# Interaction epilepsy, sleep, antiepileptics : a clinical neurophysiological study

# INTERACTION
# EPILEPSY - SLEEP - ANTIEPILEPTICS

A Clinical Neurophysiological Study

CIP-GEGEVENS

Declerck, August

Interaction epilepsy, sleep, antiepileptics : a clinical neurophysiological study / August Declerck ; [ill. Chris Vereijken]. - Lisse : Swets & Zeitlinger. - Ill., tab., fig.
Proefschrift Maastricht. - Met lit. opg. - Met samenvatting in het Nederlands
ISBN 90-265-0471-3
SISO 606.1 UDC 616.85
Trefw. : epilepsie.

Cover design: Chris Vereijken
Printed in the Netherlands by Offsetdrukkerij Kanters B.V., Alblasserdam


ISBN 90 265 0471 3

# Interaction

# Epilepsy - Sleep - Antiepileptics

## *A Clinical Neurophysiological Study*

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE RIJKSUNIVERSITEIT LIMBURG, OP GEZAG VAN DE RECTOR MAGNIFICUS PROF. DR. H. C. HEMKER, VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN IN HET OPENBAAR TE VERDEDIGEN OP DONDERDAG 2 JUNI 1983 DES NAMIDDAGS OM 16.00 UUR PRECIES, IN DE AULA DER UNIVERSITEIT

DOOR

**AUGUST DECLERCK**

GEBOREN TE WESTKERKE (B)

1983

SWETS & ZEITLINGER B.V., LISSE

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Bij het tot stand komen van het onderzoek werd apparatuur ter beschikking gesteld door de Commissie Landelijke Epilepsie Onderzoek van de Gezondheidsorganisatie T.N.O.

ACKNOWLEDGEMENT

I would like to thank all the people who played some role in the realization of this thesis, especially if I have forgotten to mention them by name.

My interest in electroencephalography and the diagnostic possibilities it offers would never have been awakened without the stimulating and friendly encouragement of Dr. A.J. Simons. My interest in research into a plethora of medical and non-medical problems has been frequently motivated and tempered by the enthusiasm or criticism of Dr. A. Wauquier.

At the start of my research investigations I have always been able to completely rely on the enthusiasm of my co-workers (Mrs. M. Pans-Raedts, Miss A.M. Schiltz, Mrs. R. Sijben-Kiggen, Mrs. J. Peeters-Sijben, Miss M. Sengers, Miss M. te Dorshorst, Mrs. E. Voets-Petiet, and Messrs. J. Vervisch, Chr. Vereijken, F.V. Renswouw, T. Lustenhouwer and F. Kums.

Special mention must also be made of the following people who played important roles in the completion of my thesis:

Prof. Dr. J.M.F. Mol, my promotor, who repeatedly urged me to rework the results of my studies into a clinically useful thesis.

Mrs. T. de Leijer-Boerenkamp my secretary, who not only repeatedly typed my corrected versions of the text, but who also helped with the cataloguing of the literature data, she could always call upon the collaboration of Mrs. Haneveer-Dingenen, the librarian.

Ir. W. Martens, who was responsible for the automatic classification of the sleep analyses and the experimental results. Further, together with Drs. G. Clincke, he completed the statistical analysis of the data.

Mr. Chr. Vereijken, who in addition to his work as EEG-technologist, took on the task of ensuring that the figures were suitably placed in the manuscript.

Drs. D. Ashton, who improved the language of the English version, and Mrs. L. Geentjens, both from Janssen Pharmaceutica, who was responsible for typing and ordening the English version of the final text.

Finally, I would like to thank the Directors of the Kempenhaeghe for their interest, and the many colleagues who gave me moral support during my research.

*Lieve*
*Els*
*Mieke*
*Stefaan*

## ABBREVIATIONS

| | |
|---|---|
| A.E. | Antiepileptic drugs |
| ARAS | Ascending reticular activating system |
| ASW | Atypical spike wave |
| Aw. | Awake |
| B.D. | Benzodiazepine derivatives |
| Carb. | Carbamazepine |
| Clon. | Clonazepam |
| Chlor. | Chlorazepate |
| c/sec | Cycle of per second |
| D.P.H. | Diphenylhydantoin |
| E. | Epileptic EEG phenomena |
| ECG | Electrocardiography |
| EEG | Electroencephalography |
| EMG | Electromyography |
| EOG | Electrooculography |
| EST | Effective sleep time |
| FSW | Spike wave of fast frequency ( $\geqslant$ 4 c/sec) |
| Gen.E. | Generalized epilepsy |
| LSW | Spike wave of low frequency ( $\leqslant$ 2.5 c/sec) |
| MSW | Multiple spike wave |
| N.A.E. | No antiepileptics |
| N.E. | No epileptic EEG phenomena |
| N.REM sleep | Non-REM sleep |
| Part.E. | Partial epilepsy |
| PSD | Partial sleep deprivation |
| PSW | Poly ( $\geqslant$ 2 spikes) spike wave |
| R | Respiration |
| REM | Rapid eye movements |
| REM sleep | REM sleep |
| RLT | REM latency time |
| RM | Respiratory movements |
| S | Spike ( > 11 c/sec) |
| SEM | Slow eye movements |
| SH | Sharp wave ( < 11 c/sec and > 5 c/sec) |
| SLT | Sleep latency time |
| Sod.V. | Sodium valproate |
| SSD | Selective sleep deprivation |
| TRT | Total registration time |
| TSD | Total sleep deprivation |
| TST | Total sleep time |

# CHAPTER I: INTRODUCTION

Almost a century ago Gowers (1885) and Fere (1890) pointed out that in some epileptics the attacks mainly occurred or increased during nocturnal sleep. Later Langdon-Down and Brain (1929) and Patry (1931) showed that there was a correlation between the occurrence of epileptic attacks and the sleep-wakefulness rhythm. This association has been studied extensively by Janz (1962) who divided the epilepsies into "Aufwach, Schlaf und Diffuse Epilepsien". Of the 2110 studied patients there were 34 % which mainly had attacks during daytime during wakefulness, 45 % with attacks during nocturnal sleep and 21 % with attacks both during the day and during the night.

After the introduction of electroencephalography (Berger, 1929) it became possible to study the association between epilepsy and sleep in a more precise way (Passouant, 1951, 1962). Gibbs and Gibbs (1942) were the first to use sleep as a method in the field of epilepsy diagnosis. Apart from the spontaneous nocturnal sleep, spontaneous sleep during daytime (siesta), drug-induced sleep, and sleep deprivation have been studied. Especially the last method has been used successfully in many laboratories (Degen, 1979) as an addition to routine EEG recording. Due to the fact that there is no uniform method of producing sleep deprivation (Gereby, 1978, Tartara et al., 1980) it is difficult to compare the results of the sleep deprivation method with those obtained with spontaneous nocturnal sleep. Therefore, it appeared desirable to investigate the conditions required for sleep deprivation recording which would result in an optimal diagnostic result.

In general it is accepted that a good night sleep is required in order to be in a good condition and to perform adequately during daytime. Many epileptics complain about a lack of fitness and subnormal performance. It is reasonable therefore, to question whether they had sufficient and adequate sleep.

Sleep can be judged by filling in a questionnaire or by carrying out a polygraphic sleep investigation. By using EEG sleep recordings, carried out in epileptic patients, in the framework of supplementary diagnosis, it is possible to study their sleep. From such studies it can be derived in what way and to which degree the sleep in epileptics differs from the sleep in normal persons and whether these differences depend on the kind of epilepsy and the kind of drug therapy. Here also the question is how to achieve an optimal sleep deprivation and recording, such that the sleep in itself can be judged.

On the basis of a literature survey and an analysis of our own investigations we will attempt to answer these two questions in the following chapters. For this purpose, data from the literature are sampled which relate to the following:

1. the epileptic EEG deviations and the polygraphic judgement of sleep;
2. the different kinds of sleep methods used to improve the diagnosis of epilepsy;
3. the changes in the epileptic EEG phenomena which may occur during sleep;
4. the sleep changes which may occur as a consequence of the epilepsy or the intake of antiepileptics.

On the basis of our own investigations we would like to know whether the polygraphic sleep recording after one night sleep deprivation:

1. is an effective and useful method for the detection of epilepsy and for the judgement of the sleep;
2. which conditions need to be fulfilled in order to approach the effect of a total night sleep recording;
3. how the sleep composition changes, because deprivation interferes with the effects caused by epilepsy or the intake of antiepileptics;
4. whether comparable morphological EEG changes are seen.

By combining the results of our own investigations with those obtained in the literature we attempted to arrive at a critical judgement of the value of polygraphic EEG investigations for diagnosing epileptic EEG phenomena and changes in the sleep in epileptics.
In addition, special attention will be given to the way in which sleep deprivation should be carried out and how the results should be interpreted. It is hoped that insight will be gained into the way certain antiepileptics exert their therapeutic effects, and a number of suggestions will be made to improve epilepsy diagnosis in the future.

## CHAPTER II: LITERATURE

The present chapter surveys findings in the literature with respect to sleep and epilepsy and is summarized in four parts:

1. polygraphic sleep investigation and the partition of sleep;
2. the electroencephalographic epilepsy phenomena and the electroclinical classification;
3. the different sleep methodologies which have been applied to diagnose epilepsy;
4. sleep changes which may occur as a consequence of having epilepsy or due to the intake of antiepileptics.

### II.1. POLYGRAPHIC SLEEP INVESTIGATION AND SLEEP CLASSIFICATION

Decades ago (Moruzi and Magoun, 1949) sleep was considered as an expression of rest of the organism and the central nervous system. It was thought that sleep was caused by a decrease in the activity of the ascending reticular formation (ARAS), a brainstem structure thought to be responsible for the maintainance of wakefulness. During such a passive rest condition the brain would function in a very simple and undifferentiated way.

Less than ten years after the introduction of the clinical use of the EEG (Berger, 1929) Loomis et al. (1935, 1937) could differentiate between 5 stages of sleep, each stage being characterized by a specific EEG picture. During nocturnal sleep these stages appeared to occur repetitively in a cyclic fashion.

Aserinsky and Kleitman (1953) discovered for the first time that rapid eye movements occurred during certain sleep periods. These eye movements could be recorded graphically by means of placing periorbital skin electrodes (electro-oculography or EOG). These eye movements appeared to be conjugated. The sleep periods during which rapid eye movements (REM) were seen, were termed by Dement (1955) as REM sleep and the other periods as non-REM sleep (N.REM). Dement and Kleitman (1957) found that REM sleep occurred in a cyclic fashion interrupted by longer periods of N.REM sleep. The total duration of the two states of sleep lasted about 90 to 100 minutes.

It appeared very soon that REM and N.REM differed from each other in many aspects. Apart from a difference in the EEG Jouvet and Michel (1959) and Berger (1961) found that the muscle activity (EMG) was strikingly low during PEM sleep. Other physiological parameters such as heart rhythm, respiration, blood pressure and body temperature behave differentially during the two states of sleep. In general, the measured values are lower and more regular during N.REM sleep as compared to REM sleep. On the basis of these differences it has been stated (Oswald, 1962) that sleep is not a simple passive process but rather an expression of a complex and active brain function. Wakefulness, REM and N.REM sleep are therefore considered as three different degrees of consciousness (Jouvet, 1962).

Because the two states of sleep: REM and N. REM sleep differ from each other in many aspects a new sleep classification was introduced taking non-EEG parameters into account. A frequently used sleep classification on the basis of polygraphic criteria was established

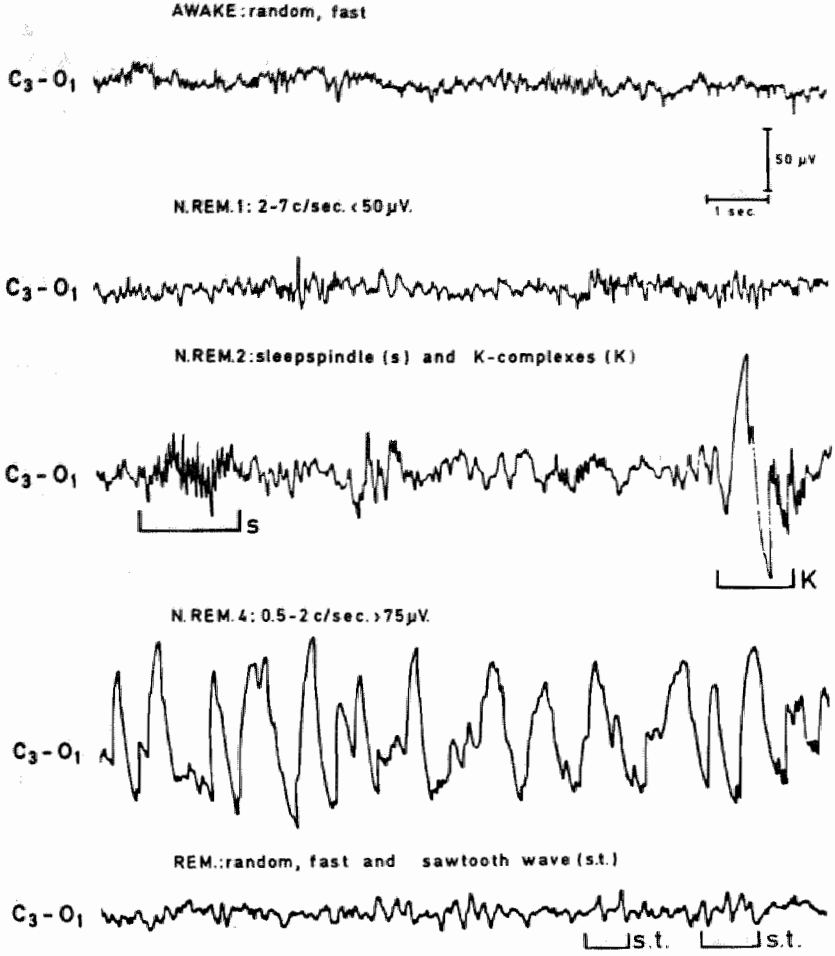


FIG. II.1.
EEG patterns according to the different human sleep stages and states (from Hauri, 1977).

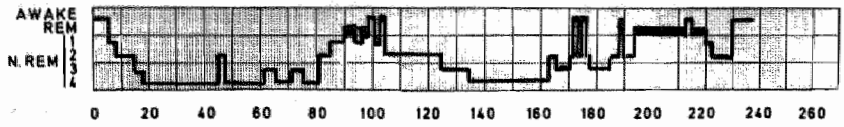


FIG. II.2.
Example of a hypnogram.

and published by Rechtschaffen and Kales (1968). On the basis of the changes in the EEG, EOG and EMG a difference was made between REM and N.REM sleep. The latter was further differentiated into 4 stages, stage 1 - 4 denoting a progressively increasing depth of sleep. An example of the different states and stages is represented in Fig. II.1.

Hereafter follows a description of each sleep stage as based on EEG and non-EEG characteristics(1).

Stage N.REM 1: The EEG is characterized by the disappearance of the wakefulness rhythms and the appearance of low voltage rhythms not exceeding 50 - 70 microvolts of varying frequencies between 2 and 7 c/sec. In the vertex region triphasic sharp waves of 100 to 200 microvolt amplitude and lasting 50 to 200 msec are seen. The EOG shows intermittent slow eye movements (SEM). The EMG shows muscle activity which is lower than during wakefulness.

Stage N.REM 2: The EEG consists of low voltage unstable rhythms, sleep spindles and K-complexes. Sleep spindles are "a group of rhythmic waves characterized by progressively increasing then gradually decreasing amplitude. The waves are monomorphic, diphasic and symmetrical with respect to the baseline with a stable frequency of 12 to 14 c/sec and variable duration of 1 - 6 sec". A K-complex is "a sharp negative high voltage EEG wave, which is followed by a slower positive component and can be elicited by external stimuli".
No eye movements are seen in the EOG and the EMG shows a further decrease of the muscle activity.

Stage N.REM 3: The EEG is characterized by polymorphic waves of 0.5 to 2 c/sec with an overall amplitude of more than 75 microvolts. These delta rhythms are present for more than 20 %, but less than 50 % of the recording time.
There are no eye movements and the muscle activity is further decreased.

Stage N.REM 4: During more than 50 % of the time 0.5 to 2.5 c/sec delta rhythms are seen, which have a high amplitude and which are more regular than during sleep stage N.REM 3. Sporadic sleep spindles occur. There are no eye movements anymore and the muscle activity remains low.

State REM : The EEG is desynchronized consisting of low voltage rhythms of varying frequencies resembling stage

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(1) - "The Sleeping Brain", Glossary, pp. 508-522 (Editor: Chase, 1971).
- "Glossary of Terms used in the Sleep Disorders Classification", Sleep, pp. 123-129, 1979.
- "Glossary of Standardized Terminology for Sleep and Biological Rhythm Research", Sleep, pp. 287-288, 1980.
- "Handbook of EEG and Clinical Neurophysiology", vol. 11, part A., pp. 58-73, 1977.

N.REM 1. However, there are no sharp vertex waves, but rather saw-tooth like waves derived from the occipital cortex (Dement, 1972). During this sleep state, many rapid conjugated eye movements are seen, often predominantly in the horizontal direction.
The EMG activity is very low, especially in the neck and chin muscles, and the postural muscles of trunk, arms and legs. In the face and fingers this low muscle activity is interrupted by short-lasting tonic contractions.

The increased depth of N.REM sleep is also expressed by a progressive decrease of heart and respiration frequency, blood pressure, body temperature and urine and gastric acid secretion (Snijder et al., 1964). Therefore, this sleep is often considered as quiet sleep. This term, however, is incorrect since during the N.REM sleep an enhanced cerebral blood flow with preservation of oxygen uptake is observed. In addition electrical skin resistance is also increased (Dement, 1972).

In contrast to the N.REM sleep during REM sleep the heart frequency and respiration become irregular and the respiratory center in the brainstem becomes less sensitive towards $CO_2$ changes (Phillipson et al., 1976). Further there is a disturbance of temperature regulation (Shapiro et al., 1974). Due to these changes REM sleep is often termed active sleep (Lena and Parmeggiani, 1964) or paradoxical sleep (Jouvet and Michel, 1965) because the desynchronized EEG picture and the presence of rapid eye movements with the eyes closed resembles wakefulness with eyes open.

Because of the characteristic EEG phenomena N.REM stage 2 is often termed spindle sleep and N.REM sleep 3 and 4 as delta sleep. Presently, the most used terms are REM and N.REM sleep, N.REM 1 and 2 and N.REM 3 and 4 respectively denoting light and deep slow wave sleep. It is common to represent the cyclic appearance of the different sleep stages in a hypnogram (Fig. II.2.).

The duration of the different stages of the sleep is changing during the course of the night: at the beginning of the night there is more deep slow wave sleep and less light slow wave sleep than at the end of the night. In normal adults the following percentage sleep partition is seen (Kales and Kales, 1970): REM: 20 - 25 %; N.REM 1: 5 %; N.REM 2: 50 - 55 %; N.REM 3: 10 % and N.REM 4: 10 - 15 %. During aging N.REM 3 and 4 slow wave sleep decreases and N.REM sleep 1 increases.

## II.2. EPILEPTIC EEG PHENOMENA AND ELECTROCLINICAL CLASSIFICATION

Interpretation of findings in the older literature on epileptic EEG phenomena is difficult since a different terminology was used. A considerable step forward has been made since the introduction of the standardized 10-20 system for electrode placement (Jasper, 1958), the establishment of criteria for an EEG investigation for clinical purposes (Kugler, 1963, Mac Gillivray, 1974), the introduction of a standardized terminology of EEG rhythms (Storm van Leeuwen et al., 1966) and a uniform interpretation of EEG rhythms in relation to the

clinic (Magnus, 1961). Since our investigations studied the relationship between polygraphic sleep patterns and epileptic EEG phenomena and their relation towards the clinic, it is necessary to define these phenomena sufficiently.

## 2.1. Epileptic EEG phenomena

The definitions of epileptic EEG phenomena were based on the terminology described in the "Handbook of EEG and Clinical Neurophysiology". Hereafter follows a description of the definitions which will be used extensively in the text.

- Epileptic discharge: A neuronal discharge characterized by the simultaneous excessive activation of a large number of cells which may be recorded by electroencephalographic techniques as a paroxysmal wave form, usually in the form of a spike (S), sharp wave (SH), spike and wave (SW) or other such complex.
- Paroxysm: A group of waves which appears and disappears abruptly and which is clearly distinguished from background activity by a different frequency, morphology and amplitude.
- Spike: (S): A wave, distinguished from background activity and having a duration of 1/12 sec or less, a prevalently negative polarity and an amplitude from 50-150 microvolt. Poly-spikes are constituted by several closely grouped spikes (usually from 2 to 6).
- Sharp waves (SH): A usually negative wave, distinguished from background activity with a duration of more than 1/12 and less than 1/5 sec, an amplitude of 100 - 200 microvolts, with a vertical ascending segment and a more prolonged descending segment.
- Complex: A group of two or more waves, clearly distinguished from background activity, and occurring with a well recognized form or recurring with consistent form.
- Spike and wave (SW): A complex of two waves, one with a duration of 1/12 sec or less (S) and the other with a duration of 1/5 - 1/2 sec (W).
- Polyspike wave (PSW): A SW complex with more than one spike.
- Sharp and wave (SHW): A complex of two waves, one having a duration between 1/2 and 1/5 sec (SH), the other between 1/5 - 1/2 sec (W).
- Sharp and slow wave (SH.SW): A complex of two waves, one having a duration between 1/12 and 1/5 sec (SH), the other between 1/2 and 1 sec (Slow W).

Paroxysmal epileptic discharges can invade both hemispheres, one hemisphere, or part of one hemisphere. In EEG terms these paroxysmal epileptic discharges can be generalized, lateralized, partial or focal. Generalized (gen.) means that the epileptic EEG phenomena are recorded simultaneously from all electrodes in both hemispheres; lateralized (lat.) means that they occur predominantly or exclusively in one hemisphere; partial (part.) means that these occur regionally but are registered from more than one electrode or focal (foc.) when these are registered only from one electrode.

Further, one defines duration of the epileptic discharges, the degree and in which way the grapho elements have a regular (reg.) or irregular (irreg.) form, frequency and amplitude and whether these occur symmetrically (symm.) or asymmetrically (asymm.) and synchronous (synchr.) or asynchronous (asynchr.) above homologous brain regions.

Finally, one can define whether these epileptic EEG phenomena possess a typical (typ.) or atypical (atyp.) aspect and whether these change during the sleep.

## 2.2. Electroclinical classification of the epilepsies

Fifteen years ago the epilepsies were mainly classified on the basis of a clinical symptomatology and a possible etiology. Later more criteria were considered of importance for a proper classification; their ictal and interictal epileptic and non-epileptic EEG phenomena played an important role. The combination of clinical and neurophysiological data were the basis of a classification system purposed by "International League against Epilepsy" (Clinical and electroencephalographic classification of epileptic seizures, Epilepsia, 1970A, 11, 102-113; Proposal for an international classification of the epilepsies, Epilepsia, 1970B, 11, 117-119).

In this classification the epilepsies have been categorized according five clinical and three neurophysiological criteria into three main forms: the primary generalized epilepsies (pr.gen.), the secondary generalized (sec.gen.) and the partial (part.) epilepsies.

The five clinical criteria are: (1) the clinical form of the epilepsy, (2) the interictal presence or absence of organic brain damage, with the presence of neurological, neuroradiological, mental or psychological deviation, (3) the age of onset, (4) the presence or absence of definable causes, (5) the degree of possible treatment with antiepileptics.

The neurophysiological criteria are: (1) the ictal EEG picture, (2) the interictal EEG picture, (3) the neurophysiological mechanisms at the origin of the epileptic discharges.

### 2.2.1. The primarily generalized epilepsies have following characteristics:

Clinical:
- The sudden appearance of clinical epileptic manifestations, either of the absence type (petit mal: P.M.), the tonic clonic type (grand mal: G.M.) or myoclonic type (mycl.), by which the muscle contractions are present from the start;
- Onset at childhood or adulthood;
- Absence of cerebral damage interictally;
- Absence of definable etiology, but often a heriditary predisposition;
- Beneficial response to antiepileptics.

EEG :
- During the ictal signs diffuse epileptic EEG phenomena are present, consisting of 10 c/sec rhythms, described as "epileptic recruting rhythm" (E.R.R.), typical and atypical SW and PSW complexes.
- Interictal appearance of epileptic EEG discharges with similar characteristics as during the attacks, the EEG background pattern shows a tendency to slow synchronization;
- The different forms of primarily generalized epilepsy cannot be divided on the basis of the etiological mechanisms of origin since these are insufficiently known.

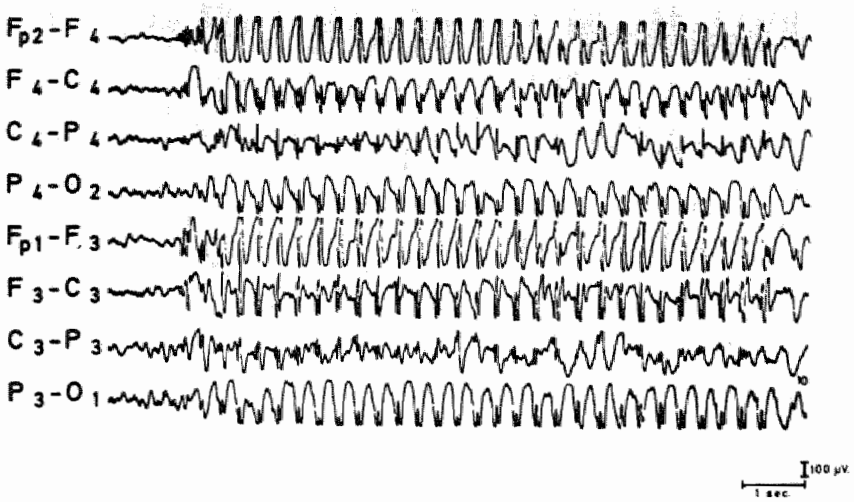


FIG. II.3.
Example of primarily generalized epilepsy (3 c/sec).

2.2.2. The secondarily generalized epilepsies have following characteristics:

Clinical: - They consist of tonic-clonic (T.C.), tonic (T), atonic (At) attacks, massive bilateral myoclonus, collapses and atypical absences. These clinical signs can be generalized from the beginning of the attack or they can be spread diffusely after a local onset.
- Interictally there are neurological, neuroradiological, psychological or mental signs of cerebral damage;
- Seldom there is an evident etiology, but often there are signs of a diffuse or multifocal cerebral damage;
- The antiepileptics of first choice have only a limited effect, benzodiazepines sometimes have better effects.

EEG : - During the ictal signs epileptic recruting rhythms, pseudorhythmic low frequency spike waves (LSW ± 2 c/sec) and isolated slow waves occur;
- Interictally, there is a diffusely disturbed EEG picture with epileptic EEG phenomena of which the former is related to the clinical picture which can be of a specific or unspecific nature;
- To the specific forms belong those which appear in combination with myoclonia such as the progressive myoclonic epilepsy of Unverricht-Lundborg and the intention myoclonic form of epilepsy such as in the syndrome of Ramsay-Hunt; aspecific is the syndrome of West or myoclonic encephalopathy with hypsarrhythmia, or by ictally as well as interictally diffuse LSW with varying localization, and the syndrome of Lennox-Gastaut or the petit mal variant, where LSW vary with fast spike waves (FSW, more than 4 c/sec).

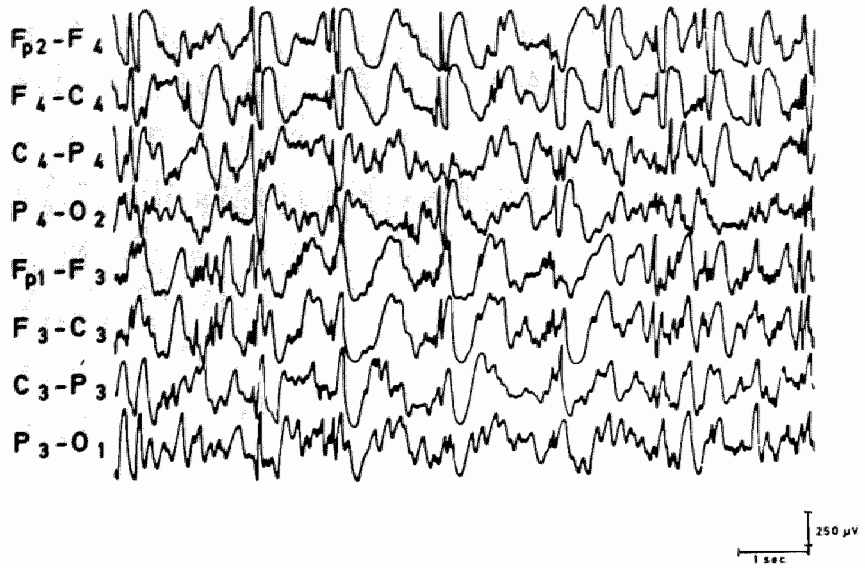


FIG. II.4.
Example of secondarily generalized epilepsy (hypsarythmie).

2.2.3. The partial epilepsies have following characteristics:

Clinical:
- The first clinical symptom as well as the most pronounced clinical symptoms are very different and depend on the anatomical localization of epileptic discharges. Depending on the complexity of the appearance, one differentiates between simple (s) and complex (c) forms.
- Interictally there are signs of the circumscribed cortical damage;
- It can appear at each age but seldom in early childhood;
- An organic injury is often at the origin;
- A reasonable to sufficient treatment with antiepileptics is possible.

EEG :
- The discharges consist of local spikes, sharp waves, typical or atypical spike waves, especially slow and sharp wave complexes. They occur isolated or in series of varying duration.
- Interictally similar paroxysmal discharges occur. The background picture is often normal in the simple epileptic form, but is associated with the slowing in the more complex form.

## II.3. SLEEP POLYGRAPHY FOR THE DIAGNOSIS OF EPILEPSY

Gibbs and Gibbs (1942) were the first to carry out the EEG sleep investigations in epileptic patients, because they observed

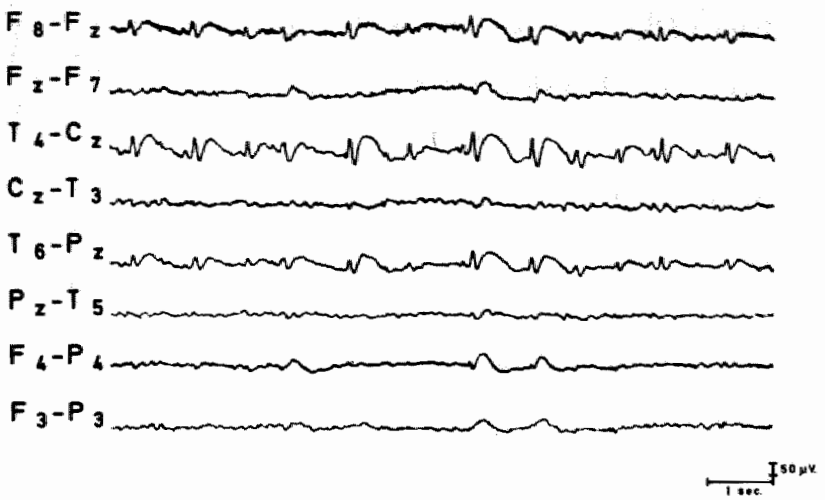


FIG. II.5.
Example of complex partial epilepsy (psychomotor type).

that epileptic EEG phenomena increased during the sleep. Thereafter sleep has been used as a diagnostic aid in the field of epilepsy by many authors (Bancaud et al., 1965; Cadilhac and Passouant, 1965; Gastaut et al., 1965a; Angeleri, 1969). Different procedures have been used: spontaneous sleep during night (all-night and interrupted sleep) or day (siesta sleep), drug-induced sleep or sleep following preceding sleep deprivation.

3.1. The spontaneous nocturnal sleep

As mentioned above Janz (1962) found that in some epileptics the attacks mainly occurred during sleep at night (sleep or S-type), in other patients during the day (awake or A-type), or in others during night and day (random or R-type).

The patients of the S-type suffer mainly from a primarily generalized attack of the tonic-clonic type and a partial complex attack, for instance of the psychomotor type. Many patients of the A-type suffer from a primarily generalized epilepsy of the absence type and those of the R-type of a focal epilepsy with secondarily generalization.

Many investigators established that the occurrence of epileptic EEG deviations depended on the depth and the kind of sleep. According Broughton (1972) the EEG abnormalities fitting with primarily generalized epilepsy of the grand mal type increased during N.REM and decreased during REM sleep. According Sato et al. (1973) and Schwartz et al. (1964), diffuse 3 c/sec spike waves fitting with primarily generalized epilepsy of the absence type, remain present during REM sleep. The features of the grand mal as well as of the petit-mal

type are mainly seen during falling asleep (Delangh et al., 1962; Kazamatsuri, 1964).

The increase of epileptic abnormalities during sleep of the secondarily generalized epilepsies is dependent on the syndrome. With the specific syndrome of Unverricht-Lundborg and Ramsay-Hunt there is an increase during N.REM 1-2 sleep and a decrease during N.REM 3-4 sleep. REM sleep is often lacking in these patients (Passouant and Cadilhac, 1970). The aspecific syndromes such as the syndrome of West (hypsarrhythmia) and the syndrome of Lennox-Gastaut (petit-mal variant) are differentially affected by the sleep. In the syndrome of West the long series of aspecific spike waves paroxysms are interrupted during the N.REM sleep and suppressed during the REM sleep. In the syndrome of Lennox-Gastaut they increase during the light N.REM 1-2 sleep and decrease during N.REM 3-4 sleep (Gastaut et al., 1975; Inoue et al., 1977).

The partial epilepsies may be increased during N.REM 1-2 sleep, and the abnormalities often tend to spread. In contrast, REM repetitively leads to a better limitation of the spread (Findji et al., 1978). According Broughton (1972) partial epilepsies with superficial cortical temporal discharges would increase during N.REM 1-2 sleep, whereas the deeper situated temporal and frontal foci would be expressed especially during REM sleep.

Measuring the spike activity in the focus as a function of time, it appears that there is an increase during N.PEM 1-2 sleep and even more during N.REM 3-4 sleep (Gozukirmizi et al., 1982; Montplaisir, 1980). This has been confirmed by Lieb et al. (1980) who found that in deeper laying cortical foci, there was a three-fold increase during N.REM 1-2 and a six-fold increase during N.REM 3-4 sleep, and none or a very limited increase during REM sleep.

The findings by Schwartz et al. (1964) are of importance: they found that the increase of focal epileptic EEG abnormalities do not only depend on the depth of sleep but also on their localization. They found an increased spike activity during N.REM 1 sleep when the injury was localized in the left occipital cortex and an increase during N.REM 2-3 and 4 sleep when the injury was localized in the right temporal region.

Many investigators pointed at the importance of REM sleep for the localization of the primarily epileptic focus, since this becomes more circumscribed during REM sleep (Montplaisir et al., 1979; Perria et al., 1966; Rossi et al., 1974).

Apart from the quantity of the epileptic EEG abnormalities also their form can change during sleep. Broughton (1972) pointed at the tendency to the formation of polyspike wave complexes during N.REM sleep, with a greater preponderance during N.REM 1-2 than during 3-4 sleep. Sato et al. (1973) categorized the morphological changes of the spike waves according depth of N.REM sleep.

During the N.REM 1 sleep the 3 c/sec spikes retain their regularity but the duration of the paroxysms becomes shorter. During N.REM 2 sleep the spike waves become irregular with changing frequencies between 2 and 4 c/sec and a more pronounced polyspike wave formation. Simultaneously these paroxysms shorten and their number increases. The decreased duration and increased number of spike-waves is even more pronounced during N.REM sleep 3-4, during which they remain irregular but their frequency changes to 2.5 - 1.5 c/sec.

Passouant (1975) has demonstrated that the changes in spike-waves are linked to the associated clinical form of epilepsy. Thus, the generalized 3 c/sec spike waves seen in the primarily generalized epilepsy of the absence type, increased during N.REM 1-2 sleep and developed towards polyspike wave formation. These changes would not occur during deep N.REM 3-4 sleep, and also possibly not during REM sleep.

In contrast, the spike wave paroxysms which occur in the primarily generalized epilepsy of the tonic-clonic type increased during all stages of N.REM sleep. In absence of the myoclonic type, the polyspike wave paroxysms are seen during wakefulness, and retain or increase their appearance during all stages of the N.REM sleep. According Erba and Moschen (1980) also the aspecific spike wave complexes are influenced by sleep. This is manifested by the formation of polyspike wave complexes during N.REM 1-2, the aspecific aspect increases during N.REM 2-3 sleep and is suppressed during N.REM 4 and REM sleep. The most important findings in the literature concerning the influence of the different sleep stages on epileptic EEG phenomena are summarized in the following table (Table II.6.).

Table II.6.
Summary of some literature findings concerning the influence of the different sleep states and stages on epileptic EEG phenomena.

| Type of epilepsy | Type of sleep | | | | |
|---|---|---|---|---|---|
| | N.REM | | | | REM |
| | 1 | 2 | 3 | 4 | |
| Prim.Gen.: Absences (P.M.) | ↑ SW | ↑↑ PSW | - | - | = or ↓ SW |
| Ton.clon. (G.M.) | ↑ PSW | ↑↑ PSW | ↑↑ LSW + irreg. | ↑↑ | ↓↓ ? |
| Sec. Gen. : Specific | ↑ PSW + irreg. | ↑↑ | ↓ irreg. | ↓ | -- |
| Aspecific | ↑↓ | ↑↓ fragmentation + irreg. | ↑ | ↓ | ↓↓ |
| Partial : Simple | ↑ spreading | ↑↑ | ↓ | ↓ | ↑ focalization |
| Complex | ↑ spreading + generalization | ↑↑ | ↓ | ↓ | ↑↑ focalization |

From this incomplete summary large differences between N.REM and REM sleep are apparent for both general and for partial epilepsy. It is therefore not surprising that one has assigned convulsive features to the N.REM sleep and anticonvulsant features to the REM sleep (Meiert-Ewert, 1978). An explanation has been sought in the difference in the level of activity of the reticular activation system during N.REM and REM sleep. This system would be less active during N.REM sleep, through which the inhibition of cortical neurons decreases and thalamocortical hypersynchronous mechanisms increase. The activity of this system increases again during REM sleep, though the cortical inhibition would be comparable with that found during wakefulness (Feemey et al., 1977; Gloor, 1980 and Montplaisir et al., 1980).

From the literature summarized above, it is clear that the recording of a total night sleep during which all sleep stages are present to a sufficient degree, can be a considerable contribution to the affirmation of, and a better description of the different forms of epilepsy. With the aid of this procedure Jovanovic (1966) found that there was a diagnostic gain of 34 % in subjects suspected of having epilepsy. Unfortunately, this method is very labour intensive and too expensive to be used routinely. Therefore, many investigators have applied it fairly selectively. Broughton (1972) advised to use this method for the detection of an epileptic focus not seen during wakefulness or which rapidly gives rise to secondarily generalization. Sometimes the sleep recording is restricted to the first part of the night (interrupted sleep). This procedure is based on the experience that in many patients the epileptic EEG phenomena are mainly seen during the first part of the night (Marosfi, 1980).

### 3.2. Spontaneous sleep during the day or siesta sleep

The possibility to record sleep during daytime is large in small children and promoted in countries where siesta sleep belongs to the normal life pattern. Different investigators made use of this need or habit to detect epileptic EEG abnormalities by recording during siesta sleep (Cadilhac and Passouant, 1965; Gastaut et al., 1965a; Knight et al., 1977).

This procedure has the disadvantage that this kind of sleep is mainly restricted to N.REM 1-2 sleep, whereby the presence or absence of REM sleep depends on the precise point of time of the recording. Berger et al. (1971) have demonstrated that the opportunity to record REM sleep is largest in the morning and decreases during the course of the day, with an increased opportunity to record deep N.REM sleep. The constitution of sleep is further dependent on all sorts of factors like environmental noice (Zimmerman, 1970), temperature (Schmidt-Kessen and Kendel, 1973), the kind and time of the proceeding meal (Jacobs and McGinty, 1971; Karacan et al., 1975) and the use of alcohol (Rundell et al., 1972). Further taking the large individual differences into account it is clear that the siesta sleep is not well suited for comparative investigations.

### 3.3. Drug-induced sleep

Preceding or during a routine investigation a short-acting barbiturate is taken orally (Kuyer and Buit-Gutter, 1974). This results mainly in N.REM 1-2 sleep and sometimes a N.REM 3-4 sleep, stages during which epileptic EEG phenomena, fitting with different forms of epilepsy are often increased. Because the dose used is low (e.g. 50 mg secobarbital), adults will have no or limited inconvenience, except for a light sleepiness (Potvin et al., 1975). The disadvantage of these substances is that they are antiepileptics (Longo, 1977), which might suppress the epileptic EEG phenomena and in addition they may influence the interictal EEG pattern as well as the polygraphic sleep pattern in an unnatural way (Gabriel and Albani, 1977; Montagu, 1971). For similar reasons benzodiazepines, mainly suppressing generalized epileptic EEG abnormalities (Boyer, 1966) are not advised (Greenblatt and Shader, 1973).
Some investigators (e.g. Degen, 1982) used phenothiazine-derivatives to promote light slow wave sleep. This superficial sleep can be favorable for the detection of partial epilepsy and the many transitions from wakefulness to sleep can favour the occurrence of generalized epilepsy. These products, however, have the disadvantage that they mainly promote brainstem lability, by which artificial abnormalities are induced which are not normally seen in these persons.

