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Reviews

The organization and regulation of sleep

A review of the experimental evidence and a novel integrated model of the organizing and regulating apparatus

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1. Introduction

Sleep, of homoiothermic animals including man, is *not* a condition during which all 'systems' are uniformly and constantly inert or dormant; it should *not* be defined – as still often is done – as a state characterized by generally lowered vigilance. Sleep rather impresses by a mixed phenomenology, exhibiting moderate to high, often quite precise, activity in some systems, and low, often completely suppressed activity in others. Moreover, the distribution of activities is by no means constant, but rather varies, under given conditions, in an almost predictable manner with the passage of time, giving rise to the well-known phases and stages of sleep. Furthermore, sleep has been found to respond with variations in duration and in structure to changes in internal and external conditions, such as displacement of sleep-onset time, partial, selective, or total deprivation, and the type and intensity of the activities that fill the preceding waking period. This, under given conditions and in a given species, so well-fixed and sturdy time-intensity-space-pattern of activities (and inactivities), clearly indicates that sleep cannot be explained by a mere passive dropping away from the waking state; it must be viewed as an actively induced and homeostatically controlled, organized function. Most definitely, this 'second existence' in its basic structure must be the result of activity – the proper information handling – in a sleep-organizing apparatus. If one concedes that the induced modifications subserve the adjustment to a variety of exigencies or functional needs, one must infer that said sleep-organizing apparatus must include a set of regulatory mechanisms.

Neurophysiological, -biochemical, and -pharmacological research of the past 50 or so years has produced an ever increasing amount of evidence on a variety of neural and neurohumoral mechanisms and processes suspected to be implicated in one way or the other in the organization and regulation of sleep. Some of these experimentally discovered processes have been found to actively promote sleep, the one or the other of its phases, or single signs thereof. Other such mechanisms or processes have been noted to inhibit sleep or even to promote waking. The role of this latter variety of mechanisms in the induction of sleep could be assumed to be a passive or permissive one, as they would promote sleep through their very inactivity. Obviously, everyone of these experimentally discovered mechanisms can be presumed to be a part of the sleep-organizing and -regulating apparatus (SORA); that is to say, they would contribute through their own specific and coordinated action (or inaction) to the organization of sleep. Some of these partial mechanisms will be described in section 2 of this paper.

However, all these experimental findings, as numerous and detailed as they are, give us little information on the exact role, the functional location of everyone of these partial processes within the putative organizing and regulating apparatus. Nor do they furnish any first-hand information about the ways and means (the necessary interfaces) through which such an apparatus could produce those particular space-intensity-time patterns of activities in the effector systems which we refer to as sleep. There is little concrete evidence about the functional, let alone the anatomical, structure of this SORA, and there has been a paucity of efforts in the past – aside from some attempts towards the establishment of 'partial models'[20,96,97,115,120,153,164] – to even theorize and speculate about this machinery. Still, some advanced knowledge about the whole organizing apparatus, and about the mode and principles of operation of its functional elements would be extremely welcome in our endeavor to better understand the very nature of sleep. Moreover, such advanced knowledge would be of considerable help for a deeper insight into the pathogenesis or even the etiology of abnormal sleep. This in turn could provide a sound foundation for the development of new (and better) remedies for the treatment of abnormal sleep patterns.

In this treatise we describe and discuss the result of our effort to produce a *Realistic Model* that could represent the quasi-complete apparatus supposed to organize and

regulate sleep. Being aware that purely experimental procedures – the accumulation of a large number of yet functionally unrelated data – cannot, and never will, be very helpful for the establishment of an integrated concept of this machinery, we have decided on a mixed theoretical/practical – deductive/inductive – approach. We construed first, based on some general rules of bio-organization and on a set of functional properties, derived from the quantitative, qualitative, temporal and adaptive characteristics of the function under consideration, a *Theoretical Model,* a Block-Diagram (section 3). With this conceptual framework at hand we proceeded by 'filling-in the blanks' of this diagram with those experimentally established partial processes which, with their particular functional properties in mind, appeared to be best suited to perform the tasks assigned to anyone of the Blocks (section 4). In some instances, where experimental evidence was not sufficiently detailed, we had to make some educated guesses about the quantitative and/or temporal characteristics of these processes; in others, where experimental data were found to be completely missing, we had to use hypothetical elements. After completion of the model we made an attempt to test its suitability by reviewing its activity patterns as they could be expected to occur in the course of a normal sleep period, as well as in their response to artificially deranged sleep patterns (section 5). In the discussion (section 6) we outlined the progress made with this new concept, but also had to point out a number of shortcomings which, hopefully, can be corrected once new and better evidence becomes available.

2. A review of the experimental evidence for mechanisms involved in the organization and regulation of sleep

The discovery of everyone of the many neural and neurohumoral mechanisms believed to be involved, as active or permissive instruments, in the organization and regulation of sleep always has been accomplished through the use of 1, 2, or all 3 of the experimental procedures of traditional neuro- and psychoneuro-physiology: the *lesion-*, the *stimulation-*, and the *recording-technique.*

With the *lesion-technique* one reduces or completely eliminates (in experimental animals) the activity in a network or in a transmission channel and observes short- and/or long-term, quantitative and qualitative changes in the function under consideration – in this case, sleep or anyone of its stages and phases, or waking. Lesions can be made either electrolytically, with the knife, by local cooling, by injection of a local anesthetic, or by inducing a spreading depression through the use of KCl. Nowadays, one reduces – more specifically – neurotransmitter activity or efficacy through pharmacological techniques, such as inhibition of synthesis or release, through neurotoxins, or then via a block of the neurotransmitter-receptor or second messenger activity. Through *stimulation,* provided it is adequately done, one increases activity in a particular network or transmission channel, and checks for enhancement of sleep (or any one of its phases or stages) or of any one of the waking activities. Activity can be enhanced by 1) biophysical means, through electrical stimulation and cathodal polarization, or 2) pharmacologically, by facilitating transmitter release (or slowing down the metabolism of transmitters), augmenting synthesis, or by increasing receptor sensitivity. Using the *recording mode,* one measures by either biophysical (mainly electrophysiological) means or by biochemical techniques the activity in networks or transmission pathways putatively involved in the organization and/or regulation of sleep, or of the various waking activities, while the behavior under consideration is underway, or in animals sacrificed while exhibiting such behavior. A variety of biochemical methods are at hand to investigate the activity in the many aspects of 'wet' transmission; one can measure transmitter concentration or turnover in discrete loci; one can monitor release or local synaptic concentration with implanted chemtrodes or voltametry; or one can measure binding or sensitivity of receptors.

2.1. Evidence for processes involved in the promotion of waking and/or in the suppression of sleep

In his classical experiments Bremer[21] has shown that transection of the brain stem of cats at the mesencephalic level is followed by the appearance of slow waves in the cortical EEG. Yet, such signs of sleep in transected animals seem to be of rather transitory nature; Batzel[16] observed in dogs transected at the midbrain level that after a few days of recovery arousal patterns began to reappear and to alternate with slow-wave patterns. Moruzzi and Magoun[165], in turn, have demonstrated that high-frequency stimulation of the midbrain reticular formation of cats leads to a characteristic arousal pattern in the electrocorticogram. When this experiment is done in freely moving animals, reticular stimulation in naturally sleeping or lightly sedated subjects induces not only EEG-arousal but also behavioral awakening followed by a whole package of enhanced motor activities, including the orienting response. Also, typically ergotropic vegetative reactions such as mydriasis and accelerated heart rate occur. These and other findings have led to the establishment of the concept of the ascending, diffusely projecting reticular activating system[217–219]. Electrostimulation of the reticular core was also found to be followed by a negative-going shift of the cortical DC-potential[13], by an increased theta output in the hippocampus[107], by improved visual discrimination[58], by enhanced excitability of the motor cortex[141], and by an increase in amplitude of the potentials evoked by specific thalamic stimulation[23]. Landfield[135] investigated in rats the effect of driving or blocking the hippocampal theta rhythm as accomplished by low and high frequency electrical stimulation of the septum. He noted that low rate theta driving improved retention in a 1-way active avoidance task in comparison with animals receiving high frequency stimulation or nonstimulated controls. In a 1-way passive inhibitory task 'driven' animals performed better than the 'blocked' ones. Low frequency stimulation during testing also improved performance in the active avoidance task. On the basis of his results Landfield suggested

that the theta rhythm is associated with memory storage processes. Lesions placed in the reticular part of the thalamus (through which passes a considerable portion of the ascending arousal system) are followed by electrographic signs of deactivation – slow waves and spindles – with little evidence, though, of a loss of primitive motor activity, nor of a loss of the basic sleep-waking cycle[11,167,236].

More recent work, done mainly with pharmacological and biochemical tools, yielded a wealth of evidence on specific *neurohumoral* transmission mechanisms liable to be involved in the local realization of these various ascending activating influences. Amphetamine, known to exert its action through facilitation of release, mainly of noradrenaline (NA) and dopamine (DA), has been shown to improve avoidance behavior and intracerebral selfstimulation[76,220], and to enhance activity in the open field[244]. More recently, Goetsch and Isaac[65] found that d-amphetamine (0.2–0.8 mg/kg) in male hooded rats produces a slight, yet significant decrement in detection of light stimuli. The authors use their results to suggest that the catecholaminergic drug would reduce visual input (possibly acting at the level of the retina) and would not modify detection threshold through motivational changes. An increase of the concentration of NA ad DA at synaptic sites, as induced by pretreatment with L-DOPA, is followed by enhanced ambulatory activity and a shift in the cortical EEG towards low voltage, fast activity in cats[34,90]. Increasing more specifically the release of NA from (central) nerve terminals by such preferential a_2-receptor blocking agents as yohimbin or piperoxan prolongs waking time in rats[255]. Injection of NA or of DA into the ventricular system or into the hypothalamus of rats enhances orienting activity[17,63,212]. Similar results were obtained through the systemic administration of apomorphine, a DA-receptor agonist[228]. Electrical stimulation of the locus coeruleus of cats, the point of origin of important ascending (and descending) NA-pathways, is followed by an electrocorticographic, behavioral, and autonomic arousal pattern, not unlike the one produced by the classical reticular stimulation[118,120]. In these studies one also observed that the cortical effect of coeruleus stimulation is reduced, if not completely suppressed, by either local or systemic application of β-adrenergic blocking agents. Redmond and co-workers[193] were able to show that electrical stimulation of the locus coeruleus elicits alerting responses in macaques. Tanaka et al.[225] demonstrated that electrical stimulation of the coeruleus drives release of NA from the cerebral cortex.

Solomon and Staton[216] noticed that microinjection of d-amphetamine (10 µg) into the nucleus accumbens – but not into the striatum – disrupts the rat's ability to learn to ignore irrelevant stimuli in the latent inhibition paradigm. These authors suggested that a local hyperdopaminergic state could be the reason for this failure in attentive behavior.

Of interest in the present connection is a recent study by Aou and co-workers[12] who tested the reaction of single cells in the orbito-frontal cortex of monkeys *(Macaca mulatta)* to microiontophoretically applied NA or DA. They noted that 40 out of 103 cells reduced their firing rate in response to NA, 1 enhanced it and 62 did not respond. Of 80 cells tested with DA 10 increased, 5 decreased and 65 did not change their firing rate. Furthermore, the authors showed that the majority of the NA-sensitive units reduced, and most of the DA-sensitive ones increased their firing rate during a food acquisiton behavior. The authors' results suggest that catecholamines 'could be involved in the reward-related neuronal activity in the monkey orbito-frontal cortex'. Fibiger and Phillips[52] reported that stimulation of the pars compacta of the substantia nigra of rats impairs long-term retention of a passive avoidance step-down task. They showed, furthermore, that lesioning of the nigro-striatal bundle (with 6-OHDA) is liable to counteract the stimulation-induced memory deficit. This has, however, little influence on the acquisition or retention of the task. In the authors' view 'excessive release of DA would interfere with neurochemical and -physiological events in the neostriatum which is an important substrate for long-term memory'.

Lowering of central catecholaminergic activity is followed by signs of reduced waking. Inhibition of the synthesis of DA and/or of NA through the application of a-methyl-p-tyrosine in rats and cats leads to sedation[59,244] and produces EEG-signs of a de-activated cerebral cortex[111,145,243]. Poisoning of the NA-pathways with local intracerebral application of 6-OHDA in rats leads to selective slowing of the cortical EEG, without affecting to any marked degree motor activity[140,152]. Depletion by 6-OHDA of central NA has been found to potentiate barbiturate anesthesia[10].

Reduction of the release of NA by activation of the mainly presynaptic a_2-receptors with such substances as clonidine is followed by sedation in rats and cats[112,139,209]. Mason and Iversen[148] observed that lesions of the coeruleo-cortical NA-system elevates resistance to extinction of a previously learned runway respinse for food reward. The same authors[149] suggested that NA is involved in attentional behaviors. Mason and Fibiger[147] noted that depletion of brain NA (through infusion of 6-OHDA into the dorsal bundle of rats) leads to the impairment of the animals' ability to ignore irrelevant stimuli. The authors concluded that the dorsal NA-bundle plays a role in the 'attentional filtering process'. Dahlöf and co-workers[33] showed that repeated i.p. administration of dl-propranolol to rats produces a significant and dose-dependent decrease of the average firing rate of locus coeruleus neurons. The authors proposed that there is a stimulatory, mainly β_2-adrenergic, control mechanism for the (noradrenergic) neurons in the locus coeruleus. In turn, an a-adrenergic input to the locus coeruleus neurons seems to convey inhibitory influences[27].

Interruption of DA-pathways by injection of 6-OHDA into the nigro-striatal channels is followed by a marked reduction of motor activity in rats[200]. According to Jones and co-workers[91,92], stereotactic lesions of the nigro-striatal pathways of cats are followed by akinesis and a drop in what these authors refer to as 'motor initiative', without any change in the basic sleep-waking cycle and in the reaction of the cortical EEG to sensory stimuli. Montaron and co-workers[160] have shown that beta-activity in the frontal cortex of cats is reduced and immobile attention behavior is eliminated after lesions

in the ventral tegmental area. According to Vanderwolf et al.[235], rats pretreated with reserpin and atropine exhibit, in response to 80 mg/kg of β-phenylethylamine, head movements and stepping, in addition to an arousal pattern in the neocortical EEG. This may indicate that this traceamine, i.e. pathways using this agent as transmitter or modulator, is involved in the control of reactivity and vigilance in some possibly more primitive functions.

The cerebral content of NA varies in a circadian fashion and in phase with general activity[194]. Chu and Bloom[28,29] noted a drop in the discharge rate of single units of the locus coeruleus of rats with the transition from active – attentive – to quiet waking and to sleep. Kovačević and Radulovački[130] demonstrated that the DA-turnover in the striatum and thalamus of cats drops with the shift from waking to sleeping. Åkerstedt[3] noted that in shiftworkers noradrenaline (and adrenaline) excretion correlates negatively with total sleep time and positively with sleep latency and the number of stage changes.

Injection of acetylcholine (Ach) into the carotid artery of encéphale isolé preparations (cats) were found to reduce slow-wave output and to increase beta-activity in the cortical EEG[22]. Similar effects are inducible by the administration of nicotine, physostigmine, and prostigmine[43,253]. According to Bättig et al.[15] nicotine (0.2 mg/kg) increases activity and the number of U-turns, shortens the latency, and lessens the likelihood of entering radial alleys in RHA-rats tested in a Dashiell-type hexagonal maze. Wikler[247] and after him many others described the ultra-high and -slow waves in the cortical EEG of cats treated with atropine. Animals under atropine are deficient in conditioned behavior and in memory performance[38,197,203], while still highly vigilant as far as primitive activities, such as locomotion, grooming, and feeding are concerned. Atropine also was found to reduce the amplitude of the Contingent Negative Variation (CNV) in man, and the Slow Cortical Potential (SCP) in rats[46,227]. In cats and dogs there is an increased Ach-release from the neocortex during waking (and during REM-sleep) as compared with slow-wave sleep[60,73,89].

While alluding to a rather local functional area within the group of mainly waking activities, one may mention that 4-methylhistamine, a powerful H_2-receptor agonist, given intraventricularly, enhances the fighting score of paired rats[192]. There is evidence too that some polypeptides are liable to exert an activating influence. Injection of D-ala, metenkephalin into the ventral tegmental area leads to enhancement of motor activity in rats[105]. Both the thyrotropin-releasing (TRH) and the growth-hormone-releasing hormone (GHRH) antagonize the sedating effect of phenobarbital[181,184]. TRH injected systemically, or into the Nc. accumbens, drives locomotion and induces grooming in rats[157]; haloperidol and pimozide – both powerful DA-receptor blocking agents – antagonize the effect of the polypeptide. According to de Wied[41] the ACTH 4–10 fragment facilitates retention of conditioned responses and drives theta-output from the hippocampus[234]. De Wied[39,40] has also shown that vasopressin improves some memory functions.

