HANDBOOK OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

EDITOR-IN-CHIEF A. REMOND

VOLUME 7

Physiological Correlates of EEG

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Department of Pharmacology, School of Medicine, Davis, Calif. (U.S.A.)

PART A

EEG and Sleep

EDITOR: P. PASSOUANT

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ELSEVIER

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Elsevier Scientific Publishing Company – Amsterdam – The Netherlands

International Federation of Societies for EEG and Clinical Neurophysiology

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ISBN 0-444-41385-5

Elsevier Scientific Publishing Company, Jan van Galenstraat 335, Amsterdam
Printed in The Netherlands

Sole distributor for Japan:
Igaku Shoin Ltd.
5-29-11 Hongo Bunkyo-ku
Tokyo

All other countries:
Elsevier Scientific Publishing Company
Amsterdam, The Netherlands

International Federation of Societies for EEG and Clinical Neurophysiology

A great need has long been felt for a Handbook giving a complete picture of the present-day knowledge on the electrical activity of the nervous system.

The International Federation of Societies for EEG and Clinical Neurophysiology is happy to be able to present such a Handbook, of which this is a small part.

The decision to prepare this work was made formally by the Federation at its VIIth International Congress. Since then nearly two hundred specialists from all over the world have collaborated in writing the Handbook, each part being prepared jointly by a team of writers.

The Handbook begins with an appraisal of 40 years of achievements by pioneers in these fields and an evaluation of the current use and future perspectives of EEG and EMG. The work subsequently progresses through a wide variety of topics—for example, an analysis of the basic principles of the electrogenesis of the nervous system; a critical review of techniques and methods, including data processing; a description of the normal EEG from birth to death, with special consideration of the effect of physiological and metabolic variables and of the changes relative to brain function and the individual's behaviour in his environment. Finally, a large clinical section covering the electrical abnormalities in various diseases is introduced by a study of electrographic semeiology and of the rules of diagnostic interpretation.

The Handbook will be published in 16 volumes comprising 40 parts (about 2500 pages altogether). For speed of publication most of the 40 parts will be published separately and in random order.

ISBN 0-444-41385-5

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PART A

EEG AND SLEEP

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Section I. Introduction

Electroencephalography has profoundly modified the studies on sleep formerly limited to the observation of man sleeping. With the classification of Loomis *et al.* (1938) a criterion was for the first time given on the course and depth of spontaneous sleep in man.

After the discovery of a sleep stage with eye movements by Aserinsky and Kleitman (1953), it became clear that sleep was composed of two states; one ordinary sleep or "slow" sleep, in which the deep sleep periods, chiefly occurring in the early hours of the night, seem to offset the day's fatigue. The other one, REM sleep, a dream time in man, is nearer to a primitive wakefulness than to a sleep. This finding of a duality of sleep has upset the previous conceptions and led to a great deal of clinical and experimental research.

Variations in the characteristics and the organization of night sleep that come with age are now much better known. Sleep anomalies are better understood and the 24 h recordings have specified the relationship between the three levels of vigilance: wakefulness, slow sleep and REM sleep. On the other hand, a pharmacology of sleep little by little has become clearer and has brought new information on the effect of drugs on the central nervous system.

Research into sleep covers nowadays such a large range that it would be materially impossible to explore all the problems concerned. In this book whose aim is mainly practical and intended specially for electroencephalographers, a large part is devoted to normal and pathological sleep. The various sections written by sleep specialists are divided into four parts.

The first part deals with the electroclinical study of sleep and its variations according to age and species. The second one treats of mechanism of sleep. The third part is about narcolepsy, hypersomnia, minor incidents of sleep such as enuresis, alterations of sleep in some neurological, medical and mental diseases as well as the relations of coma to sleep. Finally the last part is concerned with the pharmacology of sleep.

The various terms used in the different sections to describe the two kinds of sleep have a similar meaning but are not completely synonymous. Each of them is related to one or only a few characteristic patterns of both kinds of sleep.