### 3.4. Sleep after sleep deprivation

Every person restricted from fulfilling his need to sleep will compensate as soon as the possibility is given to do so. This method known as the sleep deprivation method is applied for instance, to know how a subject reacts to lack of sleep and how subsequent sleep is modified. Depending on the procedure applied one differentiates between total, partial and selective sleep deprivation. Total sleep deprivation means that one stays awake for 24 consecutive hours and minimally lacks one night sleep. Partial sleep deprivation means that one shortens abruptly or gradually the nocturnal sleep by some hours. Selective sleep deprivation means that one prevents the occurrence of a particular sleep stage. This is mainly restricted to REM sleep or to N.REM 4 sleep.

Selective REM sleep deprivation was applied for the first time by Dement (1960). According Hartman (1973) REM sleep is important for the storing and assimilation of information and for the maintainance of emotional stability and good social adaptation. According Albert (1975) and Vogel (1975) REM deprivation has no immediate implications for psychological functioning and learning capacity, but adjustment to new situations is hampered (Glaubman et al., 1978). When REM sleep is deprived, N.REM sleep retains its usual composition and sleep cyclicity (Dement, 1960).

The effects following partial sleep deprivation depend on whether the sleep reduction is applied abruptly or gradually. Abruptly means that the sleep is suddenly shortened by 3 to 4 h, and gradually means that the sleep is shortened by half an hour to 1 h weekly. By a gradual reduction it is feasible to shorten the sleep by 4 to 5 h without influencing daily performance (Friedman et al., 1974; Johnson and McLeod, 1973). According Naitoh (1976) this is based on the fact that each person has his own minimal sleep requirements. Reaching

this minimal level one still feels that one has had a good sleep and the performance on the subsequent day is normal. In contrast to gradual sleep reduction an abrupt sleep deprivation leads to an immediate decrease of alertness and attention (Hartley and Shirley, 1977). This negative effect is however short lasting, disappearing after a few days (Webb and Agnew, 1974). After partial sleep deprivation the compensatory sleep is characterized by a decreased N.REM 1-2 and REM sleep and a maintainance of N.REM 3-4 sleep (Spijkers, 1980).

The effects of total sleep deprivation have been studied extensively (Jovanovic et al., 1971; Naitoh et al., 1971). Following total sleep deprivation the performance of tasks lasting more than 20 min decreased (Wilkinson, 1965). Often, there is a slight prolongation of the reaction time towards sensory stimuli (Lisper and Kjellberg, 1972; Williams et al., 1964); or learning is disturbed as evident from retention difficulties (Glenville et al., 1978).

Physical or biochemical changes are minimal or absent (Webb and Cartwright, 1978). This is evident for instance from the fact that autonomic functions such as heart rhythm, blood pressure, respiration and body temperature remain stable. An abnormal degree of fatigue most often occurs only after total sleep deprivation of 48 h, often being associated with a slight decrease of cortisol and of 17 hydroxy steroid concentration in plasma (Akerstedt et al., 1980).

After a total sleep deprivation of 24 h the ensuing sleep is characterized by a shortening of the sleep latency, an increase of deep N.REM 3-4 sleep, with or without a decreased REM sleep (Berger et al., 1971). The increase in N.REM 3-4 sleep is age-dependent and largest in young persons (Webb, 1972). The moment at which the compensatory sleep during the day takes place is important: more REM sleep would occur in the morning and more N.REM 3-4 sleep in the evening (Fukuda et al., 1981). The cyclicity of this compensatory sleep is maintained, but certain sleep phenomena such as K-complexes and sharp vertex waves might occur in a somewhat modified form (Rothova et al., 1980).

In view of the small number of side-effects following a total sleep deprivation of 24 h and the fact that the effects on the compensatory sleep are well studied, it is not a surprise that sleep deprivation has been applied as a procedure for the diagnosis of epilepsy. For it allows to perform a sleep recording of limited duration, because of a fast onset of sleep, rapidly attaining N.REM 3-4 sleep while retaining light N.REM 1-2 sleep and REM sleep (Berger et al., 1971).

If one accepts that 2/5 (Janz, 1962) of the epileptics mainly have their seizures at night and that epileptic discharges mainly occur during N.REM 1-2 sleep (Patry et al., 1971) then one has to answer the following two questions:

1. Are the nocturnal seizures determined by a circadian rhythm or do they occur in relation to sleep?
2. Does the compensatory sleep of epileptics contain a sufficient amount of N.REM 1-2 and REM sleep to diagnose and localize epileptic abnormalities?

Therefore, the literature with respect to the methodology and the diagnostic results obtained with total sleep deprivation was investigated. (The findings here are restricted to total sleep deprivation, TSD, which means that the subjects were continuously awake for at least 24 h).

By means of TSD Scollo-Lavizarri et al. (1973) could confirm the diagnosis of epilepsy in 57.1 % versus 16.7 %, as compared to a routine EEG registered during daytime. Comparative results were obtained by Clemens and Mezey (1980) and by Degen and Degen (1980). Studying a group of 115 patients suspected of having partial complex epilepsy of the psychomotor type, Degen and Degen (1980) diagnozed epilepsy in 47.8 % using a normal night sleep recording and 55.3 % following a TSD carried out 24 h after the normal sleep in the same patients. With the two procedures combined, the authors confirmed the diagnosis in 62.2 % of the cases.

Schwarz and Zangemeister (1978) compared the total recordings in which epileptic seizures, fitting with generalized and partial epilepsy of the psychomotor type, were present during a routine EEG recording, with those found during routine EEG recording combined with provocation tests and those obtained during sleep following TSD. The percentage increased from 11.5 % to 48 % and 88 % for the generalized epilepsy and from 16 % to 39 % and 83 % for the psychomotor type of epilepsy.

The extent of the registered diagnostic gain depends on a number of factors such as type and severity of epilepsy, intake of antiepileptics, the presence of epileptic and non-epileptic EEG abnormalities found in the routine EEG, the age, and whether or not this sleep procedure is combined with other provocation tests.

As mentioned above Degen and Degen (1980) found epileptic EEG phenomena in 54 % of their patients during sleep following TSD. Hereof, 78 % of them had generalized epilepsy and only 22 % of their patients had partial epilepsy. Clemens and Mezey (1980) which also arrived at a positive diagnosis in 53 % of their patients found a slightly different proportion. Of the epileptics suspected of having a generalized epilepsy 52 % had EEG abnormalities fitting with this form, 64 % had EEG abnormalities fitting with partial epilepsy with a temporal localization and 29 % had EEG abnormalities fitting with the partial epilepsy with a non-temporal localization.

The diagnostic gain of the generalized seizures of the grand mal type was largest when the seizures were short-lasting ( < 5 min) and occurred several times a month (Degen, 1980). Depending on whether or not clinical seizures were present (Rothova et al. 1980) epileptic EEG abnormalities were found respectively in 10 % and 6 % during a routine EEG recording, increasing to 52 % and 41 % during sleep following TSD.

When antiepileptics are taken regularly, fewer sleep recordings in which epileptic EEG phenomena are present, are found than when antiepileptics are not taken (Deisenhammer and Klingler, 1978). These authors could confirm epilepsy as detected by the EEG in only 15 % of the patients which were treated and in 52 % in a non-treated group.

When EEG abnormalities of non-epileptic nature were present, then epileptic EEG phenomena increased from 34 % to 56 % during sleep after TSD (Mattson et al., 1965). When epileptic abnormalities were found during a routine EEG, then they mostly were found in all sleep stages. However, when these abnormalities were absent during a routine EEG, then they were recorded mostly during N.REM 2 sleep (Degen, 1980).

The degree of activation present during a routine EEG recording appeared of importance. In persons in which the EEG indicated the

high activity (fast low voltage activity as an expression of desynchronization) Clemens and Mezey (1980) found an increase to 23 % of the recordings with epileptic EEG phenomena after TSD. In relaxed persons, of which the EEG was characterized by a well-formed and high voltage alpha rhythm, an increase to 35 % was found and a further increase when the routine EEG showed signs of lability.

The age of the patients is also of importance: the diagnostic gain is larger in persons below 18 years than in adults and it decreases gradually above 40 years (Tartara et al., 1980).

In some laboratories (Ritter et al., 1977) the TSD procedure is combined with provocation tests such as hyperventilation and intermittent light flashes. Ritter et al. (1977) obtained an additional gain of 13 % when they used TSD in combination with hyperventilation.

Very important is the observation made by many investigators (Heineman, 1966; Johnson, 1969; Jovanovic et al., 1971; Scarpalezos et al., 1980; Tartara et al., 1980) that TSD of 24 h in non-epileptics never provoked clinical or electroencephalographic epileptic manifestations.

It appears thus that sleep after TSD is a very useful and efficient method for the diagnosis of epileptic EEG manifestations. Oller-Daurella (1966) mentioned the following advantages: 1. it is a simple method, 2. epileptic EEG phenomena not detected in a routine EEG are found, 3. activation of EEG phenomena fitting with generalized as well as partial epilepsy are found, 4. it induces sleep in a physiological way, 5. it is a burdensome test comparable to the supplementary severe effort of daily life. Also Passouant (1975) described this method as a very useful procedure in the field of epilepsy diagnosis because: 1. one night sleep deprivation is sufficient, 2. antiepileptic drug medication does not have to be stopped, 3. the method can be used in combination with other provocation methods such as hyperventilation and intermittent light flashes, 4. false positive results are obtained only seldomly, 5. the effect is based on deprivation itself.

Up to the present, it is not known which biochemical and physiological changes occurring during sleep following sleep deprivation are the cause of a decreased threshold for epileptic EEG phenomena. The longer duration of sleep recordings as compared to a EEG routine recording cannot explain the diagnostic gain (Pratt et al., 1968). The forced wakefulness leading to an increased sleepiness can also not explain the diagnostic gain (Geller et al., 1969).

Finally, a short survey of differences in duration and the method of sleep recording following 24 h TSD is given hereafter. Gereby (1978) records for 20 min, Wittenbecher and Kubicki (1977) record for 30 min, Degen (1980) records for a variable duration between 17 and 47 min depending on the results, Schwarz and Zangemeister (1978) for 40 min, Scollo-Lavizarri et al. (1977) 60 min, whereas Tartara et al. (1980) start with a period of wakefulness for 20 min, including intermittent light flashes, followed by a sleep recording of about 60 min, whereafter the patients are wakened and asked to hyperventilate. Due to these differences, the results obtained in the different laboratories are difficult to compare.

It has to be mentioned that in young children one deviates from the absolute rule that a total sleep deprivation has to consist of wakefulness for at least 24 h. Instead a partial sleep deprivation

is applied. Bechinger and Kornhuber (1976) keep children below the age of 3 years awake for half a night. Wittenbecher and Kubicki (1977) allow children, younger than 4 years to sleep from 22 to 6 h and those between 4 and 14 years between 24 and 6 h, whereas Rothova et al. (1980) prescribed a sleep deprivation of 4 h in children below the age of 8 years, six hours in children between the age of 8 and 12 years and a total night for children above the age of 12 years.

## II.4. SLEEP AFFECTED BY EPILEPSY AND ANTIEPILEPTICS

Epileptic phenomena result from sudden massive discharges of large groups of cortical cells, occurring when the inhibiting influences are becoming weak. The degree of this inhibition depends to a large extent on the activity of the ascending reticular activating system (ARAS). Likewise, this structure is responsible for the maintainance of wakefulness during daytime. Its level of activity is much lower during N.REM sleep, which may be the reason why clinical and subclinical (electroencephalographic) epileptic events may easily occur during sleep (Gloor, 1980; Montplaisir et al., 1980). Since the ARAS system is as important for sleep wakefulness regulation as for the occurrence of epileptic manifestations, it is admissible that a disturbance in its function can give rise to epileptic as well as sleep disturbances.

### 4.1. Sleep affected by the appearance of epileptic phenomena

There exists a variety of opinions in the literature concerning the sleep changes which may occur as a result of "having epilepsy". For instance Passouant (1975) stated "the nocturnal sleep of epileptics is often normal: the number of cycles, the stages of slow wave sleep, the duration of REM sleep, compared with the total sleep are not modified. However, in some cases the organization of sleep is abnormal".

Among the changes in N.REM sleep Passouant (1975) mentions a decreased number of K-complexes and sleep spindles and a decrease of N.REM 3-4 sleep. These findings have been confirmed by others (Findji et al., 1978), but other researchers found an increase in K-complexes (Halasz, 1979) and of sharp vertex waves (Clemens and Mezey, 1980) in patients having generalized epilepsy.

Abnormalities in REM sleep have also been mentioned. According Passouant (1975) REM sleep in epileptics is often associated with a decreased density of rapid eye movements and of EEG rhythms with saw tooth form. In addition REM sleep is less stable, being interrupted repetitively by short periods of N.REM 1-2 sleep or wakefulness. Also non-EEG parameters might change being characterized by the presence of more muscle and movement artifacts (Jovanovic, 1966).

According certain investigators the sleep composition would be different depending on the time of preference of the occurence of epileptic attacks and the severity of epilepsy. According Jovanovic (1966) the sleep in patients which have their fits during the night is characterized by a fast onset of sleep, the fast occurrence of much deep N.REM 3-4 sleep and very few moments of wakefulness. The opposite would occur in patients mainly having wakefulness epilepsy.

According Declerck et al. (1980) patients which have two forms of epilepsy have the tendency to sleep more superficially and awake more frequently. Analogous findings were described by Horita et al. (1981) who also found a relationship between the degree of the disorganization of sleep and the severity of the abnormalities found in the routine EEG. Further Arguner (1977) found that an aggravation of epilepsy was proceeded by a disorganization of the sleep.

The effects on sleep in patients having clinical attacks is dependent on the type and the number of these attacks. Thus Cohen and Dement (1965) found that generalized epilepsies of the tonic-clonic type do not influence N.REM sleep but give rise to suppression or delay of REM sleep. Partial epilepsies which have their origin in the amygdala or hippocampus appear not to affect sleep according Montplaisir (1979). Such abnormalities are present in epilepsies which have a frontal or occipital cortical focus, but the sleep abnormalities are not specific for one of these localizations. However, Kubicki (1969) found sleep abnormalities, especially of REM sleep, in partial epilepsies with a temporal localization.

The value of the findings in the literature are difficult to judge, because many of the mentioned deviations in sleep also occur in other non-epileptic diseases and some of these even have a physiological origin. For example, Niedermeyer (1970) and Wittenbecher and Kubicki (1977) have pointed out that many sharp K-complexes and sharp vertex waves can be found in young subjects below the age of 16 years without implicating that these indicate an epileptic predisposition. The strong suppression or the absence of sleep spindles is a regular experience in severe mentally retarded children (Shibagaki et al., 1980).

### 4.2. Sleep affected by the intake of antiepileptics

Antiepileptics are described as medicines which increase the firing threshold of nerve cells, shorten the duration of afterdischarges and prolonge the refractory period (Longo, 1977). By this they may more or less break the excessive neuronal discharges. On the basis of their specificity they are divided into antiepileptics of first and second choice. To antiepileptics of first choice belong barbiturates, hydantoins, succimides, valproate and carbamazepine. The majority of antiepileptics of second choice belong to the benzodiazepine derivatives. Sleep changes caused by the latter group have been studied extensively, in contrast to the first choice antiepileptics of which only the effect of barbiturates and to a lesser degree hydantoins are relatively well-known.

Following the intake of barbiturates the first visible effect is a decreased REM sleep (Röder and Wolf, 1980). With prolonged intake (longer than 6 months) an increase of N.REM 1-2 sleep appears whereas N.REM 3-4 sleep remains the same or decreases (Potvin et al., 1975). In certain persons barbiturates lead to a pronounced increase in sleep spindles, often correlating with a positive treatment result (Sengoku and Wolf, 1981).

Following the intake of hydantoin derivatives sleep becomes steadier i.e. the subjects awake less, and sleep less easily switches from one stage to another (Fukuyama et al., 1979). Long term intake leads to a sleep pattern similar to that seen following barbiturate intake, because N.REM 1-2 sleep increases and REM sleep decreases.

Succimide derivatives are antiepileptics mainly administered for the treatment of primarily generalized epilepsy of the absence (petit mal) type. Röder and Wolf (1981) demonstrated that these compounds increased the degree of activation by which patients tend to waken up during the sleep, increased the amount of N.REM 1 sleep and decreased the amount of N.REM 3-4 sleep.

Valproates are antiepileptics which are mainly applied for the treatment of generalized epilepsies. Apart from an increase in N.REM 1 sleep and a decreased REM sleep, no other changes are known.

In healthy persons, carbamazepine can give rise to a decrease in REM sleep (Wachner, 1980). In subjects with sleep disturbances, as a consequence of withdrawal of phenytoin (Murray, 1977) or alcohol (Hasan et al., 1980), or due to psychic disturbances (Ballenger and Post, 1980) carbamazepine can improve sleep by decreasing the number of awakenings and by increasing the total amount of sleep.

Depending on their potency and duration of action, all benzodiazepines to a more or less degree, affect sleep. Often they give rise to a fast onset of sleep, less awakening and a prolongation of the duration of the first sleep cycle. An increase in N.REM 1-2 sleep and a decrease in N.REM 3-4 sleep is also seen (Gaillard et al., 1973). Further it is known that long-acting benzodiazepine-derivatives such as nitrazepam, may postpone or suppress REM sleep. In how far these changes can also be demonstrated by polygraphic recordings in epileptic patients treated with antiepileptics could not be determined from the literature.

## II.5. SUMMARY

On the basis of the literature we aimed at answering the following questions:

1. How can sleep and epileptic abnormalities be judged electroencephalographically?

In order to judge sleep adequately, polygraphic recording including EEG rhythms, eye movements and muscle activity, is a necessity. According criteria set up by Rechtschaffen and Kales (1968), which make use of these three measures, sleep can be divided into N.REM 1,2,3 and 4 and REM sleep. By setting out the duration and time of occurrence of the different sleep stages in sequence in a time diagram, sleep composition can be judged adequately. In this respect it is desirable to describe the sleep composition using the internationally accepted terminology. Also the description and interpretation of epilepsy requires uniformity of the applied terminology. For the description of epileptic abnormalities, we made use of the definitions which are mentioned in the "Handbook of EEG and Clinical Neurophysiology" (11A, 58-73; 13A, 7-20). For the description of the different forms of epilepsy, we made use of the electroclinical classification proposed by the International League against Epilepsy.

2. Which sleep procedures have been used to diagnose epilepsy?

Polygraphic sleep recordings as an expedient to confirm epilepsy was introduced by Gibbs and Gibbs in 1942. At the outset different sleep procedures have been used: siesta sleep, all-night sleep, drug-

induced sleep and sleep following preceding sleep deprivation. At present the most applied method is total sleep deprivation for a period of 24 h, followed by a polygraphic sleep recording, of which the duration differs in the different laboratories.

3. How large is the diagnostic gain by sleep investigations?

The data from the literature mainly concern the all-night sleep and sleep deprivation methods. The results obtained by these two methods are comparable: they provide a diagnostic gain of about 30 % to 40 % as compared to the routine EEG investigation carried out during daytime. The size of the gain is dependent on the kind of sleep as well as on the type of epilepsy. The size of the gain is largest during light N.REM 1-2 sleep, for all forms of epilepsy, often somewhat larger for the generalized epilepsies than for the partial epilepsies. The gain is also dependent on the quantity and severity of the clinical and subclinical epileptic manifestations, the presence or absence of non-epileptic EEG abnormalities, the regular or irregular intake of antiepileptics and eventually combination with other provocation methods.

4. How do the epileptic EEG phenomena change during the sleep?

There is a tendency towards the formation of polyspike waves during the N.REM 1-2 sleep, the spike wave paroxysms become shorter but their frequency of occurrence increases. The same tendencies, but to a lesser degree, exist during the N.REM 3-4 sleep, but there is a propensity towards formation of low frequency and irregular spike waves, long-lasting paroxysms undergoing fragmentation.

5. Which sleep changes may occur by 'having epilepsy'?

It is generally accepted that subclinical epileptic discharges hardly affect the sleep pattern. Following clinical attacks of the generalized type, the sleep pattern can be disturbed for some minutes and REM sleep can be temporarily suppressed. This, however, is almost never associated with a loss of cyclicity.

The effects on sleep caused by partial epilepsy would be dependent on the localization of the primary focus, whether temporal, non-temporal, or superficial or deep cortically.

Subjects in which the epileptic attacks occur preferentially during the sleep or during the day, would have a different sleep composition.

6. Is sleep affected by the intake of antiepileptics?

Of the first choice antiepileptics, only the effects of the barbiturates and hydantoins on the sleep are well studied. These substances increase light N.REM 1-2 sleep, all or not associated with a decreased REM sleep. Of the antiepileptics of second choice, the effects of benzodiazepines on the sleep are well-known. Apart from an increase in effective sleep, they affect the ratio between the N.REM 1-2/N.REM 3-4 sleep in favour of the light N.REM 1-2 sleep. The barbiturates as well as the benzodiazepines give rise to an increase in the number of sleep spindles.

## CHAPTER III: AIMS OF THE STUDY

Own investigations were started in order to clarify a number of questions of which the findings in the literature were unclear. These questions were necessary to evaluate precisely the advantages and disadvantages of the total sleep deprivation method, and then to use this information to set up criteria which need to be fulfilled in order to ascertain an optimal diagnosis. To this belongs not only the recording and interpretation of epileptic EEG abnormalities, but also sleep disturbances, caused by epilepsy or the intake of antiepileptics. In this view the following questions were considered of essential importance for our investigations.

1. Which are the conditions which need to be fulfilled for sleep following sleep deprivation resulting in the highest possible yield for the diagnosis of epilepsy (Chapter V)?
2. How and to which degree does the sleep in epileptics differ from healthy persons and which factors determine these differences (Chapter VI)?
3. How and to which degree sleep deprivation affects the subsequent sleep in epileptics and on which factors does this depend (Chapter VII)?
4. Do antiepileptics differentially affect sleep (Chapter VIII)?
5. Which morphological changes in the epileptic EEG phenomena occur during the sleep and which are the changes of the polygraphic sleep pattern as a consequence of epilepsy (Chapter IX)?
6. What is the best method of sleep deprivation (Chapter X)?

## CHAPTER IV: MATERIALS AND METHODS

### IV.1. SUBJECTS

During the period 1976-1981, more than 6000 subjects were investigated electroencephalographically in our Department of EEG and Clinical Neurophysiology of the Epilepsy Centre "Kempenhaeghe" Heeze, with the aim of confirming the existence or absence of epilepsy or to better define its form. All the subjects were referred by a general practitioner, a neurologist or paediatrician. Only at the request of the specialist were additional EEG investigations carried out, the order of these is represented in Table IV.1.

TABLE IV.1.
"Diagnostic procedures".

| | |
|---|---|
| 1. Routine EEG (100 %): | - Registration time 40 - 60 min<br>- Hyperventilation during 5 min<br>- Intermittent light stimuli<br>- Spontaneous sleep (± 30 %) |
| 2. Special EEG (10 %) : | - Nasopharyngeal or other special electrode placements<br>- Drug administration<br>- During special time or activity<br>- Polygraphic recording (EEG, EMG, ECG, etc.) |
| 3. Sleep recordings (25 %): | - Sleep after 1 night sleep deprivation (3-5 h; 2 cycles)<br>- Interrupted sleep (3-4 h; 1 cycle)<br>- All-night sleep (7-11 h) |
| 4. Long term EEG registration (15 %) : | - Ambulatory 4 channel cassette EEG monitoring (24-48 h)<br>- EEG telemetry and videomonitoring (2-24 h) |

In all subjects a routine EEG recording lasting 40-60 min was carried out. In about 30 % of these, short-lasting N.REM 1-2 and sporadically N.REM 3-4 sleep were recorded. In those cases where this routine investigation did not provide enough information to answer the query, additional EEG investigations were done.

In about 10 % of the subjects this additional investigation consisted of a second EEG recording differing from the routine EEG recording in certain aspects: 1) a different electrode localization, e.g. applying nasopharyngeal electrodes; 2) the recording at times or in conditions during which the complaints mainly occur, e.g. during

eating; 3) applying drugs to check their efficacy on epileptic EEG abnormalities; 4) polygraphic recording of physiological changes together with the EEG in order to better study their association.

In about 25 % (1500) of the subjects a sleep recording was carried out as a supplementary investigation. Depending on the presumed clinical form of epilepsy, a choice was made between spontaneous sleep recording, either an all-night sleep (7-11 h) or an interrupted sleep (3-4 h), or sleep (3-4 h) after sleep deprivation (an interrupted period of 24 h wakefulness).

The sleep deprivation method was applied in 65 %, all-night sleep recordings in 18 %, and interrupted sleep in 17 % of the subjects. The predominance of the sleep deprivation method is due to the fact that this was our method of first choice. The interrupted sleep was applied in children below the age of 7 years, and in persons with a psychomotor retardation or with behavioural disturbances, in which no effective sleep deprivation could be applied. Total night sleep recordings were carried out in subjects in which seizures mainly occurred during the night, or in those in which the attacks were clearly associated with sleep and of which this association was not sufficiently confirmed during a sleep deprivation recording.

Since 1978, the number of patients in which a long-lasting EEG recording was carried out increased from 3 % to 15 %.

More than 80 % of the patients, in which a sleep recording was carried out in the period 1976-1981 were between 7-50 years of age, and were of either sex. At the moment of the sleep investigation 2/3 of them stayed in our clinic mostly for a short period, and 1/3 were investigated as outpatients. In no case was antiepileptic medication interrupted and a sleep recording was only carried out when drug treatment had not changed for minimally one week.

## IV.2. METHODS

### 2.1. Recording method

For the all-night sleep recordings, the sleep habits of the patients concerning time and way of sleeping were taken into account. For the sleep deprivation recordings, great emphasis was given to the demand that the subjects should be awake for an uninterrupted period of 24 h. In the clinic, wakefulness was continuously controlled by paramedical personnel, whereas for the outpatients, it was checked whether this condition was sufficiently fulfilled. If not, these persons were asked to come to the clinic on the night preceding the investigation, where the same paramedical staff actively controlled wakefulness.

The polygraphic recordings were carried out by experienced technicians in three specially adapted recording rooms. Each was equipped with a 16 or 21 channel mingograph (Elema-Schönander, Siemens). These were connected to a minicomputer (PDP 11/34) for on-line analysis or to a 7-channel instrumentation recorder (Racal Store 7D) for off-line analysis.

Twelve to sixteen channels were used for recording the EEG rhythms, the remaining channels were used for recording eye movements (EOG), electrocardiogram (ECG), muscle activity of the chin (EMG) and respiratory movements (RM). In order to enhance the comparability between sleep recordings a standard electrode placement according the

internationally proposed 10/20 configuration was chosen, as shown in Figures IV.2. and IV.3.

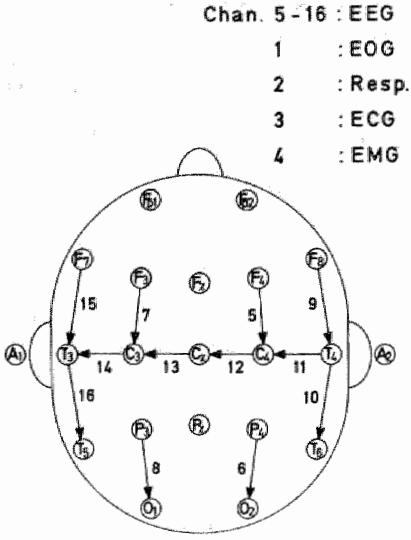


FIG. IV.2.
Position of electrodes by using a 16-channel recorder

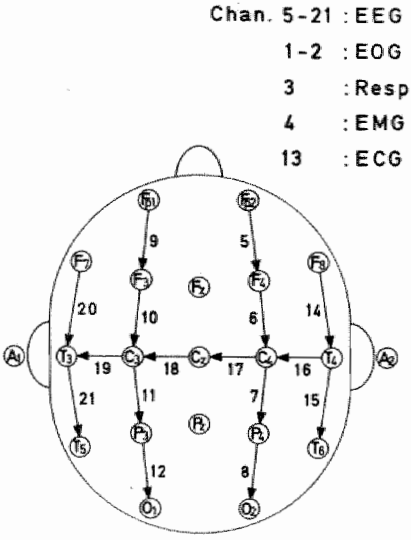


FIG. IV.3.
Position of electrodes by using a 21-channel recorder.

With the selection of above derivations it was aimed to optimalize the EEG phenomena of importance for an adequate judgement of epilepsy and of sleep.

For defining epilepsy, it is important to differentiate diffuse from partial forms. This means that for the generalized forms, one should be able to record the fitting EEG phenomena simultaneously from the anterior (F4-C4 and F3-C3) and the posterior (P4-O2 and P3-O1) brain regions of right and left hemisphere. For the partial forms or the epilepsies caused by discharges originating from a restricted brain area it is known that they are predominantly localized in the temporal region, which is the reason for which these regions are represented by 6 derivations in the used configuration (F8-T4 and F7-T3, T4-T6 and T3-T5, T4-C4 and T3-C3).

In order to partition the sleep in REM and the different stages of N.REM sleep, it is important to record the EEG phenomena optimally. During sleep the regionally specific wakefulness rhythms disappear, for instance the occipital and central alpha rhythms and locally or difusely other EEG phenomena or rhythms occur. Thus light slow wave sleep is characterized by the presence of sharp vertex waves and sleep spindles, localized maximally in the prerolandic region. Deep slow wave sleep is characterized by the occurrence of diffuse delta activity, through which local differences are less expressed. This requires a recording with a sufficiently large number of channels.

## 2.2. Analyses

### 2.2.1. Visual analysis

The polygraphic recordings of EEG, EOG and EMG were analyzed according to the criteria of Rechtschaffen and Kales (1968). The partition into wakefulness, N.REM 1 to 4 sleep and REM sleep was done for each 60-sec period and based on the kind and depth of sleep predominantly present during this period. The results were represented in a hypnogram drawn on the form, on which different parameters were indicated in a standardized way: the sleep procedure, data concerning the subject studied, clinical and diagnostic data and medication. In addition, the time of occurrence of epileptic activity during sleep was indicated, as shown in Figure IV.4.

The duration of each stage of wakefulness and sleep in minutes and in percentage of the total recording time were indicated below the hypnogram. Further the following parameters were recorded: total recording time (TRT), sleep latency (SLT) i.e. the time lapsing between the beginning of the recording and the occurrence of at least 5 min uninterrupted sleep, the total sleep time (TST) i.e. the total recording time minus the sleep latency, the number of awakenings during the sleep and their total duration (N + T), the effective sleep time (EST) i.e. the total sleep time minus the time of awakenings during the sleep and, the REM latency (RLT) i.e. the time elapsing between the beginning of the recording and the beginning of the first REM period.

For each of the non-EEG parameters it was indicated how they were related to a specific stage of the sleep in so far they were of importance for judging the sleep and epilepsy. This allowed to indicate whether the muscle tone, density of rapid eye movements, heart function and respiration during N.REM and REM sleep conformed to the expectations.

Apart from the polygraphic phenomena of importance for the classification of sleep the epileptic activity was also described in a detailed way. The type of epilepsy was indicated with the aid of symbols mentioned in chapter II.2. Also, the duration of the epileptic discharges was noted and the percentage of the recording time during which these occurred as compared to the total amount of wakefulness, N.REM 1-2, N.REM 3-4, or REM sleep was calculated.

The interpretation focused on the diagnostic meaning of the epileptic EEG phenomena and on the quantitative and qualitative partition of the polygraphic sleep picture.

### 2.2.2. Automatic sleep analysis

The automatic sleep analysis of long term EEG recordings, by means of a digital computer, was started routinely in 1979. Therefore we used a modified software program, developed by Wauquier *et al.* (1979), to analyse on-line the sleep of one subject, based on two EEG-channels, derived from T4-C4 and P4-O2, one EOG and one EMG channel. These four signals were analysed in epochs of 30 seconds and from each epoch eight parameters were extracted, which could be displayed afterwards.

The computer plot of such an analysis is shown in Fig. IV.5. The time course, in minutes, is indicated in the abcissa, and in the ordinate from the bottom (1) to the top (8) the eight parameters and

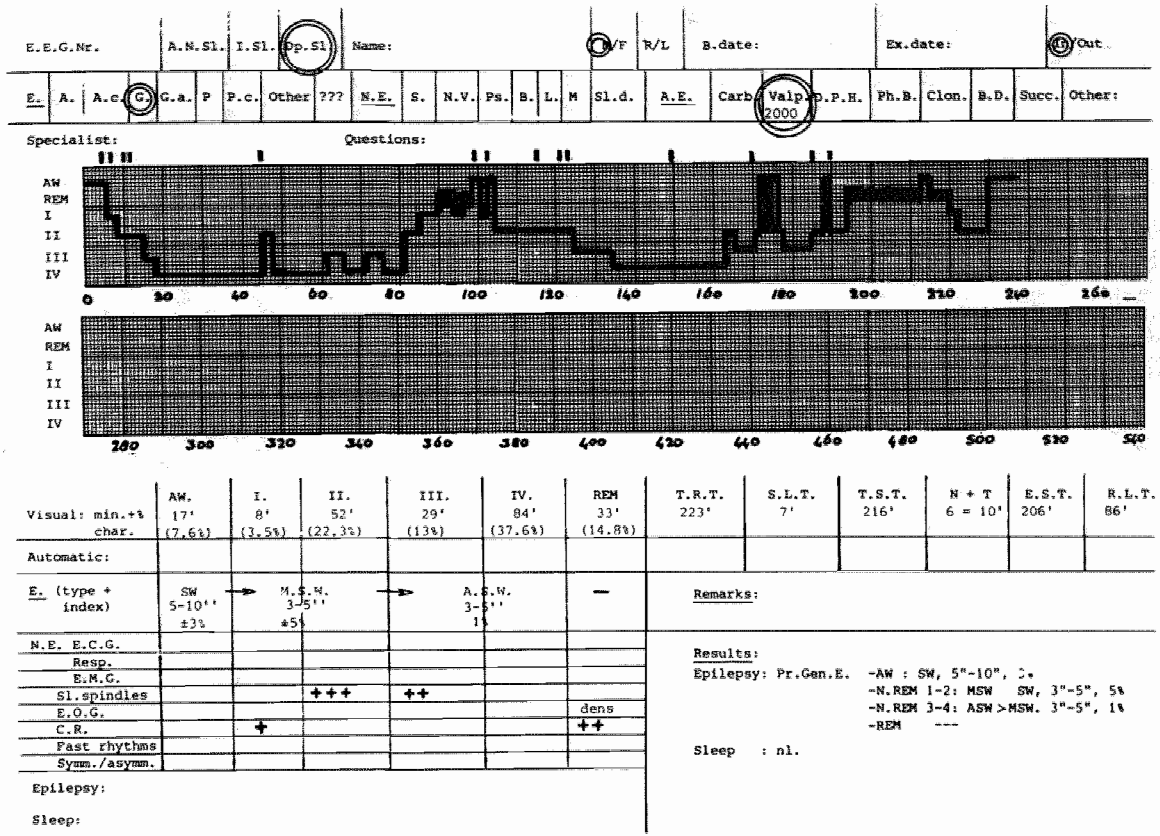


FIG. IV.4.
Standard report of a polygraphic sleep recording carried out in an epileptic patient.

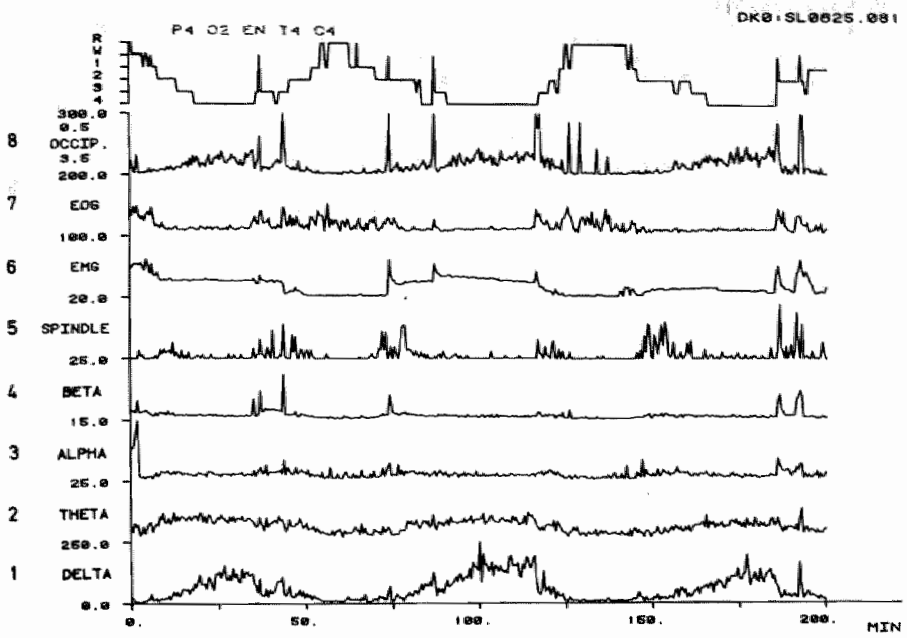


FIG. IV.5.
Example of automatic sleep analysis with sleep classification (Wauquier et al., 1978).

at the top (9) the automatic sleep classification. Below the significance of each parameter is briefly commented on but a more detailed explanation can be found in addendum 1.

1. The first parameter represents the power of the delta rhythms (0.5 Hz-3.5 Hz) derived from T4-C4, calculated for every 30 seconds in succession. This delta time course is closely related to the depth of the N.REM sleep.
2. The second parameter represents the time course of the theta waves as determined by summing the power density from 3.5 Hz to 7.5 Hz. This time course was mostly very similar to the delta activity and was not so important for the sleep classification.
3. The third parameter represents the time course of the alpha waves (7.5 Hz-11.5 Hz), which was very useful for the detection of awake periods.
4. Finally, the fourth parameter indicates the time course of the beta waves (11.5 Hz-25 Hz).
5. The fifth parameter shows the occurrence of sleep spindles. They are detected by a further segmentation of each 30-second epoch into 0.8-second periods, followed by spectral analysis and an evaluation of the power density of the EEG activity between 11.25 Hz and 15 Hz. It was the most important parameter for the identification of the N.REM 2 sleep.

6. The sixth parameter represents the time course of the chin or submental muscle activity based on the mean amplitude of the EMG signal. This parameter was used for detection of movement artefacts.
7. The seventh parameter is calculated on the same way as the EMG and indicated the occurrence of eye movements. This parameter is necessary for the recognition of REM sleep.
8. Finally, the eighth parameter shows the time course of the delta waves derived from P4-O2 and was important to confirm the diffuse presence of delta activity during the N.REM 3-4 sleep.
9. To classify the sleep recording in stages, 6 epochs were chosen visually as being representative examples for the different sleep stages. Using these individual examples, the classification is carried out automatically, based on minimal distance criteria (Wauquier et al., 1979).

In general there was a good agreement between the automatic and the visual classification of the N.REM 2 and the N.REM 4 but only a moderate agreement of the N.REM 1 and N.REM 3 (Martens et al., 1980). One of the reasons could be the suboptimal quantification of the parameters resulting into a high sensitivity for artefacts (see also addendum 1). Therefore, we attempted to develop a method which could also be applied to at least three subjects simultaneously. In August 1981 the new method (Martens et al., 1981) reached the operational stage and figure IV.6. shows an example of such an analysis.

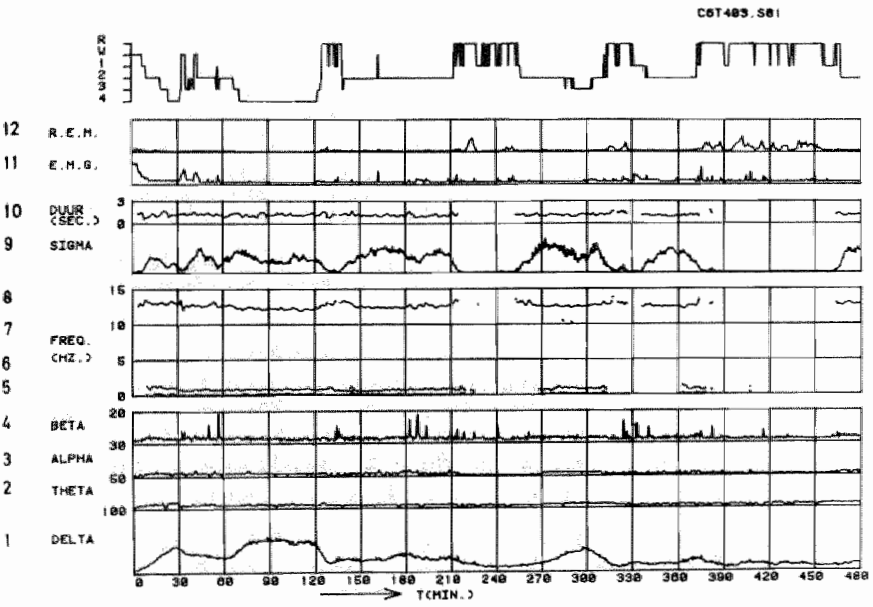


FIG. IV.6.
Example of automatic sleep analysis with sleep classification (Martens et al., 1981).

Again the time course is indicated in the abscissa and the different parameters subdivided into four groups in the ordinate from the bottom (1) to the top (12).

In the lowest rectangle, parameter 1 to 4 represent the time course of the delta, theta, alpha and beta rhythms, calculated on amplitudo base (for a detailed explanation is refered to addendum 1).