2.2. Evidence for processes promoting the onset and maintenance of sleep, mainly its slow-wave phase

Hess[78], and a host of subsequent investigators[7,8,77,126] have shown that low-rate stimulation of the midline thalamus, mainly the intralaminar nuclei of cats and dogs elicits sleep. According to Sterman and Clemente[221], high- and low-rate stimulation of the basal forebrain induces slow-wave, followed by activated sleep. Parmeggiani[175] and Magnes et al.[144] have produced evidence that low-rate stimulation of the fornix, of the hippocampus, and of the region of the solitary tract nucleus induces sleep, or at least isolated signs of sleep, such as presomnic symptoms, and increases slow waves in the cortical EEG. Low-rate stimulation of the reticular formation at the mesencephalic level also is liable to have EEG-synchronizing effects, and, if applied repeatedly, to induce clinical sleep including some of its autonomic signs[48,185]; so does, according to Peñaloza-Rojas and co-workers[180], low-rate stimulation of the cerebral cortex.

As to 'wet' transmitter systems, it is well established that serotonin (5-HT) plays an important role as a hypnogenic – or vigilance-reducing – factor. Injected in doses as small as 10×10^{-9} g into the fourth ventricle of freely moving cats, 5-HT invariably induces sleep, mainly of the slow-wave variety. The same treatment, as well as direct application of the indoleamine to the area postrema, or injection of 5-HT into the carotid or vertebral artery in immobilized cats brings about spindles and slow waves in the cortical EEG and miosis[116,117,122]. Close arterial injection of 5-HT (to the area postrema) induces synchronization of the electrocorticogram[202]. Signs of reduced local vigilance characteristic of sleep can be induced in cats by injection of 5-HT into the thalamus or into the basal forebrain[252]. Elevation of the central nervous concentration of serotonin through treatment with 5-HT-precursors – L-tryptophan or 5-OH-tryptophan – or with monoaminooxidase inhibitors, increases slow-wave sleep in rats, rabbits, and cats[34,94–96,98,124,224,251]. Electrical stimulation of the raphe nuclei, the area of origin of the ascending (and descending) serotonergic pathways, induces sedation and sleep in rats[129]. In turn, injection of p-chlorophenyl-alanine (PCPA) – a 5-HT-synthesis inhibitor – in cats, rats and monkeys leads to reduction, if not complete suppression of sleep[34,124,229,245]. According to Froment et al.[55] and to Kiianmaa and Fuxe[110], the destruction of the central serotonergic pathways with 5,6-, or 5,7-dihydroxytryptamin is followed by reduction of sleeping time in rats and cats. Ross et al.[201], though, were not able to confirm these results. However, electrolytic lesions of the (rostral) raphe nuclei are followed invariably by insomnia whose degree was found to correlate positively with the size of the lesion, and negatively with the amount of remaining 5-HT in the forebrain[95,96,195].

Finally, serotonin and its metabolite (5-OH-indoleacetic acid) vary in a circadian fashion; 'highs' coincide with periods of rest and greater densities of sleep[25,130,188,189,208]. Toru and co-workers[231] noted an increased turnover of 5-HT in the thalamus of rats during the sleep period following a 24-h sleep deprivation. Trulson and Jacobs[233] found – in contrast to the present notion – an

increase in the firing rate of dorsal raphe neurons with arousal; they assume, however, that this apparent paradox is the manifestation of a serotonergic mechanism preventing hyperarousal in response to a variety of stimuli.

Melatonin, an indole derivative evidently synthesized in the pineal organ, also seems to participate in the organization of sleep. Evidence for such a notion was produced by Menaker and Zimmermann[154]. Cramer and collaborators[30] showed that in man, melatonin reduces sleep latency without affecting (to a marked degree) total sleep time or the various stages of sleep. Of interest in this connection is Åkerstedt and collaborators' recent observation[6] of a significant (negative) correlation between performance and urinary melatonin levels. According to Radulovački and co-workers[190], N^6(L-phenylisopropyl)adenosine elevates slow-wave sleep and reduces waking time in rats. More recently Radulovački et al.[191] have demonstrated that deoxyformycin, a potent adenosine diaminase inhibitor, in a dose of 2.0 mg/kg, increased SWS in rats while a smaller dose only enhanced paradoxical sleep. The authors inferred from these results and also from other, similar experiments that adenosine has a hypnotic action.

In connection with what was mentioned earlier with respect to histamine, we can cite Ray et al.[192] who produced evidence that (central) stimulation of mainly H_1-receptors with intraventricular application of histamine reduces fighting activity of paired rats. A number of *polypeptides* should also be mentioned in this context. Pappenheimer[173], Pappenheimer et al.[174], Fencl et al.[51], and Krüger et al.[132, 133] isolated from the cerebro-spinal fluid of sleep-deprived goats, and, more recently, from human urine and from the brain of cattle, goats and rabbits, a polypeptide, *Factor-S*, which, if injected into the ventricular system of rats, exhibited sleep-promoting abilities. Hypnotic effects were obtained also in cats. This factor is a small glycopeptide, composed of glutamic acid, alanine, diaminopimelic acid, and muramic acid[133]. According to Pappenheimer[173] Factor-S is produced in the brain; its concentration increases with time of (enforced, and possibly also natural) waking. Following earlier findings of Kornmüller et al.[128], Monnier and Schoenenberger[159] and Schoenenberger et al.[210] have succeeded in isolating and chemically characterizing a nonapeptide, the *Delta-Sleep-Inducing Peptide* (DSIP) which, if administered to rabbits in intermediate doses (around 25 µg/kg i.v.) enhances delta-wave output in the cortical EEG, and brings about signs of sedation. In cats, as will be mentioned again later, DSIP rather enhances paradoxical sleep. Kastin and co-workers[103] identified a DSIP-like compound, by radio-immune assay, in the brain and the pineal organ of rats. Highest concentrations were noted in the pineal and in the thalamus. According to Pavel et al.[178] *vasotocin*, a nonapeptide from the epiphysis, has sleep-inducing abilities, if given in extremely small doses to cats. In man, this nonapeptide appears to promote mainly REM-sleep[177]. Riou et al.[199] have found that the injection of the *vasoactive intestinal peptide* (VIP) which also occurs in the brain, facilitates the onset of sleep in rats.

In connection with the description of generally (behaviorally) sedating or even depressing agents and processes, one also has to allude to *gabaergic mechanisms*. Muscimol, a powerful gabaergic agonist, reduces, if injected in small doses into the nigro-striatal or the mesolimbic system, locomotor activity in rats[206]. Andén et al.[9] observed a marked decrease in locomotor activity in response to muscimol injection into the Nc. accumbens. Pycock and Horton[187] initially primed rats for high locomotor activity by locally injecting DA into the Nc. accumbens or by systemic administration of amphetamine. GABA (50–5000 µg) or 3-aminopropane sulphonic acid injected bilaterally into the accumbens was found to antagonize in a dose-dependent fashion the drug-induced hyperactivity. A reduction of locomotor activity was obtained also through intracysternal application of GABA[54]. File[53], after intracysternal administration of ethanolamine-O-sulphate (EOS, an inhibitor of GABA-transaminase) noted a drastic decrease of the 'head dips', a manifestation of exploratory behavior of rats. With the doses used, this drop in exploratory activity, however, was not paralleled by a reduction in mean motor activity (light beam interruptions). Grimm and collaborators[66] injected (ip) amino-oxyacetic acid (AOAA) or di-n-propyl-acetate (DPA) into rats. These treatments (leading to an elevation of cerebrocortical and cerebellar GABA-levels) impaired 'smooth execution of learned locomotor acts; especially where balancing and coordination of the hind limbs were necessary'. In unrestrained, 'conscious' rabbits, intraventricularly administered GABA or muscimol were found to cause hypothermia and muscular hypotonus and to synchronize the EEG in the cerebral motor cortex and in the limbic cortex[213]. GABA-receptor blockade by picrotoxin (0.5–2.0 mg/kg i.p.) or bicuculline (1.0–4.0 mg/kg i.p.) slowed down intracranial self-stimulation, but had no effect on lever pressing in an escape test[108].

2.3. Evidence for processes involved in the promotion of paradoxical or REM-sleep

Jouvet[93] has shown that electrical stimulation of sites in the pontine reticular formation of cats (preferably if already in slow-wave sleep) induces a shift towards paradoxical sleep. The same author[96] demonstrated that in cats, after slow-wave and paradoxical sleep has been suppressed by pretreatment with reserpine, l-DOPA is liable to restore the latter. Increasing the NA-release from central noradrenergic nerve terminals by the α_2-receptor blockers yohimbine or piperoxan enhances signs of paradoxical sleep in cats and rats[99, 139]. Reduction of NA-release through administration of such α_2-agonists as clonidine is followed by a decrease of PS in rats and cats[112, 139]. Leppävuori et al.[139] and Hilakivi[80] used such evidence to suggest that controlled or restricted enhancement of central (in particular α_1 and β-mediated) NA-activity is liable to promote the emergence of paradoxical sleep whereas more pronounced enhancement of NA-activity would support and promote the activities of waking. Masserano and King's[150] findings, though at first glance somewhat contradictory, do not militate against this interpretation; they noted that once phentolamine is infused into the locus coeruleus region

of cats, it tends to increase the number (per time unit) of REM-periods and to reduce light slow-wave sleep. They also found that epinephrine given by the same route, favors waking and reduces both deep SWS and REM-sleep. According to Chu and Bloom[28] neurons in the locus coeruleus of rats increase their discharge rate with the shift from low-wave sleep to paradoxical sleep. In a later paper the same authors[29] claimed that 9 out of 30 LC-cells reduced their firing rate with the onset of sleep.

A special case, possibly, has to be made with respect to the role of *serotonin* in the organization and induction of paradoxical sleep. On the basis of their findings with two 5-HT-receptor antagonists, methiotepin and metergoline, Sallanon et al.[205] and Jouvet[97] have suggested that the injection of 5-OH-tryptophan into PCPA-pretreated cats enforces the occurrence of a (non-indolaminic) 'PS-factor', which is capable of inducing paradoxical sleep in the absence of slow-wave sleep. The nature of this factor, however, is not known as yet.

George et al.[62] and Karczmar et al.[101] found that injection of cholinomimetic agents makes cats and rats shift from SWS to PS. According to Sitaram et al.[215], arecholine, a muscarinic cholinergic agonist, given 35 min after sleep onset, shortens REM-latency and increases the number of REM-periods in man. This effect is blocked by scopolamine. Hobson and co-workers[82] have shown that microinjection of bethanechol, a muscarinic agonist, into the pontine gigantocellular tegmental field (FTG) of cats is capable of inducing signs of paradoxical sleep-reduced muscle tone and ponto-geniculo-occipital spikes. In cats and rats, atropine was found to suppress paradoxical sleep[95,109,142]. Hemicholinium-3, an Ach-synthesis inhibitor, also reduces paradoxical sleep[75]. According to Jasper and Tessier[89], Gadea-Ciria et al.[60], and Haranath and Venkatakrishna-Bhatt[93] Ach-release from the cortex is increased during paradoxical sleep in comparison with slow-wave sleep. Finally, as already mentioned earlier, DSIP tends to promote paradoxical sleep more than it affects slow-wave sleep, in the cat[207].

2.4. *Timing devices*

The obvious, though plastic, temporal structure of sleep with its characteristic 24-h or then circadian rhythm requires (in any modelling procedure) a 'clock'. This timepiece must be capable of producing a rhythmical output either in the entrained condition (signalling the day-night alternation, according to outside cues) or then, autonomously in the free-running condition, with a normally somewhat longer than 24-h periodicity. Body temperature is assumed to be a major target of such timing impact, with the sleep-waking alternation possibly constituting a facultative target. Such a free-running (and entrained) timing device has been suggested already by Kleitman[113], Mills[155], and more recently by Wever[246]. Richter[198] was the first to locate the clock, on the basis of extended lesion experiments, somwhere in the hypothalamic region. More recent investigations[57,68,69,161,162,196,204] clearly established that essential parts of this timing device are situated (at least in rodents and some primates) in the suprachiasmatic nuclei (SCN). The SCN in fact seems to include all the components and characteristics necessary to produce not only a free-running circadian rhythm, but also, via optic nerve collaterals, an entrained rhythm as well. Both the intrinsic and the extrinsic beat are capable of governing the oscillation of body temperature and, when present, the synchronous alternation of waking and sleeping. Another interesting observation[72] is that a variety of signs of the sleep-waking cycle are maintained in animals with high mesencephalic transection, i.e. independent of hypnogenic areas in the lower brain stem. The knowledge about the machineries responsible for the establishment of the ultradian oscillations (the subperiods) of sleep or the sleep cycle is considerably less clear. Many authors, often quite tacidly, assume that this rhythm is generated by a continuously running clock which has a beat considerably faster than the one of the circadian time piece, and which is capable of producing what Kleitman[114] refers to as the Basic Rest-Activity Cycle (BRAC). This interpretation is supported by another observation[64] that in man (during waking and during sleep), there is a roughly 90-min alternation between episodes of higher and lower activity – in our terminology: higher and lower vigilance in a variety of systems. Still, there are no experimental observations that suggest the existence of a consolidated oscillator akin to the one incorporated in the SCN. However, there is some evidence (and the necessary theoretical considerations) that this ultradian rhythm may be generated or at least supported by the cooperation of 2 networks. On the basis of experimental results obtained with microelectrode recordings in cats, McCarley and Hobson[153] proposed a 2-component model consisting of the locus coeruleus (LC) and the pontine gigantocellular tegmental field (FTG). This oscillator was assumed to be capable of producing, through mutual interaction of the 2 components and through collateral feedback, a non-sinusoidal, phase-shifted rhythm of the LC- and the FTG-cell discharge. It has been proposed by those same authors that this oscillator exerts *sleep cycle control*. The rhythm of both components has been found to be synchronous to, but more or less out of phase with, the onset of desynchronized sleep; the FTG-discharge starts to rise in advance of PS-onset, and the LC-discharge shortly afterwards. This suggests, in the authors' view, that the increase in the (cholinergic) FTG-output causes the onset of the PS-episode. In turn, the increase in (noradrenergic) LC-output, once reaching a critical level, would stop desynchronized sleep, i.e. noradrenergic activity is assumed to serve as a PS-self-limiting device. Borbély[20] proposed a (theoretical) model machinery similar in its basic concept to that of McCarley and Hobson, He replaced the FTG- and LC-pools by 2 blocks representing NREM- and REM-sleep propensity but maintained the inhibitory and facilitatory interconnections between the 2 blocks, as well as the (inhibitory and facilitatory, respectively) recurrent feedback lines, as already postulated by the Harvard group. Assuming that REM- and NREM-propensities were under the modulating influence of both a circadian and a sleep-dependent factor, Borbély established the (at least theoretical) basis on which one could explain the sys-

tematic changes in the structure of the sleep-cycle in the course of a whole sleep period. There also is some possibility that Jouvet's[97] PS-factor, DSIP, and vasotocin if they were to include a proper delay-link and a properly timed decay course may play a role in the production of the NREM-REM alternation. Finally, there is some evidence that, at least in man, there are additional oscillators of still shorter periodicity. Lavie[137] investigated the rapid eye movement output, and noted that in 58% of all REM-periods the REMs would peak at either 0.1 or at 0.05 cycles/min; eye movements seem to cluster every 10 to 20 min. He concluded that REMs are governed by at least 3 generators: an isolated eye movement generator, a burst generator and a 10–20 min generator (in addition, it seems to this writer, to the 90–100 min NREM-REM oscillator). Little is known, though, about the location and characteristics of these generators.

3. The development of a theoretical model

3.1. General considerations

To begin with, we postulate that the Sleep-Organizing and -Regulating Apparatus (SORA) in its functional structure is a reflex-type machinery, consisting of an *input-*, a *central coordinating,* and an *output-component.* A variety of sensors – not unlike the sense-organs supplying the afferent signals in other reflex mechanisms – are assumed to feed pertinent steering and regulating information through input paths to the central component. The levels of activities in the various behavioral systems, together composing the phenomenology of sleep, are assumed to be the (reflexly) controlled variables; the 'systems' thus constitute the effector organs at the output terminal and complete the typical 5-station reflex arc.

Seen in this manner, the problem of the organization and regulation of sleep can be reduced to the problem of induction and holding, in response to a set of input signals, of the profiles of activities in the various systems. However, with this ostensible organizational simplification, another difficulty arises: the various activities (and inactivities) that together form the phenomenology of sleep, are rather heterogeneous in nature. In defining and measuring sleep one deals with, and has to estimate the intensity and/or quality of, such incongruous activities as motor patterns, instinctive acts, autonomic tonus, particular EEG-forms, and evoked responses to sensory signals. If, for proper and quasi-complete description of sleep one expands the meaning of the term behavior, one also has to include a variety of higher internal functions, such as cognition, association, acquisition, read-out, strategies in problem solving, and moods. Every attempt to gather the intensities and qualities of all these so different types of activities into meaningful profiles, makes it mandatory to supply a common and uniform scale. This scale cannot be based on the type of activity – e.g. precision of a motor act, width of the pupil, correctness of an associative performance, or number of correctly memorized test-words – but rather on a relative measure where intensity and quality is expressed in fractions (or percentage) of maximal or optimal performance. We think we have supplied, with our recently introduced 'modern neurobiological concept of vigilance'[119,121] the very instrument capable of uniformly gauging activities of even widely diverging functional nature.