Sleep with slow waves = "slow" sleep = synchronized sleep = "orthodox" sleep = non rapid eye movement (NREM) sleep.

Sleep with fast waves = "fast" sleep = desynchronized or activated sleep = paradoxical sleep = rapid eye movement (REM) sleep.

Section II. Electro-Clinical Semeiology

In the study of nocturnal sleep, once the REM stage had been recognized, the EEG has become routinely integrated with polygraphic recordings, especially of eye movements, muscle tone, respiratory movements and heart rate.

Polygraphic data make it possible to follow the spontaneous course of the two main types of sleep and their periodic alternation during the night. In addition the neurological, vegetative and psychic features proper to each kind of sleep emphasize the electrographic differences that exist between the two states of sleep.

A. POLYGRAPHIC CHARACTERISTICS OF THE TWO SLEEPS

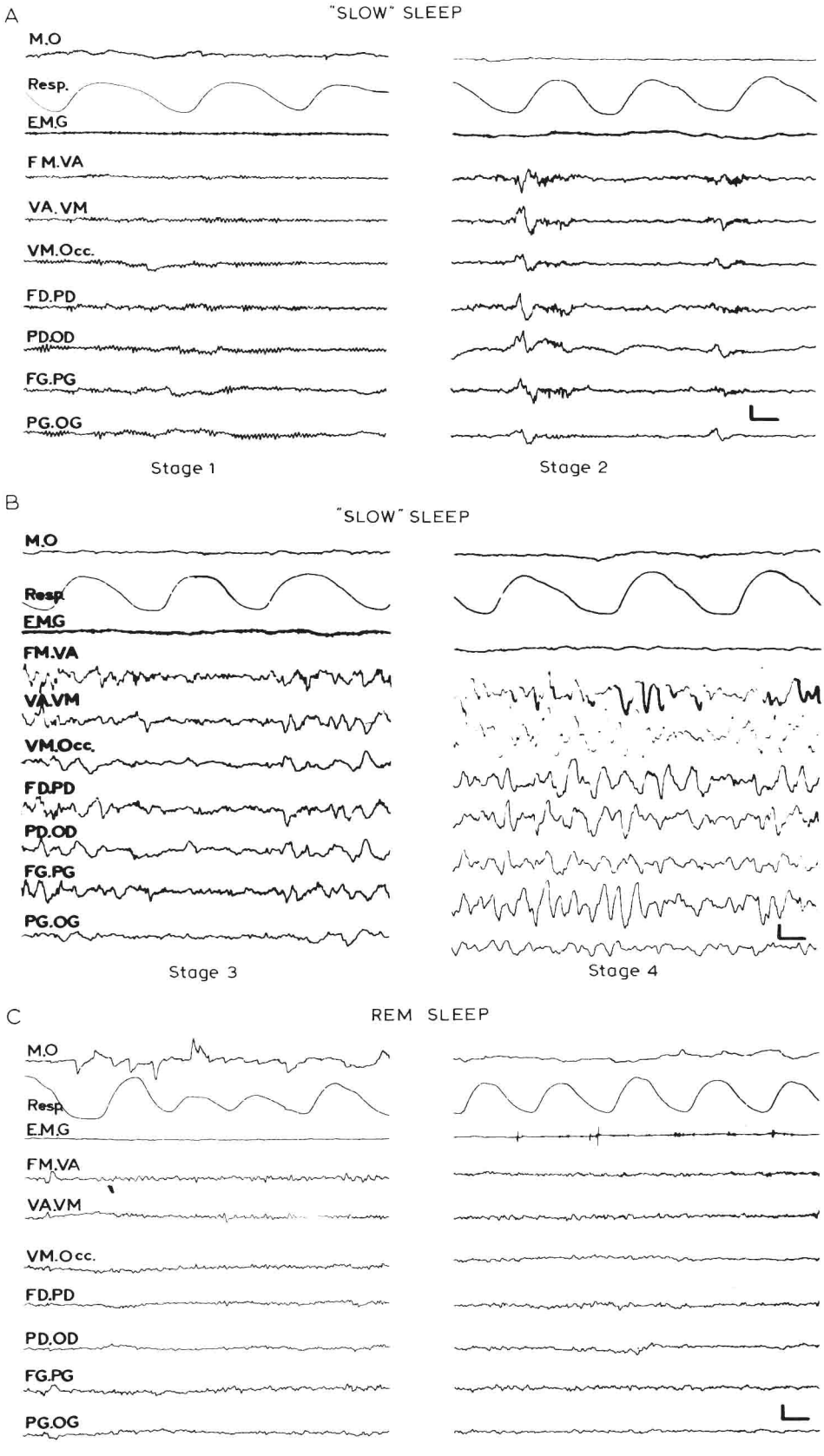
The EEG patterns of sleep were originally classified in five stages (A, B, C, D, E) according to sleep depth (Loomis *et al.* 1938). After the discovery of REM sleep a new classification of "slow" sleep into four stages was proposed by Dement and Kleitman (1957) and this has been generally adopted.