In the second rectangle, the frequency characteristics (5, 6, 7) of the delta, theta and alpha rhythms, are indicated only if they exceed certain determined levels. If this is the case the peak frequency and band width of the rhythms are represented by two lines. A narrow trace reflects a very stable rhythm (like a pure sine-wave) and a broad trace corresponds to a high variability. In the upper part the peak frequency of the sleep spindles is indicated by one simple line (8).

In the third rectangle, the time course (9) of the sleep spindle activity is established together with their time duration (10).

In the fourth rectangle, the mean amplitude of the muscle activity (EMG) is depicted in the lower part (11) and the time course of the rapid eye movements, as detected from the EOG, in the upper part (12).

On the top of figure IV.6. the hypnogram is plotted, calculated on the same way as described in the first method. The computer plots have been used by the physician as an aid to the visual analysis which can be done more easily and more quickly (50 % to 80 % less).

In the future the material stored on a magnetic disk, will be used for more detailed quantitative and qualitative studies to analyse some special sleep features.

## IV.3. MATERIAL

In order to answer the questions posed by the aims of the study (Chapter III, p. 34) the visual analysis and reporting of the sleep recordings carried out in the period 1976-1980 were used. The reasons for diagnosing epilepsy electroencephalographically during sleep recordings were due to an insufficient confirmation, description or the lack of evidence for the all or none existence of epileptic EEG abnormalities gained during a routine EEG investigation.

In order to determine the diagnostic gain, the number of sleep recordings containing epileptic EEG phenomena of a selected group of patients were counted. Further, it was studied in what percentage of the patients which had a known clinical form of epilepsy, epilepsy could be confirmed on the basis of a sleep recording, versus those of which the diagnosis was doubtful, and how many sleep recordings without epileptic phenomena were found, in subjects for which no clinical grounds existed to diagnose epilepsy.

Further, the gain of epilepsy diagnosis with respect to the applied sleep procedure and the clinical form of epilepsy was determined. In addition, it was investigated to what extent the epileptic EEG phenomena depended on the sleep stages and recording time. In order to find out whether the presence of epileptic EEG phenomena or drug therapy influence the sleep, a group of patients were studied in which spontaneous night sleep recording was taken and a sleep recording following 24 h sleep deprivation. The sleep deprivation effect was measured by comparing the duration and composition of the first and second cycle of both types of sleep.

From our patient material, groups of patients were selected which were treated with either one or maximally two antiepileptics, in order to study whether sleep changes were drug-dependent. Finally, apart from the quantitative aspects attention was also given to the morphological changes which epileptic EEG phenomena might undergo (Chapter IX).

## IV.4. SUMMARY

During the period 1976-1981, sleep recordings were carried out in about 1500 patients with the aim of investigating whether the clinical complaints were due to epileptic discharges. In 65 % of the cases sleep after 24 h sleep deprivation and in 35 % spontaneous nocturnal sleep was studied. Sleep was polygraphically recorded by means of 16 or 21-channel mingographs, of which 12 to 16 channels were used for recording EEG rhythms and 4 or 5 channels for recording non-EEG parameters. The large number of EEG channels was necessary on the one hand to differentiate partial from generalized forms of epilepsy and on the other hand to adequately partition the sleep into the different sleep stages on the basis of visual analysis. The result of this analysis was registered on a standardized way on a form on which the hypnogram and a number of quantitative and qualitative aspects of the sleep were noted. Also, the type of epileptic EEG phenomena, their time of occurrence and their duration were noted on the same form.

Therefore, it was possible to judge epileptic EEG phenomena in function of the sleep and vice versa for each sleep investigation. This report also allowed to solve the problems of our investigations as mentioned in Chapter III.

With the aid of a computer (PDP 11/34) 25 % of the sleep recordings made since 1979 were analyzed and automatically classified. This resulted in an improved method by which it became feasible to analyse sleep on-line in 3 patients simultaneously since 1981. With the aid of automatic reporting, the time required to visually analyse the sleep could be reduced to 1/3.

## CHAPTER V: EPILEPSY DIAGNOSIS DURING THE SLEEP

In this chapter an answer is sought for the following question: What is the value of long term polygraphic sleep investigations for determining epileptic EEG phenomena fitting with epilepsy and what are the conditions which need to be fulfilled for this polygraphic sleep investigation?

The material used to answer this question consisted of a total of 1503 sleep recordings carried out during the period 1976-1981 as a supplement to the routine EEG recording, to confirm the existence or absence of epilepsy, or to better describe its form. The general question has been divided into a number of smaller questions which are dealt with in sequence hereafter.

### V.1. DIAGNOSTIC GAIN

The number of sleep recordings made since 1976 are shown in Table V.1. The number of epileptic EEG phenomena found in routine and sleep recordings, in number and percentage of the total number of subjects investigated, are indicated for each year. The difference between both indicates the absolute diagnostic gain.

Studied over the total period the diagnostic gain ranged from 24.7 % (1979) to 32.1 % (1977). The equal gain of 26.2 % in 1976 and 1981 can be ascribed to a comparable increase in positive EEG findings in routine and sleep recordings. Of the 1503 patients, 566 (37.6 %) had epileptic EEG phenomena in their routine EEG recordings. Nevertheless a supplementary sleep EEG recording was done in these patients because the number and specificity of epileptic EEG phenomena found during the routine EEG recording was too small to define the form of epilepsy precisely. By means of the complementary sleep investigation an additional diagnosis was possible in 311 (54.9 %) of the 566 patients, denoted as a relative gain.

TABLE V.1.
Number (n) and percentage (%) of routine and sleep EEG recordings during the period 1976-1981 with epileptic EEG phenomena.

| Number of patients 1976-1981 | Epileptic phenomena in routine EEG | | Epileptic phenomena in sleep EEG | | Gain | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| 1976 = 99 | 30 | 30.3 | 56 | 56.5 | 26 | 26.2 |
| 1977 = 237 | 75 | 31.6 | 151 | 63.7 | 76 | 32.1 |
| 1978 = 234 | 82 | 35.0 | 150 | 64.1 | 68 | 29.9 |
| 1979 = 267 | 109 | 40.8 | 175 | 65.5 | 66 | 24.7 |
| 1980 = 326 | 118 | 36.2 | 218 | 66.9 | 100 | 30.7 |
| 1981 = 340 | 152 | 44.7 | 241 | 70.8 | 89 | 26.2 |
| = 1503 | 566 | 37.6 | 991 | 65.9 | 425 | 28.3 |

In 9 patients (1.6 %), no epileptic EEG phenomena were found during the sleep recordings although, they were present in routine EEG. Of these, seven had generalized low frequency spike waves and two focalized spikes in the routine EEG.

## V.2. ELECTROENCEPHALOGRAPHIC CONFIRMATION OF THE CLINICAL DIAGNOSIS

The patient population was divided into 3 subgroups on the basis of anamnestic and clinical findings mentioned on the request form by the demanding specialist. The first group consisted of patients of which the existence of epilepsy was considered very possible (+), the second group consisted of patients of which the diagnosis epilepsy could neither be confirmed nor denied (?), the third group consisted of patients of which the existence of epilepsy was rejected (-). In an analogue way the polygraphic sleep recordings were divided into three categories. The positive category consisted of recordings in which EEG deviations occurred, which even without knowledge of anamnestic and clinical data, immediately suggested the diagnosis of epilepsy. In the doubtful category EEG abnormalities are too small or unspecific to allow diagnosing a specific form of epilepsy. However, in relation to the clinical findings these abnormalities are valuable in order to support the diagnosis of epilepsy. The negative group consisted of patients in which neither specific nor aspecific epileptic EEG deviations were found during the recordings. The combination of the clinical and electroencephalographic partition, allows to find out whether the EEG diagnosis correlates with the clinical findings as shown in Table V.2.

The large percentage of sleep recordings with EEG confirmation of the clinical diagnosis in which the presence (+) or the absence (-) of epilepsy was stated with a high probability, is striking. For the clinical subgroup of which the existence of epilepsy was considered very likely (+) or possible (?), it is apparent that a larger percentage of specific epileptic EEG abnormalities was found during the sleep than during the routine EEG recording, this is 84.2 % versus 35.1 % for the positive group and 56.4 % versus 20.5 % for the doubtful group.

TABLE V.2.
Electroencephalographic confirmation of epilepsy according to the clinical diagnosis.

| Clinical diagnosis | % of EEG registrations with positive (+), doubtful (?) and without (-) epileptic EEG phenomena during | | | | | |
|---|---|---|---|---|---|---|
| Period 1976-1981 | Routine EEG | | | Sleep EEG | | |
| | + | ? | - | + | ? | - |
| + n: 654 | 35.1 | 19.3 | 45.6 | 84.2 | 7.0 | 8.8 |
| ? n: 454 | 20.5 | 25.6 | 53.9 | 56.4 | 28.2 | 15.4 |
| - n: 395 | - | 0.5 | 99.5 | 0.75 | 2.0 | 97.25 |

## V.3. DIAGNOSTIC GAIN AS A FUNCTION OF THE SLEEP PROCEDURE

For the calculation of the diagnostic gain in function of the sleep procedure, restriction was made to 666 sleep recordings carried out in the period 1980-1981, of which 108 were all-night, 101 interrupted and 404 sleep recordings following sleep deprivation. 53 (8 %) sleep recordings were not considered further because the patient slept for less than 1 whole sleep cycle. Concerning the clinical probability of having or not having epilepsy, this group was randomly selected and was comparable with the total patient population (V.2.). For each of the sleep procedures, the number of recordings during which EEG phenomena were found fitting with generalized or partial epilepsy, were calculated as summarized in Table V.3.

TABLE V.3.
Gain of electroencephalographic epilepsy diagnosis depending on the sleep recording method versus the clinical form of epilepsy.

| Sleep methods | | Generalized epilepsy | | Partial epilepsy | | Total | |
|---|---|---|---|---|---|---|---|
| | n | n | % | n | % | n | % |
| All-night | 108 | 42 | 38.8 | 26 | 24.0 | 68 | 62.9 |
| Interrupted | 101 | 33 | 32.6 | 27 | 26.7 | 60 | 59.4 |
| Deprivation | 404 | 131 | 32.4 | 102 | 25.2 | 233 | 57.6 |
| Total: | 613 | 206 | 33.6 | 155 | 25.3 | 361 | 58.7 |

Independent of the sleep procedure used more patients have an electroencephalographic diagnosis of epilepsy in the generalized epilepsy group than in the partial epilepsy. The diagnostic gain for the generalized epilepsy is about 6 % higher using the all-night sleep procedure than the other two methods. Such difference is not found for the partial epilepsy.

## V.4. DIAGNOSTIC GAIN AS A FUNCTION OF THE SLEEP STAGE AND DEPTH OF SLEEP

Of the 404 subjects of which sleep following sleep deprivation was recorded during the period 1980-1981, 233 had epileptic EEG abnormalities, of which 131 fitted with generalized epilepsy and 102 fitted with partial epilepsy. 233 times N.REM 1 and 2 sleep was recorded of which 211 (90.5 %) was combined with N.REM 3-4 sleep and 143 times (61.3 %) with REM sleep.

For both types of epilepsy it was studied how much epileptic EEG phenomena were found during light N.REM 1-2, deep N.REM 3-4 sleep and REM sleep, as shown in Table V.4.

TABLE V.4.
Diagnosis of epilepsy according to the sleep states and stages during sleep deprivation registration.

| Sleep stages | EEG signs of generalized epilepsy (Gen.E.) | | EEG signs of partial epilepsy (Part.E.) | |
|---|---|---|---|---|
| | n: 131 | % | n: 102 | % |
| N.REM 1-2 | 118 | 90.0 | 100 | 98.0 |
| N.REM 3-4 | 70 | 54.4 | 41 | 40.2 |
| REM | 7 | 5.3 | 35 | 34.3 |

For both types of epilepsy epileptic EEG phenomena predominantly occurred during N.REM 1-2 sleep, but were also found extensively during deep slow wave sleep. There is a striking difference as far as REM sleep is concerned: here predominantly EEG phenomena fitting with partial epilepsy were found. In this respect it should be mentioned that the percentages described in the table were calculated for the total group. In the group with generalized epilepsy 81 out of 131 had REM sleep and in the group of partial epilepsy 62 out of 102. Recalculating the percentage occurrence of epileptic EEG phenomena in those having REM sleep, epileptic EEG phenomena were present in respectively 8.6 % and 56.4 % for the generalized and partial epilepsy.

## V.5. DIAGNOSTIC GAIN AS A FUNCTION OF THE SLEEP CYCLE

If during the first cycle of a sleep recording no epileptic EEG abnormalities are seen, one can doubt whether further recording makes sense. Of the 233 TSD recordings (Table V.4.), 127 consisted of two well formed sleep cycles during which well recognizable interictal EEG phenomena fitting with generalized or partial epilepsy occurred either in both or in one sleep cycle. The results of this comparative investigation are summarized in Table V.5., in which epileptic

TABLE V.5.
Electroencephalographic confirmation of epilepsy during the first or second sleep cycle.

| Cycle | | Gen.E. | Part.E. | Gen. + Part.E. | Total |
|---|---|---|---|---|---|
| 1st | 2nd | n: 58 | n: 42 | n: 27 | n: 127 |
| + | + | 43 | 34 | 26 | 103 |
| + | - | 6 | 1 | - | 7 |
| - | + | 9 | 7 | 1 | 17 |

+: sleep cycle with epileptic EEG phenomena.
-: sleep cycle without epileptic EEG phenomena.

EEG abnormalities are indicated by a + respectively during the first and second cycle for both types of epilepsy.

From this Table it appears that EEG abnormalities were present in both sleep cycles in 81 % (103/127) of the subjects investigated, though generally more abundant during the first cycle. If the sleep recordings had been interrupted systematically after the first cycle, the diagnosis of epilepsy would have been insufficient in 17 (13.4 %) of the investigated subjects.

## V.6. DIAGNOSTIC GAIN IN FUNCTION OF THE RECORDING TIME

On the basis of the literature it was impossible to obtain a clear answer to the question of how long sleep recordings following TSD had to be carried out, in order to obtain a sufficiently high electroencephalographic confirmation of epilepsy. In many laboratories the recordings were restricted to a maximum of one hour independently of the kind and depth of sleep. Therefore it was considered of interest to know the size of the diagnostic gain following a 30-min recording time and to which extent this gain increased following a successive prolongation of the recording time with 30-min periods. To answer the posed question the group of 666 patients (V.3.) was extended to 933 by adding those patients recorded during 1979.

In 626 (67 %) sleep was investigated following TSD. Of these 626, 38 (6 %) had insufficient sleep because of continuous interruptions by wakefulness and the lack of an uninterrupted period of 30 min of sleep. The remaining 588 sleep recordings lasted for a mean of 3-4 hours and all consisted of at least 1, but mainly 2 sleep cycles. Their hypnogram was divided into successive 30-min periods, the first one starting at the onset of the polygraphic sleep recording.

In 270 of the 588 investigated persons, epileptic EEG abnormalities were found during the first 30-min period of which 124 fitting with generalized epilepsy, 97 fitting with partial epilepsy and 49, which had EEG abnormalities fitting with generalized epilepsy with in addition abnormalities fitting with partial epilepsy. For each of the following 30-min periods the number of recordings during which for the first time epileptic abnormalities were seen were counted, and summarized in Table V.6.

From the Table it appears that in 270 or 45.9 % of the investigated subjects, epilepsy could be confirmed during the first 30-min period. This is the period during which many changes occur since in most patients transitions from wakefulness to N.REM 1-2 and N.REM 3-4 sleep appear. The gain achieved during the second period (31-60 min) is 1/5 (24/124) for the generalized epilepsy and 1/6 (16/97) for the partial epilepsy as compared to the gain of the first period, which still is half of the combined group (27/49). The additional gain of 9.9 % (58/588) achieved during the third period is still considerable and might be associated with changes occurring at the end of the first sleep cycle, i.e. a transition from N.REM 3-4 to N.REM 1-2 or REM sleep. Calculating the positive diagnostic findings in function of time, the following is obtained: after 1 h 57.3 %, after 2 h 69.4 % (+ 12.1 %), after 3 h 73.15 % (+ 3.75 %) and after 4 h 74.5 % (+1.35 %). The figure between brackets is indicating the gain as compared to the preceding hour. These results are summarized in Fig. V.7.

TABLE V.6.
Number of polygraphic sleep registrations, recorded after 1 night sleep deprivation, with epileptic EEG phenomena, subdivided into periods of 30 min.

| EEG type of epilepsy | Sleep registration in periods of 30 min (n: 588) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1st 0-30 | 2nd 31-60 | 3rd 61-90 | 4th 91-120 | 5th 121-150 | 6th 151-180 | 7th 181-210 | 8th 211-240 | Total 0-240 |
| Gen.E. (243) | 124 | 24 | 23 | 6 | 9 | 4 | 2 | 1 | 193 |
| Part.E.(204) | 97 | 16 | 25 | 6 | 4 | 1 | 5 | - | 154 |
| Gen.+Part.E. (141) | 49 | 27 | 10 | 1 | 4 | - | - | - | 91 |
| Total 588 | 270 | 67 | 58 | 13 | 17 | 5 | 7 | 1 | 438 |

TABLE V.8.
Number of sleep deprivation recordings with complementary epileptic EEG phenomena, which allow a better epilepsy diagnosis, subdivided into periods of 30 min.

| EEG type of epilepsy | Sleep registration time in periods of 30 min | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1st 0-30 | 2nd 31-60 | 3rd 61-90 | 4th 91-120 | 5th 121-150 | 6th 151-180 | 7th 181-210 | 8th 211-240 | 1st-8th 0-240 |
| Gen. E. | - | + 7 | + 3 | + 1 | + 1 | - | - | + 1 | 13 |
| Part. E. | - | +12 | + 3 | - | + 2 | - | - | - | 17 |
| Gen.+Part.E. | - | + 6 | + 5 | + 3 | - | - | - | + 1 | 15 |
| Total | - | +25 | +11 | + 4 | + 3 | - | - | + 2 | 45 |

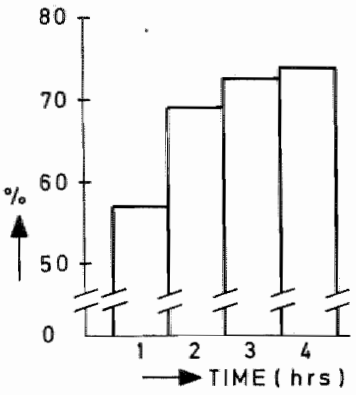


FIG. V.7.
Percentage of sleep recordings with epileptic EEG phenomena in relation to the registration time.

With the present material it was further investigated how the epilepsy diagnosis could be improved by recording other epileptic EEG phenomena. These additions could consist of changes in localization, fitting more with a partial complex than with a simple form of epilepsy, the occurrence of secondary generalization or the appearance of a second type of epilepsy. In analogy with Table V.6. we calculated the number of supplementary epilepsy diagnostic findings for each 30-min period as summarized in Table V.8.

These figures demonstrate that the diagnosis could be improved in 36 (6.1 %) patients during the first additional hour (31st-90th min). The further improvement in 7 patients (1.2 %) was found by recording the second hour (91st-150th min).

## V.7. DIAGNOSTIC GAIN DURING THE SLEEP LATENCY PERIOD

In order to investigate the supposition that an increase of epileptic EEG abnormalities following sleep deprivation is a consequence of a shortage of sleep unrelated to the subsequent sleep, the results of all-night sleep were compared with those obtained following the TSD. The percentage recordings with epileptic EEG findings during the sleep latency period using both methods was calculated. The sleep latency is the time period of wakefulness lapsing between the start of the recording and the occurrence of uninterrupted sleep for at least 5 min. As shown in Table V.9. this percentage was respectively 26.5 % and 11.6 % for the all-night sleep and the sleep following TSD. For the interpretation of these percentual values one has to consider that the mean sleep latency during the all-night sleep is longer than during the sleep following sleep deprivation. Using the sleep recordings taken during 1980-1981, the mean sleep latency is 41.3 min following all-night sleep and 6.3 min following sleep after sleep deprivation.

TABLE V.9.
Mean duration and percentage of positive (+) epileptic EEG findings during the sleep latency period (S.L.T.) for the all-night sleep and the sleep deprivation method.

| | All-night | Sleep deprivation |
|---|---|---|
| S.L.T. in min. | 41.3 | 6.3 |
| % + E. | 26.5 % | 11.6 % |

From Table V.9. it appears that the sleep latency of the deprivation method is 6.5 times smaller than the latency during all-night sleep recordings. The percentage epileptic EEG phenomena, however, is only 2.3 times smaller during the sleep deprivation method than during the all-night sleep recordings. This might indicate that the deprivation of sleep to a certain degree facilitates the occurrence of epileptic manifestations.

## V.8. DIAGNOSTIC GAIN DURING N.REM 1-2 AND N.REM 3-4 PERIOD

From the literature it is known that following TSD sleep latency is short and N.REM 3-4 is reached rapidly. In addition, there is a marked change in the composition of the first sleep cycle, i.e. an increase in N.REM 3-4, a decrease in N.REM 1-2 and eventually a postponement of REM sleep. The question therefore was whether the changed sleep pattern was associated with an increase in epileptic EEG abnormalities.

To answer this question, it was studied in how many subjects epileptic EEG phenomena were found during the first N.REM 1-2 and N.REM 3-4 period, using 100 all-night sleep recordings and 500 sleep deprivation recordings carried out before the end of 1981. The results are given in Table V.10.

TABLE V.10.
Positive diagnostic findings of epilepsy during the first N.REM 1-2 and N.REM 3-4 periods: all-night versus sleep deprivation method.

| Sleep stages | Number and percentage positive findings | | | |
|---|---|---|---|---|
| | All-night (n: 100) | | Sleep deprivation (n: 500) | |
| N.REM 1-2 | 47 | 47 % | 211 | 42.2 % |
| N.REM 3-4 | 30 | 30 % | 137 | 27.4 % |

From Table V.10. it can be seen that the number of sleep recordings containing epileptic abnormalities during both light and deep slow wave sleep are almost equal using both sleep recording procedures. This argues against the hypothesis that the increase in EEG findings are due to the changed sleep pattern following sleep deprivation.

## V.9. SLEEP DEPRIVATION AND HYPERVENTILATION

The hyperventilation test is considered as a good provocation test which promotes the occurrence of diffuse spike wave paroxysms, especially the typical 3 c/sec spike waves and polyspike wave complexes. This test can be combined with a sleep investigation.

In order to evaluate its effects, 60 patients in which a sleep deprivation investigation had been carried out were asked to hyperventilate for 5 min preceding and following a sleep recording. In 26 patients generalized spikes or spike wave paroxysms were seen during the sleep. Only in 3 of them were spike wave paroxysms also seen during the hyperventilation test, in two patients preceding and following the sleep investigation and in one patient only during the period following the sleep. In 13 patients EEG abnormalities fitting with partial epilepsy were observed during sleep. This was only seen 3 times during the hyperventilation test. In none of 60 patients, were epileptic EEG phenomena observed during the hyperventilation test which were not also seen during the sleep recording.

Although the number of patients studied is small, it is suggested that hyperventilation possibly does not provide an important diagnostic gain when combined with 3-4 h sleep recordings following one night total sleep deprivation. In addition, it appeared that at least 1/3 of the 60 patients investigated, experienced considerable difficulties in carrying out hyperventilation in a suitable way.

## V.10. SLEEP DEPRIVATION AND INTERMITTENT LIGHT FLASH STIMULI (LFS)

The occurrence of spike wave paroxysms can be promoted by LFS. The typical 3 c/sec spike waves and polyspike wave paroxysms are particularly sensitive, whereas low frequency spike wave paroxysms increase more during sleep (Dalby, 1969). On the basis of these observations it was considered meaningful to combine both tests.

In a series of 50 patients which had or were suspected of having generalized epilepsy and for which an additional sleep deprivation investigation was required, LFS was applied preceding and following sleep recording. The group consisted of 23 males and 27 females, between the age of 8 and 56 years of which 32 were younger than 30 years. Of these 36 had a clinical form of generalized epilepsy, of which 21 of the primarily type and 15 of the secondarily type and 14 subjects were suspected of having a generalized form of epilepsy.

Light stimuli of 2 msec duration of 50-130 lux, measured at the cornea, were given in alternation with 5-sec periods without LFS. The frequency of the stimuli was increased by one per second from 1 to 12 during the successive stimulation periods, followed by stimulation frequencies of 13, 16, 20, 25 and 30 per second. The test was

carried out as well with eyes open as with eyes closed. Of the 50 patients investigated 37 had spike wave paroxysms during the sleep. In 6 of them spike wave paroxysms occurred during the light flashes in 4 these were seen during both test periods and in 2 patients only during 1 test period, one preceding and one following the sleep recording. In 4 patients the spikes or spike wave paroxysms appeared generalized and were sufficiently specific to denote these as epileptogenic. These were 4 patients on which the diagnosis of primarily generalized epilepsy was posed of which 3 were of the absence type. Only in one of them were generalized spike wave paroxysms found following light flashes during a routine EEG recording. Nevertheless, all 4 had specific epileptic EEG phenomena during the sleep. In 2 patients the reaction was aspecific and consisted of unstable and often short-lasting periods of varying spikes, localized maximally parieto-occipitally.

As with the hyperventilation test, it can be concluded that light flashes combined with long term sleep recordings (minimally 3 h) do not further contribute to the diagnosis of epilepsy. However, the sensitivity of some patients to intermittent light flashes (5/50) is increased due to the shortage of sleep.

## V.11. SUMMARY

In order to confirm or to deny the diagnosis of epilepsy electroencephalographically a long term EEG recording (3-10 h) as a supplement to the routine EEG investigation was performed in 1503 subjects during the period 1976-1981. The number of patients in which epileptic EEG abnormalities were found during the routine EEG recording was 566 (37.6 %) and 991 (65.9 %) during the sleep recording, which is a diagnostic gain of 28.3 %. The epileptic abnormalities seen in 566 patients during the routine EEG could be better described following sleep in 311 patients. In 9 patients no epileptic abnormalities were found during the sleep.

The percentage sleep recordings containing specific epileptic abnormalities depended to a large degree on the probability by which epilepsy could be confirmed or denied on the basis of anamnestic and clinical findings. When the epilepsy was considered very probable, specific epileptic abnormalities were observed in 84.2 % of the sleep recordings, this in contrast to the recordings of patients of which the diagnosis of epilepsy was unlikely, where specific abnormalities were only found in 0.75 % of the cases. When the diagnosis was doubtful, then specific epileptic EEG abnormalities occurred in 56.6 % and aspecific EEG abnormalities in 28.6 % of the sleep recordings.

The EEG confirmation of partial epilepsy was independent of the applied sleep procedure. For the generalized epilepsy the confirmation was 6 % higher during all-night sleep recordings than during interrupted sleep and sleep following sleep deprivation. For each of the 3 methods, the diagnostic gain was larger for the generalized epilepsy than for the partial epilepsy. In all sleep recordings following sleep deprivation in which epileptic EEG abnormalities were present N.REM 1-2 sleep was found. N.REM 3-4 and REM sleep was present in respectively 90 % and 61 %. For both generalized and partial

epilepsy, epileptic EEG abnormalities mainly occurred during N.REM 1-2 sleep. Thus light sleep would have been sufficient to confirm the existence of generalized epilepsy in 90 % and partial epilepsy in 98 % of the cases. For the detection of the remaining 10 % of the generalized epilepsy the recording of deep N.REM 3-4 sleep was necessary and for the remaining 2 % of the partial epilepsy recording of REM sleep was necessary.

The percentage sleep recordings during which EEG abnormalities were discovered depended on the duration of the recording. During the sleep following sleep deprivation epileptic EEG phenomena were found 86.4 % during the first sleep cycle and in 13.6 % only during the second cycle. This result was supported by an investigation from which it appeared that epileptic abnormalities were present in 77 % during the first hour and in 93.1 % following a 2-h recording. This means that epilepsy would have been insufficiently demonstrated in respectively 23 % and 7 % of the patients, if the recordings had been interrupted after 1 or 2 hours. Further, it appeared that it was not indicated to stop the recording following the appearance of the first epileptic manifestations, since in these patients other epileptic EEG abnormalities were found during a later phase, by which the diagnosis could be further improved.

The mean latency in subjects kept awake for 24 h was only 6.3 min, which is much shorter than the mean sleep latency of 41.3 min following a spontaneous night sleep. During this short period of wakefulness preceding the onset of sleep epileptic EEG phenomena were only observed in 11.6 % of the recordings. This finding argues against the assertion that the short wakefulness period following one night sleep deprivation is sufficient to diagnose epileptic EEG abnormalities.

The EEG confirmation of epilepsy was not improved by combining the sleep recording following one night sleep deprivation with hyperventilation or with light flashes. All patients in which epileptic EEG abnormalities were found during these tests also had them during the sleep recordings. In addition, in 1/3 of the patients the hyperventilation test could not be performed following one night sleep deprivation because of an excessive sleepiness.

On the basis of our results, it can be stated that the sleep recording following 24 h uninterrupted wakefulness is a valuable method to diagnose epilepsy electroencephalographically. In order to be optimally effective the following conditions should be fulfilled:

1. The recording has to be made following a total night sleep deprivation. Otherwise, the duration and depth of sleep will often be insufficient.
2. The duration of the recording has to be sufficiently long in order to register minimally one complete sleep cycle (1.5-2 h), but preferentially 2 sleep cycles (3-4 h).
3. It is desirable that sleep is composed of light N.REM 1-2 sleep, deep N.REM 3-4 sleep and REM sleep.
4. With the aid of a large number of EEG derivations it must be possible to detail the localization and spread of epileptic abnormalities and to classify the sleep, in conjunction with non-EEG parameters, into N.REM 1, 2, 3 and 4 and REM sleep.

It is often thought that the listlessness of some epileptics may be associated with sleep disturbances, caused by the appearance of epileptic discharges or by the long term intake of antiepileptics. According a number of data from the literature this line of thought is incorrect. In this chapter it is aimed to answer the following questions: (1) whether the composition of sleep in epileptics differs from that of healthy persons and whether these differences depend on (2) the presence (E.) or absence (N.E.) of epileptic EEG discharges, (3) the type of epilepsy with which they concur (Gen. E.; Part. E. and Gen. + Part. E), (4) the presence or absence of antiepileptic medication (+ or - A.E.) (5) especially with regard to benzodiazepine derivatives (+ B.D.) and (6) whether the differences are age-dependent.

## VI.1. MATERIALS AND METHODS

Two groups of subjects were investigated: one group of patients (clinical group or CL) and a group of non patients (control group or CO). The patients (n = 113) were subjects suspected of having epilepsy of which an all-night sleep recording was taken as a supplement

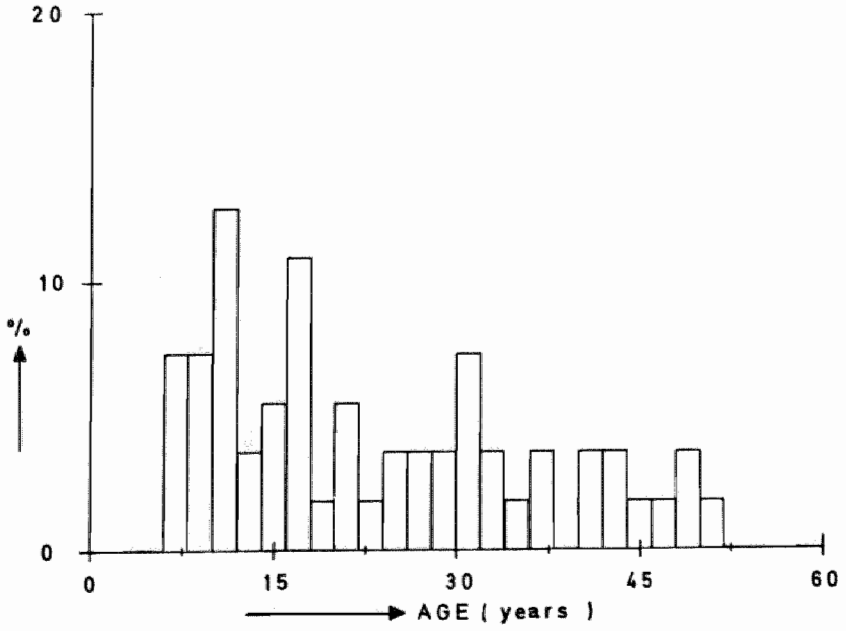


FIG. VI.1.
Age distribution in years of the 55 male patients.

to the routine EEG investigation. With the aid of hypnograms the sleep composition was studied. The sleep recording of patients during which a period of 15 min following an electroclinical fit could not be classified were disregarded. In addition cycles consisting of more than 60 min wakefulness and more than 120 min N.REM 1-2 or N.REM 3-4 sleep were not evaluated. Following this selection the CL group consisted of 55 males and 38 females of which 80 were between the age of 7 and 40 and 13 subjects were older. The age distribution for the males and females is represented in figures VI.1. and VI.2.

The CO group consisted of 9 females between the age of 21 and 30 years. At the time of the investigation all were healthy and none took medicines known to affect sleep.

The analysis has been restricted to the first and second cycle because these two cycles (1) generally consist of light as well as deep N.REM and REM sleep, (2) are comparable to the two sleep cycles recorded after applying total sleep deprivation method, (3) are often sufficient to register epileptic EEG abnormalities.

For each individual subject the sleep pattern of both cycles was described by the total duration of the cycles, the time of wakefulness, the effective sleep time and the duration of N.REM 1-2, N.REM 3-4 and REM sleep.

Of these parameters the mean, standard deviations and confidence intervals of the control and clinical group further divided into subgroups, were calculated. On the basis of the confidence intervals of the means the statistical significance of differences between both groups for the different parameters was evaluated.

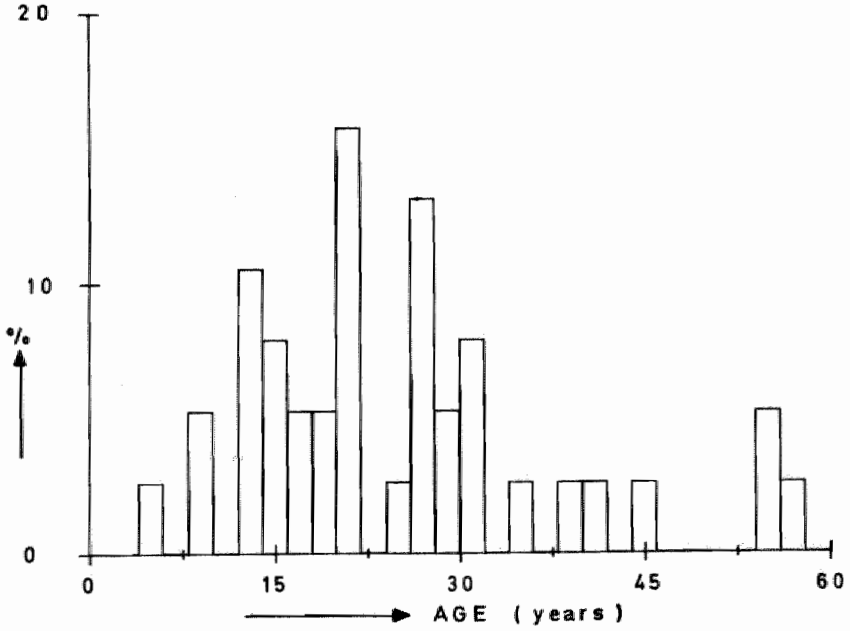


FIG. VI.2.
Age distribution in years of the 38 female patients.

In order to enhance the legibility of the following tables only the mean values and the significance of the differences are indicated. More elaborate tables including standard deviations and confidence intervals of the values are given in the addenda (chapter XIII), which in addition enter into the reasons for the choice of the statistical methods.

## VI.2. RESULTS

### 2.1. Sleep composition of the first and second cycle in the control group

The mean duration (minutes) of the different sleep parameters of the CO group for the first cycle (upper row) and second cycle (lower row) is summarized in Table VI.3.

TABLE VI.3.
Quantitative composition of the first and second cycle during all-night sleep recordings of the control population.

| CO. n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|
| Cy. 1 9 | 85.5 | 7.7 | 77.8 | 39.2 | 31.2 | 7.4 |
| Cy. 2 9 | 90.1 | 3.9 | 86.2 | 40.6 | 29.8 | 15.8 |

In both cycles there is a preponderance of light slow wave sleep, which is evident from the ratio N.REM 1-2/N.REM 3-4, being 1.26 for the first cycle and 1.36 for the second cycle. The somewhat longer duration of the second cycle is due to a higher amount of REM sleep. The sleep composition of both cycles of the CO group is in complete agreement with the values of similar age groups mentioned in other studies (Coenen, 1979; Foret and Webb, 1981; Philipson et al., 1980).

### 2.2. Sleep composition of the first and the second cycle of the clinical group

Depending on the presence or absence of epileptic EEG manifestations during the first and the second cycle, the CL group has been subdivided, respectively denoted as N.E. and E. For both categories the sleep composition per cycle as compared to the CO group is represented in Table VI.4. and VI.5.

The group without epileptic phenomena has a significantly longer duration of the total sleep cycle ($p < 0.05$) and more effective sleep, due to a tendency to have more N.REM 1-2 sleep, more REM sleep and more wakefulness. The group with epileptic phenomena has also a significantly longer duration of the total sleep cycle ($p < 0.05$) and more effective sleep ($p < 0.025$) caused by an increase of all sleep stages which individually, however, do not reach a statistically significant level. The CL group differs from each other because the

TABLE VI.4.
Composition of the first cycle of all-night sleep recordings of patients, respectively without (N.E.) and with (E.) epileptic EEG phenomena, in comparision with the CO group.

| Cy. 1 | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 9 | 85.5 | 7.7 | 77.8 | 39.2 | 31.2 | 7.4 |
| N.E. | 39 | 103.9* | 12.0 | 91.9 | 50.7 | 29.3 | 11.9 |
| E. | 54 | 104.8* | 6.2 | 98.6** | 48.6 | 39.4 | 10.6 |

* $p < 0.05$; ** $p < 0.025$

group with epileptic EEG phenomena is less awake and has more deep N.REM 3-4 sleep.

As evident from Table VI.5. the differences as compared with the control group during the second cycle are less pronounced.

TABLE VI.5.
Composition of the second cycle in all-night sleep recordings of the patients without (N.E.) and with (E.) epileptic EEG phenomena.

| Cy. 2 | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 9 | 90.1 | 3.9 | 86.2 | 40.6 | 29.8 | 15.8 |
| N.E. | 35 | 103.1 | 7.3 | 95.8 | 48.9 | 27.8 | 19.1 |
| E. | 51 | 102.1 | 5.2 | 96.9 | 52.2 | 28.7 | 16.0 |

The patients have a longer duration of the second cycle. This prolongation is mainly due to a higher amount of N.REM 1-2 sleep.
There are no important differences between both CL groups.

2.3. Sleep composition of the first and second cycle in epileptic patients which do not have epileptic EEG phenomena (N.E.) in their recordings, depending on whether (+ A.E.) or not (- A.E.) they take antiepileptic drugs

In order to trace whether the intake of antiepileptics is also responsible for the changes in the sleep composition, the CL group without epileptic EEG phenomena was subdivided into a category which did not (N.E.-A.E.) and into a category which did (N.E.+A.E.) take antiepileptics. Because of the small number (n = 4), patients treated with A.E. in combination with benzodiazepine derivatives were not considered further. The results of this comparison for the first cycle is represented in Table VI.6. and for the second cycle in Table VI.7.

TABLE VI.6.
Composition of the first cycle of all-night sleep recordings without epileptic EEG phenomena and without or with antiepileptic drug treatment.

| Cy. 1 n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|
| CO 9 | 85.5 | 7.7 | 77.8 | 39.2 | 31.2 | 7.4 |
| N.E.-A.E. 18 | 115.9** | 16.8 | 99.1 | 56.4 | 30.7 | 12.0* |
| N.E.+A.E. 21 | 94.5 | 9.5 | 85.0 | 43.8 | 29.0 | 12.2 |

** $p < 0.025$

Patients not taking antiepileptics have a significantly longer sleep cycle ($p < 0.025$). This is attributed to an increase in N.REM 1-2 sleep, in awake and in REM sleep. These changes with the exception of the REM sleep, are seen to a much lesser degree in patients which take antiepileptics.

The clinical groups differ from each other because subjects which take antiepileptics have a shorter total cycle caused by a tendency to awake less and to have less light N.REM 1-2 sleep.

TABLE VI.7.
Composition of the second cycle of all-night sleep recordings without epileptic EEG phenomena and without or with antiepileptic drug treatment.

| Cy. 2 n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|
| CO 9 | 90.1 | 3.9 | 86.2 | 40.6 | 29.8 | 15.8 |
| N.E.-A.E. 16 | 106.6 | 10.6* | 96.0 | 47.7 | 28.4 | 19.9 |
| N.E.+A.E. 16 | 98.6 | 3.1 | 95.5 | 45.3 | 31.6 | 18.6 |

* $p < 0.05$

The group not taking antiepileptics has a longer second sleep cycle, becomes more awake ($p < 0.05$) and tends to have more N.REM 1-2 sleep.

The group which takes antiepileptics has a sleep composition hardly different from non-patients.

The two clinical groups differ considerably from each other, because patients taking antiepileptics become less awake.