The main points of this concept can be summarized as follows: We view the level and the quality of activity in any one behavioral system – where the term 'behavior' is used again in its widest sense – as manifestation of the systems' degree of responsiveness, i.e. readiness to respond with an adequate behavioral act to an incoming (specific) stimulus. We refer to this (unspecific) condition as *local vigilance.* Local vigilance determines the intensity, and, mainly with more complex behavioral acts, also the quality (the precision and adequacy) of performance. Thus, the intensity and quality of such an act or the components thereof can be used to estimate the level of the local vigilance in terms of a relative scalar. Furthermore, as every behavioral act, including the higher-function varieties, is a manifestation of a well defined *space-intensity-time* pattern (SIT) of activity within the neuronal networks subserving the making of said behaviors, the local vigilance (as a measure of behavioral responsiveness) is the direct consequence of the readiness – the *local reactivity* – of this network to respond to a set of incoming (specific) signals. Local reactivity in a given network can be estimated on the basis of the quantity and quality of the behavioral act. In a number of special cases, neurophysiological recording techniques (the EEG, evoked potentials, but also DC-potentials and even single-cell recordings) can be used to directly gauge the level of the local reactivity. This neurobiological concept provides also a substrate, an 'interface', for the impact of the vigilance-controlling instruments. It can be assumed that the controlling mechanisms exert their influence at the (neuronal) network level and that they affect vigilance indirectly, i.e. by modulation of the reactivity of the underlying networks. Applying this concept to sleep, one can describe and define the various stages and phases of this 'second existence' in terms of specific profiles of local vigilances across the many behavioral systems.

This novel way of explaining and gauging the different levels of activity brings yet another advantage in terms of a further simplification of the basic theoretical construct of the machinery designated to handle the organization of sleep. The vigilance concept is applicable not only for sleep but for the waking state as well; in fact, it was initially developed to generate a functional background for the characterization (with a uniform measure) of the intensity and precision of the manifold activities of waking. Properly focussed and controlled local vigilance in selected sets of systems was assumed to be indispensible for the adequate performance of any one of the waking activities. Now, it can be postulated that waking and sleep differ from each other not by the fact that 2 entirely different sets of behavioral systems are involved; rather, the two conditions can be set apart by different local vigilances in one common set of systems. Viewed in this manner sleep and waking cannot be seen as fundamentally different 'existences'. Both

are, phenomenologically, just manifestations of different levels of responsiveness in the various systems. They differ from each other merely by their *different vigilance profiles.*

Finally, we can assume that the controlling mechanisms involved in the adjustment of the vigilance level in everyone system are the same for both states. Thus, one can conclude that the machinery responsible for the induction and holding of the sleep-specific profiles, and the one responsible for the induction and holding of the wake-specific profiles are consolidated and integrated into one common, 'general purpose', *Vigilance-Controlling Apparatus* (VCA). One could infer, furthermore, that both the sleep- and the wake-specific vigilance-controlling outputs, in their quantitative, qualitative, and temporal patterns, are preformed in 2 (or more) specific programs or 'logics', and that these programs are integral parts of the central coordinating component of the VCA. One can also postulate that the programs are activated (and inactivated) – usually in an alternating manner – by a variety of inputs, carrying timing and feedback-signals, as well as other types of information involved in the modification of the time-course of the sleep-wake sequence and, possibly, of the quantity and quality of each one of the 2 conditions. By-and-large, one can state that the organization and regulation of sleep is but 1 of the 2 main tasks of this larger VCA.

With these considerations and assumptions we have established the outlines of the structure of a *general and simple model* of the apparatus assumed to organize and regulate sleep and waking (fig. 1). From a detailed study of the phenomenology of sleep, both under normal conditions and in response to a variety of modifying factors, one can infer a number of additional properties of this putative machinery, necessary to properly perform its sleep-organizing and -regulating tasks (besides its involvement with the preparation of the various readiness levels necessary for proper performance of the manifold activities of waking). These properties then allow the inclusion of additional elements into the general model and the conversion of the latter into a true *theoretical model* of the VCA.

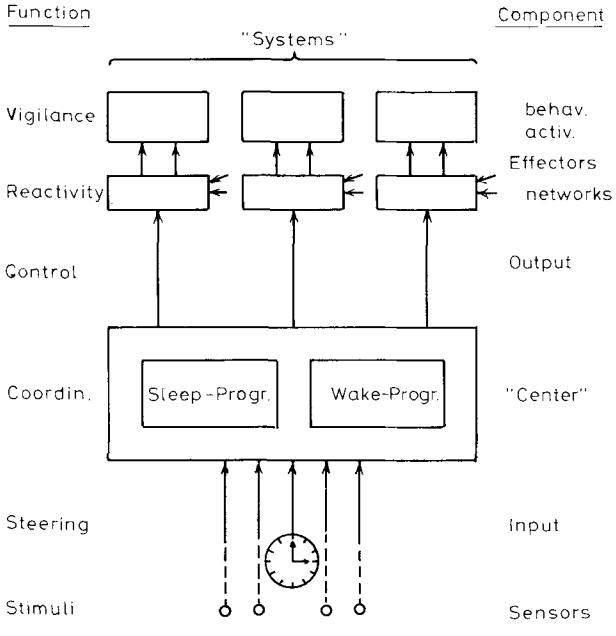

Figure 1. General model of sleep- (and waking-)organizing apparatus, i.e. the 'general purpose' vigilance controlling machinery. Note: reflex-type of design with input, coordinating 'center', and outputs; and with sensors and effector-organs in front of input-, and downstream from output-component, respectively. At left side: function of various components; horizontal and oblique small arrows, specific inputs to networks. Note: sleep- and wake-programs within central coordinating component.

3.2. The phenomenology of sleep

Behavioral observations, psychophysiological test procedures, and electrophysiological probes (e.g. the EEG) have led us to distinguish 2 different phases – NREM and REM – and, in man, within the continuum of the former, 4 different, though somewhat artificially fixed stages of sleep (NREM 1–4). In man stages 3 and 4 usually are referred to as slow-wave sleep (SWS) or, less frequently, as delta sleep. In infrahuman mammels the whole continuum of NREM-sleep usually is called SWS, and some authors[136] distinguish between SWS 2 and SWS 1, depending on whether there is more or less than 50% of slow-wave proportion. For the sake of simplicity we are using in this treatise the terms NREM- and SW-sleep interchangeably, and both to refer to the non-REM-sleep portion of the whole sleep period. Applying (for reasons already outlined) the local vigilance concept one is led to note that each one of the phases and, though to a less discrete extent, each one of the 4 or 2, respectively, stages is characterized by its own and specific vigilance- and reactivity profile. To establish a baseline, we assume that during *quiet waking* most systems exhibit an intermediate level of vigilance; they are in a 'stand-by' condition. To provide the adequate background for any one of the various activities during *active waking*, the local vigilance can be expected to increase, in a selective manner, to optimal levels to make any one of the systems involved in those activities ready to perform.

If man (for animals the evidence is less clear) drifts into *stage 1* (NREM) sleep, vigilance in the sensory and motor systems drops to some extent; arousability decreases and muscular tone and reflex excitability are somewhat attenuated. However, vigilance in some components of the cognitive and affective systems seems to remain at intermediate, or even to rise to higher levels; one experiences vivid hypnagogic hallucinations. The pronounced beta-pattern observed during this stage in the cortical EEG, can be seen as the electrophysiological evidence of elevated (local) reactivity in the networks subserving the organization of these higher functions. Heart rate, blood pressure and respiratory activity are reduced; these changes, together with the typical miosis, clearly indicate that there is a shift from the ergotropic to the trophotropic-endophylactic side of autonomic tone.

With the shift to *stages 2, 3, and 4* (NREM), vigilance in the higher function systems is markedly attenuated. Consciousness is virtually lost and it becomes increasingly difficult to awaken an individual. The motor and

some fundamental aspects of the sensory systems, however, are still held at close to intermediate levels of vigilance, as revealed by the still existing muscular tone, the ready excitability of the spinal reflexes, and the well maintained sensory evoked potentials. During 'deep' stages of sleep, man and animals are still capable of differentiating between familiar sensory stimuli on the one hand and unfamiliar ones, on the other; they continue to sleep or wake up, accordingly. We referred to the piece of machinery handling this sleep- as well as individuum-protecting mechanism (which stays awake while many other systems reveal low vigilance) as *analyzer*[115]. With the development of stages 2, 3, and 4, there is a further shift towards the trophotropic-endophylactic pattern in the autonomic functions. In mammels, the change from the (initially) desynchronized towards the increasingly synchronized pattern in the cortical EEG is the electrographic expression of a drop in the reactivity of the cortical networks. The amount of slow-wave output can be, and has been, used as an indicator of (slow-wave) sleep intensity or propensity[20]. However, one has to be aware that the synchronized pattern of the cortical EEG is merely a local sign; it indicates intensity of sleep-like low reactivity for the cortical networks only, and can therefore not be seen as a representative sign for 'intensity' of sleep in general. The fact that the arousal threshold for e.g. conditioned behaviors or for autonomic reactions is not linearly related to slow-wave output[249], clearly supports this notion.

The vigilance profile changes fundamentally with the transition from NREM- to *REM-sleep*. Responsiveness in the majority of the motor functions drops to very low levels; tonus and reflex-excitability – e.g., the H-reflex – are virtually gone. Yet, the system responsible for the organization of the rapid eye movements – which probably subserve some homeostatic, sleep-protecting function[115] – seems to retain a high level of reactivity. Also the systems handling conditioned (motor) behavior must retain a fairly high vigilance as evidenced by the fact that learned responses can be executed during REM-sleep[248, 249]. Furthermore, there is high vigilance in at least some parts of the affective, cognitive, associative and memory functions. Adequate responsiveness in the former three enables the dreamer to experience his reveries; good responsiveness in the latter is indispensible for the supplying of engrams to enrich the dreams, and for the storing of the experience for later recall. Still, some important controlling function seems to be amiss – being dormant or working at low levels of vigilance – during REM-sleep, so that associative and cognitive functions can produce the well-recognized *dereistic* (Bleuler), 'free-wheeling type of thinking'. What ever constitutes this anti-dereistic checking function, and why it should reveal such low levels of vigilance while other higher functions are wide awake during paradoxical sleep, we do not know. It is of interest, though, to note that this function's vigilance runs parallel to motor vigilance, and thus to proprioceptive feedback. Enhancement during REM-sleep of the cortical network reactivity, as the basis of heightened local vigilance in some of the higher functions, is signalled by the renewed apperance of an arousal pattern in the (cortical) EEG. In many experimental animals, it has been demonstrated that the hippocampus, during paradoxical sleep, exhibits its own and specific signs of heightened local reactivity, namely the characteristic theta-waves that otherwise are observed during the orienting response, or following reticular stimulation[107].

To these basic qualitative and quantitative properties of sleep one has to add the temporal parameters. Sleep in animals and man, under natural day-night conditions, is a 24-h, cyclic phenomenon. Periods of the highest sleep density, or the main sleep periods, coincide with one particular stretch of the natural day, and alternate with periods of low sleep output during the remainder of the day. Adult man, under natural day-night conditions, starts sleeping when the body temperature is on its descending limb, and wakes up when core temperature begins to rise; that is to say, late evening and early morning, respectively[258].

In man and animals the sleep periods are clearly divided into subperiods; in man these are of about 90–100 min duration. They typically consist of a NREM- and a REM-part. In man the duration of these subperiods varies over the course of the night in a curvilinear fashion[24]; it also varies in dependence of stage 3 + 4 and/or REM-sleep content within an individual cycle. Under natural conditions, i.e. when the subject is entrained to the normal 24-h cues, NREM-sleep is most pronounced at the beginning, while REM-sleep is preponderant in the later parts of the sleep period[50]. The peak of REM-output coincides with the trough of the body temperature curve[241]. Under free-running conditions, i.e. in the absence of (outside) time cues, the human and animal organism maintains a sleep-waking cycle; yet its frequency is somewhat slowed down. Body temperature oscillates within a period of, on the average, 25 h[246]. Sleep-onset time moves to the time of the temperature minimum, or, in particular in the course of long experiments in the 'bunker', it may exhibit its own rhythm quasi-independent of the temperature cycle. Yet, in the latter case, highest slow-wave output still occurs at, or shortly after, the time of the body temperature nadir[258]. REM-output is also highest at the time of the temperature trough[31].

Important information concerning the characteristics of the organization and regulation of sleep can be derived from experiments with artificial *somnodeprivation*. From such experiments there is evidence for a variety of compensatory phenomena. Sustained *partial* sleep deprivation, i.e. reduction of the daily sleep time, leads to a (relative) increase in slow-wave sleep, with a consecutive (relative) enhancement of slow-wave output, and to a decrease in REM-sleep[242]. *Selective* deprivation, e.g. the artificial reduction or complete elimination of stage-4, is followed by a (selective) stage-4 rebound in the first recovery night[1, 2]. Dement's[36] classical experiment demonstrated the typically long-lasting REM-rebound after selective REM-deprivation.

Similar observations have been made in animals[98]. Agnew and co-workers[2] demonstrated that the rate of stimuli necessary to prevent the appearance of stage 4 sleep increases over the course of the first deprivation night and tends to level off later in the experiment. In turn, the rate of stimuli necessary to prevent REM-sleep

increases but slowly, yet steadily over the whole course of the experiment. A differential time-course of rebound is evident when subjects are totally sleep-deprived; stages 3 and 4 are made up for, mainly in the first post-deprivation night, whereas REM-sleep recovers and overshoots preferably in the second to fourth night[249].
Finally, sleep has been shown to vary in duration and in structure depending on the quality and quantity of the various activities that fill the waking period preceding the sleep period under consideration. Bodily activity, e.g. heavy training of athletes, leads to an increase in NREM-sleep[14]. A similar effect of physical work was demonstrated in cats[81]. Bert[18] has shown that macaques' sleep is drastically changed depending on the waking activities. Torsvall and Åkerstedt[230] found that exercise (a race) enhances NREM-stage-1 and stage-2 sleep, reduces REM-sleep, and doubles the latter's latency. REM-sleep in man and animals has been noted to increase after enhanced learning efforts during the preceding waking period[47,138,257]. While these and similar findings have been challenged, they still point towards the fact that somehow the quantity and the type of waking activity projects onto the organization of sleep, and thus underlines its regulated nature.

3.3. The functional properties of the Vigilance-Controlling Apparatus

From the phenomenology of sleep, both under basic conditions and in dependence of a variety of internal and external, modifying factors, one can infer the pertinent properties of VCA necessary to perform the operations involved in the organization and regulation of this function. In particular this apparatus is
1) capable of controlling individually and selectively the local reactivity in a multitude of neuronal networks, and, thus, the local vigilance in the behavioral systems subserved by these neuronal machineries;
2) capable, relying probably on preset inherent programs, of producing the particular sequential profiles of reactivity and vigilance across the various systems which have been recognized as being characteristic for the various stages and phases of sleep;
3) capable of reacting to a variety of internal stimuli – signalling the lack of SWS and/or of PS – by varying accordingly the controlling output to the systems and thus adjusting in quantity, quality, and duration, the various reactivity and vigilance profiles;
4) capable of promoting, or hindering, the emergence of the various sleep-specific profiles in dependence (a) of outside cues, signalling (real) time of the day, (b) of an internal circadian timing device (CTD) that also controls the periodicity of body temperature, or (c) of a CTD-independent rhythm;
5) capable of producing, at least during the main sleep period, an ultradian rhythm as manifested by the alternation of NREM- and REM-sleep episodes; it can modulate in dependence of the circadian rhythm, the frequency of these subperiods and their internal structure (i.e. the relative amounts of NREM- and REM-sleep;
6) capable of reacting to a variety of internal stimuli, signalling the type and intensity of activities prevailing during the preceding waking period and, accordingly, of altering its profile-controlling output;
7) capable of reacting to a variety of external or internal (in the main, sensory) stimuli – e.g., warning, or else monotonous and familiar signals – and, accordingly, of varying its controlling output to the networks.
Though not directly concerned with the present topic, one has to mention that the VCA is also capable of establishing, in response to a variety of other signals (including the input or 'non-input' from the time-piece) the basic levels of responsiveness (i.e. vigilance) in the various functional systems necessary for proper performance of the manifold activities that fill and characterize the waking periods.