Although the EEG and polygraphic characteristics of the two main types of sleep are clearly defined, the analysis of nocturnal sleep is sometimes difficult due to numerous fluctuations that happen during the night. These difficulties, frequent in the course of pathological sleep, are also met in normal sleep and notably during the transition periods from one to the other type of sleep. Therefore a research team led by Rechtschaffen and Kales has proposed a standardization of the polygraphic signs of night sleep, and this was published in 1968 under the auspices of the U.C.L.A. Brain Service.

1. The characteristics of "slow" sleep (Fig. 1, *A* and *B*)

The four stages of this type of sleep are defined as follows: the first as drowsiness, the second as light sleep, the third and the fourth as deep sleep. These periods usually follow one after the other in the first cycle, but fluctuations are frequent and stages of deep sleep are at the end of the night.

Fig. 1. *A*: *Stage 1* (drowsiness). Alpha rhythm of 10 c/sec spread out. FM.VA = medial frontal and anterior vertex; VA.VM = anterior and medial vertex; VM.Occ. = medial vertex and occipital region of the right hemisphere; FD.PF = right fronto-parietal; PD.OD = right parieto-occipital; FG.PG = left fronto-parietal; PG.OG = left parieto-occipital. Eye movements (MO) slow and of small amplitude. Respiration (resp.) regular. Tonic activity registered by electromyogram (EMG) from chin muscles. *Stage 2* (light sleep). Bursts of slow waves (K complexes) following rapid rhythms (spindles). No eye movements, regular respiration, no modifications of EMG. *B*: *Stage 3 and stage 4* (deep sleep). Slow waves: discontinuous (stage 3) and continuous (stage 4). No eye movements, regular respiration, fall in muscle tone (EMG) during stage 4. *C*: REM sleep. *Left*: rapid eye movements (MO), irregular respiration (resp.), disappearance of muscle tone (EMG). Small amplitude EEG activity with saw-tooth waves. *Right*: brief muscular discharge (EMG) corresponding to facial twitches. EEG activity comparable to that on the left.


A
"SLOW" SLEEP
M.O
Resp.
E.M.G
F.M.VA
VA.VM
VM.Occ.
FD.PD
PD.OD
FG.PG
PG.OG
Stage 1
Stage 2
B
"SLOW" SLEEP
M.O
Resp.
E.M.G
FM.VA
VA.VM
VM.Occ.
FD.PD
PD.OD
FG.PG
PG.OG
Stage 3
Stage 4
C
REM SLEEP
M.O
Resp.
E.M.G
FM.VA
VA.VM
VM.Occ.
FD.PD
PD.OD
FG.PG
PG.OG

Stage 1 comes after wakefulness and, in normal conditions only lasts a few minutes. Alpha waves become discontinuous, diminish in amplitude and are replaced by a low voltage activity between 2 and 7/sec. At the end of this period two types of activity appear, vertex spikes (the amplitude of which can reach 200 μV) and bursts of 2–7 c/sec (from 50 to 75 μV).