2.4. Sleep composition in patients having epileptic EEG phenomena (E.) and which therefore take antiepileptics (+A.E.) or antiepileptics in conjunction with benzodiazepine derivatives (A.E.+B.D.)

Benzodiazepine derivatives may give rise to an increase in N.REM 1-2 sleep sometimes combined with a decrease in N.REM 3-4 sleep and REM sleep and with less awakenings. In a comparative investigation it was sought whether these compounds in combination with antiepileptics affect the sleep in a comparable way. Because 10 patients also take other medicines the CL group is reduced to 44 persons of which only 5 take antiepileptics in conjunction with benzodiazepine derivatives. The results are summarized in Table VI.8. and VI.9.

TABLE VI.8.
Sleep composition of the first all-night cycle in recordings with epileptic EEG phenomena, treated with antiepileptic drugs, with (E.+A.E.+B.D.) or without combination with benzodiazepine derivatives (E.+A.E.-B.D.).

| Cy. l | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 9 | 85.5 | 7.7 | 77.8 | 39.2 | 31.2 | 7.4 |
| E.+A.E. | 39 | 107.8* | 7.3 | 100.5** | 45.8 | 44.0 | 10.7 |
| E.+A.E. +B.D. | 5 | 101.8 | 4.4 | 97.4 | 52.2 | 31.6 | 13.6 |

* $p < 0.05$; ** $p < 0.025$

The group of patients which only take antiepileptics had a significantly longer sleep cycle ($p < 0.05$), more effective sleep ($p < 0.025$) and more deep N.REM 3-4 sleep.

Although the sleep composition in patients taking antiepileptics in conjunction with benzodiazepine derivatives is clearly changed, mainly because of an important increase in N.REM 1-2 sleep this group does not differ significantly from the non-patient group. This is due to the large interindividual differences within this small group.

Both clinical groups show important differences in the composition of the N.REM sleep. Patients which take antiepileptics have more light N.REM 1-2 sleep as well as more N.REM 3-4 sleep, whereas patients who also take benzodiazepine derivatives only have more light N.REM 1-2 sleep.

Patients only taking antiepileptics tend to have more N.REM 1-2 sleep. The same tendency exists for those taking also benzodiazepine derivatives, but this is associated with a decreased N.REM 3-4 sleep and REM sleep.

TABLE VI.9.
Composition of the second all-night sleep cycle in recordings with epileptic EEG phenomena, treated with antiepileptic drugs, with (E.+A.E.+B.D.) or without combination with benzodiazepine derivatives (E.+A.E.-B.D.).

| Cy. 2 | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 9 | 90.1 | 3.9 | 86.2 | 40.6 | 29.8 | 15.8 |
| E.+A.E. | 37 | 101.9 | 5.5 | 96.4 | 50.7 | 29.2 | 16.5 |
| E.+A.E. +B.D. | 5 | 92.8 | 9.0 | 83.8 | 51.8 | 22.0 | 10.0 |

2.5. Sleep composition of the first and second cycle in the presence of epileptic EEG manisfestations and the intake of antiepileptics, divided per type of epilepsy

This investigation aims at finding out whether the sleep composition is dependent on the kind of epileptic EEG phenomena fitting with respectively generalized (Gen.), partial (Part.) or a combination of both (Gen.+Part.) forms of epilepsy. The mean values of the different sleep parameters for the three categories of epilepsy are given in Tables VI.10. and VI.11. for the first and second cycle respectively.

TABLE VI.10.
Sleep composition of the first all-night cycle in recordings with interictal epileptic EEG paroxysms belonging to Generalized, Partial or Generalized with Partial epilepsy.

| Cy. 1 | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 9 | 85.5 | 7.7 | 77.8 | 39.2 | 31.2 | 7.4 |
| Gen.E. | 14 | 104.9 | 7.9 | 97.0 | 49.1 | 40.0 | 7.9 |
| Part.E. | 13 | 106.4 | 8.5 | 97.9 | 39.5 | 46.4 | 12.0 |
| Gen.+ Part.E. | 12 | 112.7 | 5.3 | 107.4* | 48.7 | 45.9 | 12.8 |

* $p < 0.05$

As compared to the CO group for all categories a longer duration of the cycle and more effective sleep is found, significant ($p < 0.05$) for the group of patients which have a combination of two forms of epilepsy. In all categories there is a tendency to have more deep N.REM 3-4 sleep, and both categories with generalized epilepsy also have more light N.REM 1-2 sleep.

TABLE VI.11.
Sleep composition of the second all-night cycle in recordings with epileptic EEG paroxysms belonging to generalized, partial or generalized with partial epilepsy.

| Cy. 2 | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 9 | 90.1 | 3.9 | 86.2 | 40.6 | 29.8 | 15.8 |
| Gen.E. | 12 | 110.1 | 5.8 | 104.3 | 55.6 | 33.1 | 15.6 |
| Part.E. | 13 | 96.2 | 6.3 | 89.9 | 46.0 | 26.0 | 17.9 |
| Gen.+ Part.E. | 12 | 99.9 | 4.3 | 95.6 | 51.0 | 28.8 | 15.8 |

For all categories there is a tendency to have a longer second cycle, consisting of more effective sleep and more N.REM 1-2 sleep. This increase is more pronounced for patients having EEG phenomena fitting with generalized epilepsy.

2.6. Sleep composition of the first and second cycle of the control group versus the clinical group

The previous tables mention differences in the sleep composition of the first and second cycle between patients and non-patients. Tables VI.12. and VI.13. summarize the various subgroups.

The different categories of patients have been divided into 3 main groups. The first group consists of patients without epileptic EEG abnormalities (categories 2 and 3), the second group consists of patients with epileptic EEG abnormalities, treated with antiepileptics (categories 4, 5 and 6), the third group consists of patients with epileptic EEG abnormalities and which are treated with antiepileptics in conjunction with benzodiazepine derivatives. The significance of differences as compared to the control group are indicated for each of the sleep parameters.

The total cycle duration is shortest for the CO group. Group 1, patients without EEG abnormalities, tend to have a longer first cycle. Group 2 has a longer cycle and a same tendency exists for group 3.

Although the duration of wakefulness for the various categories differs largely, these differences are not significant for the 3 main groups.

For the effective sleep time the differences are comparable to those of the total cycle duration.

For all 3 patient groups there is a tendency to obtain more N.REM 1-2 sleep, except for the categories which have EEG abnormalities fitting with partial epilepsy (2.5.). Deep N.REM 3-4 sleep is only increased for the group 2, patients having epileptic EEG abnormalities and which take antiepileptics. All patients have more REM sleep except for those having EEG abnormalities fitting with generalized epilepsy.

TABLE VI.12.
Comparison of the sleep patterns of the first all-night cycle: control group versus the different clinical groups.

| Gr. | Ct. | Cy. 1 | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 | CO | 9 | 85.5 | 7.7 | 77.8 | 39.2 | 31.2 | 7.4 |
| 1 | 2 | N.E.-A.E. | 18 | 115.9 | 16.8 | 99.1 | 56.4 | 30.7 | 12.0 |
| | 3 | N.E.+A.E. | 21 | 94.5 | 9.5 | 85.0 | 43.8 | 29.0 | 12.2 |
| 2 | 4 | Gen.E.+A.E. -B.D. | 14 | 104.9 | 7.9 | 97.0 | 49.1 | 40.0 | 7.9 |
| | 5 | Part.E.+A.E. -B.D. | 13 | 106.4 | 8.5 | 97.9 | 39.5 | 46.4 | 12.0 |
| | 6 | Gen.+Part.E. +A.E.-B.D. | 12 | 112.7 | 5.3 | 107.4 | 48.7 | 45.9 | 12.8 |
| 3 | 7 | E.+A.E. +B.D. | 5 | 101.8 | 4.4 | 97.4 | 52.2 | 31.6 | 13.6 |

TABLE VI.13.
Comparison of the second all-night cycle: control group versus different clinical groups.

| Gr. | Ct. | Cy. 2 | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 | CO | 9 | 90.1 | 3.9 | 86.2 | 40.6 | 29.8 | 15.8 |
| 1 | 2 | N.E.-A.E. | 16 | 106.6 | 10.6 | 96.0 | 47.7 | 28.4 | 19.9 |
| | 3 | N.E.+A.E. | 16 | 98.6 | 3.1 | 95.5 | 45.3 | 31.6 | 18.6 |
| 2 | 4 | Gen.E.+A.E. -B.D. | 12 | 110.1 | 5.8 | 104.3 | 55.6 | 33.1 | 15.6 |
| | 5 | Part.E.+A.E. -B.D. | 13 | 96.2 | 6.3 | 89.9 | 46.0 | 26.0 | 17.9 |
| | 6 | Gen.+Part.F. +A.E.-B.D. | 12 | 99.9 | 4.3 | 95.6 | 51.0 | 28.8 | 15.8 |
| 3 | 7 | E.+A.E. +B.D. | 5 | 92.8 | 9.0 | 83.8 | 51.8 | 22.0 | 10.0 |

There are no significant differences in the sleep composition of the second cycle between the three patient groups, though there is a tendency to observe less REM sleep in group 3, which apart from anti-epileptics also take benzodiazepine derivatives.

### 2.7. Sleep composition of the first and second sleep cycle in function of age

Since the control group consisted of subjects between the age of 21 and 30 years, it appeared meaningful to compare these with a group of patients of the same age. The number of patients of each clinical group is too small to be further divided into subgroups, therefore, patients having different forms of epilepsy were considered as one group, also there was no significant differences in the sleep pattern of these different subgroups (Tables VI.10. and VI.11.).

From this group, 3 subgroups were constituted respectively to the age of 10 years (n = 12), from 11 to 20 years (n = 12) and from 21 to 30 years (n = 8). The mean values for each sleep parameter for the first and second cycle and for each age group are compared with the control group in Tables VI.14. and VI.15.

TABLE VI.14.
Comparison of the sleep pattern of the first all-night cycle in patients with epileptic EEG paroxysms and treated with antiepileptic drugs: control group versus 3 clinical groups, respectively between 3-10, 11-20 and 21-30 years old.

| Cy.1. n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|
| CO 9<br>20-30 y. | 85.5 | 7.7 | 77.8 | 39.2 | 31.2 | 7.4 |
| E.+A.E. 12<br>$\leqslant$ 10 y. | 113.5 | 7.6 | 105.9* | 41.0 | 54.7* | 10.2 |
| E.+A.E. 12<br>11-20 y. | 99.7 | 4.1 | 95.6 | 44.3 | 40.7 | 10.6 |
| E.+A.E. 8<br>21-30 y. | 109.6 | 4.4 | 105.2 | 46.8 | 43.6 | 14.8 |

* $p < 0.05$

The group of patients to the age of 10 years differs most from the control group. There is a longer sleep duration and more effective sleep ($p < 0.05$) mainly caused by more deep N.REM 3-4 sleep ($p < 0.05$). In the other age groups there is an increase of all sleep stages without reaching statistical significance.

In contrast to the first cycle, the age group from 11 to 20 years has a different sleep composition as compared to the control group during the second cycle of the sleep. There is a larger cycle duration, more effective sleep ($p < 0.05$) and more light N.REM 1-2 sleep.

TABLE VI.15.
Comparison of the sleep pattern of the second all-night cycle in patients with epileptic EEG paroxysms and treated with antiepileptic drugs: control group versus 3 clinical groups, respectively between the age of 3-10, 11-20 and 21-30 years.

| Cy.2 | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO 20-30 y. | 9 | 90.1 | 3.9 | 86.2 | 40.6 | 29.8 | 15.8 |
| E.+A.E. ⩽ 10 y. | 12 | 95.3 | 5.8 | 89.5 | 47.2 | 26.0 | 16.3 |
| E.+A.E. 11-20 y. | 12 | 119.8 | 2.8 | 117.0* | 64.8 | 35.4 | 16.8 |
| E.+A.E. 21-30 y. | 8 | 105.0 | 3.2 | 101.8 | 44.8 | 37.0 | 20.0 |

* $p < 0.05$

For both the first and second cycle there is no significant difference between the control and the clinical group in the age group 21 to 30 years. Patients tend to have a longer sleep cycle duration because of an increase of all sleep stages.

## VI.3. DISCUSSION AND SUMMARY

Our investigations aimed to find out whether all-night sleep in epileptics is different from that in healthy persons. For this purpose an all-night sleep recording was carried out in 113 epileptics and in 9 carefully selected non-epileptics and thereafter analyzed and registered in a hypnogram. In 93 patients and in all 9 non-patients sleep cycles could be subdivided into light and/or deep N.REM and REM sleep.

The group of 93 patients were subdivided into categories depending on the presence or absence of epileptic EEG phenomena, the type of epilepsy, the intake of antiepileptics or antiepileptics in combination with benzodiazepine derivatives. Differences in the sleep composition of the first and second cycle could therefore be related to the criteria differentiating the different categories.

The 9 healthy persons all had a well-formed sleep pattern. The duration of the cycles as well as the relative proportion of the different sleep stages corresponded with that in normal persons as described in the literature by various authors (Coenen, 1979; Foret and Webb, 1981; Philipson et al., 1980).

Because the group mainly consisted of subjects between the age of 10 and 50 years, an age period during which the sleep pattern is relatively stable (Fischgold et al., 1959 a), it was possible to compare the different categories in patients with the sleep pattern in normals. Patients with epileptic EEG abnormalities and which took

antiepileptics did not have a significantly different sleep composition, and were therefore, considered as one group. Figure VI.16. shows the mean values (min) and confidence intervals ($1/2\alpha = p < 0.05$) of the total cycle duration, the time of wakefulness and the effective sleep time, for the first and second sleep cycle in patients as compared to the control group.

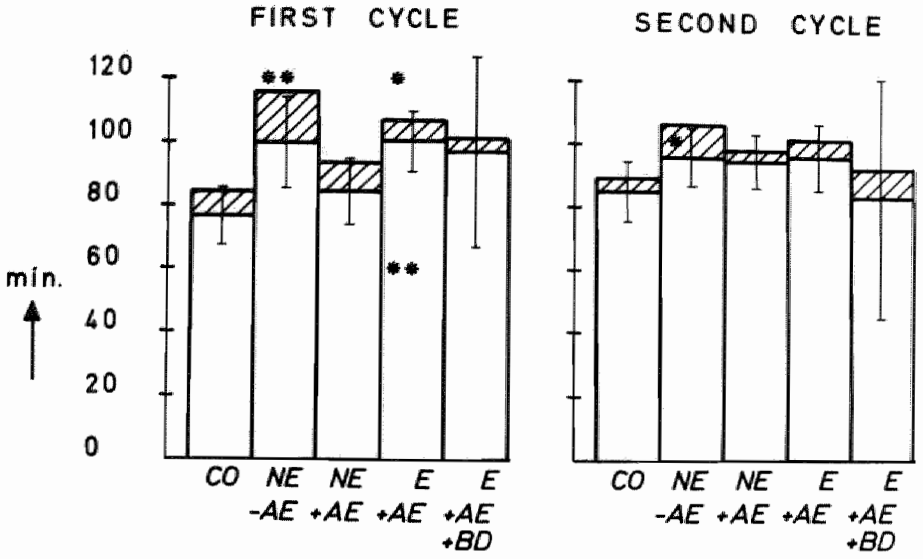


Fig. VI.16.
Mean values, in minutes, of the total sleep cycle, the time awake (▨), and the effective sleep time (□) during the first and the second sleep cycle of the control and the different clinical categories.
* $p < 0.05$; ** $p < 0.025$.

1. All patients had a longer lasting sleep cycle. The increase is largest for patients without epileptic EEG abnormalities and which do not take antiepileptics, during both the first ($p < 0.025$) and second cycle. Though somewhat less pronounced, patients with epileptic EEG abnormalities, which take antiepileptics, also have a significantly ($p < 0.05$) longer lasting first cycle.
2. Although the time of wakefulness differs considerably for the different categories of patients, these differences are statistically not significant, except during the second cycle for the patients without epileptic EEG phenomena, which do not take antiepileptics ($p < 0.05$).
3. The mean effective sleep in patients is increased as compared to the control group, which is significant for the category with epileptic EEG phenomena and which take only antiepileptics ($p < 0.025$).
4. In order to get a better insight into the sleep stability, the percentage effective sleep as compared to the total cycle duration has been calculated. This is represented in Figure VI.17.

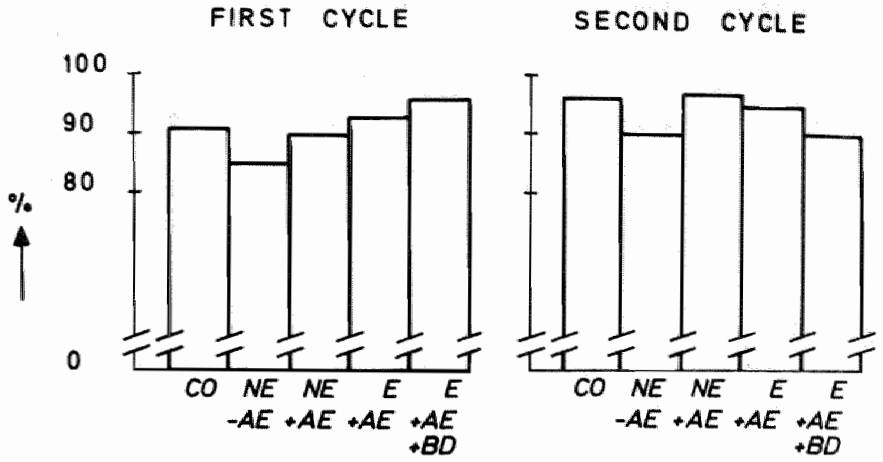


Fig. VI.17.
Percentage of effective sleep time in the control and different clinical categories during the first and second all-night cycle.

As compared to the control group, for both cycles, patients with epileptic EEG abnormalities and which do not take antiepileptics have less effective sleep. Those treated with antiepileptics only have approximately as much effective sleep during both cycles, whereas those treated with antiepileptics and benzodiazepine derivatives have more effective sleep during the first cycle and less effective sleep during the second cycle.

The effective sleep is composed of N.REM and REM sleep. The mean values of these two sleep states for the different categories of patients as compared to the control group are summarized in Figure VI.18.

5. Patients have a higher amount of REM sleep during the first cycle, but the differences are statistically not significant. During the second cycle there is a comparable amount of REM sleep, but the category treated with antiepileptics and benzodiazepines tend to have somewhat less REM sleep.
6. During both cycles patients have more N.REM sleep. This increase is only significant during the first cycle for the category with epileptic abnormalities and which take antiepileptics ($p < 0.05$).

It appeared of interest to find out whether the increased N.REM sleep was due to an increase in N.REM 1-2 sleep or N.REM 3-4 sleep. The comparison is given in Figure VI.19.

7. For both cycles, all patients have more N.REM 1-2 sleep and these differences are largest for the category without epileptic EEG abnormalities and which do not take antiepileptics, and for patients with epileptic EEG phenomena treated with antiepileptics in combination with benzodiazepine derivates.

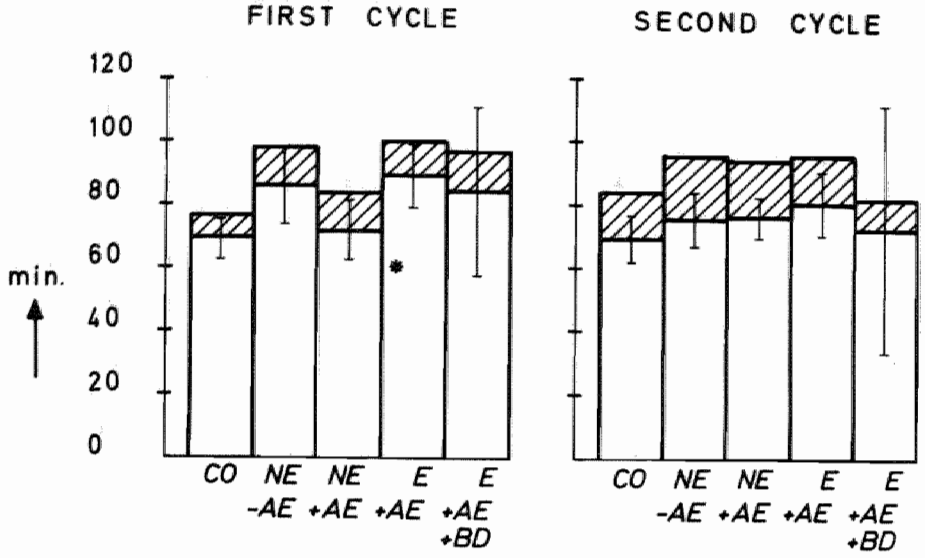


FIG. VI.18.
Mean values, in minutes, of N.REM (□) and REM (▨) sleep during the first and second all-night cycle of the control and the different clinical categories.
* $p < 0.05$

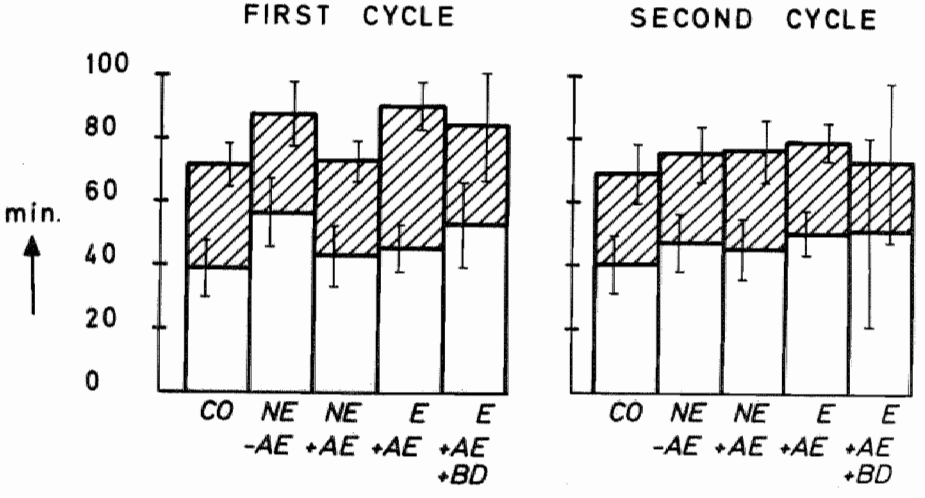


FIG. VI.19.
Mean values of N.REM 1-2 (□) and N.REM 3-4 (▨) sleep during the first and second all-night cycle of the control and the different clinical categories.

8. During the first cycle, patients with epileptic EEG abnormalities, which take antiepileptics, have more deep N.REM 3-4 sleep. During the second cycle the group treated with antiepileptics in combination with benzodiazepine derivatives tend to have less deep N.REM 3-4 sleep.
9. The changes in the quantity of light and deep N.REM sleep are best expressed by the proportion of the N.REM 1-2/N.REM 3-4 sleep as represented in Figure VI.20.

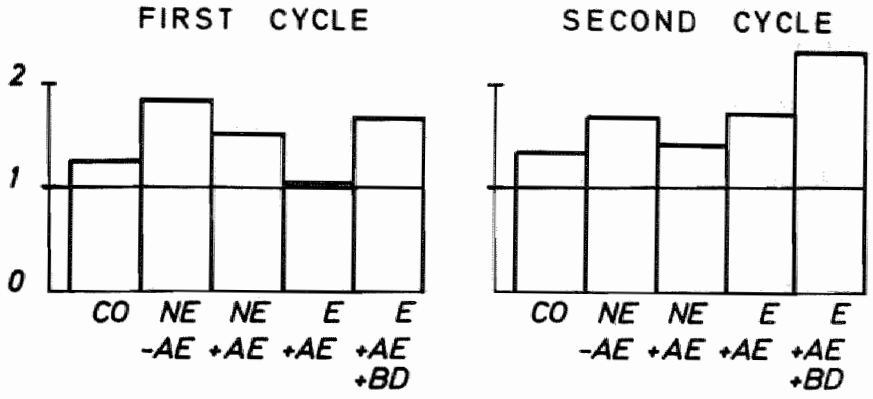


FIG. VI.20.
Ratio of the N.REM 1-2/N.REM 3-4 sleep during the first and second all-night sleep cycle of the control and the different clinical categories.

Only the category with epileptic EEG phenomena, which takes antiepileptics, has a ratio smaller than in the control group during the first cycle. All other categories have a larger ratio than the control group (1.26) respectively 1.84, 1.51, 1.65 for the group without epileptic EEG phenomena, with or without the intake of antiepileptics and for the group which take antiepileptics and benzodiazepine derivatives.
These differences are less pronounced during the second cycle where all patients groups have a somewhat larger ratio, most pronounced for the group treated with antiepileptics and benzodiazepines (2.35) as compared to the control group (1.36).

With the results summarized above the different questions can be answered as follows:
1. Is the sleep composition of the first and second sleep cycle in epileptics different from that in healthy persons?
   There is a difference because patients have a longer duration of the cycle due to an increased N.REM sleep, of which the ratio N.REM 1-2/3-4 is changed.
2. Are the differences dependent on the presence or absence of epileptic EEG abnormalities during the sleep recording?

Taking only the subclinical epileptic EEG abnormalities or the epileptic discharges which severely disturbed the sleep for less than 15 min, then it appears that the changed sleep composition cannot be associated with the presence or absence of epileptic EEG abnormalities.

3. Are these differences in the sleep composition dependent on the type of epilepsy to which the EEG abnormalities fit?
   The composition of the effective sleep is partly dependent on the kind of epileptic abnormalities seen during the sleep recording. The category which have abnormalities fitting with generalized epilepsy have more light N.REM 1-2 as well as more N.REM 3-4 sleep but no increased REM sleep. The category with partial epilepsy has more N.REM 3-4 sleep and REM sleep and an equal amount of N.REM 1-2 sleep. The category which have EEG abnormalities fitting with both types of epilepsy have an increase in N.REM 1-2, N.REM 3-4 and REM sleep.
4. Is the sleep composition dependent on intake of antiepileptics?
   Patients taking antiepileptics had a short cycle during which they awake less and thus have more effective sleep. During the first cycle there is relatively more deep N.REM 3-4 sleep for patients having epileptic EEG abnormalities.
5. Is the sleep composition further changed when benzodiazepine derivatives are added to antiepileptics?
   Adding benzodiazepines results in an increased duration of both sleep cycles, with a relatively larger increase of N.REM 1-2 sleep and a decrease of wakefulness.
6. Are the differences age-dependent?
   Epileptics only treated with antiepileptics have an age-dependent sleep composition. Subjects up to and including 10 years have a relatively higher amount of N.REM 3-4 sleep during the first cycle; subjects from 11 up to and including 20 years have a relatively high amount of light N.REM 1-2 sleep during the second cycle; the composition of the effective sleep for the age category between 20 and 30 years resembles the control.

## CHAPTER VII: COMPOSITION OF THE SLEEP FOLLOWING SLEEP DEPRIVATION IN EPILEPTICS

In chapter V it was shown that, provided specific conditions are fulfilled, the sleep deprivation method is very suitable for recording epileptic EEG phenomena. Two of these conditions were that a recording had to follow a total night sleep deprivation and that the recording had to be sufficiently long to obtain two sleep cycles.

On the basis of the literature given in chapter II, the changes in sleep composition following total sleep deprivation were described, for instance more deep N.REM 3-4 sleep especially in the first sleep cycle.

In chapter VI it was established that all-night sleep in epileptics differs in certain aspects from that in healthy persons. The difference might be associated with the presence of epileptic EEG abnormalities during the sleep and the intake of antiepileptics.

Chapter VII aims at investigating: (1) how the first and second sleep cycle are composed following sleep deprivation in epileptics; (2) whether the composition is dependent on the presence or absence of epileptic EEG phenomena during the sleep; or (3) the type of epilepsy (Gen.E.; Part.E., and Gen. Part.E.); or (4) intake of antiepileptics (+ or - A.E.), (5) in combination with benzodiazepine derivatives (+B.D.) and (6) whether the changes are age-dependent.

### VII.1. MATERIALS AND METHODS

As in chapter VI two groups were investigated: a group of patients (clinical group: CL) and a group of healthy persons (control group: CO). For the composition of the CL group, 617 sleep deprivation recordings carried out during the period 1979-1981 in subjects suspected of having epilepsy, were used. For the investigation the first and second sleep cycle were used on the condition that during one sleep cycle no more than 60 min wakefulness and no more than 120 min N.REM 1-2 sleep or 120 min N.REM 3-4 sleep were present.

After applying these criteria 548 (88.8 %) recordings of which 295 from males and 253 from females were retained. Hereof 251 (45.8 %) were between the age of 5 and 20 years, 232 (42.3 %) between the age of 20 and 40 years and 65 (11.9 %) between the age of 40 and 60 years. The age distribution is represented in Figures VII.1. and VII.2.

The control group consisted of 15 nurses between the age of 20 and 40 years. All were healthy and none took medicines known to influence sleep. They were familiar with the procedure of EEG and polygraphic sleep investigations. As in the patients, a 3-4-h polygraphic registration was carried out between 7-12 h in the morning following a total night sleep deprivation.

In analogy with the all-night sleep recordings patients were divided into a number of categories depending on the presence or absence of epileptic EEG phenomena during the recording and whether they took only antiepileptics or in combination with benzodiazepine derivatives. For each category mean values of the various sleep parameters were calculated, together with the standard deviations of the

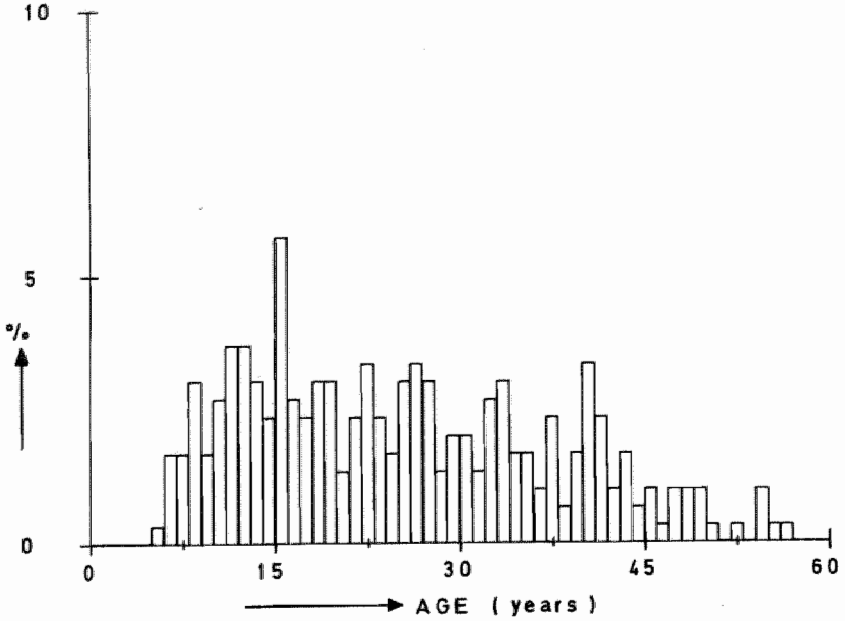


FIG. VII.1.
Age distribution in years of the 295 male patients.

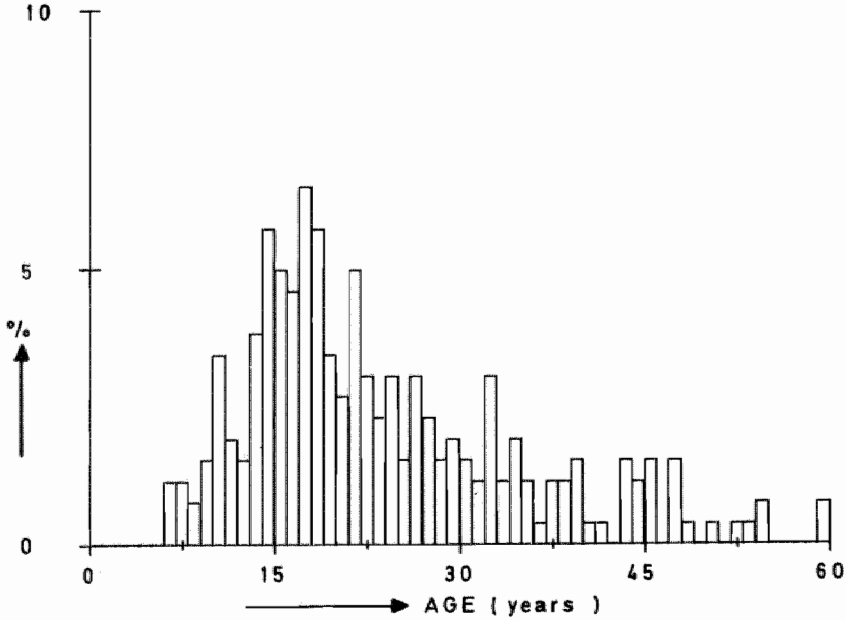


FIG. VII.2.
Age distribution in years of the 253 female patients.

mean and the confidence intervals. In the following tables only the means and significance of differences as based on the confidence intervals are given. More detailed surveys are summarized in tables of the addenda (Add. 3). The sleep composition of the total clinical group (total group: T) and for the age group 20-40 years (selected group: S) has been compared with the control group. For each comparison the most pronounced differences with respect to the first and second sleep cycle of the total night sleep are given.

## VII.2. RESULTS

### 2.1. Sleep composition of the first and the second sleep cycle in the control group

Table VII.3. shows the mean duration of the sleep in minutes during the first cycle (upper row) and of the second cycle (lower row).

TABLE VII.3.
Quantitative composition of the first and second cycle during the sleep deprivation recordings of the control group.

| CO | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|
| Cy.1 | 15 | 77.1 | 5.1 | 72.0 | 28.5 | 34.8 | 8.7 |
| Cy.2 | 14 | 84.4 | 2.8 | 81.6 | 38.8 | 30.4 | 12.4 |

The second sleep cycle lasts longer and contains more light N.REM 1-2 and REM sleep. The changed composition of the N.REM sleep is evident from the ratio N.REM 1-2/N.REM 3-4,which is 0.82 for the first cycle and 1.28 for the second cycle. Both sleep cycles are shorter than during the all-night sleep and in addition there is a different composition of the N.REM sleep. The ratio N.REM 1-2/N.REM 3-4 is 0.82 for the deprivation sleep and 1.26 for the all-night sleep. This is due to a decrease in the light N.REM 1-2 sleep by 10.7 min and an increase of the N.REM 3-4 sleep by 3.6 min.

### 2.2. Composition of the first and second sleep cycle in patients (CL group)

Patients have been divided into two categories, one with and one without epileptic EEG phenomena during the sleep recording. The sleep composition of the first and second cycle for the total group and for the selective age group of each category is summarized in Tables VII.4. and VII.5.

Both clinical groups have a significantly longer sleep cycle ($p < 0.01$), due to more N.REM sleep. In the category without epileptic EEG phenomena the significant increase in N.REM 3-4 sleep ($p < 0.05$) is observed and in the category with epileptic EEG phenomena an increase in N.REM 1-2 sleep ($p < 0.05$) and N.REM 3-4 sleep.

TABLE VII.4.
Composition of the first cycle during sleep deprivation recordings of patients without (N.E.) and with (E.) epileptic EEG phenomena, for the total group (T) and for the selective group (S).

| Cy.1 n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|
| CO 15 | 77.1 | 5.1 | 72.0 | 28.5 | 34.8 | 8.7 |
| N.E.(T) 226 | 93.6*** | 4.9 | 88.7*** | 33.2 | 46.2* | 9.3 |
| N.E.(S) 104 | 95.5 | 4.7 | 90.8 | 37.6 | 41.9 | 11.3 |
| E.(T) 322 | 93.6*** | 4.5 | 89.1*** | 36.5* | 43.8 | 8.8 |
| E.(S) 128 | 94.4 | 5.4 | 89.0 | 38.0 | 40.7 | 10.3 |

* $p < 0.05$; *** $p < 0.01$

The duration of the first cycle of both clinical groups is about 10 min shorter than that found in all-night recordings. Likewise there are differences in the ratio N.REM 1-2/N.REM 3-4 sleep. In the group without epileptic EEG phenomena this ratio is 0.72 versus 1.73 following an all-night sleep recording and in the group with epileptic EEG phenomena 0.82 versus 1.23.

TABLE VII.5.
Composition of the second cycle during sleep deprivation recordings of patients without (N.E.) and with (E.) epileptic EEG phenomena (T = total group; S = selective group).

| Cy.2 n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|
| CO 14 | 84.4 | 2.8 | 81.6 | 38.8 | 30.4 | 12.4 |
| N.E.(T) 202 | 84.7 | 5.5* | 79.2 | 36.2 | 32.2 | 10.8 |
| N.E.(S) 93 | 86.3 | 5.3 | 81.0 | 37.3 | 31.3 | 12.4 |
| E.(T) 277 | 85.5 | 5.4* | 80.1 | 36.1 | 34.0 | 10.0 |
| E.(S) 110 | 86.8 | 6.3 | 80.5 | 35.9 | 34.2 | 10.4 |

* $p < 0.05$

The composition of the second sleep cycle in both clinical groups (Table VII.5.) is hardly different from that of the control group, except for somewhat longer periods of wakefulness. As compared to

the second cycle of the all-night recording, the total sleep cycle duration is shorter (18 and 17 min), due to less N.REM 1-2 sleep (13 and 16 min) and REM sleep (8 and 6 min). This difference is also expressed in the ratio N.REM 1-2/N.REM 3-4 sleep which for the group without epileptic phenomena is 1.12 following the sleep deprivation versus 1.76 following an all-night sleep recording and for the group with epileptic phenomena 1.06 versus 1.82.

### 2.3. Composition of the first and second sleep cycle in patients without epileptic EEG phenomena, dependent on whether they take or do not take antiepileptics

The question posed here is whether the sleep deprivation effect depends on the intake of antiepileptics. Of the 226 patients without epileptic EEG phenomena in their recordings, 99 did not take medicines, 112 took only antiepileptics, 13 took antiepileptics and different medicines for psychic or somatic diseases and only 2 in combination with benzodiazepine derivatives. The sleep composition of the category which do not take medicines and the group which take only antiepileptics is represented in Table VII.6. and VII.7.

TABLE VII.6.
Composition of the first cycle during sleep deprivation recordings of patients, without epileptic EEG phenomena (N.E.) and without (-A.E.) or with (+A.E.) antiepileptic drug treatment (T = total group; S = selective group).

| Cy.1 | n | Total cycle | Time awake | Effective sleep time | N.REM1-2 | N.REM3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 15 | 77.1 | 5.1 | 72.0 | 28.5 | 34.8 | 8.7 |
| N.E.-A.E.(T) | 99 | 90.7** | 5.2 | 85.5* | 31.3 | 45.2 | 9.0 |
| N.E.-A.E.(S) | 48 | 94.7 | 5.2 | 89.5 | 34.5 | 42.7 | 12.3 |
| N.E.+A.E.(T) | 112 | 94.8*** | 3.8 | 91.0*** | 33.3 | 48.1* | 9.6 |
| N.E.+A.E.(S) | 49 | 97.2 | 4.0 | 93.2 | 39.6 | 42.9 | 10.7 |

* $p < 0.05$; ** $p < 0.025$; *** $p < 0.01$

The same differences as observed for the total group (Table VII.4.) are found here for both categories, mainly an increase in deep N.REM 3-4 sleep ($p < 0.05$). This effect is also expressed in the ratio N.REM 1-2/N.REM 3-4 sleep which for both groups is 0.69 versus 0.82 for the control group. Patients between the age of 20 and 40 years have a smaller increase in N.REM 3-4 sleep but this is compensated by a slight increase in N.REM 1-2 sleep.

Both patient categories become less awake as compared to the all-night sleep recordings. In addition the group which do not take medicines have an important shortening of the cycle duration (-25.2 min).

TABLE VII.7.
Composition of the second cycle during sleep deprivation recordings of patients without epileptic EEG phenomena (N.E.) and without (-A.E.) or with (+A.E.) antiepileptic drug treatment (T = total group; S = selective group).

| Cy.2 n | Total cycle | Time awake | Effective sleep time | N.REM1-2 | N.REM3-4 | REM |
|---|---|---|---|---|---|---|
| CO 14 | 84.4 | 2.8 | 81.6 | 38.8 | 30.4 | 12.4 |
| N.E.-A.E.(T) 99 | 82.1 | 5.1 | 77.0 | 35.9 | 30.3 | 10.8 |
| N.E.-A.E.(S) 44 | 80.9 | 5.4 | 75.5 | 35.5 | 26.3 | 13.7 |
| N.E.+A.E.(T) 101 | 86.4 | 5.8* | 80.6 | 36.6 | 33.0 | 11.0 |
| N.E.+A.E.(S) 43 | 91.0 | 5.4 | 85.6 | 39.3 | 35.3 | 11.0 |

* $p < 0.05$

Except for more wakefulness ($p < 0.05$) the sleep composition of the second sleep cycle in both patient groups is comparable to that of the control group. The category without epileptic EEG phenomena and which do not take antiepileptics differs from the all-night sleep recordings as follows: they have a shorter sleep cycle (-24.5 min), there is less REM sleep (-9.1 min), there are less awakening (-5.5 min), the ratio N.REM 1-2/N.REM 3-4 sleep is 1.18 following a sleep deprivation versus 1.68 following an all-night sleep recording. Though the differences remain they are smaller for the group which take antiepileptics: they have a shorter sleep cycle (-12.2 min), less REM sleep (-7.6 min) and the ratio N.REM 1-2/N.REM 3-4 sleep following a sleep deprivation recording is 1.11 versus 1.43 following an all-night sleep recording.