3.4. The emerging theoretical model – a block diagram

We postulate, as already mentioned, that the functional elements and, thus, the various operations involved in the organization and regulation of sleep are integrated in a larger structure which we refer to as the Vigilance Controlling Apparatus. This VCA is assumed to be designed in a fashion akin to that of the machineries that handle reflexes, in particular their more complex, modulated and mixed – proprio- and heteroceptive – variety. Accordingly, VCA can be expected to consist of 3 components: an input-, a central coordinating, and an output-part.
The *output channels* are assumed to exercise executive power for the individual and selective control of the (local) reactivity in the various networks and, thus, of the (local) vigilance in the behavioral systems subserved by these networks. It is postulated that the executive signals are conveyed in an antagonistic fashion; that is to say, every network is under the influence of an up- and a down-regulating instrument.
The *central coordinating component* is assumed to produce, in response to a variety of input signals, and on the basis of some inherent, preset programs (in its simplest version: an S- and a W-logic) that particular output through the executive channels which results in the reactivity- and vigilance-profiles characteristic for sleep, on the one hand, and necessary for proper performance of the various activities of waking, on the other. The S-program can be assumed to be subdivided into an SWS- and a PS-subprogram, interconnected by a time-dependent switching device (and/or mutual inhibitory pathways) that ascertains the alternation of the 2 phases of sleep and thus, the establishment of the subperiods of sleep or the sleep-cycle.
The *input channels* perform the actual steering and/or regulating function. These inputs are of the open- as well as of the closed-loop variety. With respect to the organization of sleep, one can postulate: (1) pathways carrying signals conveying feedback information from the tissues (in particular the CNS) about their recent 'history' (i.e. intensity, duration, and type of waking activity, but also amounts of SWS and PS) and about their present condition; (2) pathways carrying signals from a circadian timing device which produces its own beat autonomously, or oscillates in dependence of outside cues; and (3) pathways carrying signals originating

in a variety of sensory systems (with an intecallated analyzer) conveying information about conditioned and unconditioned stimuli.

A *Block-Diagram* satisfying the conditions, properties, and containing the basic functional elements just mentioned, is depicted in figure 2.

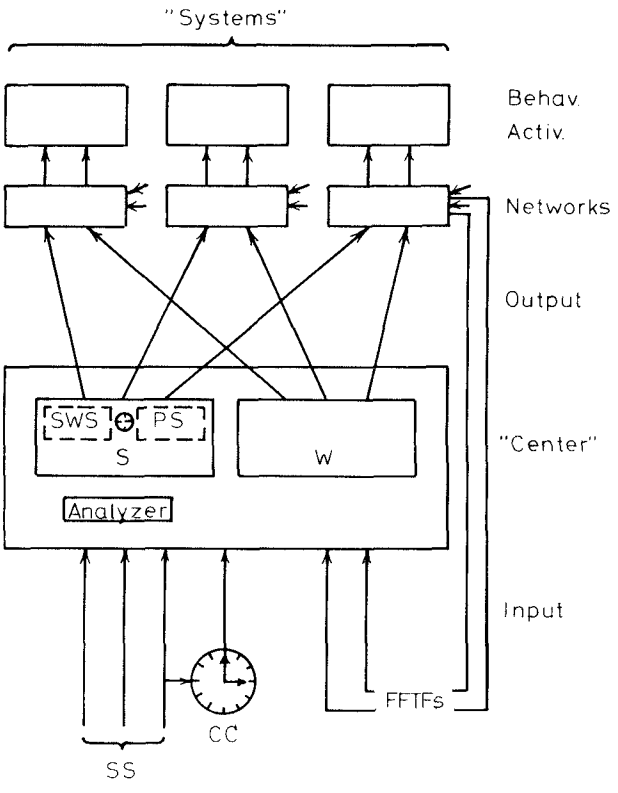

Figure 2. Theoretical model fo sleep- (and waking-)organizing apparatus, as construed on the basis of evidence presented in section 3. SWS and PS stand for slow-wave- and paradoxical sleep-subprograms, respectively, within the S-program. W, Wake-program; FFTF, feedback-from-the-tissue-factors. Note: circadian clock (on input-side) with entraining collateral from sensory afferent systems. The Analyzer is the decision-maker, downstream from sensory input. Controlling (or executive) outputs from the S- and the W-program are in charge of adjusting of reactivity in networks, and, thus, of vigilance in behavioral systems. Note: ultradian timing device between the SWS- and the PS-subprograms for generation of sleep-cycle.

4. Filling-in the blanks – Towards an integrated model

4.1. Output- or executive functions (fig. 3a)

4.1.1. Vigilance-enhancing instruments

At least 3 of the ascending (and descending), vastly diverging, transmitter-specific pathways, the noradrenergic, the dopaminergic, and the cholinergic channels, regarded by some as components of the classical activating system, appear to be 'tailor-made' to act as executive instruments subserving a reactivity- and vigilance-enhancing function. An 'alerting' role of NA was proposed already by Jouvet[96]. Mason[146] is of the opinion that noradrenergic pathways, NA-fibers in the dorsal bundle, are implicated in the making of high local vigilance in the systems that subserve selective attention. There is in fact an overwhelming variety of experimental evidence (as reviewed in section 2) to support this interpretation. Elevation of (central) *noradrenergic activity* by well-controlled electrical or pharmacological procedures is clearly followed by enhancement of vigilance in a variety of behavioral systems, known to be typically active during waking and, perhaps to some lesser degree as well as spatially restricted, during paradoxical sleep. Lesions of noradrenergic pathways affect mainly higher functions, such as the cortical EEG, memory and extinction, filtering, and attention. But such manipulations do not, or only to a minor degree, impair primitive functions, such as locomotion, grooming, or feeding; nor do they disturb the basic sleep-wake cycle. It has been demonstrated that during waking, and, to some extent, also during paradoxical sleep, noradrenergic activity is higher than during slow-wave sleep. The intimate mechanisms by which noradrenaline can improve the networks' ability to handle information, are not well understood as yet. Most investigators, e.g. Dillier et al.[42] and Olpe et al.[171], found that noradrenaline, applied or released locally, exerts an inhibitory influence on the firing rate of most of the cortical neurons, and thus assumed that this amine could not be involved in such up-regulation. There is, however, some evidence that it is not the tonic discharge rate, but rather the enhanced signal-to-noise ratio, observed in cortical neurons under the influence of locally applied NA, that constitutes an important parameter within a set of probably several such reactivity-enhancing mechanisms. Waterhouse et al.[237,238] found that microiontophoretic application of NA drives excitatory as well as inhibitory responses generated in single cells throughout the vertical extent of the forelimb region of the rat's somato-sensory cortex. The authors concluded that those results are consistent with a modulatory role, rather than a specific information transfer function, of NA. Enhancement of the signal-to-noise ratio to be the main function of NA, was also proposed by Moises and co-workers[158]. A similar interpretation is in place for the observations of Olpe and collaborators[171] and of Dillier and co-workers[42], concerning the effects of locally applied NA, or of locus coeruleus stimulation.

Cholinergic pathways also are quite likely to act as executive channels, involved in the enhancement of responsiveness in mainly higher functional systems. Elevation of central cholinergic activity leads to activation of the cortical EEG, and, under certain experimental conditions, induces the vigilance profile characteristic of paradoxical sleep. Interruption of cholinergic transmission not only leads to the appearance of a marked slow-wave output in the electrocorticogram, but also to an impairment of such higher functions as memory processes and conditioned behavior, while not affecting, or even furthering, locomotion, grooming, and feeding. Ach-release from the cortex is intensified during waking and during REM-sleep.

A third group of diffusely projecting, ascending aminergic pathways, the *dopaminergic channels,* at least their nigro-striatal part, seems to be involved in the enhancement of what one may refer to as motor vigilance. Injection of dopamine, or of other DA-receptor agonists, enhances locomotor activity. Interruption of nigro-stri-

atal DA-connectives leads to akinesis and to a loss of motor initiative. Additional, caudally projecting nigrofugal DA-pathways[74] may assume a similar role. Stereotypies, produced in rodents through manipulations that lead to hyperdopaminergia, may well be the manifestation of a hypervigilance in some parts of the central motor systems. In view of the findings of Kelly et al.[106] one may have to draw the conclusion that both the striatum *and* the limbic forebrain play a role in the making of motor responsiveness, yet, possibly with some differentiation as to the type of motor activity. In turn, high dopaminergic activity may exert a suppressive influence on attentive and conditioned behavior.

The fact that lesions in the A_{10}-nucleus are followed by a reduction of beta-output in the frontal cortex[160] does not oppose the notion of such a primarly 'motor' role of DA. It is well established that the cerebral cortex, including extra-motor-cortical regions and descending COEPS-components, plays an important role in the organization of a variety of motor activities. In turn, these lesion effects may suggest that dopaminergic pathways are also involved in the vigilance control of some non-motor, possibly primitive functions organized in part by the neocortex.

According to Vanderwolf et al.[235] *phenylethylaminergic channels,* among other traceaminergic pathways, may act as additional executive instruments. The fact that β-phenylethylamine drives 'type-2 behavior', as claimed by these authors, may suggest that this traceamine is involved in the enhancement of vigilance mainly of what we refer to as primitive functions.

There is evidence that *polypeptides,* in particular those of the activating variety, play a role as up-modulators of aminergic transmission; they may exert their influence either via co-release[83], via side-input to enhance liberation of the ligand, or by strengthening the sensitivity of the receptors. Such a modulatory role could explain the effect of Ala-metenkephalin, injected directly into the A_{10}-nucleus, or the memory-improving effect of either vasopressin or ACTH-fragments. According to Tanaka et al.[226] vasopressin increases NA-turnover in various brain regions. Olpe and Baltzer[170] have shown that (Arg)- and (Lys)-vasopressin, applied microiontophoretically, drives the firing rate of noradrenergic cells in the locus coeruleus. Vasopressin affects, if given locally to isolated hippocampal slices, the firing of (presumptive) pyramidal cells[44]. The experiments of Miyamoto and Nagawa[157] suggest an interaction of TRH with dopaminergic transmission mechanisms in the nucleus accumbens. TRH exerts an activatory influence on cerebral noradrenergic neurons[104] and facilitates the excitatory action of Ach on cortical units[254]. In turn, it has been shown that enkephalin produces excitation of pyramidal cells in the hippocampus through inhibition of supposedly inhibitory interneurons[151, 256].

Some uncertainties and even contradictory evidence notwithstanding, by far the greatest part of the evidence supports the view that the 3 (or 4) aminergic transmission systems discussed so far, probably with the cooperation of some polypeptidergic channels, are (local) vigilance-enhancing instruments. It can be assumed that, according to the particular vigilance profile prevailing during the various stages and phases of sleep (and of waking) 1, 2, or all 3 of these pathways are either selectively activated, or then inactivated in order to allow for a permissive drop of local vigilance and thus to facilitate the onset of sleep.

4.1.2. Vigilance-suppressing instruments

Serotonergic pathways – while probably also subserving a number of other central functions, such as temperature regulation, endogenous analgesia – most definitely play a pertinent role in the active induction and maintenance of sleep. They are capable of enforcing that particular low level of vigilance and reactivity in the majority of systems which we have come to recognize as typical of slow-wave sleep. Pharmacological activation of serotonergic transmission produces signs of reduced vigilance in a variety of effector systems. Destruction of serotonergic neurons, inhibition of 5-HT-synthesis, or blocking of 5-HT-receptors is followed by insomnia. Also, brain serotonin levels vary in a circadian fashion, reaching highest values during the period of highest sleep density and falling to minimal levels during the active periods. With this oscillatory pattern, serotonin exhibits a circadian rhythm which is shifted in phase by about 180° in comparison with that of NA. This interpretation of serotonergic channels as a vigilance-suppressing instrument is not in contrast to Trulson and Jacob's[233] view that this indolamine controls general arousal in that it prevents hyperarousal.

Serotonergic pathways exert their influence in an overall fashion; the 5-HT-channels are less selective and more generally effective than the vigilance-enhancing Na-, Ach-, and DA-pathways. Yet, little is known about the particular mechanism(s) through which 5-HT would lower reactivity in the networks, except that it exerts in general inhibitory influence on (single) units. Neither do we know anything about the particular quality of low reactivity in the networks as promoted by serotonin. While we are aware that the serotonergic fibers project mainly to the superficial layers of the cerebral cortex[134], we have no evidence as to how the activation of 5-HT-receptors prepares the receiver cells for a possible 'detiring' process which takes place during sleep. Yet, there is evidence that the indolamine, in addition to its (local) vigilance-reducing effect, is capable, through modulation of a feedback loop, of counteracting arousal mechanisms[116, 117, 123]; this additional mechanism will be discussed in more detail later in this paper.

The sedating or behaviorally depressing effects of treatments with GABA-receptor agonists may suggest at first glance that gabaergic channels also play a role as executive, reactivity- and vigilance-reducing instruments. Yet, this definitely cannot be the case. In the first place, there are no data suggesting the existence of long-axoned, ascending gabaergic fibers, akin to the aminergic pathways. Also, gabaergic fibers, quite unlike the aminergic pathways, do not diverge to any appreciable degree; they rather connect according to the point-to-point principle. With such a projection arrangement they would be ill-suited to act as reactivity-controlling instruments of whole networks. Thus, we rather see the majority of the (usually short) gabaergic interneurons as important operational elements within

the various networks of the effector systems. They are situated downstream from the executive channels, where they are involved in the making of those particular neuronal activity patterns which form the vary basis of particular behavioral outputs. Seen in this way, gabaergic neurons, among many others, are to be considered as receiver elements of executive regulatory output, rather than as carriers of executive signals.

4.1.3. Autonomic output

The autonomic phenomenology of sleep is characterized by a shift from the preponderantly ergotropic to the preponderantly trophotropic-endophylactic status. It is well recognized that this shift is manifested, in the vegetative periphery, by a clear decrease in sympathetic-noradrenergic tonus, paralleled by a (partial and more selective) increase in parasympathetic-cholinergic tonus. One can assume that higher central autonomic structures – in particular the hypothalamus with its posterior ergotropic, and its anterior trophotropic-endophylactic division[79] – represent again the networks of systems akin to those involved in the making of the various 'animalic' behaviors. Consequently, reactivity in these networks and thus vigilance in the (peripheral) ergotropic and trophotropic-endophylactic representatives can be assumed to be under the control of output from the W- and the S-programs, respectively. It is not unlikely, but not well established as yet, that noradrenergic, cholinergic, and possibly trace-aminergic pathways drive reactivity in the posterior hypothalamus, whereas serotonergic fibers (known to project to the diencephalon) drive reactivity in the anterior hypothalamus. With such an arrangement the autonomic regulation during waking and during sleep (at least slow-wave sleep) would appear to be well under control.

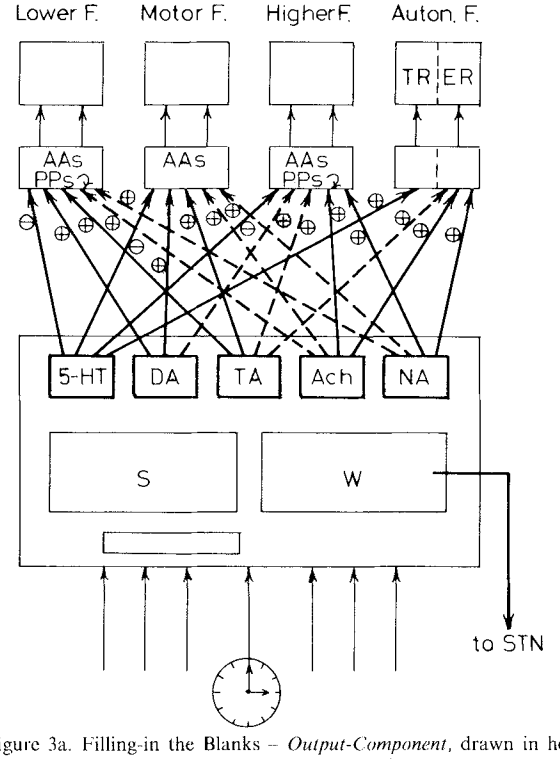

Figure 3a. Filling-in the Blanks – *Output-Component*, drawn in heavy lines. Full heavy lines indicate the (mainly) aminergic controlling pathways to the networks. ⊕ and ⊖ indicate (selective) reactivity-enhancing and -reducing, respectively, effects of these controlling instruments. Less likely controlling paths are drawn by dashed lines. NA, Ach, TA, DA, and 5-HT indicate the pools of somata of noradrenergic, cholinergic, traceaminergic, dopaminergic and serotonergic pathways, respectively. TR and ER stand for trophotropic-endophylactic and ergotropic autonomic functions. Aminoacids (AAs), for instance GABA, act as local transmission links within the networks. Local transmission-modulating polypeptidergic mechanisms at the receptor-sites of the networks are indicated by PPs. Arrow to STN: connection from the activating (part of the) reticular system to the solitary tract nucleus; it is the efferent component of the reticulo-solitario-reticular feedback system.