Slow eye movements lasting several seconds appear intermittently. Muscle tone is slightly lower than during wakefulness. This period, which groups the A and B stages in the Loomis classification has been differentiated into 1a, 1b substages to define more precisely EEG patterns of drowsiness.

Stage 2 is characterized by the presence of spindles and K complexes. Spindles (12–14 sec) have a duration of at least half a second and predominate in the central and frontal leads. Yamadori (1971) has suggested that they may reflect an active inhibition, avoiding environmental disturbances and facilitating the deep stages of sleep.

K complexes consisting of a diphasic negative–positive deflection last approximately half a second and may be associated with spindles of 12–14/sec. Their amplitude is greater at the vertex. They usually occur either spontaneously or after a stimulation and are generally linked to an arousal effect (Roth *et al.* 1956).

Stage 3 shows 20–50 per cent delta waves (2/sec) their amplitude being greater than 75 μV. Between the bursts of delta waves, the EEG activity is polyrhythmic, of medium amplitude and spindles may be recorded during this period.

Stage 4 is characterized by slow waves, fairly continuous, 2/sec or less of an amplitude of over 75 μV. Spindles may be isolated during this stage.

2. *The characteristics of REM sleep* (Fig. 1, *C*)

Low voltage EEG activity is polyrhythmic and similar to stage 1. Periods of alpha waves, slightly slower compared to wakefulness, or "periods of transient spontaneous activation", appear spontaneously or after a movement. "Saw-tooth waves", 2–6/sec, appear in short bursts in the frontal leads and in the vertex and sometimes are concomitant with ocular movements (Schwartz 1962). Spindles and K complexes are absent.

These EEG patterns are associated with a decrease or a complete loss of muscle tone (demonstrable by submental EMG), with the occurrence of rapid eye movements isolated or in bursts and with modifications in the respiratory and heart rate.

These polygraphic characteristics, despite their accuracy, sometimes fail to fix the beginning and the end of REM sleep. Indeed the transition from one type of sleep to the other is progressive and does not occur suddenly. It is evidenced by a gathering of polygraphic patterns of "slow" sleep, in conjunction with alpha waves, and may last, in normal subjects, from about 10 sec to several minutes. This period of junction between the three levels of vigilance may be related, after a rather difficult analysis, to either "slow" sleep or REM sleep according to the standards proposed by Rechtschaffen and Kales (1968). The isolation of this transitional period as an "intermediate sleep" was suggested (Lairy *et al.* 1967) and is confirmed by its long duration in cer-

tain pathological conditions, especially among mental patients.

The beginning of REM sleep is preceded by a lightening of "slow" sleep (stage 2) and it very seldom occurs immediately after a deep sleep (stages 3 and 4). The polygraphic features are variable and may be roughly classified as follows:

A loss of EMG with an EEG polyrhythmical activity associated with alpha periods or, inversely, with spindles and K complexes.

A maintained EMG with an EEG pattern of REM sleep and sometimes rare rapid eye movements.

Axial movements, followed by alpha waves and an intensification or not of muscle tone.

Vegetative modifications such as irregular respiration with an apneic phase.

The end of REM sleep is often difficult to determine. The eye movements become rare and disappear, the muscle tone grows stronger. A wide axial movement may happen; but its occurrence, always possible during REM sleep, does not necessarily confirm the end of this type of sleep. The EEG activity is faster, the bursts of "saw-tooth waves" are not identified and periods of alpha waves become more numerous. The distinction between REM sleep and stage 1 is difficult and only the appearance of spindles and K complexes mark the beginning of "slow" sleep.