### 2.4. Sleep composition following sleep deprivation in patients having epileptic EEG phenomena and which take antiepileptics in combination with or without benzodiazepine derivatives

Benzodiazepine derivatives often give rise to an increase in N.REM 1-2 sleep. It was therefore of interest to trace whether such an effect is still present in patients treated with antiepileptics and benzodiazepine derivatives following sleep deprivation.

Of the 322 patients in which epileptic EEG phenomena were found during the sleep, 221 took only antiepileptics, 37 took antiepileptics in combination with benzodiazepine derivatives, 16 took anti-

epileptics and other medicines and 48 only took other medicines. The sleep composition of patients taking only antiepileptics or antiepileptics in combination with benzodiazepine derivatives are represented in VII.8. and VII.9.

TABLE VII.8.
Composition of the first sleep deprivation cycle in patients with epileptic EEG phenomena (E.) treated with antiepileptic drugs, in combination with (+A.E.-B.D.) or without (+A.E.+B.D.) benzodiazepine derivatives (T = total group; S = selective group).

| Cy.l | n | Total cycle | Time awake | Effective sleep time | N.REM1-2 | N.REM3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 15 | 77.1 | 5.1 | 72.0 | 28.5 | 34.8 | 8.7 |
| E.+A.E.-B.D. (T) | 221 | 92.2*** | 5.0 | 87.2** | 33.7** | 44.3 | 9.2 |
| E.+A.E.-B.D. (S) | 94 | 92.7 | 5.4 | 87.3 | 33.4 | 43.1 | 10.8 |
| E.+A.E.+B.D. (T) | 37 | 104.9*** | 2.1* | 102.8** | 46.0** | 50.1 | 6.7 |
| E.+A.E.+B.D. (S) | 11 | 108.6 | 3.5 | 105.1 | 65.1 | 34.8 | 5.2 |

* $p < 0.05$; ** $p < 0.025$; ***$p < 0.01$

Both clinical categories have a significantly longer sleep cycle ($p < 0.01$) and more effective sleep ($p < 0.025$), which is based on an increase in N.REM 1-2 sleep ($p < 0.025$) and N.REM 3-4 sleep. In the group treated with benzodiazepine derivatives this increase is somewhat larger, but there is however a decreased REM sleep.

As compared to the all-night sleep recording patients which only take antiepileptics have a shorter sleep cycle (-15.6 min) and less N.REM 1-2 sleep (-12.1 min). This difference does not exist in patients of the age group 20-40 years, treated with antiepileptics in combination with benzodiazepine derivatives.

Except for a higher amount of wakefulness ($p < 0.05$), the differences in the sleep composition of patients only treated with antiepileptics as compared to the control group as well as to the patients treated with benzodiazepine derivatives, are negligible (Table VII.9). Both clinical categories have a shorter second sleep cycle (-15 min) as compared to the all-night sleep recordings, due to less N.REM 1-2 sleep. As shown in Table VII.9 ,

2.5. Composition of the first and second sleep cycle following sleep deprivation, in the presence of epileptic EEG phenomena and the intake of antiepileptics, depending on the type of epilepsy

The question here is whether the sleep deprivation effects depend on the type of the epileptic EEG abnormalities recorded during

TABLE VII.9.
Composition of the second sleep deprivation cycle in recordings with epileptic EEG phenomena (E.) with antiepileptic drug treatment, in combination with (+A.E.+B.D.) or without (+A.E.-B.D.) benzodiazepine derivatives (T = total group; S = selective group).

| Cy.2 | n | Total cycle | Time awake | Effective sleep time | N.REM1-2 | N.REM3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 14 | 84.4 | 2.8 | 81.6 | 38.8 | 30.4 | 12.4 |
| E.+A.E.-B.D. (T) | 195 | 86.2 | 5.6* | 80.6 | 36.5 | 34.3 | 9.8 |
| E.+A.E.-B.D. (S) | 83 | 87.6 | 7.0 | 80.6 | 35.9 | 34.2 | 10.5 |
| E.+A.E.+B.D. (T) | 29 | 77.8 | 2.6 | 75.2 | 30.0 | 34.8 | 10.4 |
| E.+A.E.+B.D. (S) | 8 | 79.0 | 5.2 | 73.8 | 34.1 | 30.9 | 8.8 |

* $p < 0.05$

the sleep. A difference was made between recordings containing EEG abnormalities fitting with generalized, partial or both forms of epilepsy. The sleep composition for the first and second sleep cycle for the different categories is represented in Tables VII.10. and VII.11.

TABLE VII.10.
Composition of the first sleep deprivation cycle in recordings with epileptic EEG paroxysms belonging to generalized, partial or generalized with partial epilepsy (T = total group; S = selective group).

| Cy.1 | n | Total cycle | Time awake | Effective sleep time | N.REM1-2 | N.REM3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 15 | 77.1 | 5.1 | 72.0 | 28.5 | 34.8 | 8.7 |
| Gen.+A.E. -B.D.(T) | 98 | 94.4** | 5.5 | 88.9** | 34.2 | 45.8 | 8.9 |
| Gen.+A.E. -B.D.(S) | 33 | 96.9 | 9.2 | 87.7 | 39.8 | 37.7 | 10.2 |
| Part.+A.E. -B.D.(T) | 74 | 92.1** | 4.6 | 87.5** | 31.6 | 45.5 | 10.4 |
| Part.+A.E. -B.D.(S) | 37 | 92.5 | 4.3 | 88.2 | 29.7 | 46.5 | 12.0 |
| Gen.+Part.+A.E. +B.D.(T) | 49 | 87.8 | 4.3 | 83.5 | 36.2 | 39.5 | 7.8 |
| Gen.+Part.+A.E. -B.D.(S) | 24 | 87.5 | 2.2 | 85.3 | 30.0 | 45.3 | 10.0 |

** $p < 0.025$

All 3 clinical categories have a longer sleep cycle and more effective sleep. This is largest for patients having one form of epilepsy ($p < 0.025$) and is based mainly on more N.REM 3-4 sleep. In patients which have both types of epilepsy, the prolongation of the sleep cycle is less pronounced. This is for the total group mainly based on an increase in light N.REM 1-2 sleep and for the age group between 20-40 years due to an increase in deep N.REM 3-4 sleep. This difference is also evident from the ratio N.REM 1-2/N.REM 3-4 sleep, which is 0.82 for the control group and for patients with a generalized, partial or both types of epilepsy is respectively 0.74, 0.69 and 0.91. For the 3 clinical categories the sleep following sleep deprivation differs from the all-night sleep in that the sleep cycle is shorter (-10 to 25 min), which for patients having one type of epilepsy is mainly due to less N.REM 1-2 sleep and for patients having two types of epilepsy due to a decrease in N.REM 1-2 as well as N.REM 3-4 sleep.

TABLE VII.11.
Composition of the second sleep deprivation cycle in recordings with epileptic EEG paroxysms belonging to generalized, partial or generalized with partial epilepsy (T = total group; S = selective group).

| Cy.2 | n | Total cycle | Time awake | Effective sleep time | N.REM1-2 | N.REM3-4 | REM |
|---|---|---|---|---|---|---|---|
| CO | 14 | 84.4 | 2.8 | 81.6 | 38.8 | 30.4 | 12.4 |
| Gen.+A.E. -B.D.(T) | 86 | 86.3 | 5.0 | 81.3 | 36.7 | 34.1 | 10.5 |
| Gen.+A.E. -B.D.(S) | 26 | 84.6 | 7.1 | 77.5 | 34.2 | 32.4 | 10.9 |
| Part.+A.E. -B.D.(T) | 64 | 82.9 | 5.3 | 77.6 | 34.4 | 33.9 | 9.3 |
| Part.+A.E. -B.D.(S) | 33 | 85.3 | 6.5 | 78.8 | 35.8 | 34.0 | 9.0 |
| Gen.+Part.+A.E. -B.D.(T) | 45 | 90.5 | 7.1 | 83.4 | 39.0 | 35.0 | 9.4 |
| Gen.+Part.+A.E. -B.D.(S) | 24 | 93.9 | 7.4 | 86.5 | 38.0 | 36.3 | 12.2 |

All 3 clinical groups tend to be more awake (Table VII.11.). The duration of the sleep cycle is shorter as compared to an all-night sleep recording and this decline is largest for the group which has generalized epilepsy (-24 min), caused by a decreased N.REM 1-2 and REM sleep.

## 2.6. Composition of the first and second sleep cycle in the clinical categories for the age group 20-40 years

The question studied here is whether the sleep composition of patients in the age group 20-40 years differs from the sleep composition in the total groups. The results are represented in Tables VII.12. and VII.13. Group 1 represents the control group. The different categories of patients are subdivided into 3 main groups: group 2: patients without epileptic EEG abnormalities during the sleep (categories 2 and 3); group 3: patients with epileptic EEG abnormalities and which are treated with antiepileptics (categories 4, 5 and 6); group 4: the same as the last group but treated with antiepileptics and benzodiazepine derivatives.

As compared to the control group the 3 clinical groups have a longer sleep cycle, more effective sleep and more light N.REM 1-2 sleep. The category of patients treated with antiepileptics and benzodiazepine derivatives have more light N.REM 1-2 sleep as compared to the control group and to other clinical groups. The groups cannot be differentiated statistically from each other otherwise, probably because of the relative small differences between the group and the large interindividual variability.

Though the clinical groups tend to spend more time awake, the differences in composition of the second sleep cycle are too small to differentiate these statistically from the control group (Table VII.13.).

Comparison of the sleep pattern of the first sleep deprivation cycle: control group versus the different clinical groups of patients between 20 and 40 years old.

| Gr. | Ct. | Cy. 1 | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | CO | 15 | 77.1 | 5.1 | 72.0 | 28.5 | 34.8 | 8.7 |
| 2 | 2 | N.E.-A.E. | 48 | 94.7 | 5.2 | 89.5 | 34.5 | 42.7 | 12.3 |
| | 3 | N.E.+A.E. | 49 | 97.2 | 4.0 | 93.2 | 39.6 | 42.9 | 10.7 |
| 3 | 4 | Gen.E.+A.E. -B.D. | 33 | 96.9 | 9.2 | 87.7 | 39.8 | 37.7 | 10.2 |
| | 5 | Part.E.+A.E. -B.D. | 37 | 92.5 | 4.3 | 88.2 | 29.7 | 46.5 | 12.0 |
| | 6 | Gen.+Part.E. +A.E.-B.D. | 24 | 87.5 | 2.2 | 85.3 | 30.0 | 45.3 | 10.0 |
| 4 | 7 | E.+A.E. +B.D. | 11 | 108.6 | 3.5 | 105.1 | 65.1 | 34.8 | 5.2 |

TABLE VII.13.
Comparison of the sleep pattern of the second sleep deprivation cycle: control group versus the different clinical groups in patients between 20 and 40 years old.

| Gr. | Ct. | Cy. 2 | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | CO | 14 | 84.4 | 2.8 | 81.6 | 38.8 | 30.4 | 12.4 |
| 2 | 2 | N.E.-A.E. | 44 | 80.9 | 5.4 | 75.5 | 35.5 | 26.3 | 13.7 |
| | 3 | N.E.+A.E. | 44 | 91.0 | 5.4 | 85.6 | 39.3 | 35.3 | 11.0 |
| 3 | 4 | Gen.E.+A.E. -B.D. | 26 | 84.6 | 7.1 | 77.5 | 34.2 | 32.4 | 10.9 |
| | 5 | Part.E.+A.E. -B.D. | 33 | 85.3 | 6.5 | 78.8 | 35.8 | 34.0 | 9.0 |
| | 6 | Gen.+Part.E. +A.E.-B.D. | 24 | 93.9 | 7.4 | 86.5 | 38.0 | 36.3 | 12.2 |
| 4 | 7 | E.+A.E. +B.D. | 8 | 79.0 | 5.2 | 73.8 | 34.1 | 30.9 | 8.8 |

2.7. Differences in sleep composition of the first and second sleep cycle between patients belonging to the age groups 5-20 years versus 20-40 years.

Since in our patient material 251 subjects were younger than 20 years and 232 between the age of 20 and 40 years, these groups were large enough to compare the different clinical categories with each other. The mean values for both age groups are represented next to each other in the Tables VII.14. and VII.15.

There are no important differences in the total duration of the first sleep cycle between both age groups (Table VII.14.). Patients younger than 20 years tend to become less awake, but this difference is small. Most patients younger than 20 years have less light N.REM 1-2 sleep and more deep N.REM 3-4 sleep. The difference in N.REM 1-2 sleep is significant for patients treated with antiepileptics and benzodiazepine derivatives ($p < .005$) and for patients which have no epileptic EEG abnormalities in their sleep recording and which take antiepileptics ($p < 0.01$) and is less for patients having generalized epilepsy.

Below the age of 20 years there is significantly more N.REM 3-4 sleep for patients which do not have epileptic EEG abnormalities and which take antiepileptics ($p < 0.01$), and for those which have EEG abnormalities fitting with generalized epilepsy ($p < 0.01$). Except for those which take antiepileptics in combination with benzodiazepine derivatives, all patient categories of the age group below 20 years have a shorter REM sleep.

There are no substantial differences in the sleep composition of the second sleep cycle of both age groups (Table VII.15.). Just as for the first sleep cycle, patients below the age of 20 years tend to become less awake, except for subjects which do not have epileptic EEG abnormalities and which take antiepileptics.

TABLE VII.14.
Comparison of the first sleep deprivation cycle: control group versus the different clinical groups depending on the age (5-20 versus 20-40 years).

| Cy.1 | n | | Total cycle | | Time awake | | Effective sleep time | | N.REM 1-2 | | N.REM 3-4 | | REM | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | <20 | 20-40 | <20 | 20-40 | <20 | 20-40 | <20 | 20-40 | <20 | 20-40 | <20 | 20-40 | <20 | 20-40 |
| N.E.-A.E. | 46 | 48 | 88.9 | 94.7 | 4.6 | 5.2 | 84.3 | 89.5 | 28.6 | 34.5 | 49.7 | 42.7 | 6.0 | 12.3 |
| N.E.+A.E. | 48 | 49 | 92.4 | 97.2 | 1.8 | 4.0 | 90.6 | 93.2 | 26.3 | 39.6 *** | 55.8 | 42.9 ** | 8.5 | 10.7 |
| Gen.+A.E. | 55 | 33 | 94.0 | 96.9 | 3.8 | 9.2 | 90.2 | 87.7 | 29.6 | 39.8 | 52.1 | 37.7 ** | 8.5 | 10.2 |
| Part.+A.E | 27 | 37 | 87.2 | 92.5 | 3.5 | 4.3 | 83.7 | 88.2 | 24.2 | 29.7 | 50.7 | 46.5 | 8.8 | 12.0 |
| Gen.+Part.+A.E. | 21 | 24 | 83.8 | 87.5 | 4.8 | 2.2 | 79.0 | 85.3 | 36.5 | 30.0 | 37.3 | 45.3 | 5.2 | 10.0 |
| E.+A.E.+B.D. | 19 | 11 | 98.4 | 108.6 | 0.4 | 3.5 | 98.0 | 105.1 | 31.8 | 65.1 **** | 57.7 | 34.8 | 8.5 | 5.2 |

** $p < 0.025$; *** $p < 0.01$; **** $p < 0.005$

TABLE VII.15.
Comparison of the second sleep deprivation cycle: control group versus the different clinical groups depending on the age (5-20 versus 20-40 years).

| Cy.2 | n | | Total cycle | | Time awake | | Effective sleep time | | N.REM 1-2 | | N.REM 3-4 | | REM | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | <20 | 20-40 | <20 | 20-40 | <20 | 20-40 | <20 | 20-40 | <20 | 20-40 | <20 | 20-40 | <20 | 20-40 |
| N.E.-A.E. | 47 | 44 | 82.6 | 80.9 | 4.6 | 5.4 | 78.0 | 75.5 | 36.6 | 35.5 | 33.2 | 26.3 | 8.2* | 3.7 |
| N.E.+A.E. | 47 | 43 | 84.1 | 91.0 | 6.4 | 5.4 | 77.7 | 85.6 | 34.1 | 39.3 | 32.3 | 35.3 | 11.3 | 11.0 |
| Gen.+A.E. | 50 | 26 | 85.8 | 84.6 | 3.8 | 7.1 | 82.0 | 77.5 | 36.1 | 34.2 | 35.1 | 32.4 | 10.8 | 10.9 |
| Part.+A.E. | 25 | 33 | 78.8 | 85.3 | 3.7 | 6.5 | 75.1 | 78.8 | 31.8 | 35.8 | 35.4 | 34.0 | 7.9 | 9.0 |
| Gen.+Part. +A.E. | 18 | 24 | 87.0 | 93.9 | 4.1 | 7.4 | 82.9 | 86.5 | 39.4 | 38.0 | 36.6 | 36.3 | 6.9 | 12.2 |
| E.+A.E.+B.D. | 17 | 8 | 77.6 | 79.0 | 1.4 | 5.2 | 76.2 | 73.8 | 27.9 | 34.1 | 36.7 | 30.9 | 11.6 | 8.8 |

* $p < 0.05$

The amount of light N.REM 1-2 sleep and deep N.REM 3-4 sleep is comparable for both age groups except for subjects between 20 and 40 years which do not have epileptic EEG phenomena and which do not take antiepileptics, which have less deep N.REM 3-4 sleep. The ratio N.REM 1-2/N.REM 3-4 is about 1 in the other clinical groups. REM sleep of subjects younger than 20 years which do not have epileptic EEG abnormalities and which do not take antiepileptics is significantly ($p < 0.05$) higher than for the patients of the age group 20-40 years.

### 2.8. Composition of the first sleep deprivation cycle in subjects below the age of 25 years in periods of 5 years

The sleep composition of patients younger than 25 years was studied, in order to find out to which degree the sleep deprivation effect is age-dependent. The results are represented in Tables VII.16. (no antiepileptics), VII.17. (only antiepileptics) and VII.18. (antiepileptics and benzodiazepines)

There are no large differences in the composition of the first sleep cycle for the different age groups (Table VII.16.). The deprivation effect consisting of a preponderant deep N.REM 3-4 sleep is most pronounced for subjects younger than 20 years. The ratio N.REM 1-2/N.REM 3-4 sleep of the age group 20-24 years is comparable to the ratio of the control group between the age of 20-40 years (0.77 versus 0.82).

The youngest (5-9 years) and the oldest group (20-24 years) have respectively the shortest and the longest sleep cycle (Table VII.17.). The deprivation effect is least pronounced for the youngest groups which also shows less deep N.REM 3-4 sleep. For the other groups the deprivation effect is increased or comparable to the effect in patients which do not take antiepileptics.

For all age groups there is an increased total cycle length and a decrease in wakefulness, which is to be expected when benzodiazepine derivatives are taken (Table VII.18.). This also gives rise to an increase in N.REM 1-2 sleep, this is only seen here in patients older than 20 years.

For the age groups below 20 years, there is no increase in light N.REM 1-2 sleep but an increase in deep N.REM 3-4 sleep (deprivation effect), which for all groups is larger than in patients which do not take or only take antiepileptics. The deprivation effect is sustained for the patient group between 20-24 years, but complemented by benzodiazepine effects since an increase in N.REM 1-2 sleep is observed.

TABLE VII.16.
Composition of the first sleep deprivation cycle in patients of different age group, without antiepileptic drug treatment (-A.E., n = 100).

| Age n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM 1-2 / N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| 5- 9 12 | 92.1 | 4.7 | 87.4 | 34.3 | 50.2 | 2.9 | 0.68 |
| 10-14 24 | 92.1 | 2.5 | 89.6 | 32.2 | 49.8 | 7.6 | 0.64 |
| 15-19 32 | 91.3 | 4.7 | 86.6 | 30.9 | 50.2 | 5.5 | 0.61 |
| 20-24 22 | 94.9 | 5.2 | 89.7 | 35.8 | 46.2 | 7.7 | 0.77 |

TABLE VII.17.
Composition of the first sleep deprivation cycle in patients of different age only treated with antiepileptic drugs (+A.E., n = 195).

| Age n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM 1-2 / N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| 5- 9 20 | 77.5 | 0.5 | 77.0 | 33.8 | 35.3 | 7.8 | 0.95 |
| 10-14 55 | 93.3 | 4.4 | 88.9 | 31.9 | 49.2 | 7.8 | 0.64 |
| 15-19 71 | 93.6 | 3.8 | 89.8 | 27.5 | 54.2 | 8.1 | 0.50 |
| 20-24 49 | 100.0 | 6.6 | 93.4 | 32.0 | 51.1 | 10.3 | 0.62 |

TABLE VII.18.
Composition of the first sleep deprivation cycle in patients of different age, treated with antiepileptic drugs in combination with benzodiazepine derivatives (+A.E.+B.D., n = 24).

| Age | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM 1-2 / N.REM 3-4 |
|---|---|---|---|---|---|---|---|---|
| 5- 9 | 6 | 99.0 | 0.0 | 99.0 | 32.8 | 53.0 | 13.2 | 0.62 |
| 10-14 | 8 | 100.3 | 0.7 | 99.6 | 29.5 | 64.1 | 6.0 | 0.46 |
| 15-19 | 6 | 95.1 | 0.3 | 94.8 | 34.2 | 52.8 | 7.8 | 0.64 |
| 20-24 | 5 | 126.0 | 4.6 | 121.4 | 56.4 | 58.6 | 6.4 | 0.96 |

## VII.3. DISCUSSION AND SUMMARY

This chapter deals with the composition of the first and second sleep cycle following sleep deprivation of subjects which are suspected to have epilepsy. In order to find out whether the sleep structure is dependent on the presence or absence of epileptic EEG abnormalities, the intake of antiepileptics, with or without the combination with benzodiazepine derivatives, the total population group was divided into a number of categories based on these criteria.

For the investigation hypnograms of the sleep following sleep deprivation of the total of 548 subjects were used. This group consisted of 295 males and 253 females, 251 belonged to the age group 5-20 years, 232 belonged to the age group 20-40 years and 65 were older than 40 years. The influence of medication was examined by using only the hypnograms of patients which took only antiepileptics or antiepileptics in combination with benzodiazepine derivatives, with the exclusion of all other medicines.

The influence of age was checked by studying the sleep composition of the total population and for patients between 20 and 40 years as compared to the control group, which consisted of 15 healthy persons between the age of 20-40 years.

The mean values and confidence intervals of the different sleep parameters are depicted in block diagrams in a similar way as for the all-night sleep recordings. Patients with epileptic EEG abnormalities are grouped together since there was no major difference between the different types of epilepsy. The restriction here is that only patients between 20 and 40 years are considered.

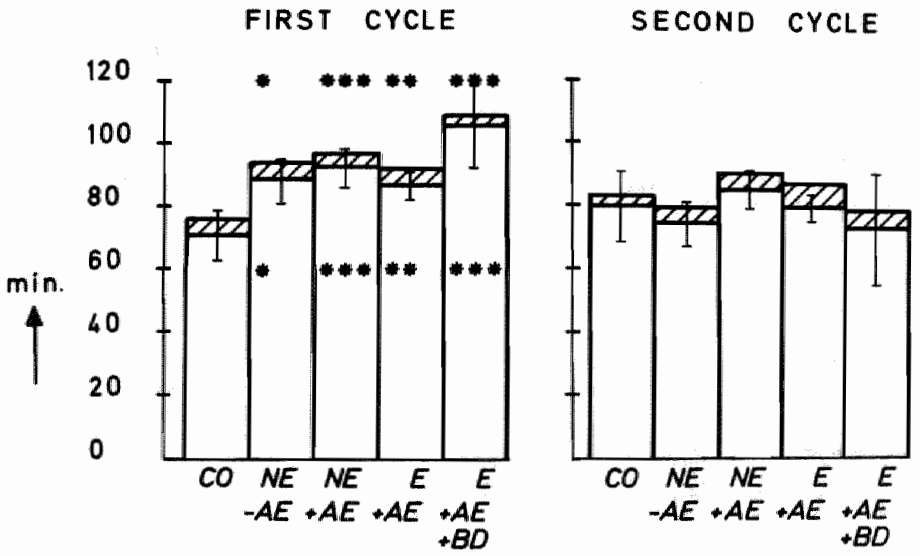


FIG. VII.19.
Mean values, in minutes, of the total sleep cycle, the time awake (▨) and the effective sleep time (□) during the first and second sleep deprivation cycle of the control and the different clinical categories (20-40 years).
* $p < 0.05$; ** $p < 0.025$; *** $p < 0.01$.

During the first sleep cycle following differences between the control group and the clinical categories exist:

1. The duration of the first sleep cycle is significantly longer for all clinical categories ($p < 0.05$ to $p < 0.01$), and is most pronounced for patients treated with the combination of antiepileptics and benzodiazepine derivatives.
2. Following deprivation there is less wakefulness as well in the control group as in the clinical group.
3. In analogy with the cycle duration, the mean effective sleep during the first sleep cycle is significantly longer in all clinical categories ($p < 0.05$ to $p < 0.01$).
4. Following sleep deprivation the control group as well as the patients have a higher percentage effective sleep, which amounts to more than 93 % during both sleep cycles (Fig. VII.20.).

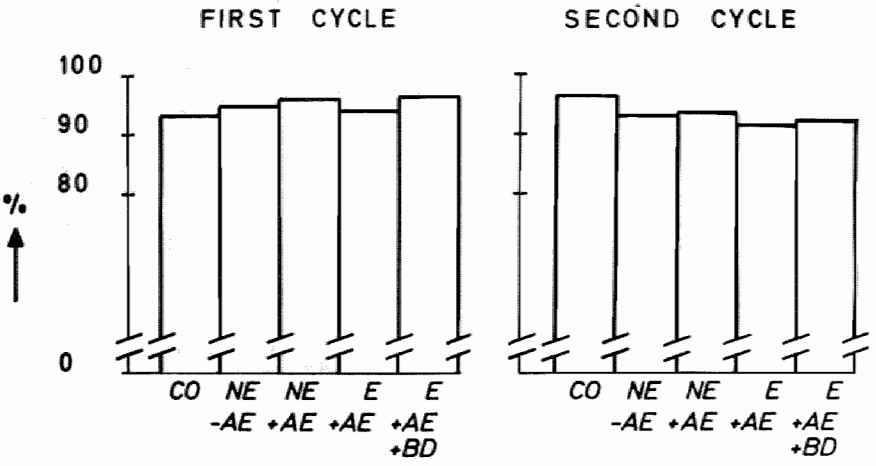


FIG. VII.20.
Percentage of effective sleep time in the control and the different clinical categories during the first and second sleep deprivation cycle.

Since effective sleep consists of N.REM and REM sleep, the ratio between both is depicted in Fig. VII.21.

5. There are few differences in the amount of REM sleep between the control and clinical groups and between the first and second sleep cycle, except for patients treated with the combination of antiepileptics and benzodiazepine derivatives, during the first cycle which tend to have less REM sleep.
6. The increase in cycle duration and effective sleep seen in patients during the first sleep cycle is based on a significant ($p < 0.05$ to $p < 0.005$) increase in N.REM sleep, which is most pronounced for patients treated with the combination therapy. In order to know which part of the sleep increased most, the mean duration of N.REM 1-2 sleep and N.REM 3-4 sleep is depicted in Fig. VII.22.

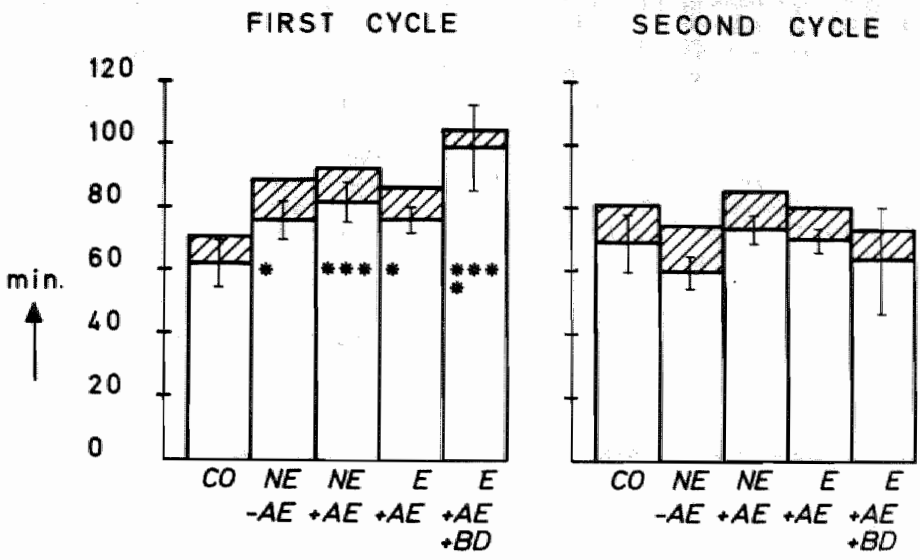


FIG. VII.21.
Mean values, in minutes, of the REM (▨) and the N.REM (□) sleep during the first and second sleep deprivation cycle of the control and the different clinical categories.
* $p < 0.05$; *** $p < 0.01$; **** $p < 0.005$.

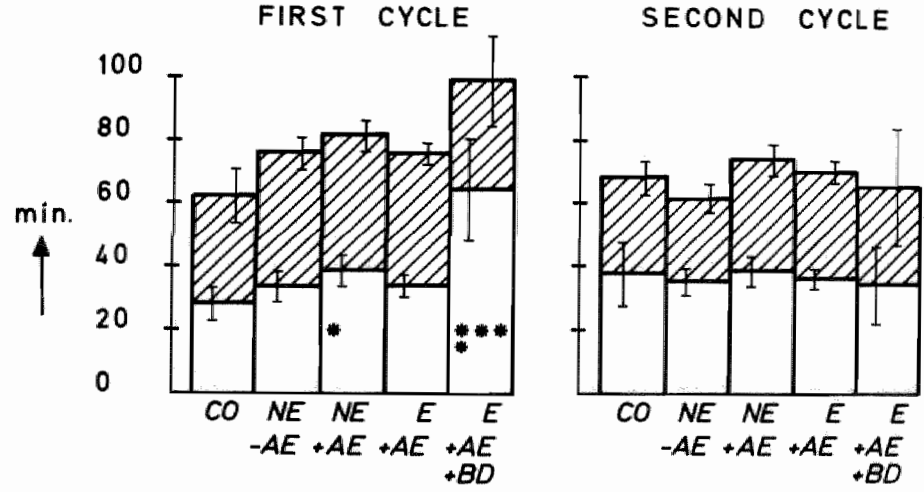


FIG. VII.22.
Mean values, in minutes, of the N.REM 1-2 (□) and the N.REM 3-4 (▨) sleep during the first and second sleep deprivation cycle of the control and the different clinical categories (20-40 years).
* $p < 0.05$; **** $p < 0.005$.

7. Patients have more N.REM 1-2 sleep during the first sleep cycle. This difference is most pronounced for patients treated with the combination of antiepileptics and benzodiazepine derivatives ($p < 0.005$) and for patients without epileptic EEG abnormalities but which take antiepileptics ($p < 0.05$). These differences are not found during the second sleep cycle.
8. In all subjects there is more deep N.REM 3-4 sleep during the first cycle than during the second sleep cycle, but this increase is not significant statistically. The duration of the N.REM 3-4 sleep is longer for both cycles as compared to an all-night sleep recording (Fig. VI.19.).
9. Since the sleep cycles are shorter following sleep deprivation than during an all-night sleep recording, an increase in deep N.REM 3-4 sleep has to result in a changed ratio N.REM 1-2/N.REM 3-4 sleep. The ratios for both sleep recording methods are depicted in Fig. VII.23.

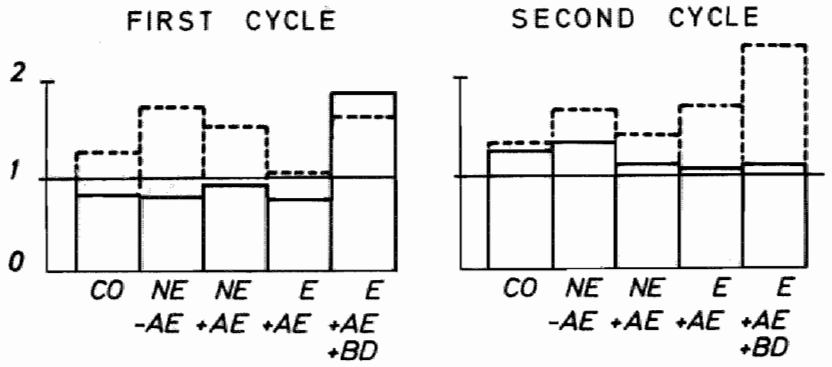


FIG. VII.23.
The N.REM 1-2/N.REM 3-4 ratio during the first and second sleep deprivation (_____) and all-night (-----) cycles of the control and the different clinical categories.

The ratio in all categories is smaller than 1 during the first sleep cycle and smaller than during the all-night sleep, except for the category treated with the combination of antiepileptics and benzodiazepine derivatives. This is due to an increase in light as well as deep N.REM sleep, but mostly to an increase in N.REM 1-2 sleep. During the second sleep cycle the ratios are between 1.05 and 1.35 and are smaller for all categories than during the all-night sleep.

With the findings described above the questions posed at the beginning of this chapter can be answered as follows.

1. What is the composition of the first and second sleep cycle following sleep deprivation in epileptics?
   There is a shortening of the cycle length. The sleep is less interrupted by awakening, whereby an effective sleep of more than 93 % is reached during both sleep cycles. This increase is mainly

based on an increase in the N.REM sleep. There is a slight preponderance of deep N.REM 3-4 sleep during the first cycle and a slight preponderance of the light N.REM 1-2 sleep during the second cycle. These cycles thus differ from the all-night sleep recordings, where a preponderance of N.REM 1-2 sleep is seen during both sleep cycles. During the first cycle this difference is very small for the categories which have epileptic EEG abnormalities and which take only antiepileptics.

2. Is the changed sleep composition dependent on the presence or absence of epileptic abnormalities?
   Both categories cannot be differentiated on the basis of this criterium, but they differ from their control groups by a significantly longer first sleep cycle, during which significantly more effective sleep occurs. These differences are not found during the second sleep cycle.
3. Is the sleep composition dependent on the type of epileptic EEG abnormalities?
   Patients which do have EEG abnormalities fitting with either generalized or partial epilepsy have relatively more deep N.REM 3-4 sleep than patients which have a combined form of epileptic EEG abnormalities. The latter group of patients have more light N.REM 1-2 sleep. This difference is also expressed in the ratio N.REM 1-2/N.REM 3-4 sleep, which is 0.69 for those having one type of epilepsy and 0.91 for those having a combined form of epilepsy. This ratio is 0.82 for the control group.
4. Is the sleep composition dependent on the intake of antiepileptics?
   Subjects taking or not taking antiepileptics differ only slightly from each other during the first as well as during the second sleep cycle. This contrasts to the large differences found following an all-night sleep recording, where patients which do not take antiepileptics have a longer sleep cycle and have more awakenings.
5. Is the sleep composition changed when benzodiazepines are taken together with antiepileptics?
   There is only a clear effect during the first sleep cycle, where a large increase in cycle length and a minimal time of wakefulness is observed. For the total age group there is a pronounced increase in light as well as deep N.REM sleep. In comparison with the control group patients belonging to the age group 20-40 years have two times as much N.REM 1-2 sleep, though the amount of deep N.REM 3-4 sleep is comparable.
6. Are the changes age-dependent?
   Patients younger than 20 years have more deep N.REM 3-4 sleep and less light N.REM 1-2 and REM sleep. In all age groups there is more deep N.REM 3-4 sleep than N.REM 1-2 sleep and this is independent of the medication. The only exception are the children below 10 years treated with antiepileptics which have as much N.REM 1-2 sleep as N.REM 3-4 sleep.
   Patients belonging to the age group 20-24 years and which do not take antiepileptics tend to have more light N.REM 1-2 and less N.REM 3-4 sleep than the age group below 20 years. The benzodiazepine effect is also clear from this age on, where a large increase in N.REM 1-2 sleep is seen in combination with the sustained large amount of deep N.REM 3-4 sleep, as if the benzodiazepine effect is added to the sleep deprivation effect.

## CHAPTER VIII: THE INFLUENCE OF ANTIEPILEPTIC MEDICATIONS ON SLEEP-WAKEFULNESS PATTERNS

This chapter is aimed at finding out whether the composition of the sleep following one night sleep deprivation depends on 1. the type of antiepileptic medication taken, 2. the type of the benzodiazepine derivatives taken.

### VIII.1. MATERIALS AND METHODS

From the patients of which an additional sleep deprivation investigation was carried out during the period 1979-1981 (n = 617), following groups of patients were selected: those treated with either sodium valproate (Sod.V.) or carbamazepine (Carb.) or diphenylhydantoin (D.P.H.) or a combination of carbamazepine with sodium valproate or of carbamazepine with diphenylhydantoin or an antiepileptic in combination either with chlorazepate (A.E. + Chlor.), or clonazepam (A.E. + Clon.).

The investigation was limited to the sleep deprivation method, since it allowed to gather a sufficiently large number of patients to carry-out a reliable analysis. Further, patients with a multiple form of epilepsy were discarded since their sleep deprivation pattern diverged from the other clinical groups.

The final group consisted of 252 patients. Their partition per category of antiepileptic medication taken, further divided into sleep recordings with or without epileptic EEG abnormalities, and the mean age of these groups are given in Table VIII.1.

TABLE VIII.1.
Number and mean age of patients treated with different types of antiepileptic drugs or benzodiazepine derivatives.

| Epileptic patients | | Sod.V. | Carb. | D.P.H. | Carb. + Sod.V. | Carb. + D.P.H. | A.E. + Chlor. | A.E. + Clon. |
|---|---|---|---|---|---|---|---|---|
| N.E. | n | 19 | 32 | 11 | 11 | 13 | 4 | 6 |
| | age | 21.2 | 27.9 | 31.5 | 18.8 | 24.5 | 18.4 | 25.2 |
| E. | n | 25 | 34 | 11 | 36 | 31 | 11 | 8 |
| | age | 17.7 | 23.2 | 23.2 | 20.9 | 31.0 | 20.9 | 23.3 |

Of the 252 patients, 123 (48.8 %) were between the age of 5 and 20 years, 113 (44.8 %) were between the age of 21 to 40 years and 16 (6.4 %) were of the age between 41 to 60 years. A nearly equal number of sleep recordings with or without epileptic EEG phenomena were found in patients taking one antiepileptic. In patients treated with two antiepileptics, a substantial higher amount of sleep recordings with epileptic EEG phenomena were found.

The different parameters analyzed are represented in Tables, significance of differences are indicated and in addition the ratio N.REM 1-2/N.REM 3-4 sleep is given, indicating the changes within the N.REM sleep.

## VIII.2. RESULTS

### 2.1. Sleep composition in patients treated with sodium valproate

Of the 44 patients studied, all had a well-formed 1st sleep cycle and in 39 also the second sleep cycle could be classified properly. The sleep composition of both sleep cycles is represented in Table VIII.2.

TABLE VIII.2.
Composition of the first and second sleep cycle after one night sleep deprivation in patients only treated with sodium valproate.

| Sod.V. n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM 1-2 / 3-4 |
|---|---|---|---|---|---|---|---|
| Cy. 1 | | | | | | | |
| N.E.:19 | 100.5 | 4.1 | 96.4 | 32.6 | 52.3 | 11.5 | 0.62 |
| E. :25 | 86.6 | 2.1 | 84.5 | 31.6 | 44.1* | 8.8 | 0.72 |
| Cy. 2 | | | | | | | |
| N.E.:16 | 93.4 | 6.3 | 87.1 | 39.6 | 34.7 | 12.8 | 1.14 |
| E. :23 | 82.4 | 8.7 | 73.7 | 33.2 | 30.0 | 10.5 | 1.10 |

* $p < 0.05$

Patients with epileptic EEG manifestations have a short sleep cycle, which is due to a decrease of all sleep stages. The difference is largest for the deep N.REM 3-4 sleep ($p < 0.05$) during the first sleep cycle, and during the second cycle less effective sleep occurs.

For both groups the sleep deprivation effect is visible in both sleep cycles, which is apparent from a small N.REM 1-2/N.REM 3-4 ratio, this in comparison with an all-night sleep recording as well as compared to a sleep deprivation recording of the control group.

### 2.2. The sleep composition in patients treated with carbamazepine

Except for a well-formed first sleep cycle, 55 of the 66 patients also have a complete second sleep cycle.

The composition of the first sleep cycle for both patient groups is nearly equal, pointing at a strong sleep deprivation effect, consisting of a preponderance of deep N.REM 3-4 sleep. Both groups have a longer lasting second sleep cycle due to more N.REM 1-2 sleep. During the second sleep cycle, the sleep deprivation effect is still

TABLE VIII.3.
Composition of the first and second sleep cycle after one night sleep deprivation in patients only treated with carbamazepine.

| Carb. n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM $\frac{1-2}{3-4}$ |
|---|---|---|---|---|---|---|---|
| Cy. 1 | | | | | | | |
| N.E.:32 | 81.9 | 2.0 | 79.9 | 24.8 | 44.5 | 10.6 | 0.56 |
| E. :34 | 78.8 | 2.9 | 75.9 | 21.4 | 43.2 | 11.3 | 0.49 |
| Cy. 2 | | | | | | | |
| N.E.:28 | 93.9 | 5.7 | 88.2 | 39.4 | 33.1 | 15.7 | 1.19 |
| E. :27 | 84.4 | 2.8 | 81.6 | 33.1 | 39.1 | 9.4 | 0.85 |

present in the group with epileptic EEG manifestations, as is apparent from the ratio N.REM 1-2/N.REM 3-4 sleep, which is 0.85 as compared to 1.28 in the control group.