4.2. Input- or steering functions (fig. 3b)

4.2.1. Clock-work

The suprachiasmatic nucleus (SCN) seems to have all the functional characteristics necessary to generate not only a free-running circadian, but also an entrained rhythm; the latter in response to outside cues. Either one of the rhythms is capable of governing the typical sleep-waking alternation so some extent. As to the connection between the clock and the 'center', it is of interest to note that the sleep-inducing vasoactive intestinal peptide (VIP) occurs in high concentrations in the cells of the SCN[26]. Based on such observations, Groos[68] put forward the notion 'that VIP and other projections to the paraventricular diencephalic nuclei and to the central gray mediate the control of the circadian sleep-waking cycle'. The fact that VIP is a sleep-inducing peptide suggests that clock activity and VIP-release should be at their zenith some time during the sleep periods. Also of interest is the observation of Shimatsu et al.[214] that serotonin (perfused in concentrations of 10^{-6}M through the ventricular system) enhances VIP-release from the hypothalamus. This may indicate that (intraventricular) 5-HT exerts an amplifying influence on the (sleep-inducing) clock-input. But then, according to Kaji and co-workers[100], cholinergic mechanisms also are involved in the processes that govern the release of VIP into the intraventricular space. Concerning the locus of impact of VIP on the center, we have learned from Hanada and Kawamura's[72] study that sleep-waking alternation is maintained (to some extent) after high transection of the brainstem; evidently VIP seems to exert its influence, at least in part, somewhere high in, or above, the mesencephalon.

It is somewhat more difficult to explain, in terms of well established mechanisms, the generation of the ultradian cycle of sleep, i.e. the subperiods of 90–100 min duration in man, of some 30 min in the cat, and of about 13 min in the rat. These subperiods clearly are manifestations of systematic alternations between episodes of slow-wave and paradoxical sleep. There is some evidence, as described earlier, that there is an oscillator based on the reciprocal interaction between 2 cellular aggregations, the locus coeruleus and the pontine tegmental gigantocellular field[153], or between 2, so far hypothetical, pieces of networks representing a NREM- and REM-sleep controlling process[20]. As these pieces of machinery would clearly have to be considered parts of what we refer to as central coordinating apparatus, we shall discuss them in more detail when dealing with the 'center'.

4.2.2. Humoral feedback from the tissues

There is enough evidence that at least 1 of the hypnogenic polypeptides, *Factor-S,* subserves a role as carrier conveying information about the recent history and the present conditions of the effector-networks toward the center. Factor-S promotes the onset, and prolongs the duration, of sleep in animals. According to Pappenheimer[173] Factor-S is produced in the brain; it is infused into the ventricular space; and it increases in concentration with the time of (enforced) waking. We may add that, in all likelihood, it is catabolized (or eliminated) during sleep; this possibly manifests what we refer to as the 'detiring' effect of sleep[115]. Factor-S can be assumed to constitute the recurrent link of one of possibly several feedback loops. Concerning the locus of impact of this feedback factor, Pappenheimer[173] claims that 'it has to reach the aqueduct or places below' to be effective; accidental blocking of the flow of CSF from the third to the fourth ventricle eliminates the sleep-inducing effect of Factor-S if injected into the ventricular system of the forebrain. However, Krueger[131] assumes, on the basis of microinjection studies, that the site of action of Factor-S lies between the basal forebrain and the meso-diencephalic junction. As to the mode of action of this hypnogenic factor, we suggested some 16 years ago[115] that 'neurons or humoral factors arising in the clock alternately enhance and depress the sensitivity of the sleep center to the action of the hypnogens and, thus, alternately facilitate the onset of sleep and the onset of waking, respectively'. Borbély[20], further developing this notion, assumes that a sleep-dependent process and a sleep-independent process (our 'time-piece') interact in an additive manner to determine sleep propensity and duration, both under entrained and under free-running conditions and after an enforced waking period. Our earlier speculations and Borbély's[20] interpretations are supported to some extent by the results of a simulation experiment performed by Daan and Beersma[32], using data generated by Åkerstedt and Gillberg[5]. In view of Krueger's[131] notion about the site of action of Factor-S, and Hanada and Kawamura's results[72] about the point of impact of the clock signals, one would have to conclude that the locus of interaction – the mixing device or *Integrator* – of the 2 inputs can be placed somewhere in the rostral brainstem.

Little is known about the point of origin, the wet pathway, and the mode and locus of action of DSIP, the delta-sleep-inducing peptide. Hösli et al.[85] noted that this substance binds with small, medium-sized, and large neurons of brainstem cultures, but not to glia. Aside from the fact that binding (if one interprets those authors' photomicrographs correctly) is overwhelming, such investigations yield little pertinent information; one knows nothing about the original function of the cultured cells and thus has no insight into the system they belong to. According to Monnier et al.[159], DSIP promotes, in rabbits, slow-wave sleep. Yet those and other authors who have worked with this compound, have failed to measure in animals the exact yield of DSIP in dependence of waking- or sleeping-time. Only Kastin and his colleagues[102] have some evidence that in man, DSIP plasma concentration is higher at 16.00 h as compared with 08.00 h. Little can be said as yet about the functional role of this putative hypnogen. It may subserve some input function akin to that of Factor-S; if so, and if one is ready to accept Scherschlicht's[207] findings, that in cats DSIP promotes preferably paradoxical sleep, this compound may assume a role as a signal carrier for REM-pressure. Such a notion may be supported by the observation that DSIP is found in high concentrations mainly during slow-wave sleep, i.e. the precursor of paradoxical sleep. The fact that DSIP in man affects, in a positive fashion, higher functions in addition to its presumed sleep-inducing effects[211] could be seen as yet another indication that this peptide is somehow involved with the generation of the higher-function experiences of REM-sleep. One may speculate that DSIP (in that case a misnomer) signals local exhaustion – after heavy learning or other higher function performance – in the tissue to promote, after delay, the putative restorative activity of paradoxical sleep.

There is also little evidence about how *vasotocin* plays its role as a (putative) hypnogenic input. This polypeptide appears to be manufactured in the pineal gland and it is not unlikely that it is released into the ventricular space to act, after transport to the fourth ventricle, at lower brainstem sites. We have postulated as will be described later such a locus of action for intraventricularly released serotonin to explain the indoleamine's role as an anti-arousal factor through an attack at the area postrema. It is possible that the pathway of vasotocin and that of serotonin run parallel and that both information channels project, in an interacting manner, to the same site. Such a notion would be supported by the findings of Pavel et al.[177] that vasotocin exerts its effect through interaction with serotonergic transmission. Jouvet's[97] PS-factor may also be listed under the heading of 'inputs from the tissues', and as such could be assumed – as already mentioned – to play a role in the establishment, or in the modulation, of the NREM-REM-cycle.

4.2.3. Additional inputs

There is evidence that the anterior brainstem which houses in all probability – as will be discussed later – the central coordinating component of VCA, is under the influence of a variety of additional (neuronal) inputs, arising at various sites of the CNS. In particular, cortico-reticular influences, as demonstrated by Tower[232], Hugelin et al.[86, 87] and many others, are of importance in the present context. This writer[125], using evidence about such downward signal flow and about ascending activating systems, has developed a model of a 'two-tailed' cortico-reticulo-cortical feedback arrangement, capable of stabilizing and concentrating the responsiveness or reactivity of cortical networks. On the basis of its very functional structure and characteristics, this system can be assumed not only to focus high reactivity to one hemisphere, but also, within one cortex, to one particular network. It stands to reason, though, that such a focussing mechanism comes into play mainly during the various activities (with their specific vigilance profiles) of waking, and, possibly, of REM-sleep, but not during slow-wave sleep.

It is well recognized that sensory stimulation, especially if intense and of particular modular specificity, is apt to

inhibit the onset of, or to interrupt, sleep; but even weak stimuli, if unfamiliar, non-habituating, and non-monotonous, are capable of suppressing sleep. In turn, sensory stimulation, if containing familiar and habituated signals, and, in particular if applied in an monotonous fashion, can in fact support or even induce sleep. Lovell and Morgan[143] observed that acoustic stimuli which were made to increase and decrease in intensity at regular intevals, produce sleep in man. Pompeiano and Swett[182,183] found that, as already mentioned, low-rate stimulation of limb nerves of freely moving (conscious) cats leads to synchronization of the cortical EEG, often followed by behavioral sleep. Oswald[172] reported that even unpleasant, painful electrical shocks, if applied at regular intervals, lead to short bouts of sleep between the stimuli, and then to continuous sleep which, at times, may reach stage C (i.e. stage 2). Such phenomena may be related to Pavlov's Internal Inhibition[179]; he has noted that animals during extinction of conditioned reactions invariably become drowsy and eventually fall asleep. The analyzer, mentioned earlier, is capable of differentiating between familiar, non-significant, and unfamiliar, potential danger-signalling stimuli[115]. It is quite probable that the sensory pathways, or collaterals thereof, feed towards this discriminating apparatus, to enhance, or else suppress, its activating influence, and thus to override, or support, respectively, the influence of sleep-inducing and -maintaining factors. In the present context one can mention also the observations of Puizillout and Foutz[186]. They noted that electrical stimulation (30 pps) of the afferent vago-aortic nerves of encéphale isolé cats prolong, or even induce, periods of paradoxical sleep. This relates – mutatis mutandis – to our own work[127]; we have reported that distension of the cat's carotis sinus, isolated from the general circulation but with intact innervation, produces in the cortical EEG signs of synchronization, i.e. of reduced local reactivity. There is an additional feedback loop, involved as a reactivity- and vigilance controlling mechanism, that deserves mentioning. This loop originates in the reticular formation; it curves through the area of the solitary tract nucleus and projects back bilaterally to the reticular formation. Magnes et al.[144] have shown that electrical stimulation of the region of the solitary tract nucleus is followed by signs of synchronization in the electrocorticogram. According to Bonvallet and Allen[19] the reticulo-solitary-reticular loop is capable of checking excessive ascending activity in the reticular core. Interruption of this feedback loop at the level of the STN releases the ascending activating system. We have shown that intraventricular or intravasal application of serotonin, probably acting at the area postrema or structures close-by, is liable to increase amplification in the STN, thus enhancing the inhibitory feedback activity to the reticular formation and, consequently, curtailing ascending arousal or vigilance-enhancing influences[123]. The findings of Roth et al.[202] are in support of this interpretation which would assign to serotonin, in addition to its executive vigilance-suppressing function, also a role on the input side of the sleep-organizing machinery.

Finally, one has to mention *recurrent pathways* connecting the projection sites of the output or executive channels with the latters' point of origin. The striato-nigral feedback tracts, which probably include gabaergic links[70] may serve as an example of such an arrangement. According to Nishikawa and Scatton[169], GABA and other gabergic agonist agents, if applied to the dorsal raphé nucleus (or given systemically) exert an inhibitory influence on (striatal) 5-HT release and transmission. Here one must mention also the recurrent collaterals projecting back to the cells of origin of the executive neurotransmitter fibers and to neighboring cell assemblies. The noradrenergic (collateral) fibers that make contact with NA-cells of the locus coeruleus and with supposedly cholinergic cells, and the cholinergic fibers that make contact with their cells of origin and with NA-cells – both arrangements realized evidently in the McCarley-Hobson model – can be cited as examples.

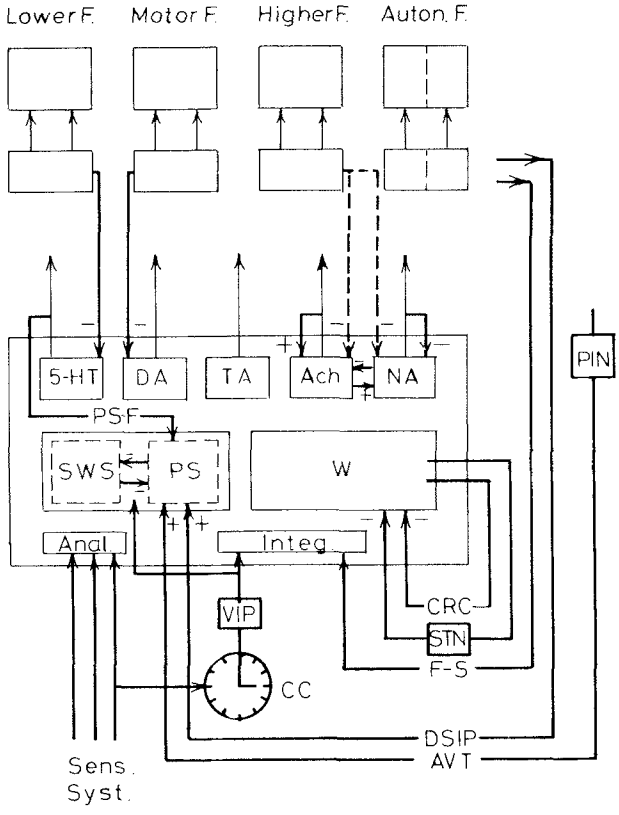

Figure 3b. Filling-in the blanks – *Input-Component*, drawn in heavy lines. Circadian Clock (CC) with – supposedly – the vasoactive intestinal polypeptide (VIP) as centripetal transmitting vehicle, and with sensory collateral input for entrainment. Factor-S (F-S) is the most likely feedback-from-the-tissue-factor, impinging, together with the Clock-Input on the summing Integrator (Integ.). DSIP, originating in the tissues and vasotocin (AVT), originating in the pineal (PIN) with facilitatory (and delayed) impact on PS-Subprogram (PS). Note: Clock-collateral, impinging on ultradian (flip-flop-)oscillator between the SWS- and the PS-subprograms. Also note: reticulo-cortico-reticular feedback-loop (CRC), and reticulo-solitario-reticular loop (STN); sensory inputs impinging on decision-making Analyzer. Included are (probaly mainly gabaergic) feedbacks from the network to the dopaminergic, serotonergic, and – less clearly established – the cholinergic and noradrenergic somata. Also included is the McCarley-Hobson oscillator with the mutual and feedback connections to the cholinergic and noradrenergic cell-body region. Finally, this figure depicts also Jouvet's indolamine-dependent PS-Factor (PS-F).

4.3. The 'Center' or integrating and coordinating functions (fig. 3c)

Observations in animals subjected to electrical stimulation of a variety of structures offer first hints concerning the location and the extent of this 'center'. Low- and high-rate stimulation of the basal forebrain, and low-frequency stimulation of the midline thalamus, of some limbic structures, of the mesencephalic reticular formation, of the area of the solitary tract nucleus, but also of the cerebral cortex and of (peripheral) afferent nerves induces sleep, or, at least, isolated signs of sleep. Electrical stimulation of pontine structures of cats, while in slow-wave sleep, is bound to induce a shift towards paradoxical sleep. Such evidence could mean that all of these central nervous 'hypnogenic' sites and afferent channels in peripheral nerves together form the center. However, it is quite obvious that this cannot be the case. Some of these structures must be excluded on the basis of their very location and/or functional characteristics. This is definitely true for peripheral sensory nerves including their central afferent projections and their many collaterals, The latter must be considered, as already discussed, to be part of the input component of VCA. The cerebral cortex is an effector organ and projection target of the output channels; at the same time it must be viewed, as also outlined, as the point of origin of feedback channels to the central coordinating machinery. Similar conclusions are in place for limbic structures such as the hippocampus. Furthermore, the area of the solitary tract nucleus, on the basis of its functional characteristics and its quasi-peripheral location, cannot be looked at as part of the coordinating center. This hypnogenic region, as already discussed, must be considered to be a substation in a reticulo-solitario-reticular, anti-arousal feedback loop; it is connected to the input- and the output components of VCA. Finally, based on anatomical and histochemical evidence, we find no compelling reason to include the basal forebrain in the center proper. The hypnogenic effects of low- and high-rate stimulation of this area are probably the result of an activation of serotonergic pathways running through this very region. The ensuing sleep can be viewed as manifestation of a wide-spread (active) suppression of the local reactivity and vigilance. Insomnia, following transections at the level of the chiasma[168], or following lesions in the preoptic area[222] would then be due to interruption of executive channels, rather than to elimination of parts of the central coordinating machinery.