B. ORGANIZATION OF THE TWO TYPES OF SLEEP DURING THE COURSE OF THE NIGHT

In adults, night sleep is made up of 4–6 cycles, beginning with a period of slow sleep. The duration of each cycle, 90 min roughly, is often variable. The first sleep cycles are longer than those of the last part of the night. In an 8 h night, "slow" sleep ranges from 75 to 80 per cent of total sleep, that is approximately 5 per cent for stage 1, 50 per cent for stage 2 and 20 per cent for stages 3 and 4. The duration of REM sleep varies from 20 to 25 per cent of the total sleep and the first period of this sleep comes at least 45 min after the onset of stage 1.

Deep sleep (stages 3 and 4) is dominant during the first third of the night. The first period of REM sleep, of short duration, with few eye movements may be replaced by a phase of light sleep (stage 2), while towards the end of the night the periods are longer and richer in phasic activities (Williams *et al.* 1964b).

The challenge between "slow" sleep and REM sleep as it exists during the course of night sleep is noticed during the rests in the day time. Morning rest includes a lengthy REM sleep, while at the end of the afternoon rest is shown as a prolonged slow sleep (Webb and Agnew 1967).

C. CLINICAL CHARACTERISTICS OF "SLOW" SLEEP

1. Motor activity

The decrease of postural tone which appears with stage 1 is more obvious as sleep becomes deeper and even more in stage 4. This hypotonia is not generalized and actually, the tonic activity of certain muscles is enhanced (orbicularis oculi, masseters, sphincters).

Tendon reflexes are first increased at the beginning of sleep; then they are reduced and may disappear during deep sleep. These variations have been linked with the fluctuations of the gamma motoneuron activity (Paillard 1955). Cutaneous reflexes persist and are sometimes enhanced. Babinski reflex and the grasping reflexes may be found in stages 3 and 4.

The movements that occur during sleep have been studied at length according to the depth of sleep and the feeling of well being when waking up (Viaud 1945; Schaff and Marbach 1960; Kleitman 1963). These movements are very greatly different according to the subjects, and may be grouped for several minutes without a periodicity being established or separated by long periods of immobility. Few at the beginning of the night, they are numerous at the end of the night since they prevail in light sleep.

The *sensory signals* are still received during sleep and the study of evoked responses to sensitive and sensory stimulations have shown modifications especially of latency with regard to stages of sleep (*cf.* Section III).

The arousal effect that lessens while the depth of sleep increases is made easier by certain sensory afferent signals; auditive in man, olfactive in animal. It is favored by the quality of the stimulus and specially by its effective significance.

Autonomic functions. They slow up during "slow" sleep. Hess (1954) links this modification to a parasympathetic or trophotropic effect illustrated by the myosis that goes with sleep. However, these variations are not specific to sleep and depend on 24 h rhythms of the vegetative functions.

The lowering of heart rate is about 10 per cent (Kleitman 1963) with variations according to the depth of sleep, as with the respiratory activity and other movements. Blood pressure decreases by about 20 per cent in the first part of the night; this reduction is more obvious with the systolic pressure than with the diastolic pressure. In the later part of the night, blood pressure returns toward waking levels. This variation is connected with the 24 h cycle.

The slowing up and the regularization of respiratory rate are well known (Pieron 1913). However, some fluctuations may appear, such as a periodic respiration, which resembles the Cheyne–Stokes rhythm, either when falling asleep, especially in older subjects, or when sleep becomes lighter for some reason. The average respiratory rate decreases progressively from the beginning to the end of the night, a change that is related to 24 h rhythm and not to sleep (Schaff and Marbach 1960).

Psychic state. When the subject falls asleep the psychic activity may be intensified and find expression in hallucinations corresponding to hypnagogic pictures. Mental activity persists during slow sleep, but is diminished.

Hypnagogic hallucinations are nearly always visual, sometimes auditive or somesthetic, rarely gustative or olfactory. Thoroughly studied by Maury (1848) and Delage (1903), these hallucinations occur periodically in certain subjects; they may be of a great intensity and even bring a state of obsession in their trail. They either appear when the subject falls asleep or they may occur during the dawn period which follows awakening.