2.3. The sleep composition in patients treated with diphenylhydantoin

This group consisted only of 22 patients, of which an equal number with and without epileptic EEG abnormalities in their sleep recording were found.

TABLE VIII.4.
Composition of the first and second sleep cycle after one night sleep deprivation in patients only treated with diphenylhydantoin.

| D.P.H. n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM $\frac{1-2}{3-4}$ |
|---|---|---|---|---|---|---|---|
| Cy. 1 | | | | | | | |
| N.E.:11 | 96.9 | 9.0 | 87.9 | 48.4 | 35.6 | 3.9 | 1.36 |
| E. :11 | 86.9 | 5.0 | 81.9 | 31.9 | 40.1 | 9.9 | 0.79 |
| Cy. 2 | | | | | | | |
| N.E.: 7 | 86.6 | 4.3 | 82.3 | 35.0 | 34.9 | 12.4 | 1.19 |
| E. : 7 | 90.0 | 9.4 | 80.6 | 36.4 | 34.3 | 9.9 | 1.06 |

The composition of the first sleep cycle is different in both groups, because this sleep deprivation effect is not evident in patients which have no epileptic EEG phenomena. However, also in patients which have epileptic EEG phenomena, the sleep deprivation

effect is less pronounced than in patients treated with sodium valproate or carbamazepine and is comparable to a sleep deprivation effect in non-patients.

The sleep composition during the second sleep cycle shows minor differences and is in accordance with the expectations following sleep deprivation.

### 2.4. Sleep composition in patients treated with carbamazepine and sodium valproate

A total of 47 epileptics were treated with a combination of carbamazepine and sodium valproate and in 36 of these epileptic EEG abnormalities were found in their sleep recordings, but none in 11 of them. Their sleep composition is shown in Table VIII.5.

TABLE VIII.5.
Composition of the first and second cycle of one night sleep deprivation in patients treated with carbamazepine and sodium valproate.

| Carb.+ Sod.V. n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM 1-2 / 3-4 |
|---|---|---|---|---|---|---|---|
| Cy. 1 | | | | | | | |
| N.E.:11 | 89.4 | 1.0 | 88.4 | 23.9 | 54.2 | 10.3 | 0.44 |
| E. :36 | 86.0 | 1.8 | 84.2 | 22.6 | 49.1 | 12.5 | 0.46 |
| Cy. 2 | | | | | | | |
| N.E.:11 | 83.6 | 1.0 | 82.6 | 26.7 | 41.3 | 14.6 | 0.65 |
| E. :35 | 86.7 | 3.0 | 83.7 | 30.8 | 38.2 | 14.7 | 0.80 |

For both sleep cycles there are no significant differences between the two clinical groups. There is a preponderance of deep N.REM sleep which is apparent from the ratio N.REM 1-2/N.REM 3-4 sleep: for both clinical groups this is respectively 0.44 and 0.46 during the first sleep cycle (in the control group this ratio is 0.82) and during the second sleep cycle the ratio is respectively 0.65 and 0.80 (in the control group the ratio is 1.28). This points at a strong sleep deprivation effect persisting during the second sleep cycle. In addition, the very few time spent awake is striking.

### 2.5. Sleep composition in patients treated with carbamazepine and diphenylhydantoin

In this group of 44 patients there are substantially more sleep recordings with than without epileptic EEG phenomena. As is apparent from Table VIII.6. there are some differences in the mean sleep composition.

The group with epileptic EEG abnormalities has a shorter first sleep cycle due to less deep N.REM 3-4 sleep, to a large extent neutralizing the expected sleep deprivation effect. The latter

VIII.6.
Composition of the first and second cycle after one night sleep deprivation in patients treated with carbamazepine and diphenylhydantoin.

| Carb.+ D.P.H. | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM 1-2 / 3-4 |
|---|---|---|---|---|---|---|---|---|
| Cy. 1 | | | | | | | | |
| N.E.: | 13 | 102.3 | 3.9 | 98.5 | 38.2 | 49.5 | 10.7 | 0.77 |
| E. : | 31 | 88.6 | 4.7 | 83.9 | 37.3 | 37.2 | 9.4 | 1.0 |
| Cy. 2 | | | | | | | | |
| N.E.: | 10 | 92.7 | 3.4 | 89.3 | 41.6 | 35.4 | 12.3 | 1.17 |
| E. : | 26 | 87.1 | 5.9 | 81.2 | 37.9 | 31.4 | 11.9 | 1.21 |

effect still exists for the group without epileptic EEG phenomena and is comparable to the control group.

The composition of the second sleep cycle is comparable for both groups and similar to the control group.

2.6. Composition of the first sleep deprivation cycle and its dependence of antiepileptic medication

From Tables VIII.2. to 6 it appears that the differences in composition of the sleep of the various clinical groups show the largest differences during the first sleep cycle independently of whether they have or do not have epileptic EEG abnormalities in their recordings. In order to have a better survey, the values of the different sleep parameters for all clinical groups in comparison with the control group are summarized in Tables VIII.7. and VIII.8.

The longest sleep cycle, the most effective sleep and the highest amount of deep N.REM 3-4 sleep are found in patients treated with either sodium valproate ($p < 0.01$ to $p < 0.05$) or carbamazepine in combination with diphenylhydantoin ($p < 0.05$).

A strikingly different pattern is seen in patients treated only with diphenylhydantoin since these have significantly more N.REM 1-2 sleep ($p < 0.05$).

The differences in the composition of the sleep as compared to the control group in patients which have epileptic EEG abnormalities are relatively small. There is, however, a tendency to awake less and to have more effective sleep, especially in patients taking carbamazepine in conjunction with sodium valproate. The latter drug combination also resulted in a significantly higher amount of N.REM 3-4 sleep ($p < 0.05$).

TABLE VIII.7.
Composition of the first cycle after one night sleep deprivation of sleep patterns without epileptic EEG phenomena in patients treated with one or two antiepileptic drugs.

| Cycle 1 N.E. | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM $\frac{1-2}{3-4}$ |
|---|---|---|---|---|---|---|---|---|
| CO | 15 | 77.1 | 5.1 | 72.0 | 28.5 | 34.8 | 8.7 | 0.82 |
| Sod.V. | 19 | 100.5*** | 4.1 | 96.4*** | 32.6 | 52.3* | 11.5 | 0.62 |
| Carb. | 32 | 81.9 | 2.0 | 79.9 | 24.8 | 44.5 | 10.6 | 0.56 |
| D.P.H. | 11 | 96.9 | 9.0 | 87.9 | 48.4* | 35.6 | 3.9 | 1.36 |
| Carb.+ Sod.V. | 11 | 89.4 | 1.0 | 88.4 | 23.9 | 54.2* | 10.3 | 0.44 |
| Carb.+ D.P.H. | 13 | 102.3* | 3.9 | 98.4* | 38.2 | 49.5 | 10.7 | 0.77 |

* $p < 0.05$; *** $p < 0.01$

TABLE VIII.8.
Composition of the first cycle after one night sleep deprivation of sleep patterns with epileptic EEG phenomena in patients treated with one or two antiepileptic drugs.

| Cycle 1 E. | n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM $\frac{1-2}{3-4}$ |
|---|---|---|---|---|---|---|---|---|
| CO | 15 | 77.1 | 5.1 | 72.0 | 28.5 | 34.8 | 8.7 | 0.82 |
| Sod.V. | 25 | 86.6 | 2.1 | 84.5 | 31.6 | 44.1 | 8.8 | 0.72 |
| Carb. | 34 | 78.8 | 2.9 | 75.9 | 21.4 | 43.2 | 11.3 | 0.49 |
| D.P.H. | 11 | 86.9 | 5.0 | 81.9 | 31.9 | 40.1 | 9.9 | 0.79 |
| Carb.+ Sod.V. | 36 | 86.0 | 1.8 | 84.2 | 22.6 | 49.1* | 12.5 | 0.46 |
| Carb.+ D.P.H. | 31 | 88.6 | 4.7 | 83.9 | 37.3 | 37.2 | 9.4 | 1.00 |

* $p < 0.05$

2.7. Composition of the sleep in patients treated with antiepileptics in combination with chlorazepate or clonazepam

In order to find out whether two different benzodiazepine derivatives affect sleep following sleep deprivation in a differential way, two groups of patients were studied: one group was treated with chlorazepate with a daily dose of 10-30 mg/day, the other group was treated with 1.5-4.5 mg/day of clonazepam. The sleep composition of the first and second sleep cycle of these groups is summarized in Table VIII.9.

TABLE VIII.9.
Composition of the first and second cycle after one night sleep deprivation in patients treated with antiepileptic drugs in combination with chlorazepate (Chlor.) or clonazepam (Clon.).

| Chlor. or Clon. n | Total cycle | Time awake | Effective sleep time | N.REM 1-2 | N.REM 3-4 | REM | N.REM 1-2 / 3-4 |
|---|---|---|---|---|---|---|---|
| Cy. 1 | | | | | | | |
| Chlor. 15 | 101.0 | 0.9 | 100.1 | 43.9 | 50.3 | 5.9 | 0.87 |
| Clon. 14 | 108.6 | 4.4 | 104.2 | 59.6 | 36.6 | 8.0 | 1.63 |
| Cy. 2 | | | | | | | |
| Chlor. 13 | 87.7 | 0.7 | 87.0 | 31.3 | 43.9 | 11.8 | 0.71 |
| Clon. 8 | 79.8 | 3.3 | 76.5 | 32.0 | 36.4 | 8.1 | 0.88 |

Both medication groups have a very long first sleep cycle, which is due to an increase in the N.REM sleep. The increase in deep N.REM 3-4 sleep is larger than the increase in the N.REM 1-2 sleep in patients treated with chlorazepate, from which it can be derived that the deprivation effect is more pronounced than the benzodiazepine effect. In contrast, there is a strong increase in N.REM 1-2 sleep in the patients treated with clonazepam, which points at an evident benzodiazepine effect. These effects are evident from the ratio N.REM 1-2/N.REM 3-4 sleep, which is 0.87 and 1.63 for patients treated respectively with chlorazepate and clonazepam as compared to 0.82 for the control group.

During the second cycle there is a predominant N.REM 3-4 sleep in both medication groups, suggesting that the possible lack of sleep deprivation effect during the first sleep cycle is compensated during the second sleep cycle. Finally, it is worth noting that both patient groups show few wakefulness during both sleep cycles.

## VIII.3. DISCUSSION AND SUMMARY

In chapter VII it was shown that the sleep in epileptics following one night sleep deprivation is changed, especially during the first sleep cycle. In this chapter it was studied whether the effects on the sleep are dependent on the type of antiepileptic medication taken. Therefore, the composition of the sleep following one night sleep deprivation was studied in epileptics, which took only sodium

valproate, carbamazepine or diphenylhydantoin or a combination of two of these antiepileptics, with the exclusion of other medicines.

Herein, different sleep parameters are depicted in block diagrams respectively for the patients with and without epileptic EEG abnormalities found in their sleep recordings as compared to the control group. Results obtained in patients taking either antiepileptics alone or in combination with chlorazepate or clonazepam are depicted.

Figure VIII.10. shows the mean values of the total sleep cycle, the amount of wakefulness and the amount of effective sleep obtained during the first sleep cycle for different medication groups.

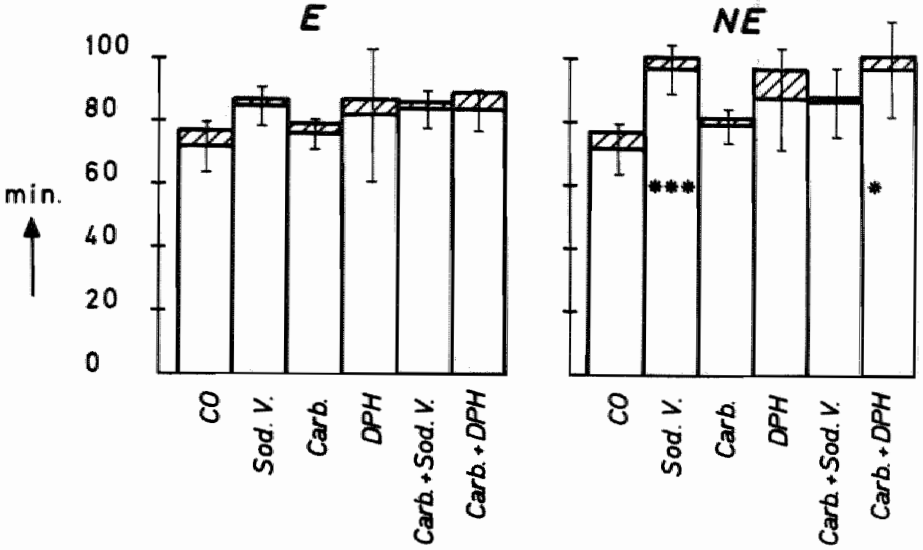


FIG. VIII.10.
Mean values, in minutes, of the total sleep time, the time awake (▨), and the effective sleep time (□) of the first sleep deprivation cycle in patients with (E.) or without (N.E.) epileptic EEG phenomena treated with one or two different antiepileptic drugs.
* $p < 0.05$; *** $p < 0.01$.

1. All patients have a longer first sleep cycle than the control group. This increase is small for patients taking only carbamazepine, but is important for those taking sodium valproate or diphenylhydantoin or drug combinations, and more so for patients which do not have epileptic EEG abnormalities.
2. There is a higher amount of wakefulness only in patients which do not have epileptic EEG phenomena and which take diphenylhydantoin.
3. All patients have more effective sleep, but this is only significant ($p < 0.01$) for patients which do not have epileptic EEG abnormalities and which are treated with sodium valproate.
4. The percentage effective sleep is higher than the 93 % of the control group, except for patients which do not have epileptic EEG phenomena and which are treated with diphenylhydantoin. This result is summarized in Fig. VIII.11.

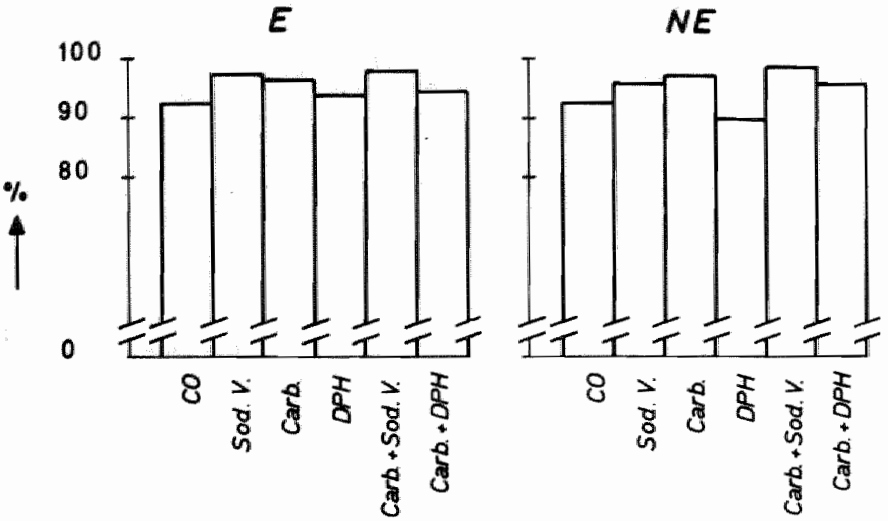


FIG. VIII.11.
Percentage of the effective sleep time in the first sleep deprivation cycle of patients with (E.) or without (N.E.) epileptic EEG paroxysms treated with different antiepileptic drugs.

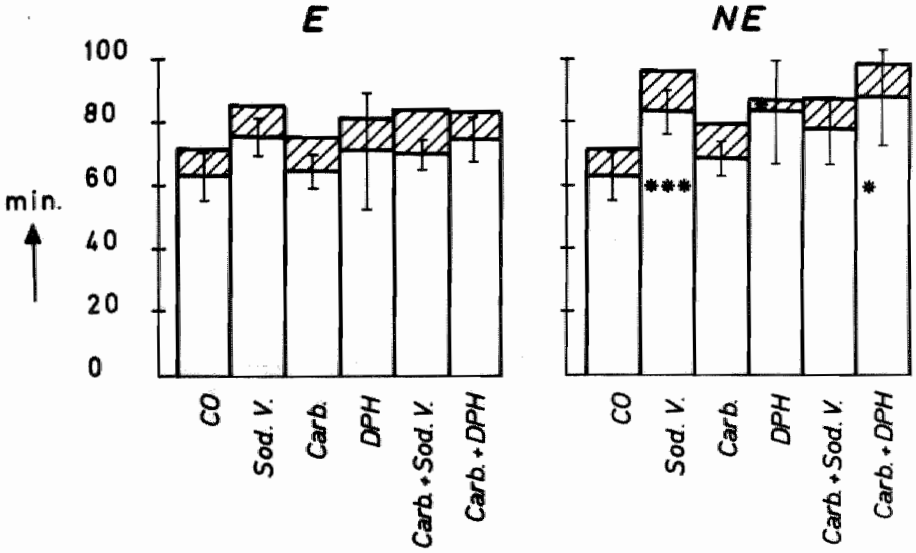


FIG. VIII.12.
Mean values, in minutes, of the REM (▨) and the N.REM (□) sleep during the first sleep deprivation cycle of patients treated with different types of antiepileptic drugs.
* $p < 0.05$; *** $p < 0.01$.

5. From Figure VIII.12. it appears that the REM sleep in all medication groups is approximately similar as in the control group, but is less for patients which do not have epileptic EEG phenomena and which are treated with diphenylhydantoin.
6. The N.REM sleep tends to be higher in all patient categories but is very small for the patients only treated with carbamazepine. This increase is largest for patients which do not have epileptic EEG phenomena.
   The two types of N.REM sleep: N.REM 1-2 and N.REM 3-4 sleep are depicted in Figure VIII.13.

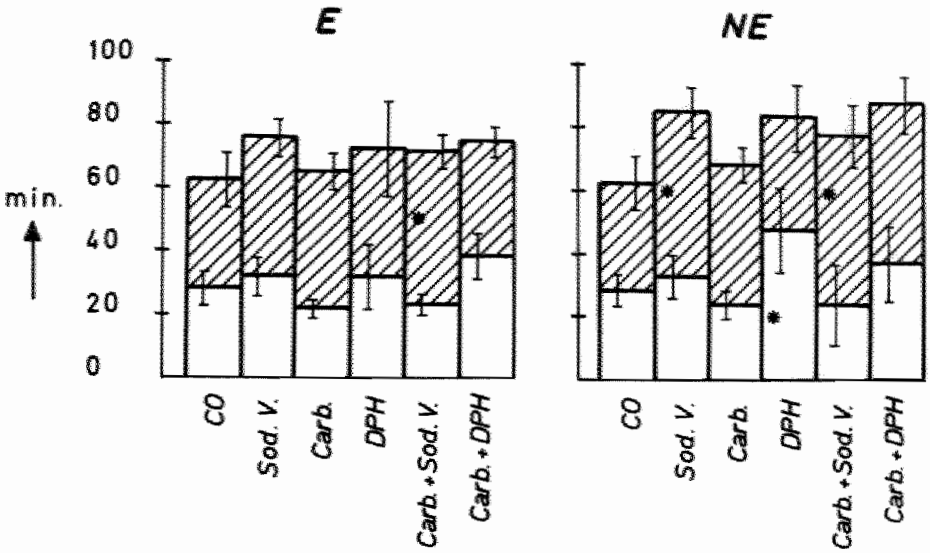


FIG. VIII.13.
Mean values, in minutes of the N.REM 1-2 (□) and the N.REM 3-4 (▨) sleep during the first sleep deprivation cycle of patients treated with three different types of antiepileptic drugs.
* $p < 0.05$.

7. Patients treated with carbamazepine either alone or in conjunction with sodium valproate have less light N.REM 1-2 sleep. In contrast, those treated with diphenylhydantoin either alone or in conjunction with carbamazepine have more N.REM 1-2 sleep.
8. Patients only taking sodium valproate or carbamazepine have more deep N.REM 3-4 sleep, an increase which becomes significant ($p < 0.05$), when both medicines are taken. Such a tendency is also present in patients which do not have epileptic EEG phenomena and which are treated with the combination of diphenylhydantoin with carbamazepine.
9. The effects caused by different medicines are best expressed by the ratio N.REM 1-2/N.REM 3-4 sleep (Figure VIII.14.). From this, a relatively strong increase in N.REM 3-4 sleep is more clear in

patients only treated with carbamazepine (0.49) or carbamazepine in combination with sodium valproate (0.46). Such an effect is also present in patients taking sodium valproate (0.72), but is negligible for those patients which do have epileptic EEG phenomena in their EEG and are treated with diphenylhydantoin, but not for patients which do not have epileptic EEG phenomena.

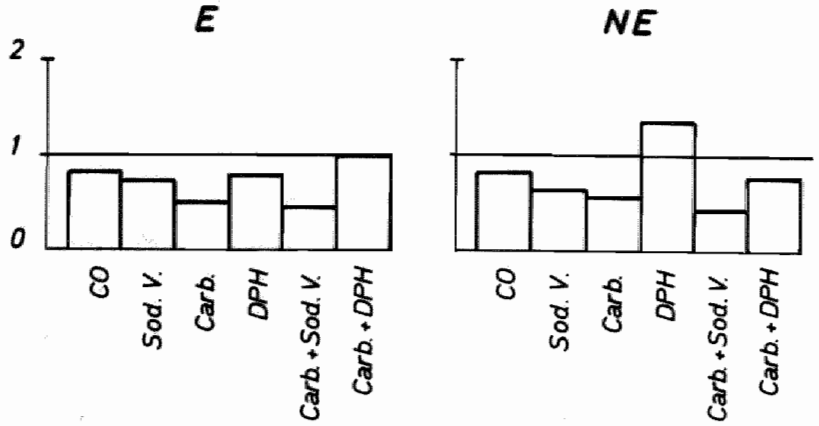


FIG. VIII.14.
N.REM 1-2/N.REM 3-4 ratio of the first deprivation sleep cycle for 3 different types of antiepileptic drugs (sodium valproate, carbamazepine and diphenylhydantoin).

10. There is a significant increase in the length of the total first sleep cycle, containing more effective sleep ($p < 0.025$) and more N.REM sleep ($p < 0.01$), in patients treated with the benzodiazepines chlorazepate or clonazepam in conjunction with antiepileptics. For chlorazepate, this is based on an increase in both N.REM 1-2 and N.REM 3-4 sleep, whereas for clonazepam this is exclusively based on a significant increase of the N.REM 1-2 sleep ($p < 0.025$). These data are summarized in Figure VIII.15.

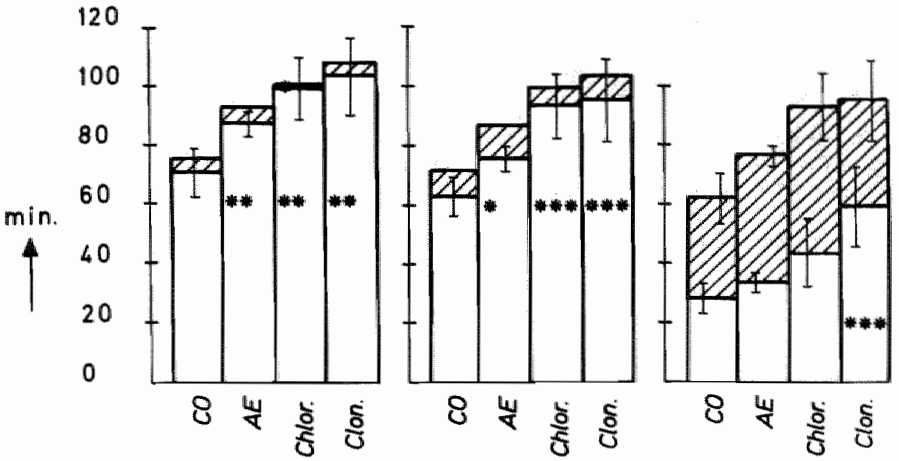


FIG. VIII.15. (a, b, c)
The mean values, in minutes, of the total cycle, divided in time awake (▨) and effective sleep time (□) (a), of the effective sleep time divided in REM (▨) and N.REM sleep (□) (b) and the N.REM sleep divided in N.REM 1-2 (□) and N.REM 3-4 (▨) sleep in patients treated with antiepileptic drugs, or in combination with or without chlorazepate or clonazepam (c).
* $p < 0.05$; ** $p < 0.025$; *** $p < 0.01$.

On the basis of these data it can be stated that the composition of the sleep following sleep deprivation differs depending on the kind of antiepileptic taken.

1. Carbamazepine gives rise to a strong change in the ratio N.REM 1-2/ N.REM 3-4 sleep by increasing deep sleep (0.49).
2. Sodium valproate increases the length of the first sleep cycle which is due to an increase in effective and N.REM sleep with a relatively larger increase in the deep N.REM 3-4 sleep (0.72).
3. Previous effects are more pronounced when both products are taken (0.46). This effect is further evident also during the second sleep cycle (0.85).
4. As a result of the treatment with diphenylhydantoin, the sleep cycle length increases, which is caused by more N.REM sleep. The amount of light and deep N.REM sleep in patients which have epileptic EEG abnormalities is comparable, but in patients which do not have epileptic EEG abnormalities, there is an increase of N.REM 1-2 sleep, such that the ratio N.REM 1-2/N.REM 3-4 sleep amounts up to 1.36.
5. Even in combination with carbamazepine, the effect obtained with diphenylhydantoin remains predominant.
6. The degree of the benzodiazepine effects on sleep following sleep deprivation is even in combination with antiepileptics dependent on the type of medication taken. This difference is especially expressed in the way by which they influence the N.REM sleep, whether only by increasing N.REM 1-2 sleep (clonazepam), or by increasing light as well as deep N.REM sleep (chlorazepate).

# CHAPTER IX: CHANGES OF THE EEG AND POLYGRAPHIC EEG PATTERNS ASSOCIATED WITH EPILEPSY AND SLEEP

In previous chapters it was shown to which degree the electroencephalographic diagnosis of epilepsy increased during sleep and how the composition of the sleep changed in function of the occurrence of EEG epileptic phenomena and the medication taken. Apart from the quantitative mutual interactions, qualitative interactions occur.

## IX.1. MORPHOLOGICAL CHANGES OF THE EPILEPTIC EEG PHENOMENA OCCURRING DURING SLEEP FOLLOWING SLEEP DEPRIVATION

It is known that the typical 3/sec spike wave paroxysms (SW; Figure IX.1.) recorded during wakefulness tend to develop to polyspike wave complexes (PSW; Figure IX.2.) during N.REM 1-2 sleep and to low frequency spike waves (LSW; Figure IX.3.) during deep N.REM 3-4 sleep. During N.REM 1-2 sleep the changes are often associated with an increase in number, and a decrease in the duration of the generalized spike wave paroxysms. During the N.REM 3-4 sleep these changes are associated with an interruption of long-lasting paroxysms, by which they obtain a pseudorhythmic aspect.

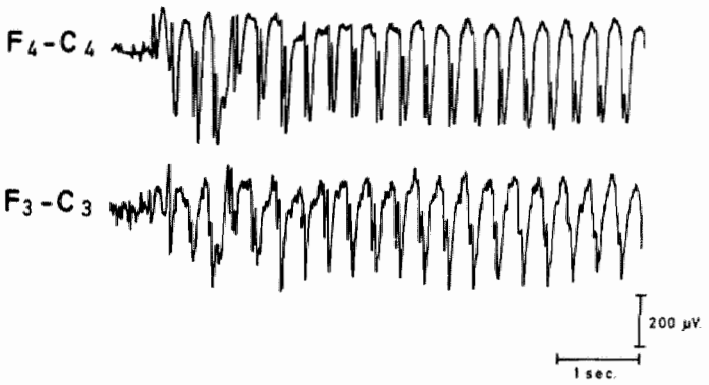


FIG. IX.1.
Example of typical spike wave complexes (SW).

In order to ascertain whether these changes also occur during sleep following sleep deprivation, we studied three groups of 100 patients each, all of which had generalized spike wave paroxysms during their awake routine EEG recording. The three groups of patients differed from each other because the spike wave complexes consisted of either regular 3/sec spike waves, polyspike waves (at least 2 or more spikes per complex), or low frequency spike waves (equal to or less than 2.5 c/sec). For each of the three groups the degree and

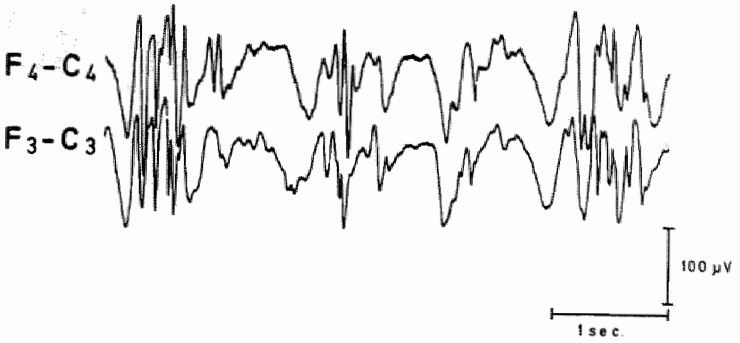


FIG. IX.2.
Example of polyspike wave complexes (PSW).

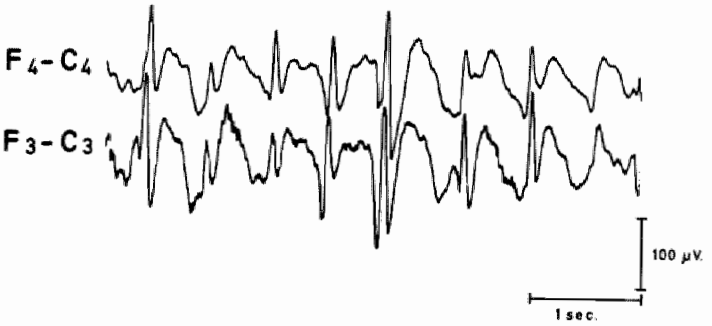


FIG. IX.3.
Example of low frequent spike wave complexes (LSW).

form of spike wave complexes were determined during N.REM 1-2 and N.REM 3-4 sleep following sleep deprivation. REM sleep was not considered in this investigation since the spike wave paroxysms did not occur in the majority of the patients or because the morphology of the spike wave paroxysms was similar as that seen during wakefulness. The results of this investigation for the three groups of patients are represented in Table IX.4.

In the group which had typical SW paroxysms, respectively 96 % and 76 % had also spike wave paroxysms during light N.REM 1-2 sleep and deep N.REM 3-4 sleep. Most SW complexes retain their form (48 %) or tend to develop to a PSW form (34 %) during N.REM 1-2 sleep. During N.REM 3-4 sleep 1/5 (21 %) of SW paroxysms developed to a PSW form, 1/3 (36 %) developed to a LSW form, but 1/4 (24 %) are not seen. In the PSW group a large percentage (62 % and 44 %) retained their polyspike wave aspect during the N.REM sleep. It is striking that approximately 1/5 (21 % and 17 %) developed to a typical SW form.

TABLE IX.4.
Percentage of typical spike wave (SW), polyspike wave (PSW) and low frequent spike wave (LSW) paroxysms during the sleep stages N.REM 1-2 and N.REM 3-4 sleep after one night sleep deprivation, and the registrations without epileptic EEG manifestations (N.E.), in comparison with the routine awake EEG.

| Epileptic EEG paroxysms | | SW 3 c/sec | | PSW ≥ 2 c/sec | | LSW ≤ 2.5 c/sec | | N.E. | |
|---|---|---|---|---|---|---|---|---|---|
| Awake | n | N.REM 1-2 | N.REM 3-4 | N.REM 1-2 | N.REM 3-4 | N.REM 1-2 | N.REM 3-4 | N.REM 1-2 | N.REM 3-4 |
| SW | 100 | 48 | 19 | 34 | 21 | 14 | 36 | 4 | 24 |
| PSW | 100 | 21 | 17 | 62 | 44 | 12 | 22 | 5 | 17 |
| LSW | 100 | 9 | 7 | 5 | 3 | 72 | 58 | 14 | 32 |

The LSW group is the most stable group, since in respectively 72 % and 58 % the LSW paroxysms continued to exist during N.REM 1-2 and N.REM 3-4 sleep.

The percentage of patients which during N.REM 1-2 sleep following sleep deprivation do not show epileptic phenomena is small, but for the LSW paroxysms group it can increase to 32 % during N.REM 3-4 sleep.

Thus, it can be stated that most spike wave paroxysms retain their form or develop to a polyspike aspect during N.REM 1-2 sleep. Very striking is the fact that 1/5 of the polyspike waves take a more typical spike wave form during the sleep. This is often associated with a strong shortening of the duration of the paroxysms, eventually restricted to 1 or 2 complexes. The low frequency spike waves constitute the most stable group, although spike waves were not seen any more during deep sleep in 1/3 of the patients. This spike wave form is often seen in subjects which have signs of diffuse organic brain damage, a disorder which apart from epilepsy may also cause psychomotor retardation and disturbances of the sleep.

## IX.2. THE INFLUENCE OF REM SLEEP FOLLOWING SLEEP DEPRIVATION ON EPILEPTIC EEG PHENOMENA

During REM sleep (Chapter II), EEG abnormalities fitting with primary generalized epilepsy are suppressed, except the typical 3 c/sec spike waves and abnormalities fitting with partial epilepsy are better localized than during the light N.REM 1-2 sleep. Because the amount of REM sleep recorded in the forenoon following one night sleep TSD does not differ substantially from the amount of REM sleep recorded during the first and second cycle of an all-night sleep recording (Chapter VII), it was checked whether the above hypothesis also accounted for the REM sleep following one night sleep deprivation.

Therefore, 100 sleep deprivation recordings of patients which have or were suspected of having primarily generalized epilepsy were investigated. In 83 of them generalized epileptic EEG phenomena were

recorded during N.REM sleep and in 13 also during REM sleep. Of these 13 patients, 11 had EEG abnormalities consisting of typical 3 c/sec spike waves, which in 8 cases clinically corresponded with an epilepsy of the absence type and 3 cases with an epilepsy of the tonic-clonic type. In the two remaining patients, which also had a tonic-clonic type of epilepsy, the paroxysms consisted of LSW.

Further, 100 sleep deprivation recordings of patients which have or were suspected to have partial epilepsy were investigated. These had typical epileptic EEG abnormalities occurring during N.REM 1-2 sleep as well as during REM sleep. An example is represented in Figure IX.5.

The EEG abnormalities were more evident during N.REM 1-2 sleep than during REM sleep in 29 patients. This was because they were seen over a larger brain area or because they occurred more frequently. In 22 patients the EEG abnormalities were localized in the left temporal region and in 6 in the right temporal region. The focus was better defined or the epileptic EEG abnormalities were better formed during REM sleep in 25 patients. In 22 patients the abnormalities were localized in the left temporal region and in 3 in the right temporal region.

From this limited evaluation it may be concluded that the REM sleep retained its characteristic influence on the epileptic EEG abnormalities also during a sleep recording following one night sleep deprivation.

## IX.3. POSTICTAL SLEEP PICTURES

When a clinical fit occurs during sleep, the sleep can become irregular for a short period, however, often without a loss of cyclicity. In order to know to which degree a clinical seizure disturbs the sleep following one night sleep deprivation, it was investigated how many clinical seizures occurred during sleep following sleep deprivation in the 404 patients investigated during the period 1980-1981 (Table V.3.). Electroclinical seizures were recorded in 22 patients: 11 of the primarily generalized grand mal type, 6 of the secondarily generalized type, and 5 of the partial complex type. The time of occurrence was partitioned over the total sleep recording time. The earliest attack occurred 4 min after the start of the recording, the last occurred after 184 min. They occurred 3 times during wakefulness, 12 times during light N.REM 1-2 sleep, 5 times during N.REM 3-4 sleep and 2 times during REM sleep. The recording period after a seizure was divided into a postictal recovery period and a postictal sleep period. The recovery period is the period during which the EEG picture does not correspond to a N.REM 1-4 or REM sleep pattern, characterized by for instance the absence of physiological sleep phenomena such as K-complexes, sharp vertex waves and spindles. An example of this is given in Figure IX.6.

The postictal sleep starts as soon as the EEG picture can again be divided into light or deep N.REM or REM sleep. The duration of the recovery period as well as the characteristics of the postictal sleep are represented in Table IX.7.

Of the 12 patients which had clinical seizures during N.REM 1-2 sleep, 7 belonged to the primarily generalized epilepsy type, and 4

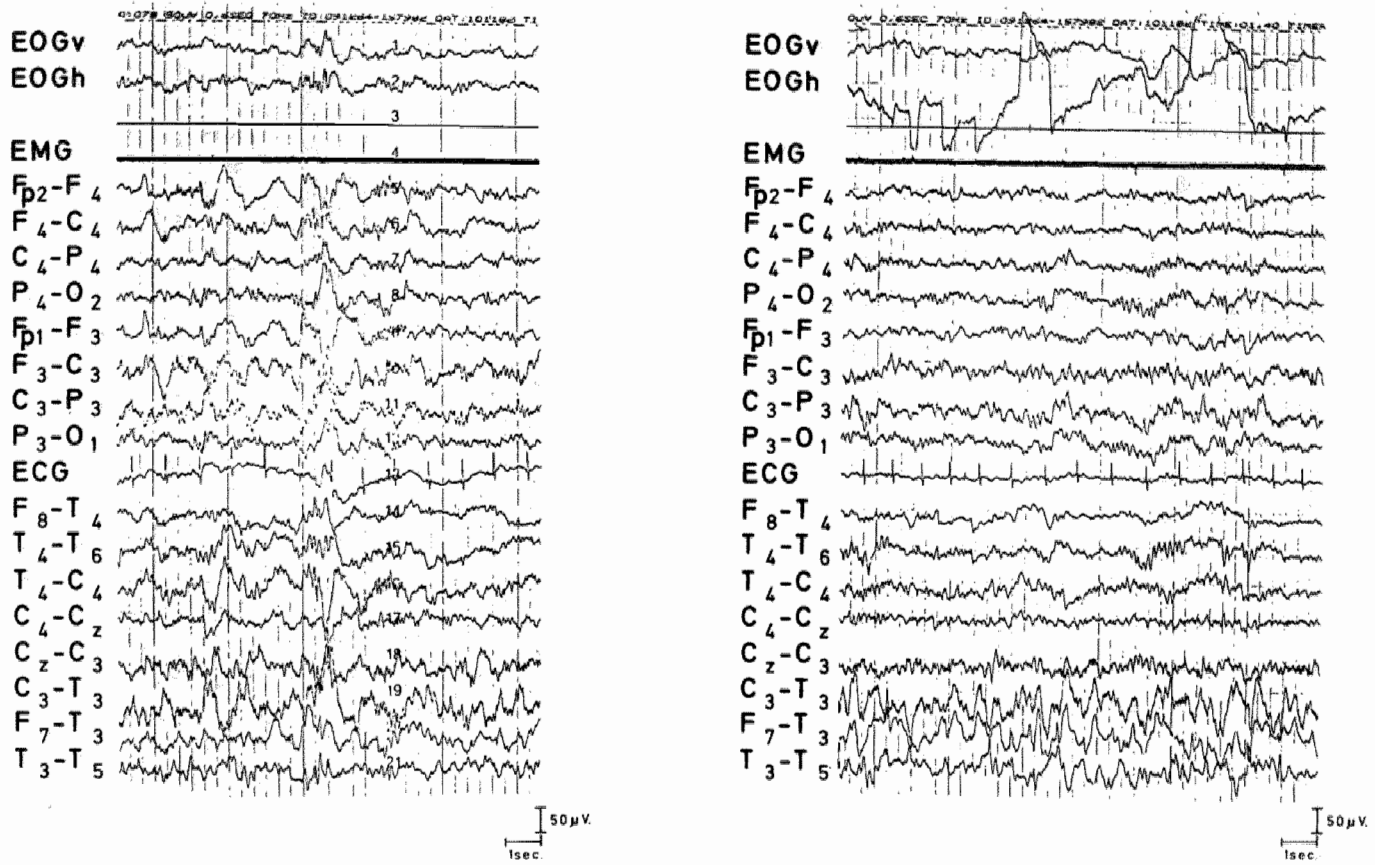


FIG. IX.5.
Example of epileptic EEG manifestations during N.REM 1-2 and REM sleep of the first sleep cycle registered after one night sleep deprivation.