In turn, we propose that the unspecific (reticular) thalamus – in particular the intralaminar nuclei and the centre médien – are to be regarded as an important part of the center. Low-rate stimulation of this structure is probably the most effective means of inducing, in experimental animals, real sleep which outlasts the stimulation by easily 1–2 orders of magnitude, and which includes all stages and phases of sleep. Also, from this same place one can produce the recruiting responses, signs of reduced cortical reactivity[37]. Findings[11,167,236] that lesions in this area do not eliminate spindles and slow waves in the cortex, are not sufficient evidence to reject this view. One has to remember that high-frequency stimulation of the intralaminar nuclei in experimental animals produces a cortical arousal pattern quite similar to the one elicited by classical reticular stimulation. Evidently, some vigilance-enhancing structures are also contained in the reticular region of the dorsal diencephalon. Thus, lesions in the region of the midline thalamus are bound not only to destroy the local hypnogenic networks, and thus to eliminate the active induction of sleep, but also to interrupt parts of the arousal machinery and thus to produce signs of 'dewaking' with its characteristic spindling and slow waves. Based on similar evidence, we assume that the reticular structures of the rhomb- and the mesencephalon, and their continuations into the hypothalamus contain an additional part of the central sleep-coordinating machinery. While high-rate stimulation of these areas elicits the characteristic arousal pattern (including a variety of behavioral phenomena), low-rate stimulation clearly produces sleep, or, at least, isolated signs of sleep. Lesions in these structures are followed – acutely – by what has been referred to as 'sleep'; these symptoms, however, are better described again as inactivity or 'dewaking'. The occurrence of spindles and of slow waves does not oppose the view that such lesions in fact eliminate 'true' sleep as well. We also propose, based on the studies of Jouvet[93] and others that the rhombencephalic part of the reticular system contains, in particular, those pieces of machinery that are involved mainly with the organization of paradoxical sleep.

It is evident that the diencephalic, the mesencephalic, and the rhombencephalic reticular formation contains networks capable of generating sets of preponderantly high local vigilance in a variety of systems, characteristic for the waking state as well as for paradoxical sleep. And it also contains networks capable of generating sets of preponderantly low local vigilances in a variety of systems, as is characteristic of slow-wave sleep. There is, in other words, *coexistence* in these reticular areas of hypnotic (for SWS and PS), and of arousal and wake maintaining networks. This conclusion, based on experimental evidence, corroborates our theoretical concept – already presented in the introduction to section 3 – that in fact there is no need to postulate the existence of an isolated central sleep-coordinating apparatus separate from a similar machinery generating and coordinating the reactivity and vigilance profiles characteristic and necessary for the various activities of the waking state. Both pieces of machinery are integral and overlapping parts of a now larger apparatus, the *Vigilance Controlling Apparatus* (VCA), i.e. its central coordinating component. The central coordinating component of VCA can be assumed to contain a *waking*- as well as a *sleep*-program bank; the latter is likely to be subdivided into an *SWS*- and *PS*-bank. Little concrete evidence is available about the actual structure of these program banks. Still, at first glance they could consist of dividing networks that transmit incoming information either as facilitatory or inhibitory signals upon the roots of the output pathways to induce there activity or inactivity, respectively. It also can be assumed that these programs contain, for delayed action, some 'hold-logic'. The whole center of VCA is evidently capable of activating, in dependence of, and in response to, a vari-

ety of neural and neuro-humoral input signals, either one of the 2 main programs (or subprograms thereof) and thus of inducing through proper use of the various output channels, the reactivity- and vigilance-profiles characteristic for either one of the 2 states, i.e. waking or sleep (including the latter's paradoxical variety).

The available evidence furthermore suggests that the wake- or the sleep-program can be called into action experimentally on the basis of their differential responsiveness to varying rates of (electrical or sensory) stimulation. The hypnogenic processes are activated mainly by low-rate stimuli whereas the wake processes are elicited mainly by high-rate stimuli. One seems to be dealing with a differential *resonance phenomenon;* the programs appear to be tuned to different 'activating wavelengths'.

In addition to these program banks, the central component of VCA contains a number of other functional elements. It houses the *receptive poles* – the perikarya or their dendritic ramifications – of the neurons constituting the output channels. The anatomical evidence, i.e. the location of the NA-, DA-, Ach-, and 5-HT-cell somata within, or very close to, the rhomb- and the mesencephalic reticular formation corroborates this notion. We can also assume that the central component of VCA contains the *Integrator* or mixer; a piece of machinery capable of summing the incoming signals carried by the (humoral) feedback information from the tissue (FFTF) and that arising in the (circadian) clock. Similarly, we can assume that this center also contains the *Analyzer,* i.e. the decision-maker that is capable of steering sensory signals according to their characteristics as facilitatory signals to the W- or to the S-program. Furthermore, the central component must include a high-frequency oscillator responsible for the establishment of the NREM/REM-cycle. This cycle represents, for instance, in man the 16th, in the mouse the 200th harmonic of the fundamental (circadian) rhythm. Both the duration and the shape the SWS/PS-ratio – of the subperiods vary systematically in the course of the sleep periods; both depend on, and appear to be modulated by, the circadian clock and, possibly, some waking-dependent, sleep-inducing factor. This suggests that the ultradian oscillator is located downstream from the point of impact of the circadian clock and the sleep-factor. Hence we have to place this fast oscillator within the central component of VCA. At this time there is not much concrete and plausible evidence about a particular set of neuronal and/or neuro-humoral mechanism responsible for the establishment of this oscillation. Still, there are some proposals for the putative structure, nature, and location of this time-piece that deserve some detailed discussion.

One of these proposals is the oscillator model of McCarley and Hobson[153] described earlier in this paper. Considered in isolation, this machinery which consists of an Ach- and a NA-cell pool with facilitatory and inhibitory collateral feedback, and facilitatory and inhibitory (respectively) projections upon the opposite pool, could be expected to produce such a sleep cycle. Those authors in fact presented some experimental evidence, obtained with microelectrode recordings, which may support their notion. Yet, if one attempts to integrate the McCarley-Hobson oscillator into the model of the compound sleep-organizing apparatus, one encounters considerable difficulties. The oscillation of the proposed apparatus is based on a rhythmically occuring, high-amplitude, slightly phase-shifted variation in activity (output and feedback) of the Ach- and the NA-cell pools. The very nature of this oscillation dictates that the *duty-cycles* – the episodes of high activity levels within the cycle – of Ach and of NA are relatively short. In turn, one has to be aware that both cholinergic and noradrenergic channels are probably the most important instruments for the elevation of the local reactivity and vigilance mainly in the higher, but possibly also in some lower function systems. Thus, if the McCarley-Hobson oscillator were to operate as originally proposed, one would have to conclude that high-level performance in those systems would be possible only for about one fourth of the total cycle length. This would be acceptable for the conditions prevailing during sleep; the animal, and in particular the human organism activates higher functions quasi-exclusively during the REM-portion of the sleep-cycle. However, such a short duty-cycle of vigilance-enhancing aminergic activity is incompatible with the behavioral patterns of the wake state. If the McCarley-Hobson oscillator were in operation during waking, the (human) organism would be able to properly attend to, and make use of, higher (and lower) functions only for, on the average, 22½ min during every 90 min period. This is definitely not the case. While there is evidence, as mentioned earlier, that there is a shallow rhythmical variation of (local) vigilance, the time of occurrence of the peaks of high readiness in the various systems is obviously dictated by the actual behavioral patterns, initiated by oscillator-independent internal and external factors. One could possibly resolve this problem by assuming that the oscillator is in high-amplitude operation only during sleep, and that during the waking state the executive aminergic outputs were controlled predominantly by the information emanating from the W-program; that, in other words, the excitatory influence from the W-program to the Ach- and NA-pools may override the inhibitory impact of, for instance, the recurrent NA-fibers. One may also speculate that supplemental inhibitory connections, arising in the W-program, impinge (possibly presynaptically) on the terminals of the recurrent collaterals of the NA-channels, and thus are capable of blocking the recurrent signals necessary for the induction of the oscillation of the system. Furthermore, one may contemplate that circadian variations in receptor sensitivity[250] may play a role in the change of the operation of the oscillator. There is, however, no evidence in support of the involvement of any one of these auxilliary mechanisms. Nor is there any concrete evidence that the McCarley-Hobson-oscillator is in operation during high performance activity in the waking state. For similar reasons, Borbély's model, as also described earlier, cannot be accepted, without any reservations, to explain the making of the sleep cycle. Borbély[20] suggests an apparatus virtually identical to the one proposed by McCarley and Hobson, except that he replaces the Ach- and NA-pools of the latters' model by 2 (hypothetical) processes referred to as REM- and NREM-propensi-

ties. He assumes that this machinery which is based in fact on a paradigm proposed by Lokta-Volterra to explain the interaction of prey and predators, could produce the step-like alternation of SWS and PS, so characteristic of the sleep cycle. Closer scrutiny of this paradigm and also the curves presented by McCarley and Hobson clearly show that such an apparatus would be inclined to produce transitory peaks of NREM- and REM-output and not a rectangular alternation. With the machinery proposed by Borbély, high REM- and NREM-output would be liable to broadly overlap and not to alternate; the main portion of the sleep-cycle would be reduced to a 'no man's land'.

The very phenomenology of the NREM/REM cycle suggests still another possibility of an oscillator. The typical step-like pattern of this oscillation makes it likely that the swing is initiated and maintained by a flip-flop-type of arrangement based on the assumption that the SWS- and the PS-subprograms are interconnected through collaterals of their output lines and intercallated delay links in a mutually inhibitory manner. Jouvet's PS-factor and – if one is ready to accept the evidence obtained in cats and man – DSIP and vasotocin could be assumed to act as primary timing links or, at least, as accessory modulating instruments. Finally, the proper operation of our model makes it mandatory to add a number of hypothetical elements where experimental evidence is not available as yet. This holds true in particular for some intrinsic connections. As already indicated and outlined, we assume that there is no separate set of output channels for the induction of any one of the specific vigilance profiles of waking and sleeping. Any particular output channel, acting as a *common endpath,* can be called into action by any one of the programs or subprograms. For instance, noradrenergic fibers could be activated to enhance (local) reactivity in the cortical and limbic networks by the W-program as well as by the PS-subprogram. Dopaminergic channels are put into action by the W-program as well as by the SWS-subprogram, to maintain responsiveness in (some of) the motor systems during the waking state and – e.g. for the organization of somnambulistic behavior – during stages 3 and 4 of NREM-sleep. Consequently, the center must contain the necessary channels for the transmission of the respective information. Thus, one can postulate activating pathways from the W-program to the pool of the noradrenergic, cholinergic, dopaminergic, and putative traceaminergic somata. Activating pathways to at least parts of the noradrenergic and cholinergic pools can be expected to arise in the PS-subprogram. In turn, from the latter, an inhibitory pathway can be expected to impinge on the DA-pool to deactivate responsiveness in the motor systems during paradoxical sleep. An activating pathway must exist between the SWS-subprogram and the roots of the 5-HT-channels. If the principle of the antagonistic innervation is realized, one can assume that the various activating (and inhibiting) pathways just mentioned are supplemented by a number of (antagonistically) deactivating (and activating) instruments.

Moreover, one has to postulate an activating as well as an inhibiting connection between the Integrator – the locus of impact and interaction between the clock input and the sleep-inducing factors (presumably Factor-S) – and the S- and the W-program. The same holds true for the Analyzer. If the flip-flop arrangement between the SWS- and the PS-subprogram were in fact to be realized one would also have to postulate (as already mentioned) some type of inhibitory and 'hold'-connection between these 2 logics. Gabaergic interneurons can be assumed to constitute important inhibitory elements within the networks, making up the W-program, and the SWS- and PS-subprograms. They must be involved in the establishment of those particular patterns of neuronal activity within these logics which eventually produce the desired output activity; proper operation of any network is virtually impossible without such inhibitory links. The sleep- and wake-programs are no exception.

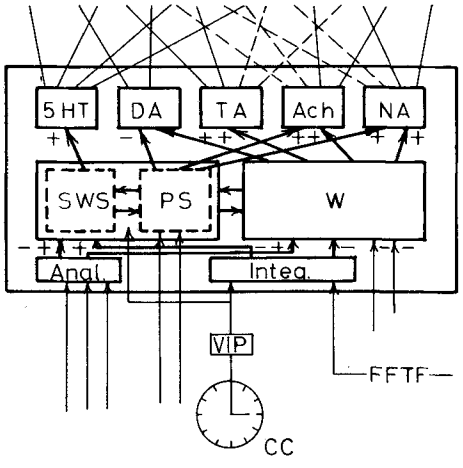

Figure 3c. Filling-in the Blanks – *central coordinating component* (the 'Center'). Note: the Wake- (W-) and the Sleep- (S-) program; the latter with the two subprograms (SWS and PS, respectively); also roots of aminergic output pathways, the Analyzer (Anal.) and the Integrator (Integ.) as important parts of the center. Included are the (in good part hypothetical) connections between the various subcomponents, with + and – symbols to indicate their facilitatory and inhibitory influence on the receiver subcomponent. Note: (supposedly delayed) mutual inhibitory connections between the SWS- and the PS-subprogram, and similar inhibitory mutual connection between the S- and the W-program.

5. The 'complete' model in operation – A recapitulation

With figure 4, the composite of figures 3a–c, we present the final result of the transformation of our initial *Theoretical* into an integrated and *Realistic Model* of the Vigilance-Controlling Apparatus. It shows in a schematic and certainly still simplified fashion all those functional elements that appear to be necessary for the proper organization of sleep. To illustrate the 'general purpose' nature of VCA and to adequately document the operational changes taking place in VCA with the transition from the waking state to sleep and vice versa, we are also including in this figure some of the (basic) mechanisms supposedly instrumental for the generation of those varied vigilance profiles that must form the

very foundation for the adequate performance of the manifold behavioral activities of the waking state. We have, however, omitted the cortico-reticulo-cortical feedback system as it is probably of less importance for the organization of sleep.

For the recapitulation to follow, we shall adhere to a functional procedure, by looking at the manifold activity patterns within VCA in their relation to the various activity patterns outside of VCA. In other words, we shall delineate certain sets of activities (as well as inactivities) among the various partial processes, as they can be expecated to coincide with everyone of the various and systematically changing stages and phases of sleep and quiet waking state. The state of inactive waking, the point of departure of both sleep and active waking will serve as reference point. For this recapitulation we will make a number of – as we hope, not too simple and unrealistic – assumptions with respect to the quantitative and temporal properties of some of the partial processes belonging, in particular to the input-component. Where relevant, we will base these assumptions on the characteristics of sleep in the adult man.

We assume, chosing the simplest case, that the circadian clock discharge (CD) and thus, presumably, the magnitude of release of VIP at the receptor sites within the center, varies in a quasi-sinusoidal fashion. As VIP is a sleep-inducing agent, one can expect that its (and, thus, the clock's) activity is lowest (i.e. zero) some time during the waking period and highest (arbitrarily set at unit level) sometime during sleep. The time course of CD, and, thus, of VIP-activity can be expressed by the following formula:

$$CD = \frac{1+\sin 15(\times - \varphi)^\circ}{2}$$

x stands (under 24 h entrained conditions) for real time (in h) and φ for phase-shift (also in h).

Concerning the phase angle of the circadian clock input, the available experimental evidence is somewhat contradictory. From data provided by Gross[67] one may deduce that in anesthetized rats (following conditioning to a particular light-dark schedule) the intrinsic (neuronal) activity of the suprachiasmatic nucleus reaches a peak in the middle of the dark (i.e. active) phase, whereas a broad nadir occurs during the rest period. In contrast, Inouye and Kawamura[88] noted that the discharge rate in the rat's SCN is highest during the day (i.e. rest and sleep) and lowest at night. In view of this equivocal evidence one has to attempt to obtain information about the phase angle of the clock (in man) again by interference from the temporal characteristics of (this species') sleep and waking behavior. Åkerstedt and Fröberg[4] have shown that the level of fatigue in the course of a 3-day sleep deprivation experiment in women (i.e. when FFTF can be expected to rise unidirectionally and linearly) varies in a typically circadian fashion with peaks (of fatigue) at about 05.00–07.00 h and troughs at about 17.00–18.00 h. Similar findings, i.e. maximal fatigue in the morning hours in the course of short-term sleep deprivation experiments, have been reported by Fröberg and co-workers[56] and more recently by Åkerstedt and Gillberg[5]. With such data as a base, it is probably safe to assume that the clock, and thus the VIP-input, runs with a phase angle of about 23 h. This suggests that there is a peak VIP-release at about 05.00 h, and zero release of about 17.00 h.

Relying on, for instance, Krueger and co-workers' data[132, 133], we can expect the concentration of the main *feedback-from-the-tissue-factor* (FFTF) in the ventricular space, and thus at the receptor site in the center, to increase during the waking period and to drop in the course of a sleep period. Assuming again the simplest condition, namely that FFTF is catabolized only during sleep, one expects a by-and-large linear rising and falling pattern for the concentration of this agent in the ventricular space. With an average waking time of 16 and a sleeping time of 8 h, and a swing between 0 and 1 unit concentration (to give FFTF and CD 'equal power'), the expected rates of increase and decrease would be +0.0625 and −0.125 units/h, respectively. With prolonged waking the FFTF-concentration can be expected to rise to levels above unity.

