates or permits ' restoration ', I think we should take into consideration a particular aspect of these hypothetical restorative processes, namely the time required for these processes to take place. As everybody knows, the time spent in sleep is different in the different animal species. These differences can be quite impressive. Does this fact contrast with the ' restorative ' hypothesis of the function of sleep? Or is it possible that restorative processes – even if they should be basically similar in the different species – require different times in the different animals? I should like to invite you to discuss this point. I might start by asking our expert in neurochemistry, Dr. FUXE, whether the difference in the temporal organization of sleep shown by different animals is compatible with a neurochemical interpretation of restoration or not.

FUXE: I certainly think it would be compatible. It is a matter of turnover of the molecules involved, and I guess it may differ from species to species. As far as I can see, there are in wakefulness continuous changes in the synapses, particularly in the cortex cerebri as the signals are coming in from the environment. This continuous activity may in some way cause changes in proteins in the synaptic membranes to leave memory traces. These processes must be very rapid. You just read a newspaper, for instance, you start to learn a lot of new things at an extremely rapid rate. I think this very rapid rate of learning must be reflected in continuous changes in the molecules in the synapses in the cortex cerebri so as to leave trends enabling some sort of a memory. Due to the high demands of the environment you have to have periods of slow-wave sleep in order to restore new energy-rich compounds which will again enable very rapid energy transfer in these synapses. I think the variations in amount of sleep from species to species may then be dependent on the type of energy-rich molecules involved and also on the extent of the learning processes.

WEBB: The point raised by Dr. ROSSI on the differences in the amount of sleep in different animals was at the basis of a particular theory of the function of sleep which I formulated some 2 or 3 years ago. According to this theory, sleep is not restorative or concerned with restoration. Rather, sleep would be a behavioral control system protecting the animal from excessive or dangerous energy expenditure. According to this hypothesis the animals are sleeping to protect themselves and to be able to collect their energy resources most efficiently. The theory that I have been exposing is non ' restorative '. I think that I can marshal together a considerable amount of evidence to suggest that, for example, ungulate animals which sleep only 1 or 2 h every 24 h are animals which must sleep only 1 or 2 h; they have no natural hiding place, they are not ferocious, they are usually quite slow and, therefore, they must stay awake to survive. Their metabolism requires an almost continuous wakefulness. On the other hand, you will find other animals which would sleep 12–14 h/day. The nature of the length of sleep, in short, seems better explored on an ecological rather than on a neurophysiological basis.

FUXE: How do you know that the animal is not asleep during very brief periods?

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WEBB: On the basis of continuous recording of the EEG.

VOGEL: I want to suggest that there are more reasons to think that sleep is not simply a source of ' restorative ' function. In the first place, let us take into consideration rapid eye movement (REM) sleep. Several studies have been done on deprivation of REM sleep: there are no findings indicating that the deprivation of REM sleep is in any way harmful to men or to animals. If REM sleep were necessary for ' restoration ' of some kind of normal function, one would think we would have seen this by now, but we have not. As far as sleep in general or total sleep is concerned, I would like to make an analogy between eating and sleeping. We eat because of the signal hunger but, biochemically, we know that the function of eating is not to relieve hunger. In some way I want to suggest that we sleep on the signal of fatigue or a need for restoration; we wake up in the morning satiated and refreshed, just as after we have finished a meal we are no longer hungry. However, while we agree that we should not say that the function of eating is to relieve hunger, I am afraid we are still saying that the function of sleeping is to relieve fatigue. What we need, it seems to me, are measures of biochemical or physiological events that really do get ' restored ' on a molecular or physiological level during sleep.

ROSSI: Don't you think, Dr. VOGEL, that what you said is fitting, in a way, with the hypothesis of sleep as an instinctive behavior?

VOGEL: I am not sure I have understood this hypothesis!

ROSSI: Sleep would be something which comes as a consummatory act at the end of a preparatory act, the latter being the appetitive phase of instinctive behavior. It is a pity that we have here nobody really expert in ethology and who might help us to discuss this hypothesis better.

OSWALD: I would like to comment on the question whether REM sleep deprivation has deleterious effects or not. I should have thought that it is fundamental in the central nervous system that if you cannot achieve your goal by one method – the normal and optimal method – you will do it in some other way, and so I am not impressed by this argument. It remains that if you deprive someone of REM sleep behaviorally, he will try to make it up to get back to the optimum.

HAWKINS: One of the main questions of this symposium is that of the rôle of sleep in the total economy of the organism. You have provided excellent indications that there are biochemical types of restitution, at least in certain types of sleep, particularly slow-wave sleep. I don't think that the instinctive notion of paradoxical sleep is necessarily a different point of view. Instinctive actions develop in organisms because they help in preservation of species. The instinctive hypothesis suggests that there is a very important function somehow served by this stage of sleep. Therefore, we are not saying anything fundamentally different from the other point of view. Sleep, particularly REM sleep, has evolved in the mammals, and this parallels plasticity and learning. After all, the most important thing about the brain is its complex information processing system. We know that you can overload the system during wakefulness so that you are not able to work efficiently. I would like to pose the notion of information processing as an important aspect of sleep function, or at least of paradoxical sleep.