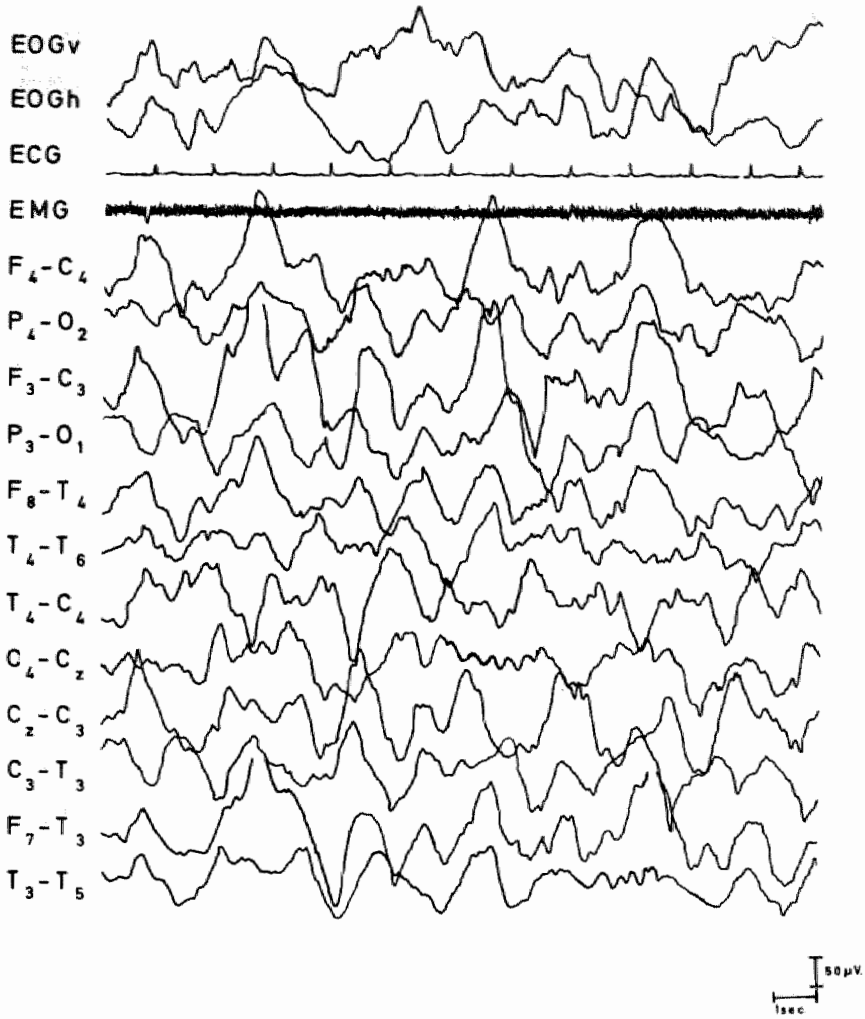


FIG. IX.6.
Example of a postictal period, two minutes after a generalized tonic-clonic seizure;

to the partial complex type. The 4 occurring during N.REM 3-4 sleep were all of the secondarily generalized epilepsy type. The postictal recovery period lasted longer than 15 minutes in only 4 subjects. Following the postictal recovery period, in 11 (50 %) sleep continued as expected and in 8 only N.REM 1-2 sleep was seen. Postictal sleep differed from pre-ictal sleep in 19 subjects, because of instability consisting of continuous transitions between the different stages of the sleep or because of long interruptions by arousal reactions or by the occurrence of delta paroxysms.

TABLE IX.7.
Duration of the postictal period and the characteristics of the postictal sleep in patients with the occurrence of an electroclinical epileptic seizure during the registration after one night sleep deprivation.

| Nr. | M/F | Age | Type of epilepsy | Sleep stage | Time of occurrence | Duration of postictal period | Characteristics of of the rest sleep |
|---|---|---|---|---|---|---|---|
| 1 | F | 24 | Pr.Gen. | N.REM 2 | 15' | 7' | unstable nl.cycle |
| 2 | F | 29 | Sec.Gen. | N.REM 2 | 155' | 30' | unclassificable -- |
| 3 | F | 21 | Sec.Gen. | N.REM 4 | 62' | 16' | unstable nl.cycle |
| 4 | F | 27 | Pr.Gen. | Awake | 61' | 5' | unstable nl.cycle |
| 5 | F | 16 | Pr.Gen. | N.REM 1 | 31' | 10' | unstable nl.cycle |
| 6 | F | 54 | Pr.Gen. | N.REM 1-2 | 25' | 10' | unclassificable -- |
| 7 | M | 50 | Part.c. | N.REM 1 | 118' | 4' | unstable nl.cycle |
| 8 | F | 32 | Pr.Gen. | N.REM 2 | 4' | 4' | unstable N.REM 1-2 |
| 9 | M | 34 | Pr.Gen. | N.REM 3 | 57' | 1' | unstable nl.cycle |
| 10 | F | 16 | Pr.Gen. | Awake | 65' | 4' | unstable N.REM 1-2 |
| 11 | M | 16 | Sec.Gen. | N.REM 4 | 54' | 4' | unstable N.REM 1-2 |
| 12 | M | 8 | Pr.Gen. | N.REM 1-2 | 36' | 4' | unstable nl.cycle |
| 13 | F | 32 | Part.c. | N.REM 1-2 | 5' | 30' | unstable N.REM 1-2 |
| 14 | M | 31 | Part.c. | N.REM 1-2 | 12' | 5' | unstable nl.cycle |
| 15 | M | 55 | Sec.Gen. | N.REM 4 | 66' | 1' | unstable N.REM 1-2 |
| 16 | M | 36 | Part.c. | REM | 184' | 5' | awake -- |
| 17 | F | 26 | Sec.Gen. | N.REM 4 | 73' | 22' | unstable N.REM 1-2 |
| 18 | M | 27 | Pr.Gen. | REM | 162' | 4' | unstable nl.cycle |
| 19 | F | 18 | Sec.Gen. | Awake | 8' | 6' | unstable nl.cycle |
| 20 | F | 25 | Pr.Gen. | N.REM 1 | 175' | 10' | unstable nl.cycle |
| 21 | F | 13 | Pr.Gen. | N.REM 1-2 | 136' | 4' | unstable N.REM 1-2 |
| 22 | F | 16 | Part.c. | N.REM 1 | 13' | 5' | unstable N.REM 1-2 |

Our findings are in agreement with data from the literature concerning the changes of the all-night sleep recordings as a consequence of electroclinical seizures. Here too, seldom was a loss of cyclicity or difficulty to partition the sleep into sleep stages found, though sometimes a suppression or delay of REM sleep has been observed.

## IX.4. FRAGMENTATION OF THE SLEEP

In about 10 % of the sleep registrations recorded following one night sleep deprivation in subjects which have or are suspected to have epilepsy, the hypnograms are characterized by a fragmentation of the sleep. This means that the sleep stages are repetitively interrupted for a short period (5 à 20 sec) by one or another sleep stage. An example of such interruption is shown in Figure IX.8.

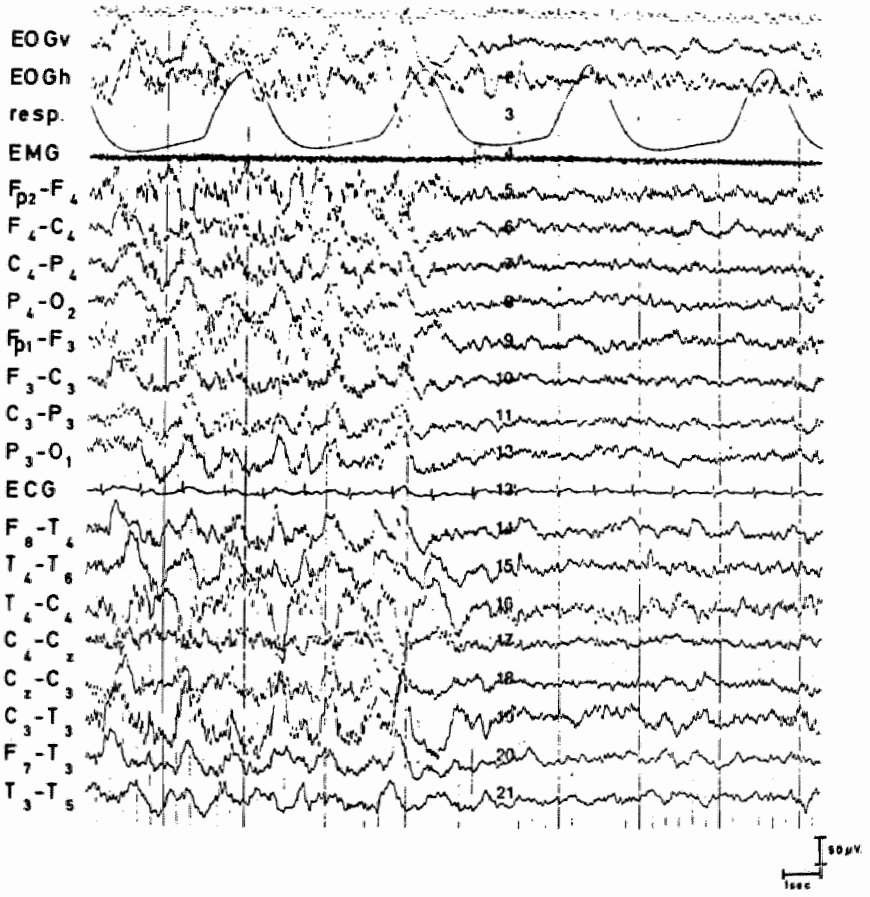


FIG. IX.8.
Example of sleep fragmentation.

This very striking event was the instigation to examine whether these events are associated with clinical complaints of a non-epileptic nature. Therefore, we selected 50 recordings demonstrating this characteristic sleep picture, from a total of 626 deprivation hypnograms recorded in the period 1979-1981 (Table V.6.). The population consisted of 26 males and 24 females, of which the age was respectively between 11 and 57 (mean: 27.9) and between 17 and 47 (mean: 29.4). Since it was known to us (Declerck et al., 1980) that the incidence of sleep fragmentation is higher in mentally retarded patients, patients were divided into 4 groups on the basis of the Wechsler Adult Intelligence Scale (I.Q.: W.A.I.S.), respectively with an I.Q. above 95, between 95 and 75, between 75 and 50, and less than 50. Of each of the 4 groups it was verified whether and in how many persons non-epileptic complaints were mentioned in their clinical dossier by the treating specialist. In addition, the number of patients in which the diagnosis of epilepsy could be confirmed and whether they were treated with antiepileptics (A.E.) or whether treated with other medication (N.A.E.) was examined. The data are summarized in Table IX.9.

TABLE IX.9.
The clinical and electroencephalographic findings of 50 patients, suspected of having epilepsy, with a typical pattern of sleep fragmentation in the sleep recorded after one night sleep deprivation, in relation with the intelligence level.

| Intelligence quotient level | n | Clinical symptoms epil. | other | Epil. paroxysms in sleep EEG | Drug treatment - | + A.E. | + N.A.E. |
|---|---|---|---|---|---|---|---|
| > 95 | 21 | 11 | 21 | 8 | 3 | 13 | 5 |
| 95-75 | 14 | 10 | 7 | 12 | 4 | 10 | - |
| 75-50 | 10 | 9 | 4 | 9 | 1 | 9 | - |
| < 50 | 5 | 4 | 2 | 4 | 1 | 4 | - |

All 21 patients, which had an I.Q. above 95 suffered from additional complaints of neurovegetative origin such as headache, vertigo, syncopes or emotional or psychic instability. The clinical diagnosis of epilepsy was only certain in 11 subjects and only 8 of them had epileptic EEG abnormalities. The diagnosis was doubtful in the remaining 10. Five of them were only treated with neuroleptics, because of complaints of a non-epileptic origin. Of the 14 subjects which had an I.Q. between 95 and 75, 10 had a well-recognisable form of epilepsy and the diagnosis was doubtful in 4 cases. Epileptic EEG abnormalities were recorded during the sleep in 12 patients of which 3 fitted with a combined form of epilepsy, with characteristics of both partial and generalized epilepsy. In 7 patients important non-epileptic complaints were mentioned, especially learning and behavioural difficulties such as attacks of aggression and hot temper.

Of the 10 patients which had an I.Q. between 75 and 50, 9 suffered from a moderate to severe form of epilepsy, confirmed during a sleep recording. In 5 patients epileptic paroxysms were registered fitting with a secondarily generalized form of epilepsy. Severe behavioural disturbances were found in 3 patients.

Of the 5 patients which had an I.Q. below 50, 2 had a hemiparesis. Other complaints, except for epilepsy, were not mentioned probably because of the predominance of the very severe mental retardation.

On the basis of these data it can be stated that, in the absence of severe mental or psychomotor handicaps, the fragmentation of the sleep is often associated with complaints of a non-epileptic nature, neurovegetative as well as psychic instability. Moreover, these complaints can persist in persons of which their epilepsy is well controlled by antiepileptic medication.

## IX.5. MORPHOLOGICAL CHANGES OF THE K-COMPLEXES IN EPILEPTIC SUBJECTS

The most evident EEG sign of arousal occurring during N.REM 1-3 sleep is the appearance of K-complexes (Fig. IX.10.). According Halasz et al. (1979) the number or density of K-complexes, would augment when the sleep becomes more profound. This tendency is absent when the sleep becomes lighter. They also found that the density is maximal during the first sleep cycle, and gradually decreases during subsequent sleep cycles. These changes do not occur in epileptics, because K-complexes exist during the whole sleep, often appearing in short series of 3 or more complexes.

In order to find out whether these changes are present in the sleep recorded following one night sleep deprivation, we calculated the density of the K-complexes in the sleep of 8 healthy persons and in 10 epileptics which had generalized spike or polyspike wave paroxysms during their sleep recordings. The transition of wakefulness via light to deep sleep and vice versa are respectively denoted as a descending and an ascending phase.

For each phase and for the first and second sleep cycle separately, we calculated the density of the K-complexes during the N.REM 1, N.REM 2 and the N.REM 3 sleep, by taking the mean of 10 x 1 minute (in as far as the sleep stage lasted 10 minutes). An example of such calculation for a healthy and an epileptic patient is represented in respectively Tables IX.11. and IX.12. All K-complexes were counted, even if they had a deviant or epileptic aspect, but they had to conform with the description given by Chatrian et al. (1974): "K-complex: a burst of somewhat variable appearance, consisting most commonly of a high voltage diphasic slow wave frequently associated with a sleep spindle. Amplitude is generally maximal in proximity of the vertex. K-complexes occur during sleep apparently spontaneously or in response to sudden sensory stimuli, and are not specific for any individual sensory modality".

In healthy persons, the number of K-complexes varied between 0-5 per minute and their density was approximately equal during the descending and ascending phase and was somewhat smaller during the first sleep cycle than during the second sleep cycle. In epileptics the density of K-complexes varied between 1 and 8 and often appeared in short series of 2 or 3 subsequent K-complexes. There was no systematic difference between the first and second sleep cycle, neither

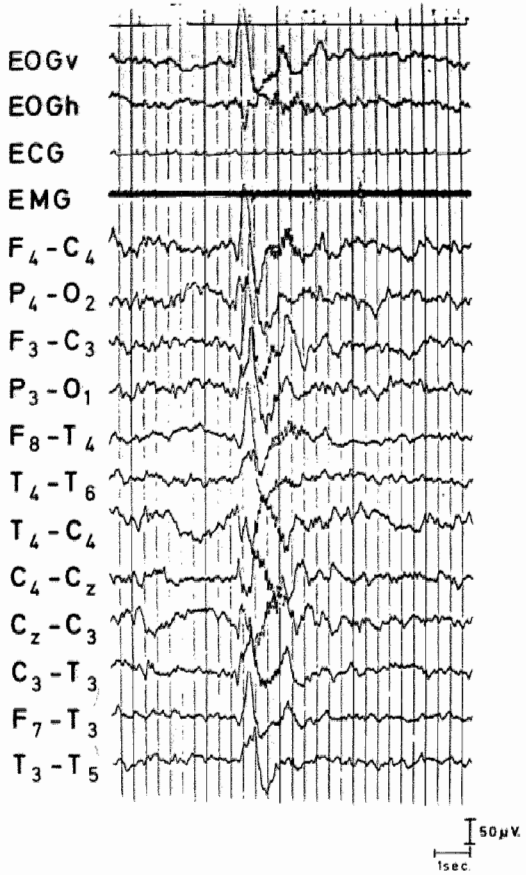


FIG. IX.10.
Normal K-complex.

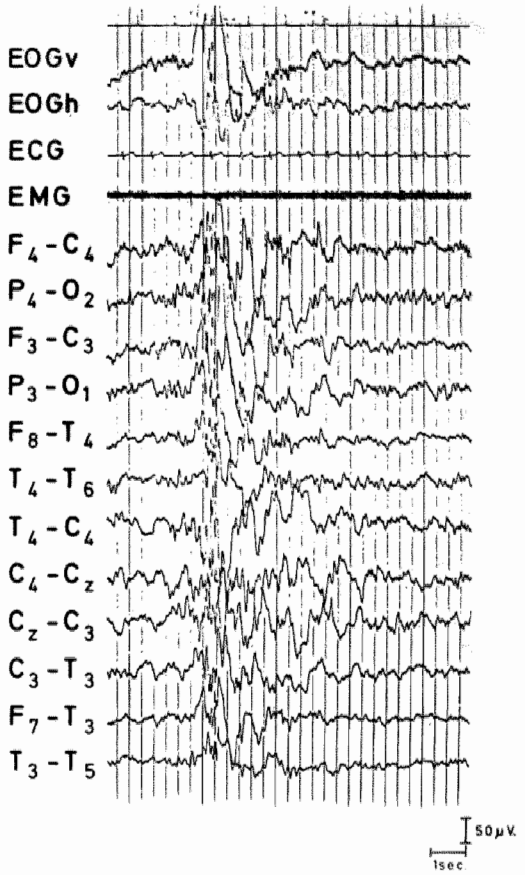


FIG. IX.13.
Example of an atypical K-complex.

TABLE IX.11.
Density of K-complexes during the descending (D) and ascending (A) N.REM phases of the first and second sleep cycle of a healthy person after 1 night sleep deprivation.

| Density of K-complexes | 1st cycle | | 2nd cycle | |
|---|---|---|---|---|
| | D1 | A1 | D2 | A2 |
| N.REM 1 | 1.2 | 1.1 | 1.5 | 1.5 |
| N.REM 2 | 1.8 | 2.1 | 2.6 | 3.1 |
| N.REM 3 | 1.6 | 1.8 | 1.8 | 2.8 |

TABLE IX.12.
Density of K-complexes during the descending (D) and ascending (A) N.REM phases of the first and second sleep cycle of an epileptic patient after 1 night sleep deprivation.

| Density of K-complexes | 1st cycle | | 2nd cycle | |
|---|---|---|---|---|
| | D1 | A1 | D2 | A2 |
| N.REM 1 | 2.2 | 2.0 | 1.6 | 1.5 |
| N.REM 2 | 4.6 | 5.4 | 5.0 | 5.5 |
| N.REM 3 | 4.1 | 3.6 | 3.5 | 3.7 |

between the descending and ascending phase. Except for a higher density, more abnormal K-complexes were found in epileptics, i.e. they were of a low amplitude and irregular or of a very high amplitude and sharp. Examples of abnormal K-complexes are represented in Figure IX.13.

In accordance with data from the literature on all-night sleep recordings more K-complexes, of which many had an abnormal character, were found in the sleep recorded following one night sleep deprivation in epileptics. In contrast to Halasz et al. (1979) no differences were found neither in density during the first and second sleep cycle nor in the ascending and descending phase of the CO group. This could go together with the sleep deprivation effect, through which sleep especially during the first sleep cycle mainly consists of deep N.REM 4 sleep which also occurs faster after falling asleep.

## IX.6. THE VALUE OF NON-EEG SLEEP PARAMETERS IN PATIENTS WHICH HAD OR WERE SUSPECTED TO HAVE EPILEPSY

As mentioned in the recording method (IV.2.) apart from recording EEG rhythms, also eye movements (EOG), chin muscle activity

(EMG), the electrocardiogram (ECG) and respiration (R) were registered. By these recordings a better differentiation can be made between the 4 stages of the N.REM sleep and REM sleep. The N.REM sleep, also termed quiet sleep, is characterized by the slowing and at some stage by a disappearance of eye movements, a decrease of muscle activity and a regular heart and respiration rhythm. Partly in contrast herewith, during REM sleep, heart and respiration rhythm becomes irregular, fast eye movements occur and a further decrease of muscle activity is seen. It appears to make sense to figure out to which degree these physiological changes are also observed during the sleep following sleep deprivation in subjects which have or are suspected of having epilepsy.

6.1. The electro-oculogram

The different types of eye movements appearing during wakefulness and sleep were recorded through skin electrodes positioned at the border of the eye. One pair of electrodes is positioned vertically, respectively with one electrode in the middle above and one electrode in the middle below the eye. Another pair of electrodes is positioned horizontally with one electrode on either lateral side of the eye corner. Around the eye there exists an electrical field based on the potential difference within the eye, since the cornea is positively charged in comparison to the retina. Because the position of the cornea and the retina changes continuously during an eye movement, one measures the continuously changing potential difference at the electrodes. From these measures one can derive the direction, speed, size and density of the eye movements (in /min). Figures IX.14. and IX.15. give examples of slow eye movements (SEM) during N.REM 1-2 sleep of rapid eye movements (REM) of a high density during REM sleep.

Based on a visual evaluation of sleep recordings, the density of REM was scored as high, moderate and low. High means that minimally a mean of 20 REMs were seen, low a maximal of 6 REMs and moderate from 7 to 20 REMs. It was found that in about 50 % of the patients, REM sleep following sleep deprivation, consists of a low density and only in 5 % of a high density. This is clearly different from the density of the eye movements in healthy persons of which 80 % scored a moderate density. Between patients with a low and moderate density of REM following differentiation could be established. In the group which had a low density there were relatively more mentally retarded patients or patients with signs of a diffuse organic brain damage. In addition, there were more patients treated with the combination of more than 2 drugs, whether antiepileptics, especially high doses of diphenylhydantoin, or antiepileptics in combination with benzodiazepine derivatives. In the 5 % of patients which had a high density of eye movements relatively more patients had additional psychiatric complaints.

In 20 to 25 % of the patients REM sleep was unstable and repetitively interrupted by short periods of light N.REM 1-2 sleep or awakening.

Finally, in patients as well as in non-patients fast eye movements appear in clusters. The density of REMs is smaller during the first sleep cycle than in the subsequent cycles.

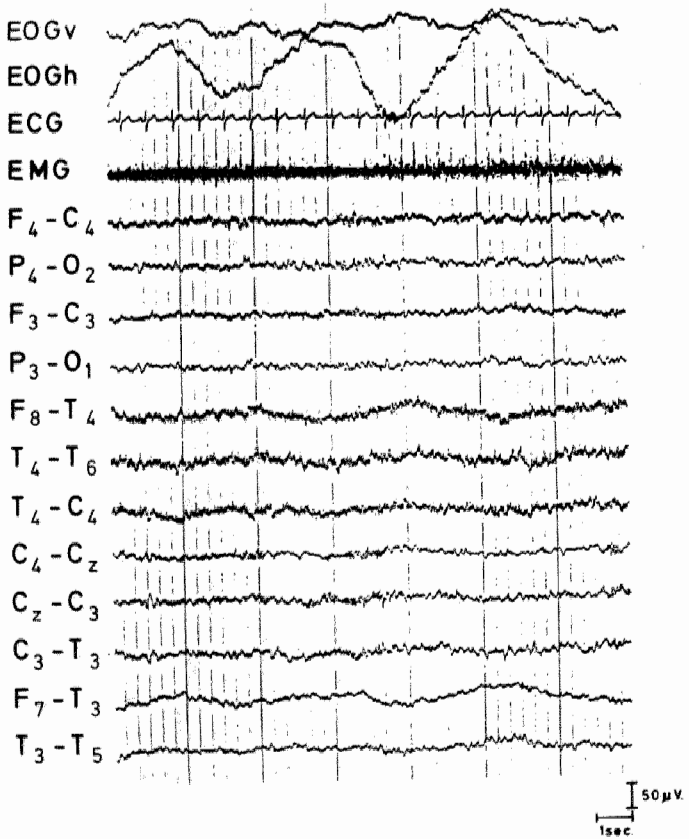


FIG. IX.14.
Example of slow eye movements during N.REM 1 sleep.

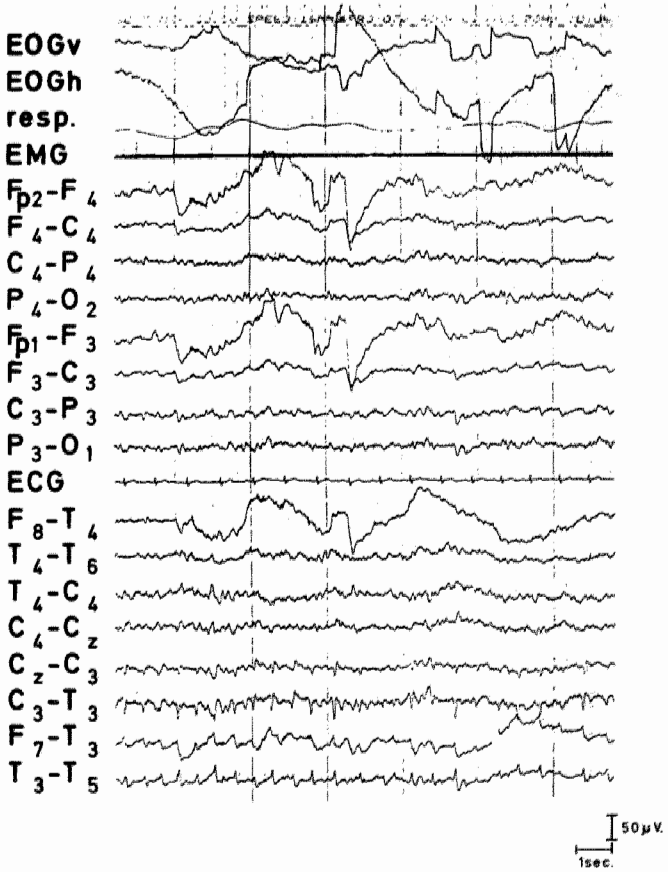


FIG. IX.15.
Example of rapid eye movements of high density during REM sleep.

6.2. The electromyogram

During sleep there is a general decrease of muscle activity and of large body movements. Though this decrease is most pronounced during REM sleep, precisely during this sleep state small short-lasting twitches in the face and fingers appear. To measure this general decrease in muscle activity and the characteristic twitches in the face, it is common to measure chin muscle activity by means of skin electrodes. We also systematically applied this method, but often in combination with a second derivation placed on the neck, the cheek or the jaw muscles.

To check the validity of an EMG measure in the evaluation, three experienced EEG assistants working for at least 3 years in our laboratory and regularly carrying out sleep investigations were asked to classify the sleep into deep N.REM and REM sleep exclusively based on the EMG signal. For this investigation 300 hypnograms of sleep recordings following sleep deprivation in epileptics were used. This independent evaluation provided following results:

1. Only in 1 patient, which had a serious sleep disturbance, was a high level of muscle activity registered during REM sleep.
2. In more than 40 % of the patients no differentiation could be made between N.REM and REM sleep only on the basis of the EMG. This was due to the fact that the muscle activity during N.REM sleep was as low as during REM sleep and because almost no muscle twitches occurred during REM sleep.
3. Following an arousal reaction occurring during N.REM 1-2 sleep, the muscle activity could reach a 2 or 3 times higher level for about 5-10 minutes (Figure IX.16.). These long-lasting changes on muscle activity do not correlate with the short-lasting changes of the EEG picture or with changes in heart or respiration frequency, of which the original pattern is often re-established within 1 minute.
4. In many patients an extremely low muscle activity is seen from the beginning of sleep onwards, a phenomenon regularly observed in patients treated with antiepileptics in combination with benzodiazepine derivatives.
5. A sudden and very strong increase in muscle activity is often associated with a short period of wakefulness or with an epileptic discharge. The latter is mainly observed in patients with psychomotor attacks and in which a second derivation at the level of the cheek or jaw muscle is used.
6. Positioning electrodes in the neck or at muscles of the extremities is less meaningful since changes in posture may greatly alter the measured muscle activity.

In summary, it can be stated that measuring the muscle activity is a less valuable parameter for the partition of sleep in epileptics, especially when they are treated with antiepileptics in conjunction with benzodiazepine derivatives, than generally proposed in the literature.

6.3. Respiration

During REM sleep respiration becomes irregular and periods of apnea may occur. A frequently applied method for recording the respiration is measuring air flow by placing a small

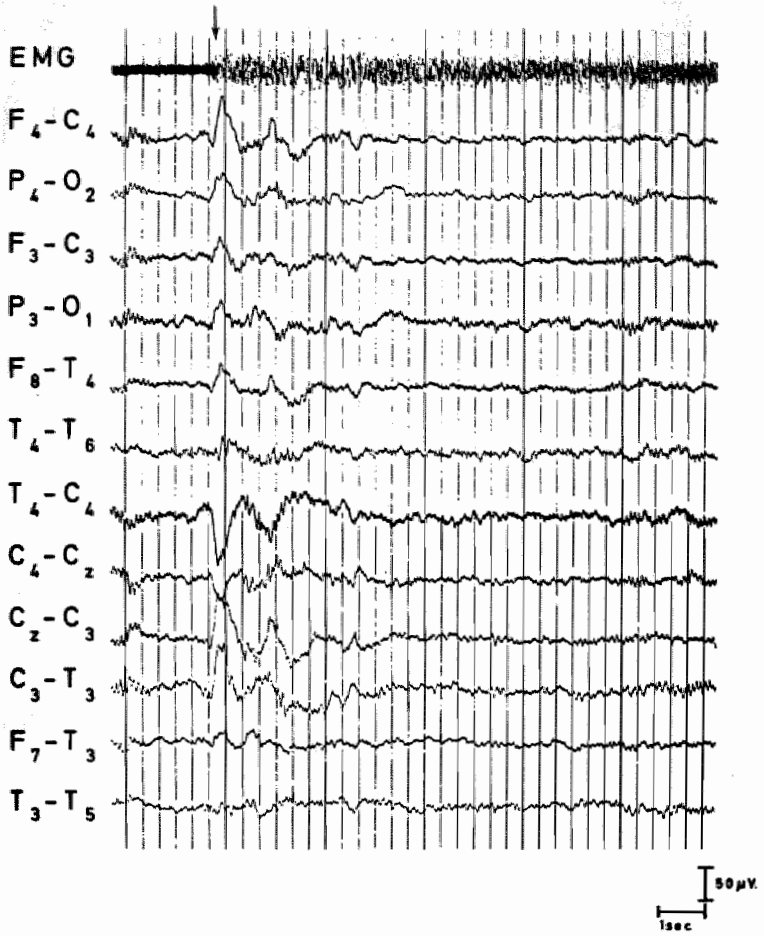


FIG. IX.16.
Level of chin muscle activity during N.REM 2 sleep before and after an arousal reaction.

temperature- sensitive plate before the nose and mouth. This method (thermistor NTC - Siemens) has also being applied by us.

A period of apnea is defined as an interruption of the air flow during minimally 10 sec. According some authors (Guilleminault et al., 1980) periods of apnea can give rise to sleep interruptions. Owing to this a shortage of sleep may occur and in reverse a shortage of sleep can favour the occurrence of apnea periods.

It was of interest to check the regularity of respiration during REM and N.REM 1-2 sleep and N.REM 3-4 sleep following sleep deprivation and how frequent apnea periods occurred in patients which had or were suspected of having epilepsy.

A total of 40 sleep recordings were studied from patients recorded in 1981, in all of which an artifact free respiration recording was present and in which 2 complete sleep cycles were found, consisting of N.REM 1-2, N.REM 3-4 and REM sleep. The data of these 40 patients are summarized in Table IX.17. The different columns contain following data: (1) age; (2) sex; (3) clinical form of epilepsy; (4) the EEG confirmation; (5) antiepileptic medication; (6) lowest and highest respiration frequency per minute respectively during N.REM 1-2, N.REM 3-4 and REM sleep; (7) the maximal duration of apnea; (8) the maximal and minimal value of the heart frequency during REM sleep.

The population consisted of 17 males and 23 females, their age varied between 9 and 42 years, 26 were epileptics and 14 patients which were suspected to have epilepsy.

The magnitude and variability of the respiration frequency in the different sleep stages was relatively stable for each individual patient. In most patients, respiration was most regular and deepest during N.REM 3-4 sleep and superficial and irregular during N.REM 1-2 sleep and especially during REM sleep. There was no firm relationship between the respiration and heart frequency. Only in 3 patients were apnea periods found (case 11, 16 and 28) with a maximal duration of respectively 15, 22 and 30 sec. These occurred mainly during the transition of deep N.REM 3-4 sleep to REM sleep or light N.REM 1 sleep. Most apnea periods give rise to a short-lasting lightening of the sleep (or wakefulness), but in most cases for less than 1 minute. They never induced clinical seizures or increased electrical epileptic abnormalities.

For comparative purposes, an evaluation was made of 30 all night sleep recordings in an analogous patient group. Apnea periods occurred in 2 patients lasting respectively 15 and 22 sec. These also occurred during the transition to REM or N.REM 1-2 sleep following a deep sleep period. From these data one can conclude that there are no major differences between an all-night and a deprivation sleep recording, concerning the appearance of apnea periods and that apnea periods do not give rise to an increase in epileptic abnormalities. Therefore, sleep deprivation in epileptics does not yield an extra risk.

### 6.4. The electrocardiogram

The ECG was derived from contact plate electrodes fixed at both wrists by means of an elastic string. The ECG was systematically recorded during a routine awake EEG as well as during the sleep recordings. Though a larger variability was found during REM sleep as compared to N.REM sleep (Table IX.17.), these differences were too small and varied to much to allow to differentiate between the different states of sleep on the basis of this parameter alone.

## IX.7. GENERAL SUMMARY

During sleep following sleep deprivation spike wave paroxysms tend to change their form: 1/3 of the typical spike waves changed

TABLE IX.17.
The respiration rate and the occurrence of apnea periods in a group of 40 epileptic patients during the different types of sleep and awake after one night sleep deprivation in relation with the form of epilepsy and the antiepileptic drug treatment.

| | 1 | 2 | 3 | 4 | 5 | 6 | | | | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Respiration rate | | | | Apnea | |
| | Age | M/F | Clin. | EEG | A.E. | AW. | N.REM 1-2 | N.REM 3-4 | REM | > 10 sec | ECG |
| 1 | 31 | F | Pc. | + | Teg. 600 | 10-12 | 10-12 | 10-12 | 8-12 | | 68- 76 |
| 2 | 36 | M | ? | - | -- | 14-16 | 12-16 | 12-16 | 12-16 | | 70- 78 |
| 3 | 17 | F | ? | - | -- | 12-16 | 12-16 | 14-16 | 12-18 | | 54- 68 |
| 4 | 9 | M | P.G. | + | Teg. 700 | 14-20 | 14-20 | 14-20 | 14-20 | | 68- 90 |
| 5 | 35 | M | ? | - | Dep. 900 | 16-18 | 16-18 | 14-16 | 12-16 | | 104-112 |
| 6 | 36 | M | ? | - | -- | 14-16 | 14-16 | 14-16 | 14-20 | | 80- 88 |
| 7 | 32 | F | Pc. | + | Teg. 400 | 16-20 | 16-20 | 16-20 | 16-22 | | 64- 72 |
| 8 | 18 | F | Ga. | + | Eth.1000 | 18-20 | 18-20 | 18-20 | 18-22 | | 80- 90 |
| 9 | 24 | F | Ga. | - | Teg. 800 | 18 | 18 | 18 | 18 | | 74- 80 |
| | | | | | Dep.1800 | | | | | | |
| 10 | 26 | F | Pc. | + | Teg. 400 | 16-18 | 16-18 | 14-16 | 14-18 | | 64- 72 |
| 11 | 30 | F | Pc. | + | Diph.450 | 22-24 | 20-24 | 20-24 | 20-24 | 15 sec | 78- 84 |
| | | | | | Lum. 50 | | | | | | |
| 12 | 10 | M | Ga. | + | Dep.1500 | 20-21 | 18-20 | 18-20 | 18-20 | | 64- 76 |
| 13 | 27 | M | Ga. | + | Teg. 600 | 20 | 14-16 | 14-16 | 12-16 | | 76- 84 |
| 14 | 9 | M | ? | - | -- | 16-18 | 16-18 | 16-18 | 14-20 | | 60- 90 |
| 15 | 42 | M | Pc. | + | Teg. 700 | 16-18 | 13-17 | 15-17 | 14-16 | | 48- 64 |
| | | | | | Dep. 700 | | | | | | |
| 16 | 21 | F | P.G. | + | Teg. 800 | 18-20 | 16-20 | 16-18 | 16-22 | 22 sec | 44- 78 |
| | | | | | Dep.3000 | | | | | | + E.S. |
| 17 | 29 | F | Pc. | + | Diph.300 | 18-20 | 16-20 | 14-20 | 14-20 | | 82- 90 |
| 18 | 30 | F | ? | - | Dep. 900 | 20-24 | 18-24 | 20-22 | 16-24 | | 80- 90 |
| 19 | 38 | F | ? | - | Lum. 50 | 14-16 | 14-18 | 14-16 | 12-16 | | 66- 74 |
| 20 | 24 | M | G of Pc | +(G) | -- | 16 | 14-16 | 14-16 | 14-18 | | 52- 64 |

TABLE IX.17. (continued)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | 37 | M | G | + | Teg. 600 | 16 | 14 | 12 | 12-14 | | 64- 76 |
| 22 | 11 | F | Ga. | - | Teg. 400 | 18-20 | 18-22 | 18-20 | 14-20 | | 72- 80 |
| 23 | 23 | F | G. | - | Dep. 900 | 14-16 | 12-16 | 12-16 | 12-16 | | 70- 78 |
| 24 | 19 | M | Pc. | - | Teg. 600 | 20 | 20-24 | 20 | 20-24 | | 60- 68 |
| | | | | | Dep.2000 | | | | | | |
| 25 | 11 | M | ? | - | -- | 16 | 16 | 16 | 12-18 | | 70- 90 |
| 26 | 13 | F | Ga. | + | Dep.1000 | 18-20 | 18-20 | 18 | 18-24 | | 96-108 |
| | | | | | Eth.1000 | | | | | | |
| 27 | 19 | F | G | + | Dep.1200 | 14-18 | 14-18 | 12-16 | 12-16 | | 52- 64 |
| 28 | 38 | F | Pc. | + | Teg.1400 | 10-14 | 10-16 | 12-16 | 12-18 | 30 sec | 70- 80 |
| | | | | | Diph.300 | | | | | | |
| 29 | 14 | F | Pc. | + | Teg. 600 | 16-18 | 14-18 | 14-18 | 14-18 | | 50- 70 |
| 30 | 16 | M | ? | - | Dep. 600 | 18 | 15-18 | 15 | 16-20 | | 72- 80 |
| 31 | 27 | F | ? | - | Teg. 600 | 14-16 | 14-16 | 14-16 | 14-18 | | 70- 74 |
| 32 | 16 | F | Ga. | + | Dep. 300 | 18-20 | 18-20 | 18 | 18-22 | | 80- 88 |
| 33 | 20 | M | ? | - | -- | 16-20 | 14-20 | 14-18 | 14-16 | | 48- 64 |
| 34 | 14 | F | Pc. | + | Teg. 600 | 15 | 12-18 | 12-14 | 20-24 | | 76- 80 |
| | | | | | Dep. 500 | | | | | | |
| 35 | 26 | M | ? | - | -- | 14 | 12-16 | 14 | 14-18 | | 60- 90 |
| 36 | 32 | M | G | + | Teg.1000 | 18 | 14-18 | 18 | 14-18 | | 56- 70 |
| 37 | 26 | M | G | + | Dep.1200 | 12-16 | 10-16 | 12 | 12-16 | | 60- 72 |
| 38 | 16 | F | ? | - | -- | 18 | 14-18 | 18 | 14-18 | | 78- 90 |
| 39 | 25 | F | G | + | Teg. 600 | 16 | 14-16 | 14-16 | 14-18 | | 68- 70 |
| | | | | | Dep. 600 | | | | | | |
| 40 | 24 | F | ? | - | -- | 16-20 | 16-20 | 16-18 | 16-20 | | 68-82 |

into polyspike waves and 1/5 of the polyspike waves to typical spike waves during N.REM 1-2 sleep. During N.REM 3-4 sleep 1/3 of the typical spike waves and 1/5 of the polyspike waves changed to a low frequency spike wave form. The latter demonstrated the most stable aspect, but these occurred especially in patients which have a diffuse brain damage.

The abnormalities fitting with partial epilepsy are better localized and better formed during REM sleep. This influence also occurs during REM sleep following sleep deprivation in epileptics.

With the occurrence of an electroclinical seizure during a sleep deprivation investigation, sleep can be partitioned only with difficulty, but such periods seldom last longer than 15 minutes. In the subsequent periods, sleep is often less stable than before the seizure.

When sleep following sleep deprivation is characterized by a striking fragmentation, especially in epileptics which have a normal intelligence (I.Q. W.A.I.S. $> 95$) one often has to consider complaints other than epilepsy, especially those of a neurovegetative or psychic origin. These complaints do not disappear after treatment with antiepileptics, even if these regulate the epilepsy.

A larger density of K-complexes is often seen in epileptics. They occur during light N.REM sleep or when sleep becomes deeper or lighter, respectively at the start and at the end of a sleep cycle. In addition, these K-complexes can take an abnormal form because they are blunt and have a low amplitude or because they are sharp and of a high amplitude or because they appear in short series. In these cases a differential diagnosis with aspecific spike waves can be extremely difficult.

Half of the patients treated for epilepsy have less than 6 fast eye movements per minute during REM sleep. Such a low density is especially seen in epileptics which have a subnormal I.Q. or when they are treated with more than 2 antiepileptics of which one is hydantoine or with antiepileptics in combination with benzodiazepine derivatives.

In 20 to 25 % of the epileptics REM sleep is interrupted by short periods of light N.REM 1-2 sleep.