The EEG recordings have shown that these hallucinations occurred during stage 1a, persisted during stage 1b and were then experienced less often or disappeared

during stage 2 (Foulkes and Vogel 1965; Fischgold and Safar 1967). These hallucinations that recall those of dream and were called "dreamlet" by Foulkes and Vogel (1965) are of a different kind. They are of short duration, are not accompanied by anguish and the subject who perceives them is most often indifferent or surprised at this sight in which he does not take a part as in a dream.

Psychic activity is reduced during "slow" sleep. According to Dement and Kleitman (1957) an induced awakening during this sleep is followed by a dream report only in 7 per cent of the cases. According to Rechtschaffen *et al.* (1963) mental state would be translated by "sleep thoughts" linked to a diurnal activity, more abstract and more logical than the hallucinatory activity of the dream.

D. CLINICAL PATTERNS OF REM SLEEP

1. Motor activity

The absence of muscle tone proper to REM sleep is accompanied by short and sharp movements in eyeballs, face, and limbs.

The absence of tonic EMG activity is noticed in most muscles and most clearly, in man, in the neck and chin muscles. It is associated with the loss of spinal reflexes and with a reduction of H-reflex (Hodes and Dement 1964). In addition short spells of muscular jerks and large movements happen during REM sleep, most frequently at the beginning or at the end of this sleep.

Rapid eye movements occur in bursts; few during the first period of this stage of sleep, they are more numerous at the end of the night. They are bilateral, conjugated, and go in every direction, although horizontal movements are more frequent than vertical. They look like some ocular movements of wakefulness; movements of pursuit, movements associated with the recalling of a visual scene.

2. Exteroceptive stimulations and depth of REM sleep

As a result of the lowering of peripheral afferents, the arousal threshold is considered elevated during REM sleep. This increase would be of the order of 200 or 300 per cent in the cat either for tactile or auditive stimulations, or after stimulation of the ascending reticular activating system.

However, a reactivity persists, according to the affective meaning of the stimulus. For instance calling someone in a low voice by his first name may lead to an arousal effect, with a reappearance of alpha waves, and a mewing may induce a hippocampal and cortical desynchronization in the cat (Passouant *et al.* 1965c).

It seems illusory to compare REM sleep to "slow" sleep according to the threshold arousal for the two sleeps correspond to different states. The quality of every deep sleep cannot be given to REM sleep which in fact is a peculiar state different from ordinary sleep.

E. AUTONOMIC FUNCTIONS

Autonomic activity begins to increase several minutes before the onset of REM sleep and is more important during the periods of REM sleep at the end of the night.

This appears as an increase of 6 per cent in the heart rate, of 7 per cent in the respiratory movements and of 4 per cent in systolic blood pressure (Snyder *et al.* 1963). However, this increase is not constant and in some subjects a lowering of heart rate and blood pressure may be noted.

The irregularity of somatic functions, more than their increase, characterizes REM sleep. The respiration, often light, may have a periodic pattern with apneic periods from 10 to 20 sec. The heart rate may be irregular with bursts of extra-systoles. The blood pressure may be irregular with sudden rises of 30 mm Hg. These circulatory variations may, in older subjects or people suffering from vascular diseases, encourage the heart or brain attacks of the night. The vegetative fluctuations may be influenced by the eye movements and the wealth of dreams. But this relationship is not complete, since the autonomic modifications appear before REM sleep and are noticed in newborn infants and during comas with decortication.

In addition to the variations of heart rate, blood pressure and respiration, other autonomic modifications accompany REM sleep.

Penile erection occurs with REM sleep (Fischer *et al.* 1965). Constant in young adults, it may be observed in newborn infants and in older people. It comes before the onset of REM sleep and is maintained throughout this sleep. Sexual dreams are not necessary for this to happen, but they influence the amount of erection. The male hormone may have an influence because of the increase of erection in adults and its reduction in older subjects. This periodic erection produced during REM sleep may help a sexual regulation (Karacan *et al.* 1972).