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BANQUET: There is not only variation in duration of sleep from species to species but even within the same species. Such variations can be related to stress and fatigue. People who go to sleep stressed and fatigued, just after getting tired or stressed, need less sleep than others who have accumulated stress or fatigue. I would like to suggest that slow-wave sleep is particularly affected by body fatigue and REM sleep by mental stress. Finally, I think we did not speak enough in this symposium of the classical studies of psychiatrists and psychologists. We did not touch, for instance, on dreams which have an important function in the maintenance of the psychological equilibrium.

KOELLA: I would like to make a short comment to what Prof. MONNIER has told us. He mentioned activation and inhibition of the cortex following stimulation of the thalamus with different parameters. In spite of the evidence he provided, I wonder whether it is really pertinent to talk here of cortical activation and inhibition. One should recall some already classical experiments by EVARTS who has shown that, with transition from waking to sleep, there is a kind of dedifferentiation in the discharge rate of cortical neurons. While during waking there are neurons discharging at all kinds of different frequencies, during sleep they come together, somehow at a ' happy ' median level. EVARTS talks of ' loss of gradients '. Because of this we might have less information content in the brain and we may speculate that loss of information content at cortical level may explain loss of consciousness. We should keep in mind that at least one aspect of sleep is this dedifferentiation, this temporary loss of information, perhaps this increase in entropy. This may bring us a little bit further towards understanding the nature of sleep and possibly also the function of sleep.

BERTINI: Prof. ROSSI said that we have two different hypotheses: ' restoration ' or ' repair ' on the one hand and the ' instinct ' hypothesis on the other. Now, what I would simply like to point out is that these two hypotheses should not be considered as alternatives; they might represent two equally sound lines of reasoning but at two different levels of analysis. While the one hypothesis considers sleep from a behavioral point of view and defines it as an instinct, the other hypothesis might be viewed as an attempt to indicate the functional meaning of it. In theory, therefore, there is no contradiction; on the contrary it could be relevant to assess how far a deepening of the analysis at one level can contribute to the understanding of the other level and *vice versa*. The conceptualization of sleep as an instinct should go much further than simply defining it along the lines of a preparatory and consummatory act. Instinct, indeed, is a very complex psychobiological entity; what are its specific structural components besides biological components (cognition, motivation and so on) and what are its dynamics? Also very vague till now has been the elaboration of the ' restoration ' construction. What does restoration or repair really mean? It may very well be that an analysis of restoration within a framework of a better elaborated hypothesis of sleep as an instinct will positively contribute to our knowledge. Just as an example, Dr. VOGEL was reluctant to accept REM sleep as a period of brain restoration since restoration is a very important matter. However, REM sleep deprivation is not followed by severe consequences as the core of recent research has shown. But which consequences? FREUD has shown, for instance, that repression of sex does not eliminate the related instinctual energy; its discharge simply takes different routes not recognizable without a clear knowledge of the characteristics and of the dynamic evolution of the instinct itself. Following this line of reasoning it might be possible to speculate that an

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appropriate elaboration of the assumption of sleep as an expression of an instinctual need of repair could reveal the distorted or transformed routes along which repair finds its instinctual gratification once blocked at its proper site.

PARMEGGIANI: Thank you for your stimulating question which gives me the opportunity to clarify that my position with regard to sleep as an instinct is not exactly the same as Prof. MORUZZI's. In fact, I approached the problem of sleep from the behavioral point of view because I think that behavior is a kind of language of the organism that we can understand directly. On the other hand, at the present time we still have great difficulties to decode the patterns of neuronal discharge. Thus, the behavioral approach to sleep is justified also by methodological reasons. This does not mean, however, that I have attained an explanation for sleep, I am only compelled by experimental results to use this method in order to define the nature of sleep. In brief, my aim is to put the problem into a logical frame. So, following this line of thinking, I have concluded that the consummatory act should be paradoxical sleep.

Concerning a question of Prof. JUNG, the consummatory act of sleep would be remarkably long if it were not distributed into short episodes. The reason for this may be that without this fractionation the organism would be endangered. The results I have presented today suggest that this danger may consist in the fact that the regulation of homeostasis is altered during the consummatory act of sleep.

ROSSI: I am sorry that we cannot go on with this discussion; our time is over. As I said at the beginning, it was unlikely that we would reach in this symposium a satisfactory definition of the ' physiological rôle of sleep ' and, indeed, an agreement on the physiological rôle of sleep acceptable for everybody has not yet been obtained. I do not think that we should feel ashamed of that. Let us hope that the next time we meet again to discuss this intriguing subject, some more data which might facilitate our discussion will be available. I thank all of you for your participation.

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