As we have no indication for higher order interrelations, we assume as mentioned earlier (and as does Borbély[20]) that the clock- and the FFTF-inputs combine in their impact on the integrator in an additive manner, so that activity in the latter at any particular time point reflects the sum of the 2 inputs. With these (simple) quantitative and temporal specifications as a base, one obtains time courses of (1) FFTF (with an assumed

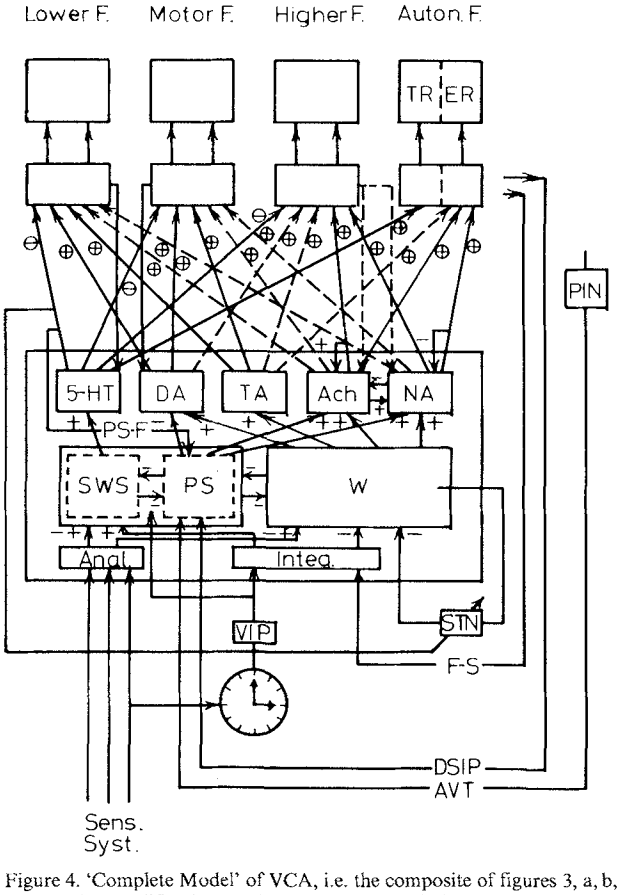

Figure 4. 'Complete Model' of VCA, i.e. the composite of figures 3, a, b, and c. The amplification-modulating serotonergic input to the solitary tract nucleus area (STN) is added, but the reticulo-corticoreticular feedback loop is ommitted. Symbols as in figures 3 a–c. Not included are gabaergic mechanisms in networks and programs.

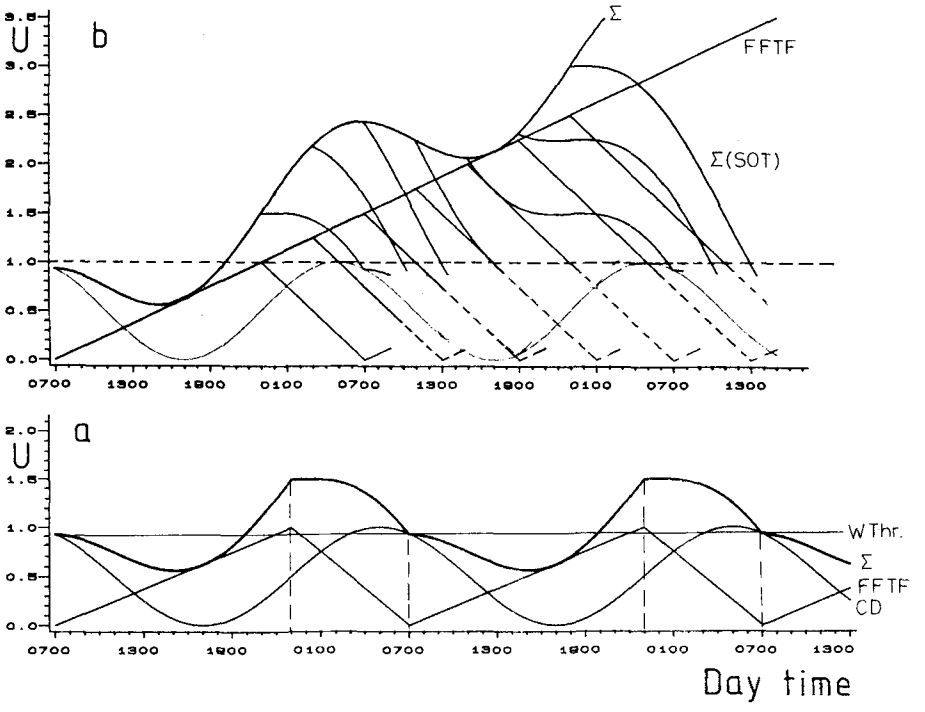

Figure 5. Presumed time-courses (1) of clock-discharge (CD, i.e. supposedly VIP-activity), (2) of the feedback-from-the-tissue-factor (FFTF, supposedly Factor-S), and (3) of the sum of the 2 former parameters (Σ) as obtained by computer processing. Arbitrary units (double amplitude of CD-sine wave) on ordinate scale; time (h) on abscissa. dFFTF/dt assumed to amount, during waking, to 0.0625 units/h and during sleep, to −0.125 units/h. *a* (lower part), under entrained conditions, with (normal) sleep-onset time (SOT) at 23.00 h and waking-up time at 07.00 h. WThr = waking- or sleep-maintaining threshold of Σ (FFTF + CD). *b* (upper part), when SOT is increasingly delayed (by multiples of 4 h). Note: curvilinear (and for every SOT specific) decay of Σ (FFTF + CD) as depicted by Σ (SOT).

sleep-onset time at 23.00 h and a waking-up time at 07.00 h), (2) the clock discharge, and (3) the sum of these 2 quantities as shown in figure 5a. The sum reaches a plateau-like maximum at the time of sleep-onset and drops by the time of awakening to about $^{9}/_{10}$ units. From this one can infer that with the proposed specifications this level of the summed FFTF and clock discharge represents the lowest quantity of the integrator's activity necessary to maintain sleep, or, to put it the other way around, the awakening threshold. Figure 5b depicts the time courses of (1) the FFTF-concentration, (2) clock input, and (3) the sum of these 2 quantities, anticipated if sleep-onset time is artificially delayed in steps of 4 h (as was done, for instance, in the experiment of Åkerstedt and Gillberg[5]) while still adhering to the basic parameters – phase-angle, amplitude, and level of the clock-oscillation, and the rising and decaying rates of FFTF – as specified earlier. It is not unexpected that during a prolonged waking period the sum (FFTF+CD) follows an oscillating, though generally rising pattern. It is also obvious that starting at every one of the various sleep-onset times (SOT) (23.00, 03.00, ..., 19.00, 23.00 h) the sum drops in its own curviliear, SOT-specific fashion.

With these assumptions as a base, we can now take a closer look at the operation of the model. During the *quiet waking* state (for instance during a rest period in the early afternoon) the concentration in the CSF-space of the feedback-from-the-tissue-factor (FFTF, presumably Factor-S) has reached intermediate levels. The activity of the (entrained) circadian clock, and thus the level of VIP release is close to its minimum. The combined impact on, and thus the level of activity in, the Integrator is at about half-unit level (fig. 5a). There is little activating input to the S-, and little inhibitory input to the W-program. The ensuing activity in the latter is maintained, if not further enhanced, by sensory signals, carrying a high amount of novel, non-habituating information. Activity in the W-program exerts an inhibitory influence on the S-program, and an activating influence on the NA-, Ach-, DA-, and TA-pools. These hold the level of reactivity in the effector neuronal networks of the systems, and thus the level of vigilance in the respective behavioral functions at 'stand-by' condition. The same output also maintains an adequate sympatho-adrenal tonus in the periphery. During this situation some polypeptidergic mechanisms can be expected to exert an amplifying influence on the aminergic transmission functions. The active W-program also inhibits the 5-HT pool; yet, it may reverse this to an activating influence under conditions of exagerated activity. In the absence of released 5-HT, the negative feedback loop, originating presumably in the W-program and projecting to the nucleus tractus solitarius and back to the anterior brainstem, is at a low level of responsiveness, and thus not bound to exert a strong dampening influence on anyone of the arousing processes. Heavy higher function activity – for instance, intensive learning – can be expected to be signalled, possibly via DSIP, to the S-program and to initiate storage of an as yet unknown agent used later as PS-enhancing and -prolonging factor.

Towards and at the expected time of *falling asleep* (23.00 h) the FFTF-concentration in the CSF-space and at the central receptor sites reaches unit level. The circadian clock discharge and, thus, probably VIP-release at the central receptor sites, passes through its steepest phase and moves toward its maximum (also unit-level). The summed activity of the 2 processes has reached levels of about 1.5 unit-points and remains there for a few hours (fig. 5a). Integrator activity also has increased accordingly and is transmitted to the S-program. At the same time the W-program becomes progressively deactivated, due to lessened novel and arousing sensory input (in the quiet, familiar, and habituated surroundings) and, presumably, to a progressively increasing inhibitory influence from the Integrator and from the S-program. The now considerably increased tonus in the latter, particularly in its SWS-division, activates the 5-HT-output, simultaneously inhibits the vigilance-enhancing aminergic channels, and enhances parasympathetic-cholinergic activity in the periphery. Serotonin, released into the intercellular space, and, eventually, into the ventricles, exerts an amplifying action on the reticulo-solitario-reticular feedback system and thus adds further to the general suppression of the vigilance-enhancing instruments.

At the time of the start of the first REM-period, the combined impact of FFTF and VIP still is fairly high; yet the activity within the S-program is flipped from the SWS- to the PS-subprogram. With the drop in tonus in the SWS-subprogram the 5-HT-output is lowered and the vigilance-enhancing instruments are disinhibited. The increased activity in the PS-subprogram further activates the output through the noradrenergic and cholinergic channels while probably inhibiting DA-output (and other pathways involved in the active suppression of muscular tone and reflex activity). DSIP, through its delayed action, may further enhance responsiveness of the PS-subprogram to activating influences; so may, possibly, the impact of Jouvet's PS-Factor. The reduced tonus of the SWS-subprogram leads to reduction of (peripheral) parasympathetic-cholinergic activity; together with the already deactivated sympathic-adrenergic tonus, one may see here the ultimate cause for the autonomic 'anarchy', the loss of vegetative homeostasis, during paradoxical sleep, emphasized so much by Parmeggiani[176]. Again due to the impact of the aforementioned flip-flop arrangement (and/or of an intercallated ultradian clock) the activity in the PS-subprogram is flopped back, within a few minutes, to the SWS-subprogram which, possibly after a short abortive awakening, produces again the output pattern described for the first NREM-episode. This *switching of activity* from the SWS- to the PS-subprogram and back is bound to repeat itself several times in the course of the whole sleep period. Yet, while the alternation continues, the summed activity of FFTF and the clock drops to such an extent (fig. 5a) that the SWS-subprogram is progressively less activated. This makes it increasingly easier to switch from the SWS- to the PS-subprogram and to keep the latter active for increasingly longer periods of time. It is the gradual drop in SWS-propensity (and we agree here entirely with Borbély[20]) which is responsible for the typically increasing PS/SWS-ratio within the series of sleep cycles in the course of a (normal) sleep period. By about 07.00 h the combined power of FFTF and the clock input drops to intermediate levels, i.e. towards what one may refer to as the *awakening* (or sleep-maintaining) threshold. The now lowered activity in the Integrator leads to a reduction of its activating influence on the S-program and of its putative inhibitory influence on the W-program. The latter's tonus is further increased by the lessened inhibitory influence from the (now less active) S-program and by the more intensive impact of sensory stimuli, for instance the alarm clock, other noise in the surroundings, the smell of breakfast coffee, light, and social activity. The W-program is ready to resume its activating influences on the NA-, Ach-, DA-, and TA-channels, thus up-regulating the organism's overall level of (behavioral) responsiveness, and making it ready to cope with the exigencies of the waking state. An increased output to heighten the tonus in the sympathic-adrenal functions supports the performance of these activities.

Our model also applies for the explanation of some cases where abnormal sleep patterns follow a variety of experimental manipulations. Åkerstedt and Gillberg[5] investigated the changes in the duration of the sleep periods following displaced (by multiples of 4 h) sleep-onset times (SOT). They found that (total) sleep lengths, as well as stage-2 and REM-sleep, varied in a circadian fashion. Long sleep periods followed (normal) SOTs at 23.00 h and, after deprivations of 20 and 24 h, respectively, SOTs at 19.00 and 23.00 h of the following day. In turn, minimal durations were found with SOTs at 07.00 and 11.00 h. We noted, if we plotted the various waking-up times on the respective descending curves of the summed (FFTF + clock discharge)-values of figure 5b, that Åkerstedt and Gillberg's data grouped themselves along a slightly rising straight line (b = + 0.044 units/h). This line starts at about 0.9 units elevation at 0 h deprivation time (fig. 6). This indicates – if our temporal and quantitative assumptions are not too unrealistic – that the awakening threshold (i.e. the minimal sleep-maintaining summed (FFTF + CD)-activity slowly rises in the course of a short-term sleep deprivation; a phenomenon that may suggest a process of adaptation. Åkerstedt and Gillberg have shown also that slow-wave sleep percentage varies – though not in a statistically significant fashion – along a pattern almost diametrically opposed to the one of total sleep duration. This pattern appears to be directly related to the summed (FFTF + CD)-values at any one of the various SOTs. From this one may be led to assume that the total 'load' of (FFTF + CD), and thus of sleep-pressure at sleep-onset time is responsible in a positive fashion for SWS-participation in the sleep period following that particular SOT, while it seems to inhibit the occurrence of Stage-2 and REM-sleep. Such a conclusion may not be too far-fetched in view of Borbély's[20] contention that the intensity of his S-process can and should be measured in terms of slow-wave sleep output.

The present model is also apt to explain the behavioral depression, if not sleep-like condition, induced by the systemic or intraventricular administration of directly as well as indirectly acting GABA-receptor agonists. We assigned to gabaergic interneurons the role of oper-

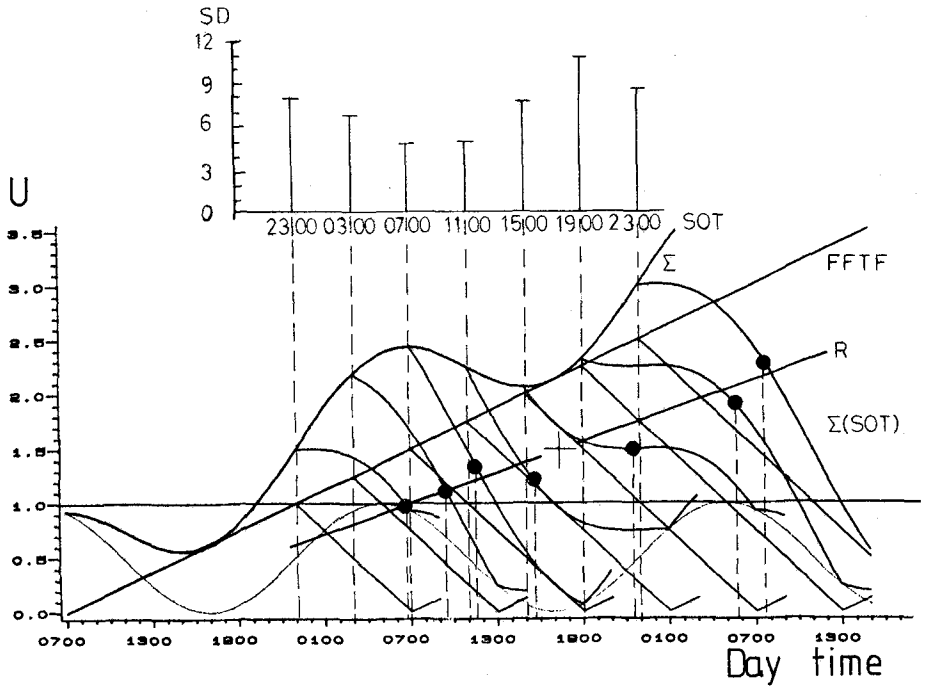

Figure 6. Time course of Σ (FFTF + CD) expected with increasingly delayed sleep-onset time, as shown also in figure 5b. On each one of the descending curvilinear (SOT)-curves starting at the various SOTs from the (FFTF + CD)-line, we plotted the waking-up times (●) as observed by Åkerstedt and Gillberg[5]. Note: these points group themselves along a straight line (R) with a 'b' of 0.044 units/h. Insert: sleep durations (SD in h) as observed by Åkerstedt and Gillberg, when SOT was delayed by multiples of 4 h.

ational elements within the effector networks (the 'systems'), within the reticular networks that constitute the S- and the W-programs, and within the feedback channels from the effector networks to the roots of the various aminergic executive output channels. It is obvious that artificially enhanced gabaergic transmission in the neocortical and limbic structures leads to exagerated inhibition within these effector networks which reduces their output, and produces generalized and unspecific reduction of behavioral activity – a symptom usually referred to as sedation. Hypergabergia in the (inhibitory) feedback lines impinging on the somata of the vigilance-enhancing channels is bound to further depress in an unselective fashion vigilance. Enhancement of gabaergic transmission further back in the reflex arc – i.e. in the program-networks – is liable to induce more systematic faults in the organizational patterns. Such hypergabergia in the programs can be expected to disorganize the activity in these networks by enhancing the intrinsic inhibition and curtailing any facilitatory (and inhibitory) output to and through the executive channels. The organism is, at least partially, deprived of its capabilities of producing the vigilance profiles characteristic of sleep (including PS) and of the waking state. With this inerpretation as a basis it comes as no surprise that benzodiazepines – indirectly and only partially acting GABA-transmission enhancers[71] – not only curtail the output from the various behavioral systems and thus exert a deactivating or sedating influence, but also hinder the development of the characteristic, mainly low, vigilance profiles of slow-wave sleep (reduction of stages 3 and 4) and the mixed profiles of REM-sleep.