The cerebral blood flow as measured by the thermocouple technique, is increased by 30–40 per cent in REM sleep when compared with slow sleep (Kanzow 1965). This modification might reflect the increase of the cerebral metabolism and of the CO_2 which is a vasodilating agent. At the same time an increase of cerebral temperature has been noted (Kawamura and Sawyer 1964).

Cutaneous resistance increases with the depth of slow sleep and reaches the highest level during REM sleep; this result has led Hawkins *et al.* (1962) to accept REM sleep as the deepest sleep. Short fluctuations of the electrical conductivity may reappear during REM sleep facilitated by a movement or the emotional intensity of the dream. Electro-dermic responses may reappear sporadically, often following a movement.

Psychic activity. REM sleep is the state of dreaming and subjects awakened while exhibiting REM sleep recall dreams in 80 per cent of the cases (Dement and Kleitman 1957). The hallucinatory imagery and the emotional intensity are greater if awakening is induced at the time of a burst of eye movements. Dreams are more elaborate at the end of the night, as sleep lightens (Foulkes 1964).

Some correlation would seem to exist between mental activity and somato-vegetative modifications that go with REM sleep. It has been suggested that the content of

a dream has a link with the direction and the frequency of eye movements, with the associated movements and the importance of vegetative variations (Dement and Wolpert 1958; Roffwarg *et al.* 1962). However, such a connection could not be exclusive. Indeed the somato-vegetative expressions of REM sleep are definite in the newborn and may be found in some comas in which the possibility of dreaming would seem rather unlikely. The duration of a dream cannot be confused with that of a REM sleep period. Several dreams are possible and the transition from one to the other is marked by a waking effect associated with a movement. Stimuli received during REM sleep may be inserted in the content of the dream but do not start it off.

The dream-recalling mechanism has not been satsifactorily explained and depends on many personal factors which cannot always be defined. The importance of vegetative modifications and respiratory irregularity has been retained (Snyder 1960; Shapiro *et al.* 1963). The frequency of eye movements and the duration of EEG arousal that follows a phase of REM sleep seem to play a role in the recollection of dreams in narcoleptics (Passouant 1967).

Section III. Evoked Responses and Automatic EEG Analysis in Human Sleep

During recent years computers have been used for the automatic analysis of EEG in humans, especially for: (i) evoked responses to peripheral stimulation, recorded by conventional scalp EEG electrodes; the responses are analyzed by applying "on line" averaging techniques (see for references Katzman 1964; Bergamini and Bergamasco 1967; Cobb and Morocutti 1967; Gastaut *et al.* 1967a; Jonkman 1967); (ii) frequency components in spontaneous activity of the brain; auto- and crosscorrelation functions are computed to establish the frequency power spectra of the EEG waves.

These new concepts and new methods have been applied also to the analyses of the EEG events during sleep. Although the data still appear fragmentary heterogeneous and often discordant, it is unquestionable that they have provided new and important knowledge concerning sleep.

A. EVOKED POTENTIALS

The evoked potential (EP) consists of a polyphasic sequence of waves, presumably related to particular neuronal events. It is common opinion that the EP is the expression of a certain type of reactivity (responsiveness) of the central nervous system, or, at least, of the reactivity of the structures involved in the mechanisms of reception, transmission and integration of the evoking stimuli.