There is a phenomenon, though, that cannot be explained by the present model, namely the phase shift of (ad lib.) sleep-onset time, under free-running conditions, to the trough of the body temperature curve and thus the (relative) phase advance of the period of highest REM-output to the early phases of the sleep periods. As REM-sleep propensity, under entrained and free-running conditions oscillates synchronously and with a phase angle of about 180° (12 h) with body temperature, one can contemplate that there is a direct input – bypassing the Integrator – form the clock to the PS-subprogram; future research may demonstrate that this is true. Neither can we explain the phenomenon so aptly demonstrated and discussed by Wever[246], namely the internal desynchronization, the dissociation of the sleep-waking rhythm from the 'strong' oscillator that governs REM-propensity, body temperature (the 180° reversal of our clock-rhythm), and cortisol secretion. Minors and Waterhouse[156] have recently again discussed this problem. One may contemplate though that under some extreme conditions the sleep-waking rhythm is detatched from the clock and runs entirely in dependence of the beat generated by the mutual inhibitory interaction between the S- and the W-program in cooperation with the FFTF.

6. Discussion and critique

We postulated that sleep, in its phenomenology, is the functional result of a set of *reflex mechanisms*. That is to say, the particular quantitatively, qualitatively, and

temporally well defined patterns of activities (and inactivities) in the organism's various functional areas that together make up what we refer to as sleep, are to be considered as being the reflex response to a variety of hetero- and proprioceptive input signals. This implied that the (Theoretical) Model of the sleep-organizing apparatus had to be designed in a manner akin to other (motor) reflex machineries. It was assumed to be composed of an input-, a 'preprogrammed' central coordinating, and an output-component. To provide a uniform measure for the various activities in the many heterogeneous effector systems we applied a recently introduced new concept of vigilance. According to this concept the intensity and quality of activity in any one of the systems that participate in the making of sleep should be viewed as being the manifestation of their instantaneous level of responsiveness, for which we proposed the term *local vigilance*. The latter, a basically behavioral parameter, was assumed to be the direct consequence of the responsiveness – the *local reactivity* – of the neuronal networks subserving the making of a given behavioral component. Network reactivity was then assumed to be the variable controlled by the output channels of the sleep-organizing apparatus. Thus, the whole organization of sleep was reduced to the problem of the establishment, in proper temporal sequence, of the characteristic vigilance- (and reactivity-) profiles, as they have been found to be typical for the state of sleep.

Furthermore, in the development of the Theoretical Model, we rejected the original and generally held opinion that there is a separate sleep-controlling and -regulating apparatus apart from a (similar or dissimilar) machinery responsible for preparing the 'stage' for all the activities of the waking state. Closer scrutiny of the phenomenology of sleep quite clearly indicated that all the systems that participate with a particular quantity and quality of activity in the making of sleep, also participate, though with different activities, in the making of the so varied phenomenology of the waking state. That is to say, sleep differs from waking mainly, if not exclusively, by the particular levels of vigilance in every one of the systems; or, seen as a whole, by its particular (stage- and phase-specific) vigilance profiles. Thus we could postulate that the vigilances in the manifold systems that characerize the various phases and stages of sleep, and those that characterize the various activities of the waking state can be assumed to belong to, and move within, the same, common, and non-discontinuous space. Consequently it could be postulated that the generation of the vigilance profiles of sleep and those of the waking state are morely 2 different tasks of one common piece of machinery; the 'general purpose' Vigilance-Controlling Apparatus (VCA). From this we inferred that the adjustment of the proper vigilance level in any one system, regardless whether it be for sleep or for waking, is accomplished by common mechanisms. The vigilance profiles of sleep, on the one hand, and those of waking, on the other, can not be assumed to be governed by their own private set of controlling instruments; the very same executive channels, in the sense of common endpaths, can be expected to be used to engender the profiles of both states. The production of the proper activation patterns in the output paths of the whole reflex machinery, i.e. the direction of activity to the adequate executive channel is the main task of preprogrammed networks – program banks – contained within the central component of the VCA.

By-and-large, the model of the apparatus that is supposed to organize sleep (in alternation with the production of the vigilance profiles of wakefulness), although multifaceted at every component level and complicated by a multitude of interactive processes, turned out to be relatively simple in its basic and general design. The entire sleep-organizing mechanisms can be looked at as a series of *switching processes*, an organizational principle well known for every mixed, proprio- and heteroceptive, modulated reflex. Switching, through program networks, towards the characteristic vigilance profiles occurs in response to a variety of input signals, such as feedback-from-the-tissue-factors (supposedly Factor-S), carrying information about 'fatigue' of the brain, transmitter agents (supposedly VIP), carrying information about the time of the day, and low-rate, low-intensity, monotonous sensory signals. Switching from slow-wave sleep to paradoxical sleep and back is accomplished, possibly, through the interaction of an additional – ultradian – time piece, or a slow flip-flop arrangement between the SWS- and the PS-subprograms. The switching from sleep to waking occurs in response to a transposition of activity from the S- to the W-program; a change-over that may be due in part to attenuation of the impact of the summed FFTF and clock-discharge to levels below the sleep-maintaining threshold. The S- to W-switch is probably further facilitated by enhanced sensory input, in particular, more intense, higher-rate and less monotonous afferent signals.

With this design our model offers a new opportunity to interpret, in functional terms, the role of the many partial processes played within the whole of the organizing apparatus. For instance, noradrenergic channels, usually viewed as 'generally arousing' and/or PS-inducing instruments[61] are now clearly diagnosed as (local) vigilance-enhancing factors, coming into play as executive mechanisms during the waking period as well as during sleep, in particular during its paradoxical phase. Serotonin must not be considered a sleep-inducing agent. It deserves its nickname 'Somnotonin' (as suggested rather light-heartedly by us[116]) only in as much as serotonergic channels are involved, as executive instruments, in the suppression of local vigilance. They are bound to be active during SWS; but they also come into play during the waking state, namely to counteract excessive levels of local reactivity. In turn, the feedback-from-the-tissue-factor(s) can be designated as true sleep-inducing agent(s), although it (they) may become active in this direction only in combination with other inputs, such as the circadian clock and its putative (input-) transmitter VIP. Still, there is reason to assume that agents, such Factor-S, while slowly increasing in concentration during waking, may represent what Moruzzi[163] referred to as the *appetitive phase* of the 'instinct' sleep, while the elimination or metabolization of this agent during sleep, may represent the *consumative phase* of this instinctive behavior. Moreover, with the introduction of the local vigilance as a measure of

activity and responsiveness in the various systems there is no more need to use the ill-defined and often misleading term 'depth of sleep'. We rather can describe now the functional state in every one system on the basis of its own 'alertness' and can define particular phases and stages of sleep through their particular vigilance profile. Thus one can avoid the unpleasant experience of having (so-called overall) depth of the sleep (at one particular point in time) turn out to be quite different, depending on the test procedure used and the system investigated. In fact, it is not unlikely that the vigilance profile may offer itself as an advantageous and convenient base for a new (more functional) principle of defining the various phases and stages of sleep.

Opposite these various positive aspects of our new concept and model, we are aware of some shortcomings, if not oversimplifications, omissions, and possible misinterpretations. For instance for the description of the vigilance profiles of sleep as well as those of the waking state we divided the whole universe of behaviors into only 3 groups: the *higher functions,* mainly, but not exclusively what we refer to as 'internal behaviors' such as association, cognition, advanced learning processes, read-out and extinction; the *lower functions,* including moods, drives, instinctive behaviors, feeding, grooming, and sexual activities (with precopulatory patterns); and *motor functions,* including teleokinetic and ereismatic activities and, as a special case, rapid eye movements. It is obvious that this grouping is far from being adequate to describe the many different behavioral forms. Also it separates where there is obvious overlap and cooperation. One has to be aware of motor activity in connection with, e.g., instinctive or sexual behavior; one has to be aware of the coexistence of higher (mental) activity with primitive functions (moods) and with motor activities (vocalization and/or skilled movements). Furthermore, any one of these 3 groups of functions should be subdivided into a variety of more specialized activities which, in the course of different behavioral patterns, can be expected to come into play with entirely different intensities. This is true particularly for the various higher functions, not only during waking but also during dreaming. This is true also for the more primitive functions and for different types of motor activities. As to the latter, one should distinguish (still allowing for overlap) between conditioned motor acts (for instance, in connection with performance tests during sleep), many types of skilled muscular activities, sensory-motor activities involved in locomotion (in connection with somnambulistic behavior), and of course the rapid eye movements that seem to subserve a homeostatic function. It is quite likely that the vigilance in any one of the systems involved in the making of these activities is very unequal at anyone point of time in the course of sleep. A recent paper by Duron and Marlot[45] illustrates the need for an even higher resolution. These authors have studied the respiratory and the postural functions of the intercostal musculature. They noted that during REM-sleep (in the cat) the networks handling respiratory functions seem to retain an adequate level of reactivity, whereas the ones attending to the postural function revealed quite low reactivity levels, as manifested by virtually complete loss of tonus of the posturally active muscles. With such better resolution within any one of the three main (behavioral) groups, one would be able to observe a more selective handling of the local vigilances; that is to say for the many behavioral patterns occurring during, the waking state for instance, one could expect a more detailed and more specific patterning of the vigilance profiles. But even for sleep, in particular its paradoxical variety, a more detailed differentiation (specifically for the higher functions) would be desirable for the description of the vigilance profiles prevailing in the course of a dream experience. While being fully aware of the need for such expansion in terms of more detailed phenomenology, we preferred – being interested mainly in the principles of organization – to keep things as simple as possible.

As a direct consequence of this trend towards (over-) simplification at the effector level, we also had to simplify the issue with respect to vigilance control. Of the 3 supposedly vigilance-enhancing aminergic pathways we assigned (with some experimental evidence to support this) to the noradrenergic and the cholinergic systems a role mainly for the control of the responsiveness in the higher function systems. There also was some evidence that polypeptides act as local amplifiers of the (reactivity-enhancing) action of said amines; but there are few, if any, experimental data indicating a more detailed selectivity of these executive instruments. We also assumed, based again on some experimental evidence, that dopaminergic channels handle (mainly) motor vigilance. But again we had to refrain from going into further details about a possibly more selective action with respect to particular types of motor activities. Still, one may suspect that the striato-petal and the accumbo-petal DA-pathways subserve different tasks with respect to different motor functions. Moreover, dopaminergic channels, possibly of the neocortico-petal and the limbo-petal variety, may subserve – in, or not in connection with any overt motor activity – a role as vigilance enhancers in some lower if not even higher functions. In turn, there is some evidence pointing towards a role of descending noradrenergic and dopaminergic pathways in the adjustment of reactivity in spinal motor networks.

Furthermore, as the 4 or 5 mainly aminergic output instruments considered quite adequately explain the principles of operation of our model, we did not find it necessary to include additional executive instruments, although there is some evidence that, e.g., histaminergic and adenosinergic transmission mechanisms may play a role not unlike the one played by the aforementioned transmission systems. We also did not consider (again, mainly to simplify the structure of the model) the influence of hypoxia and of hypo-, as well as hypercapnia on the setting of particular vigilance levels. We also avoided, for similar reasons, mentioning the certainly powerful impact of hormones (aside from some neurohormones), although one has to be aware that, for instance sexhormones play an important role in the adjustment of vigilance in the systems that handle sexual behavior, and that such agents as cortisol are indispensible for the setting of proper vigilance levels in the 'stress systems'.

Finally, we deliberately avoided going into any details

concerning the intimate mechanisms of synaptic transmission at the terminals (and varicosities) of the executive channels. While being aware of recent developments about 'cross-talk' and interaction between the various pathways, about autoreceptors, about presynaptic homo- and heterotypical receptors and about the circadian dynamics of receptor sensitivity, we assumed that inclusion of such additional local modulatory mechanisms would only further complicate the already complicated structure of our model. And in fact, it is unlikely that the inclusion of such detailed mechanisms would fundamentally alter the main operational concept of this sleep-organizing apparatus.

With all these simplifications we have to be aware that the Realistic Model, presented in figure 4, is not so 'complete', possibly in part incorrect. This state of uncertainty is further aggravated by the fact that some of the elements, for instance the programs in the center and a variety of horizontal and vertical interconnections, are still hypothetical without much experimental evidence to support their very existence, let alone their functional characteristics.

Yet, as the analysis of the 'Model in Operation' clearly indicates, our VCA seems to 'work'; a machinery composed in a way described in section 4 apparently could produce, at least in first approximation, something that looks like (human) sleep and the great advantage of, and the advance obtained with the present model, must be seen in the fact that it is plastic; any one of the functional elements within and between the 3 components can be replaced by others that may be better suited for the particular task. Also, additional elements can be inserted. And the qualitative, quantitative, and temporal parameters of every single element can be changed where new experimental evidence makes this mandatory. Yet, all this can be done without affecting the whole apparatus' overall concept of operation.

This very concept and the ensuing model also allow the explaining of the experimental results of Nakamura et al.[166] and to challenge their conclusions, namely that there would be 'no support to the notion of a hypnogenic center that maintains sleep through an increase in neuronal activity'. Those authors, using the 2-dioxyglucose (2-DG) method, noted that glucose utilization in virtually all 24 areas of monkeys' brain tested was reduced during (NREM-) sleep as compared with quiet and alert waking. Such findings may make sense for the many regions, we refer to as effector structures – such as parts of the limbic system – which can be expected to reveal, during synchronized sleep, low levels of local reactivity and, thus, of overall neuronal activity. The same would hold true for neocortical sites. However, the fact that the basal forebrain also shows reduced glucose utilization during sleep cannot be taken as proof against the 'hypnogenic center' theory. This area must not be included in the series of structures that constitute such a center. As outlined earlier, the basal forebrain is hypnogenic only in the sense that it contains executive ascending vigilance-suppressing (i.e. serotonergic) pathways. The fact that stimulation and lesioning of this area promotes and inhibits, respectively, the onset of sleep is adequately explained by assuming that such interventions affect merely output functions. Also, the resolution of the 2-DG method is not good enough to distinguish between 'en-passant' structures and local neuronal networks. Similarly, the area of the solitary tract nucleus is by no means part of the sleep-organizing center, but rather an extra-central substation of a feedback loop. Slightly reduced (supposedly) neuronal activity in this area during sleep is, in part, due to attenuated firing in the transmission lines to this substation from the (less active) reticular system; this attenuation is not completely compensated for by the amplification-enhancing impact of intraventricular serotonin. Finally, the finding that there is reduced local neuronal activity, as manifested by reduced glucose utilization in such areas as the reticular thalamus and the mesencephalic reticular core, must be viewed and interpreted in the light of our contention, that these structures contain both the Slow-Wave-Sleep-subprogram *and* the Wake-program. Enhanced neuronal activity in the former is probably more than only made up for by reduced activity in the latter. This disbalance is certainly aggravated by the fact that the typical activity in the W-program appears to be of the high-frequency type, whereas that in the SWS-subprogram is slow, calling for high or low rates of glucose utilization. And again, the resolving power of the 2-DG method is not good enough to single out elements that belong to the one or the other of the 2 programs. Consequently, the data of Nakamura and his colleagues yield no sufficient evidence to reject the notion of an active induction and maintenance of sleep.

There is, however, one important shortcoming in our concept – and the vigilant reader may have noticed already – that the organization and regulation of sleep, and the development of our model were based entirely on phenomenological parameters. We accepted particular sets of local vigilances and reactivities as typical signs of sleep, or even as measures of the 'intensity' of sleep; but we never alluded to the real 'product', the function, of sleep. And yet, some insight into the functional output of this second existence would be of paramount importance for a true understanding of regulatory interventions and adjustments. However, there is little, if any, unequivocal evidence about the function of sleep and its various phases. As Horne[84] puts it: 'the putative functions of mammalian sleep range from non-restorative 'non-behavior' occupying unproductive hours, providing safety and conserving energy, to an essential and special restitutive process for the body and the brain'. Thus, to avoid making a fundamental mistake about the product measured, we *had* to base our organization and regulation on phenomenological indicators. We can only hope that these 'signs' in magnitude and time course do not deviate too much from the functional measures, once they become available.

But then, if sleep is interpreted as being merely an adaptive non-behavior[239,240], the various but mainly low vigilances in most of the various behavioral systems (sparing mechanisms for alarm) could be considered as the proper signs to gauge the functional result of the sleep-organizing and -regulating efforts of the organism.

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