Therefore, the investigation of the EP and of their alterations during sleep can also afford information concerning certain functional alterations of the cerebral mechanisms underlying them and, presumably underlying sleep itself. During sleep in humans, visual (Vanzulli *et al.* 1960; Cigánek 1961, 1965; Evarts 1961; Ebe and Mikami 1962a, b; García-Austt *et al.* 1962, 1963; Kooi *et al.* 1963, 1964; Guilbaud *et al.* 1965a, b; Bergamasco *et al.* 1966b; Corletto *et al.* 1966a, b, c, 1967; Kudinova and Myslobodoskii 1968; Saier *et al.* 1968a, b), auditory (Vanzulli *et al.* 1961; Williams *et al.* 1962, 1964a; Guilbaud *et al.* 1956a, b; Weitzman *et al.* 1965a, b; Ornitz *et al.* 1967a, b; Tepas 1967; Nodar and Graham 1968) and somatosensory (Giblin 1964; Goff *et al.* 1966) evoked responses have been studied in normal adults, in newborns and children (Barnet and Goodwin 1965; Weitzman *et al.* 1965b; Kassabgui *et al.* 1966; Rapin and Graziani 1967; Ornitz *et al.* 1968; Suzuki and Taguchi 1968; Weitzman and Graziani 1968; Hrbek *et al.* 1969), as well as during some pathological situations (Broughton *et al.* 1966; Ritvo *et al.* 1967; Jonescu and Dolce 1970) and in pharmacologically induced sleep (Cigánek 1961; Kugler and Doenicke 1965; Bergamasco *et al.* 1968c).

The visual evoked potential (VEP) has been most investigated. Probably due to the use of different techniques and to the different evaluation and analysis criteria applied, some discrepancies still exist between the data of different authors. However, the common characteristics of the VEP during sleep can be summarized as follows:

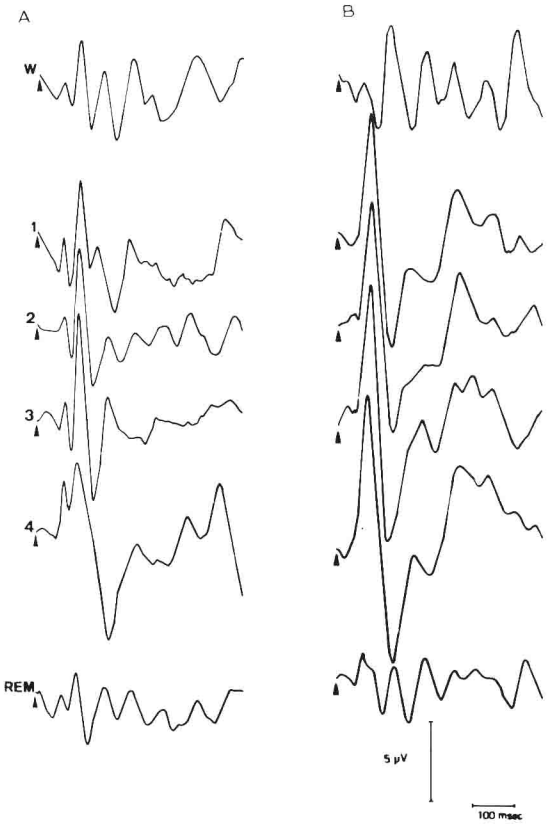


Fig. 2. Visual evoked potentials in wakefulness (W) and during different sleep stages (1, 2, 3, 4 and REM). Stimulus at the arrows. Each trace represents the computed average of 50 successive responses to stimuli given at 0.5 c/sec. Two different subjects: in *A*, without obvious morphological differences between responses in wakefulness and synchronized sleep; in *B*, morphological changes during synchronized sleep. Note: progressive increase of the amplitudes occurs during synchronized sleep; on the contrary, during desynchronized sleep the amplitudes are decreased, becoming even more reduced than in wakefulness. For further explanation see text.

1. The (peak-to-peak) amplitude of the VEP considered as a whole, increases after sleep onset and, usually, also continues to increase during the progression of sleep and EEG synchronization (synchronized EEG: sleep stages 2, 3 and 4) (Rechtschaffen and Kales 1968). On the contrary, during the sleep stage with desynchronized EEG and rapid eye movements (REM sleep stage), the amplitude decreases to values even lower than those recorded during wakefulness (Fig. 2, *A*).

The increase might be more conspicuous in the positive components (Vanzulli