Many epileptics have a strikingly low chin muscle activity during all sleep stages, such that this is as low during N.REM as during REM sleep. This especially occurs in patients treated with the combination of antiepileptics and benzodiazepine derivatives. Otherwise, arousal reactions which shortly disturb the sleep picture (less than 1 minute) can triple the muscle activity for several minutes.

The influence of N.REM and REM sleep on the regularity and frequency of heart and respiration does not differ between epileptics and healthy persons. Of practical importance is the fact that sleep deprivation does not increase the frequency of periods of apnea. In addition, when these occurred they did not provoke clinical or electro-encephalographic epileptic abnormalities. This means that the sleep deprivation method is also a safe method for epileptics.

# CHAPTER X: PROCEDURES FOR THE APPLICATION OF THE TOTAL SLEEP DEPRIVATION METHOD (TSD)

In chapters IV-IX it was shown that the diagnostic yield of long-term polygraphic sleep registrations following one night TSD is determined by a multiplicity of factors. Different procedures of TSD have been applied. Depending on the practical possibilities of an EEG department and the aims of the investigation, one can make a differentiation between the following:

1. A simple routine TSD procedure, with the sole aim of improving the epilepsy diagnosis.
2. A complex long-term TSD procedure, to be carried out in those cases where it is extremely difficult to make a differential diagnosis between the presence or absence of epilepsy, and in those cases where it is wished to study, not only the epileptic, but also the non-epileptic EEG abnormalities in relation to the composition of the sleep.
3. A directed TSD procedure, where the recording and the processing is adapted in order to better analyze certain aspects of epilepsy during sleep, or sleep itself in epileptics.

## X.1. THE SIMPLE ROUTINE TSD PROCEDURE

When on the basis of the clinical investigation and of a routine EEG examination it is desirable to carry out a sleep recording after sleep deprivation, the following procedure can be proposed:

1. Preceding the investigation the patient, preferentially under guidance, remains awake for the whole night.
2. The patient is present in the EEG department in the morning. The recording has to be carried out in the forenoon, since the opportunity to record a sufficient amount of REM sleep decreases towards the end of the day (Fukuda et al., 1981).
3. Normally a 12-, but preferentially a 16 (or more)-channel electroencephalograph is used for the polygraphic sleep recording. Three or 4 channels are used for the recording of non-EEG parameters, the other channels serve for recording EEG rhythms. The electrodes have to be positioned in a configuration by which epileptic EEG as well as sleep phenomena can be recorded optimally (chapter IV). During the technical preparation the patient has to be kept awake.
4. After the start of the recording, the patient has to be kept awake for minimally 10 minutes, for this purpose external stimuli are often necessary. This period of lowered alertness continuously interrupted by arousal reactions, is considered as very provocative for the appearance of epileptic EEG abnormalities. Moreover, during this period, it is ideal to check whether all EEG and non-EEG parameters are recorded artifact free. A correction is then feasible without having to additionally awaken the patient.
5. After the sleep onset minimally one sleep cycle is recorded. In epileptics, the first sleep cycle lasts between 80 and 110 minutes, often containing somewhat more deep N.REM 3-4 sleep than light N.REM 1-2 sleep and a short REM period at the end of it.

6. If by the end of the first sleep cycle no epileptic EEG abnormalities have been recorded, than it is meaningful to prolong the recording for minimally 15 minutes in order to find out whether epileptic EEG abnormalities occur during the initial phase of the second sleep cycle, i.e. the transition of REM sleep to N.REM 1-2 sleep.
7. The recording has to continue for an additional 10 to 15 minutes after awakening the patient. Most patients have difficulties in remaining awake. The variations in the degree of vigilance favour the occurrence of epileptic EEG manifestations.
8. In patients suspected of having a form of epilepsy sensitive to light stimuli or hyperventilation, the investigation can be complemented by one or both provocation tests.

In applying this procedure, the duration of the registration lasts 120-150 minutes. With this recording procedure we achieve more than 90 % of the total positive diagnosis, which could be attained by prolonging the recording to two sleep cycles or about 4 hours recording. The most obvious reason responsible for an insufficient sleep, apart from other demonstrable causes of sleep disturbances (for example organic brain damage), is an insufficient sleep deprivation.

## X.2. THE COMPLEX LONG-TERM TSD PROCEDURE

During short-lasting observations allowing to confirm, differentiate, or exclude the existence of epilepsy, the following neurophysiological procedures can be proposed:

1. Carrying out a routine and specific EEG investigation on the basis of clinical and anamnestic findings, preferentially during the morning.
2. Linking-up with this routine EEG investigation and based on the recorded findings, the patient is further investigated with the aid of a continuous ambulatory EEG registration, using a minitape recorder. Herewith one can find out whether the patient remains awake at night and whether epileptic EEG abnormalities occur during this period. Keeping the patient awake is done in the clinic under the guidance of the nursing staff. The day/night activities are noted by the patient or by the staff.
3. During the next morning a polygraphic sleep investigation is carried out, conforming to the procedure proposed for the simple routine TSD procedure. The duration of the recording, however, is prolonged to two sleep cycles or when there is an insufficient cyclicity of the sleep to minimally 4 hours.
4. Following the sleep investigation again an ambulatory EEG recording is carried out during the next 24 hours. When necessary, the electrode position is adapted according to the epileptic EEG findings established during the sleep investigation. By this means it is possible to check whether the effects of the sleep deprivation persist because the appearance of day sleep, through which the sleep in the subsequent night becomes superficial and less stable.

   Such registration continued during 48 to 60 hours is not burdensome to most patients.

## X.3. THE DIRECTED TSD PROCEDURE

Many investigators mentioned that during the sleep in epileptics more sharp vertex waves (Passouant, 1975) and K-complexes (Halasz et al., 1979) are present, eventually even with the appearance of epileptic K-complexes (Niedermeyer et al., 1981). An increase of well-formed spindle activity would otherwise point at a better regulation of the epilepsy (Sterman et al., 1979). Recently Naitoh et al. (1982) pointed at the antagonism which would exist between brain mechanisms responsible for the production of sleep spindles and the synchronizing mechanisms responsible for the appearance of sharp vertex waves, K-complexes and delta sleep. An inhibitory function is assigned to sleep spindles (Johnson et al., 1976) giving rise to an increase of the arousal threshold and stability of the sleep. Sharp vertex waves and K-complexes, on the other hand, are considered as an expression of enhanced cortical exitability (Raynal et al., 1974), by which arousal reactions interrupting the sleep are facilitated. According Gaillard and Tissot (1976) one may expect that an increase of spindle activity is associated with a decrease of vertex waves, K-complexes and delta sleep.

If it is desirable to study such associations, it is necessary to derive these specific EEG phenomena from those regions where they are maximally present. For an adequate detection of K-complexes, recordings have to be made not only from the vertex but also from more frontal, medial, and parasagittal cortical regions. For the detection of the spindle activity recordings have to be made precentrally as well as central-temporally and parieto-occipitally. These are the regions where these rhythms may differ largely from each other during the N.REM sleep.

Though such investigation offers perspectives for an improved evaluation of brain functioning and antiepileptic treatment, adequate soft-ware methods are required for an optimal processing of the EEG signals

## CHAPTER XI: DISCUSSION

This study was designed to find the optimal method of carrying-out a polygraphic sleep recording following one night total sleep deprivation (TSD) in epileptics, in order to obtain a maximum in diagnostic gain. By this we not only mean the recording of epileptic EEG abnormalities, but also the sleep changes which can originate from having epilepsy or from the intake of antiepileptics. Therefore, we carried out a literature survey and an investigation in which sleep of epileptics and healthy subjects, whether during the night, or during the day following one night total sleep deprivation were registered and subsequently analyzed. By comparing the obtained results, it became possible to judge the diagnostic validity of our TSD method. In order to better understand the differences in the diagnostic gain depending on the applied sleep procedure, first a short description of the neurophysiological background, which might be of importance in epilepsy and sleep, will be considered.

### XI.1. NEUROPHYSIOLOGICAL BACKGROUND OF THE INTERACTION SLEEP AND EPILEPSY

Nearly all investigators (II.3.) agree that epileptic EEG abnormalities are mostly seen during the light N.REM 1-2 sleep. Also, during N.REM 1-2 sleep the probability of developing polyspike waves increases and the spread of focal discharges from the focus increases. This does not occur during REM sleep and a decrease in generalized epileptic discharges and a better circumscription of partial epileptic discharges is better observed. These apparently contradictory influences show that cortical functioning during N.REM and REM sleep differs and further, that both types of sleep are differently controlled.

The activity of neurons, localized in the brain stem, are responsible for the neurophysiological organization of wakefulness and sleep. They can be divided into two systems on the basis of their antagonistic function. One system is responsible for wakefulness and arousal, the other one for the induction of sleep and between both systems a continuous reciprocal interaction exists (Hobson et al., 1975). The first or activation system is responsible for a continuous activation and control, through an adequate inhibition of cortical neurons. Herein the ascending reticular activating system fulfils an important role. This system is also responsible for a high cerebral catecholaminergic activity; an action which is also expressed in a desynchronized EEG picture and a high level of muscle activity. In the second or sleep inducing system, the midline nuclei of the thalamus and raphe nuclei play an important role, whether by a direct influence on cortical neurons, or indirectly by suppressing the subcortical activating systems. This influence is associated with an increase in cerebral serotonergic activity, which is especially expressed during N.REM 3-4 sleep (Hartmann, 1967) and give rise to a synchronized EEG picture consisting of high delta waves. The organization of the REM sleep is sustained by a complex mechanism in which the locus coeruleus plays an important role. Similarly, as during

wakefulness though less pronounced, during REM sleep the catecholaminergic activity is high (Gaillard, 1979) by which this desynchronized EEG picture can be explained. Further during REM sleep there is a low serotonergic activity and a high cholinergic activity. Finally the EMG picture is characterized by a low level of muscle activity, which is ascribed to an inhibition of alpha-motor neurons. Although the cited regulatory mechanisms are very simplified it is possible to better understand the similarity between wakefulness and REM sleep, both typified by a desynchronized EEG, and deep N.REM 3-4 sleep with a synchronized EEG. Wakefulness and REM sleep as well as deep N.REM 3-4 sleep are considered as actively induced states (Hess, 1925; Monnier and Schönenberger, 1977) whereas light N.REM 1-2 sleep is often considered as a passive condition, which originates from a decreased or even suppression of the functioning of activating systems (Bremer, 1935; Koella, 1981). In this conception, light N.REM 1-2 sleep can be viewed as a passive transition phase between the inability to maintain the conditions of wakefulness and REM sleep and the inability to induce a stable deep N.REM 3-4 sleep. During this activation, the control of cortical neurons is lessened, however, the thalamo-cortical activity is maintained. Due to the decreased inhibition, afferent stimuli produce a more pronounced cortical reaction which is expressed in the EEG by the appearance of sharp vertex waves and K-complexes (Naitoh et al., 1982). Because of the existence of large physiological differences at cortical and subcortical level during the conditions of wakefulness, light and deep N.REM sleep and REM sleep, it is likely that epileptic discharges will occur more easily during conditions which promote their origin.

Gastaut and Tassinari (1975) defined an epileptic EEG discharge as "a neuronal discharge characterized by the simultaneous excessive activation of a large number of cells which may be recorded by electroencephalographic techniques as a paroxysmal wave form, usually in the form of a spike (S), sharp wave (SH) and spike and wave (SW) or other such complex". The spike is considered as "a sign of neuronal membrane depolarization and unit activity facilitation under conditions of enhanced positive pyramidal cell feedback and increased activity of excitatory interneurons". The slow wave is described as "a hyperpolarization with inhibition of pyramidal cell unit activity" (Steriade, 1974). Conditions of an enhanced cortical excitability which allow the appearance of excessive neuronal discharges, may be based on a congenital predisposition (Metrakos and Metrakos, 1961) or an acquired pathological condition of the gray brain matter (Gloor, 1969). This disturbs the normal rhythmic interplay between excitatory and inhibitory postsynaptic potentials, which are the basis of the EEG rhythms (Pollen et al., 1964), and give rise to abnormal EEG phenomena.

Gloor (1979) differentiates between epileptogenesis of the first and second order, depending on the degree of the disturbance. In the first degree the rhythmic interplay between excitatory and inhibitory postsynaptic potentials is disturbed without instigating an increasing depolarization of the cell membrane potential. This disturbance is clinically expressed mainly in a generalized epilepsy of the absence type and electroencephalographically in generalized spike wave paroxysms. During the second degree the neuronal discharges give rise to a further depolarization by which the discharge frequency of cells

further increases. This disturbance is electroencephalographically expressed by the appearance of series of spikes, sharp waves or polyspike waves. Clinically, this is expressed in generalized epilepsy of the grand mal type or partial epilepsy if the disturbance is restricted to a part of the brain cortex. These excessive focal discharges however, can invade neighbouring normal neurons. Calvin (1972) showed that "even a normal neuron can become epileptic if more than 1 % of the synaptic input receives high frequency discharges from other epileptic neurons".

When as described above, epilepsy is based on a too high and simultaneous discharge frequency of large groups of cortical neurons, this tendency will be further reinforced by physiological conditions of diminished cortical inhibition (N.REM 1-2 sleep) or by pathophysiological conditions of enhanced cortical excitability (postanoxic or metabolic). As a consequence of this it is comprehensible that epileptic EEG abnormalities will more easily appear during N.REM 1-2 sleep with an enhanced possibility for the formation of polyspikes and a spread to adjacent neurons. Due to the high activation and control of cortical neurons during REM sleep an opposite effect can be understood. These are the reasons why in the literature REM sleep is sometimes assigned anticonvulsant properties and the N.REM sleep convulsant properties. This claim cannot fully be sustained because focal discharges though sharply circumscribed sometimes occur more frequently during REM sleep than during wakefulness or N.REM sleep. This might be connected with the finding that focal epileptic sources, localized in the limbic system or in the supplementary motor area, show a higher incidence of spiking during REM sleep, this is in contrast to other cortical areas (Wieser, 1982). The enhanced cerebral cholinergic activity during REM sleep might play a role in this according to some authors (Celesia and Jasper, 1966).

If one accepts that one of the basic mechanisms for the origin of epilepsy is an acquired or innate enhanced cortical excitability and that the degree of cortical excitation differs depending on the kind and depth of sleep, then it is acceptable that this can change the structure of the sleep in epileptics.

During N.REM 1-2 sleep many authors observed more sharp vertex waves in patients with a generalized form of epilepsy (Clemens and Mezey, 1980). Similarly, more sharp to epileptic K-complexes (Niedermeyer, 1981) which may even occur in series (Halasz, 1979) or which may be expressions of excitation and synchronization have been reported (Naitoh et al., 1982). This enhanced cortical excitation can give rise to a too strong arousal reaction resulting in frequent and long-lasting awakenings from light N.REM 1-2 sleep, which hamper the induction of a stable N.REM 3-4 and REM sleep. Through this one can explain the many transitions and even interruptions seen during N.REM 3-4 sleep and REM sleep in epileptics. These stages of sleep can then be replaced by light N.REM 1-2 sleep and even by awakening (Passouant, 1975).

Taking into account, that according to certain authors (Chadwick et al., 1978; Rolf et al., 1982) epileptics, especially those which suffer from a grand mal type, produce few biogenic amines such as serotonin (activity engaged in the induction of deep N.REM 3-4 sleep) a deviant sleep structure can be understood.

## XI.2. DISCUSSION OF OUR OWN INVESTIGATION PROCEDURE AND RESULTS

On the basis of the outlined interactions between epilepsy and sleep, we will discuss hereafter the investigation procedures we applied and the results obtained. Where our findings deviate from the literature we attempt to explain them.

### 2.1. The TSD procedure (Chapter IV)

The most important differences between our procedure and those mentioned in the literature are the following:

a. The systematic utilization of 16 or 21 recording channels through which the epileptic and sleep phenomena can be described and classified precisely;
b. Controlling, by the nursing staff aided by the members of the family or relatives, that the patients remain continuously awake during the night preceding the investigation . By this, one prevents the occurrence of "microsleeps" through which the aimed deprivation effect can be mitigated;
c. Starting the sleep recording in the morning between 7.00 and 8.00 hours because the opportunity to record REM sleep is greater during the forenoon than in the afternoon or evening (Fukuda et al., 1981);
d. A 3 to 6 times longer recording time than the 30-60 minutes recording used in the literature;
e. Mentioning the type, localization and the quantity of epileptic EEG abnormalities depending on the sleep stage and depth, with in addition, mentioning the sleep partition in a hypnogram and the most striking sleep phenomena, such as K-complexes, sleep spindles, and of sleep patterns of delta and REM sleep.

Thanks to the measures mentioned in b, c, d the recording period was often sufficiently long to obtain two complete sleep cycles and to record REM sleep and all stages of N.REM sleep in patients. This provided the opportunity to relate the epileptic EEG abnormalities with the kind and depth of sleep during the first and second cycle and to compare the two sleep cycles with each other and with the all-night sleep, which allowed the deprivation effect in epileptics to be studied.

The measures mentioned in a and e made it possible to analyze the changes in the aspect of epileptic EEG phenomena with respect to the sleep and of the sleep phenomena with respect to the epilepsy, or the intake of antiepileptics.

### 2.2. The value of TSD for the electroencephalographic diagnosis of epilepsy (Chapter V)

This discussion is restricted to some differences which are mainly of practical importance.

a. The percentage sleep recordings in which epileptic EEG abnormalities were found in an aselective group of patients suspected of having epilepsy was 63.7 % in 1977 and 70.9 % in 1981. During the of 3-4 hours following TSD, this percentage was 4 to 5 % lower than during an all-night sleep recording lasting 7-9 hours. The percentage of 60 to 65 % is 5 to 10 % higher than those found in

most of the literature (Degen and Degen, 1980). This gain can be ascribed to the longer duration of the recording time and to a strict control of wakefulness during the period preceding a sleep recording.

b. Besides the percentage diagnostic affirmation depending on the clinical form of epilepsy we aimed to determine the diagnostic gain in function of (1) the probability by which the referring specialist (neurologist of pediatrician) could confirm or deny the existence of epilepsy on the basis of anamnestic and clinical data and (2) the specificity by which the epileptic EEG abnormalities were seen during the sleep recording.
When the existence of epilepsy was clinically considered as certain, then the percentage of recordings with specific epileptic EEG abnormalities increased from 35.1 % during wakefulness to 84.2 % during sleep. When however the diagnosis of epilepsy was clinically rejected than only 3 (0.75 %) of the 395 patients had specific epileptic abnormalities during the sleep. Such a differentiated comparison of such a large patient population has not been reported in the literature (Deisenhammer and Klingler, 1978). This also points at the importance of precisely observing and describing the clinical as well as the electroencephalographically recorded epileptic phenomena.

c. In accordance with the literature (Marosfi, 1980) most epileptic EEG abnormalities were determined during the first sleep cycle. Though it has to be mentioned that 13.4 % of the positive findings were only seen during the second sleep cycle. This can be the consequence of the sleep changes which may occur during the first cycle following one night TSD and which consist of a much shorter onset of sleep and a decrease in the light N.REM 1-2 sleep.

d. The mean sleep latency was 6.3 min in our population. During this short period wakefulness was characterized by a low and instable vigilance, which favours the occurrence of epileptic EEG abnormalities (Faber, 1978). Some data from the literature suggest that recording only the wakefulness following one night TSD without sleep is sufficient to determine the epileptic EEG abnormalities. In order to evaluate this we systematically kept 100 patients awake for 30 minutes during TSD recordings. The number of registrations with epileptic EEG abnormalities during this wakefulness period was 29 %. This is 17 % lower than the percentage established during the first 30-min period of recordings following TSD when patients were allowed to fall asleep spontaneously. This higher percentage makes a sleep recording desirable. Furthermore, artificially keeping patients awake is unpleasant for the patient.

e. Because of the long recording time we were able to calculate the percentage diagnostic gain in relation to time. The diagnostic gain was 57.3 % following one hour recording time, this increased to 69.4 % after 2 hours and to 74.5 % after 4 hours. The additional gain of 5.1 % achieved during the third and fourth recording hour was independent of the type of epilepsy.

f. The higher percentage positive diagnostic findings using our TSD procedure is in our opinion not only the consequence of a longer duration of the recording but also of the changes in wakefulness and sleep which result from the preceding sleep deprivation. Thus during the sleep latency period, wakefulness is characterized by a

changing and often low degree of vigilance, whereby "micro-arousals" need to be continuously given to prevent the occurrence of sleep. It is known that such variations in vigilance (Faber, 1978) favour the occurrence of epileptic EEG abnormalities. Apart from this, we observed during the sleep following TSD in epileptics larger variations and more series of sharp vertex waves and sharp to epileptic K-complexes as compared to an all-night sleep. These findings point respectively at an increased instability of the sleep, through which more intermediate sleep stages occur (Halasz, 1982) and to an increase of cortical excitability during light N.REM 1-2 sleep (Niedermeyer, 1981) or changes which favour the occurrence of epileptic EEG abnormalities.

2.3. Sleep structure of the all-night sleep in epileptics (Chapter VI)

According to the literature the presence of epileptic EEG abnormalities hardly changes the sleep structure. In our investigations which were restricted to do the first and second sleep cycle of an all-night sleep some differences between epileptics and a control group were found.

a. Epileptics often have a longer-lasting first and second sleep cycle, almost completely due to an increase in light N.REM 1-2 sleep. Further, epileptics become more frequently awake and sleep fractionations often occur. This might be associated with the existence of a high degree of cortical hyperexcitability during light N.REM 1-2 sleep, through which the arousal reactions are more violent and can easily give rise to more awakenings and by which deep sleep is less easily induced and maintained.
b. The mentioned differences are less pronounced when antiepileptic medication is taken. From this one can derive that these medicines carry out their action by reducing the cortical hyperexcitability through which the sleep stabilizes and epileptic EEG abnormalities diminish. This is linked up with the experience that the sleep abnormalities of the epileptics which have epileptic EEG abnormalities are often larger than in those which do not have epileptic EEG phenomena.
c. When the sleep is not disturbed by other diseases (e.g. severe organic brain damage, depression, etc.) then the sleep changes are only moderately dependent on the type of epilepsy. There is somewhat more N.REM 1-2 sleep in patients having a generalized form of epilepsy, somewhat more REM sleep in those having a partial form of epilepsy and when both forms of epilepsy exist, both forms of sleep increase.
d. In contrast to some findings in the literature (Findji et al., 1978) we did not find an absolute, but a relative decrease, of deep N.REM 3-4 sleep, due to a prolongation of the cycle length. In many epileptics, the delta activity during deep N.REM 3-4 sleep had a strikingly low amplitude or there was a strong spread in the frequency with more fast delta waves of 2-3 c/sec. This can be associated with an insufficient functioning of sleep mechanisms, which induce deep N.REM 3-4 sleep, and which can be based on epilepsy, or the intake of antiepileptic medication.

2.4. The sleep structure of TSD sleep in epileptics (Chapter VII)

There is a consensus in the literature that the changes in sleep following one night TSD are mainly restricted to the first sleep cycle, which consists of a decrease in light N.REM 1-2 sleep or an increase in N.REM 3-4 sleep, sometimes associated with a decrease of the REM sleep. We found similar changes in our control population, but some of these changes were different in epileptics.

a. As compared to an all-night sleep, in both control and the clinical group, there was a shortening of the cycle length during the sleep following TSD. In the control group, the effect was restricted to the first cycle in which there was a relatively larger decrease of N.REM 1-2 sleep. In epileptics, there was a shortening of the first cycle and to a lesser extent of the second cycle. In the first cycle, this was mainly due to a decrease of N.REM 1-2 sleep, and a less strong increase of N.REM 3-4 sleep as compared to the control group and in the second cycle due to less REM sleep. It seems as if epileptics can only move slowly and less effectively recuperate from the consequences of a one night wakefulness. This is not surprising, since the changes induced by sleep deprivation are opposite to the changes established during an all-night sleep in epileptics. Therefore, these sleep changes need to be neutralized before the deprivation effect can be expressed.

b. All patients, except for the clinical group treated with the combination of first choice antiepileptics and benzodiazepine derivatives, had a longer sleep cycle following TSD than in the control group. Though this was also established during spontaneous nocturnal sleep, whereby the prolongation was only due to an increase of N.REM 1-2 sleep, this was mainly due to an increase of light and deep N.REM sleep following TSD.

Further, the differences in sleep structure of the first sleep cycle following one night TSD are much less than during the spontaneous nocturnal sleep. It is reasonable to assume that precisely the strong decrease of light N.REM 1-2 sleep following TSD, or the sleep which is most sensitive to different influences, is therefore responsible.

However, in conformity with the all-night sleep, also during sleep following TSD, we found small differences in the composition of the sleep between the clinical groups which have either generalized or partial epileptic EEG abnormalities, or which have phenomena of both. In the patient group between 20-40 year there was relatively somewhat more light N.REM 1-2 sleep in the presence of generalized epilepsy and somewhat more REM sleep in the presence of partial epileptic EEG abnormalities and an increase of N.REM 1-2 sleep as well as REM sleep when both forms of epilepsy co-exist. The latter pattern was not found in patients younger than 20 years, which had both forms of epilepsy. In comparison, with patients which have generalized epilepsy, they only had more light N.REM 1-2 sleep. This finding fits with the clinical data that certain forms of generalized epilepsy preferentially occur at an early age. The preponderance of this form of epilepsy would then explain the observed sleep pattern.

c. The sleep structure following one night TSD is age-dependent and can be influenced strongly by the intake of benzodiazepine derivatives. When these factors are excluded, then one can state that one night TSD also affects the sleep in epileptics in a stereotyped way. The absence of this influencing pattern, appears to be based mainly on an incomplete sleep deprivation (for instance a not well-controlled total sleep deprivation during the night) or the existence of a serious sleep disturbance caused by a non-epileptic disease.

2.5. Sleep structure following TSD depending on the antiepileptic medication (Chapter VIII)

Long-term intake of barbiturates, hydantoins and benzodiazepine derivatives can give rise to an increase in N.REM 1-2 sleep, a decrease of N.REM 3-4 sleep and REM sleep, and a prolongation of the cycle length (II.2.4.). This can be accompanied with an increased need for sleep which according to Feinberg et al. (1979) originates "by slowing the metabolic processes of sleep so that longer sleep duration is required for the same biological effects". Hitherto, no extensive studies have been carried out on how sleep in epileptics is affected by long-term intake of carbamazepine and valproate, and of antiepileptics in combination with benzodiazepine derivatives (Johnson, 1982). In order to evaluate this we sampled a patient group in which a sleep recording following TSD was performed and which had a well-partitioned first sleep cycle. Further, the patients were treated only with carbamazepine, sodium valproate, diphenylhydantoin, or with two of these antiepileptics, or first choice antiepileptics in conjunction with the benzodiazepine derivatives chlorazepate or clonazepam. An advantage of this study appeared to be the fact that the interindividual differences in the composition of the first sleep cycle largely disappear following one night TSD. This increases the likelihood that the measured differences are medication-dependent.

a. The effects of first choice antiepileptics on the sleep structure . Such a study appeared reasonable since most data from the literature concern the chronic use of barbiturates. These drugs, together with benzodiazepine derivatives, are often prescribed for their hypnosedative effects and less frequently because of their anticonvulsant properties. Our investigation concerns those drugs which are taken in the first place for their anticonvulsant properties. In accordance with the structure of the all-night sleep in patients taking only diphenylhydantoin (Sengoku and Wolf, 1981) we found the following changes in the sleep after TSD: a prolongation of the cycle length caused by an increase in N.REM 1-2 sleep, deep N.REM 3-4 sleep stays the same, however, the patients become awake for shorter periods. Also the intake of sodium valproate gave rise to a longer cycle length caused by an increase in N.REM 1-2 sleep and an even more pronounced increase in deep N.REM 3-4 sleep. The effects of the intake of carbamazepine on sleep differed in that a stronger increase in N.REM 3-4 sleep was compensated by an equal decrease in the amount of N.REM 1-2 and REM sleep, through which the cycle length remained the same. Such differential influences on the structure of the sleep suggest that the mechanisms of action of these antiepileptics differ.

Hydantoin derivatives are known as drugs which raise the neuronal firing threshold at thalamocortical level and which stabilize the cell membrane potential (Englander et al., 1977). By this they are able to suppress the chance of, or the presence of increasing cortical hyperexcitability. Long-term usage of these drugs can by continuously suppressing hyperexcitability lead to a slowing of brain functioning. This is clinically expressed during the day by a lower degree of vigilance and electroencephalographically in a diminishing of the frequency of the EEG rhythms or with a mixing of slow waves (Longo, 1977). During the night there is a slower recovery, through which the need for sleep increases and the cycle length increases (Feinberg et al., 1979).
Sodium valproate derivatives are compounds which enhance the cerebral GABAergic activity, a neurotransmitter which has inhibitory properties. This drug is indicated in conditions of a lowered cortical inhibition. This can exist in patients which have a generalized form of epilepsy (Metrakos and Metrakos, 1961). It might be that this medical readjustment of the brain can also be responsible for an effective recuperation following TSD, which is expressed in a stronger increase of the deep than the light N.REM sleep.
The influence of carbamazepine on the sleep pattern is somewhat more than the influence of TSD itself in the control group. It seems as if carbamazepine activates the compensatory mechanisms in patients, which result in a recuperation within the first sleep cycle, just as is seen in healthy persons. From many investigations (e.g. Ballenger and Post, 1980) it appears that carbamazepine is able to suppress the cortical epileptic discharges originating in the limbic system and spreading to the diencephalon. Recently (Sillanpää, 1981) it has been suggested that the specific mechanism could be attributed to the anticholinergic properties of carbamazepine. Therefore, it is not surprising that this antiepileptic is especially useful for partial epilepsy of temporal origin. The mechanism of action can be partially understood from the fact that carbamazepine resembles imipramine, a tricyclic amine known to cause comparable EEG changes (Jovanovic, 1974).
As mentioned earlier it is not excluded that the differences are partially connected with the form of epilepsy for which these antiepileptics are prescribed. The group only treated with carbamazepine in our population, are almost exclusively normal to slightly subnormal functioning subjects which have a psychomotor form of epilepsy. This signifies that only a small part of the cortex is disregulated and that the majority can be considered as normal. This might also be the reason why the sleep structure in these patients hardly differs from those in the control group.
Patients treated with valproic acid derivatives suffered almost exclusively from a generalized form of epilepsy and had a normal to subnormal (I.Q. > 75) functioning level. This means that all parts of the brain cortex are subject to epileptic discharges, through which sleep can be more affected.
Finally, the diphenylhydantoin group consists of subjects which have a severe form of epilepsy (mostly partial epilepsy with secondary generalization), and of which the epileptic abnormalities are only part of more generalized disturbances in cerebral functioning.

When the treatment with antiepileptics was unable to control the epilepsy, patients were treated with two antiepileptics. From our investigations it appeared that both antiepileptics affected the sleep though unequally. With the combination of carbamazepine and sodium valproate there was a predominant carbamazepine effect and with the combination of hydantoin and sodium valproate, there was a predominant hydantoin effect.

Because an antiepileptic can affect the epileptic EEG manifestations as well as the sleep, it is not surprising that some authors are of the opinion that a better adjustment of the epilepsy is accomplished also by an improved sleep regulation (Röder and Wolf, 1980) and further, that a disregulation of the sleep can precede a deterioration of the epilepsy (Arguner, 1977).

b. The influence of a combined therapy of antiepileptics and benzodiazepine derivatives on the sleep structure.

It is now generally accepted that part of the activity of benzodiazepines is brought about by an activation of a GABA system and through an influence on the limbic system (McCarley, 1982; Gallager, 1982). Most benzodiazepine derivatives give rise to an increase of the light N.REM 1-2 sleep and a prolongation of the first cycle length (Johnson and Spinweber, 1981). We found similar effects in epileptics treated with antiepileptics in combination with chlorazepate and clonazepam on the sleep following one night TSD. Both groups, however, differed clearly from each other. The expected rise in the deep N.REM 3-4 sleep as a consequence of sleep deprivation, was seen when chlorazepate was taken, but not following the intake of clonazepam. There too the problem exists that patients treated with clonazepam often had a more severe form of epilepsy, mainly based on generalized organic brain damage.

One could wonder whether the sleep changes are directly the consequence of the action of antiepileptics and benzodiazepine derivatives on cortical neurons, or to which degree they are based on a suppression of the regulatory mechanisms and the release of neurotransmitters (e.g. serotonin), which are of importance for the induction of deep N.REM sleep and REM sleep. However, it remains of interest that benzodiazepine derivatives, given in therapeutic doses and even in combination with high doses of antiepileptics, change the sleep following TSD in epileptics in such a way that one can derive their mechanism of action from these.

### 2.6. Age and the influence on sleep (Chapter VI-VII)

Brain maturation is a gradual process which can proceed till the age of 15-20 years. An age-dependent effect on the sleep structure is known (Fischgold et al., 1959) as well as the age-dependent occurrence of certain forms of epilepsy (van Heycop ten Ham, 1974; Jeavons, 1977; Matthes, 1969).

The first and second sleep cycle of an all-night sleep is on the average longer in patients below the age of 20 years than in healthy subjects of the same age. This prolongation is due to an increase of N.REM sleep which in subjects below the age of 20 years is predominantly due to a very strong rise in the amount of deep N.REM 3-4 sleep. This increase can be associated with a pronounced somatic growth during this age period in which there is a greater need of

substances such as the growth hormone mainly released during N.REM 3-4 sleep (Monnier and Gaillard, 1980).

The deprivation effect following one night TSD was more pronounced in patients below the age of 20 years. Below the age of 20 years, and when no antiepileptics were taken, the deprivation effect was age-independent. When antiepileptics were taken, there was a reinforcement of the deprivation effect (more deep N.REM 3-4 sleep), but this effect diminished with aging. The patient group between 5 and 9 years old differed, but this population group consists of severe brain damaged children which often have multiple handicaps. It seems as if the treatment with antiepileptics allows young epileptics to compensate faster for the deprivation effect.

The effect of benzodiazepine derivatives is strikingly age-dependent. The deprivation effect is reinforced below the age of 20 years, but above 20 years it is complemented by a benzodiazepine effect. This gave rise to a strong prolongation of the cycle length, respectively due to an increase of deep N.REM 3-4 sleep with respect to the deprivation and an increase of N.REM 1-2 sleep and a decrease of the REM sleep with respect to the benzodiazepine derivatives.

Our data show that the age limit of 20 years is important for the way the brain reacts to the medication as well as to the sleep deprivation. The latter is in agreement with the findings in the literature (Ritter et al., 1977). The age factor has, therefore, to be taken into account in evaluating sleep structure.

### 2.7. Changes of the morphological aspects of the EEG fitting with epilepsy and sleep (Chapter IX)

It is known since a long time that sleep can change the electroencephalographic configuration of epileptic EEG abnormalities and that certain sleep patterns and phenomena in epileptics have a-specific characteristics. We found analogous changes during the sleep in epileptics following one night TSD.

a. Changes of the epileptic EEG phenomena.

Since brain functioning during N.REM and REM sleep differs from each other in many aspects, it is not surprising that both forms of sleep differentially affect the epileptic EEG phenomena. During light N.REM 1-2 sleep, a stage considered as a condition of deactivation and diminished cortical inhibition, spikes developed to polyspike wave paroxysms and focal discharges spread to other areas in many patients.

It is likely that this process is favoured during N.REM 1-2 sleep if one accepts that the spike is based on a summation of a large number of excitatory postsynaptic potentials occurring simultaneously in large groups of cortical neurons. One can state that when these changes occur to a moderate extent they point at an adequate functioning of cortical neurons. For a clinical interpretation it is of great importance to take these changes into consideration. In our own investigations (Declerck et al., 1982) we found that in 32 % of the patients, which had generalized spike wave paroxysms during a routine EEG recording, only had spike wave paroxysms during N.REM 1-2 sleep. Further, when epileptic EEG abnormalities were present only during N.REM 1-2 sleep, 70 % of the PSW paroxysms correlated clinically with a primarily generalized form of epilepsy.

We often observed that the epileptic focus was better circumscribed during REM sleep (in accordance with the literature), but also an increment in the quantity and specificity of the epileptic abnormalities was found. The latter almost exclusively concerned temporarily localized foci. This finding agrees with findings of Wieser (1982) which established a decrease of cortical spiking during REM sleep, except in foci localized in the limbic system and the supplementary motor area. Though not yet statistically confirmed in our material, these changes appear to correlate with the stability and density of REM sleep.

b. Changes of the sleep parameters.
Apart from the epileptic EEG abnormalities also the sleep parameters can undergo changes. To the most cited ones belong an increase in sharp vertex waves and sharp K-complexes, EEG phenomena which can be present to an even more frequently during sleep following one night TSD (Klingler et al., 1982). We can confirm this finding. In addition, we found that when the epilepsy was well-controlled the sleep became more stable and this was associated with an increase in sleep spindles (Sengoku and Wolf, 1981; Declerck et al., 1982).
Except for an increased number in K-complexes we would like to draw attention also to the sharp aspect of the K-complexes found in epileptics. It is often difficult to differentiate these from the very short generalized aspecific spike wave paroxysms especially when they occur in short series. We have as yet been unable to investigate whether both phenomena are based on a similar hypersynchronous mechanism (Niedermeyer, 1981).

2.8. The value of the total sleep deprivation method (Chapter X)

Within the scope of supplementary epilepsy investigations we studied whether the sleep recording following one night TSD is an effective and practical diagnostic method. On the basis of our experience we proposed three procedures which, depending on the indication, were sufficient to study the epileptic EEG and the sleep changes in relation to each other as well as with respect to the treatment.

The first or simple procedure was especially focussed on the diagnosis of epileptic EEG abnormalities. During this procedure a sleep cycle is recorded during which all sleep stages are normally present. These are required to promote the occurrence of epileptic EEG abnormalities and changes in their morphology. In addition, their occurrence is promoted by the changes of wakefulness occurring during the sleep latency period as well as of the sleep occurring during the first sleep cycle, as a consequence of the sleep deprivation. Following TSD, wakefulness is characterized by continuous fluctuations of vigilance, during which continuous microarousals are necessary to keep awake. These arousal reactions are based on hypersynchronization of mechanisms which mainly favour the occurrence of generalized epileptic discharges. Similar fluctuations occur in a more pronounced way during the sleep following TSD and give rise to the appearance of more sharp vertex waves (Wittenbecher and Kubicki, 1982), more sharp and epileptic K-complexes (Niedermeyer, 1981) and delta paroxysms (Naitoh et al., 1982) or phenomena which are also based on hypersynchronization.

Although the mentioned morphological changes following sleep deprivation can also occur in subjects which do not have epilepsy (Klingler et al., 1982) especially in young people (Ritter et al., 1977), we never observed specific epileptic EEG phenomena in patients which do not have epilepsy (Arné-Bess et al., 1982). It is therefore of utmost practical importance to clearly differentiate both types of EEG abnormalities in order to avoid a wrong diagnosis. If we applied only this simple method, then the percentage diagnostic confirmation would have been about 80 % of the results achieved from a long-term investigation consisting of two or more sleep cycles.

The second or complex method is focussed on the one hand on forms of epilepsy which can only be diagnosed and differentiated with difficulty and on the other hand, on evaluation of the sleep in relation to the epileptic EEG abnormalities present and the drug treatment.

The results obtained during the sleep latency period and the first sleep cycle are obviously equal to those obtained using the simple procedure. The absence of the expected sleep deprivation effect during the first sleep cycle can point at a severe brain disturbance or at the presence of a non-epileptic disturbance of the sleep or at the intake of antiepileptics. Especially the second sleep cycle following TSD is very useful for the study of sleep since its structure hardly differs from the second sleep cycle of an all-night sleep. On the basis of the composition of second sleep cycle it is possible to find out how and to what degree sleep in epileptics differs from that in healthy subjects of the same age, depending on the kind and degree of the epilepsy and its treatment.

Such an analysis is not only of importance for quantifying the sleep but also for determining the epilepsy. It has been established that a deterioration of epilepsy can be preceded by a disregulation of the sleep (Arguner, 1977) and that normalization of sleep can be an early sign of an effective treatment with antiepileptics (Sterman and Shouse, 1980).

The third or directed method is required especially for a detailed study of EEG phenomena which can help in making a better differential diagnosis, or to better evaluate a therapeutic effect. Therefore it can be necessary to extend the method of recording (number and localization of skull electrodes) and of the methods of analysis (automatic). By way of example we mention the evaluation of sharp K-complexes, which may occur in youths or in epileptics. In youths, these physiological sharp K-complexes are maximally localized on the vertex region whereas in epileptics they appear more in the frontal area (Niedermeyer et al., 1981). One could also study the relationship between K-complexes and sleep spindles, two phenomena occurring during the light N.REM 1-2 sleep, but which are based respectively on an excitatory and an inhibitory mechanism (Naitoh et al., 1982).

## XI.3. CONCLUSIONS AND PERSPECTIVES

From our study we can conclude that a sleep recording following one night TSD, under certain conditions, is a very suitable method to establish epileptic EEG abnormalities and to evaluate these in relation to sleep in epileptics and, to evaluate the sleep in function of the presence or absence of epileptic EEG abnormalities and the medi-

cation taken. We consider that the following conditions are very important: (1) a sufficient control on the efficacy of remaining awake during the TSD period, (2) carrying out a sleep recording according one of the three procedures proposed (Chapter X) depending on the indication made, (3) describing and analyzing in a standardized way the epileptic and non-epileptic EEG abnormalities, (4) being familiar with the EEG changes which may occur with respect to the interaction between epilepsy, sleep, sleep deprivation and antiepileptics and (5) taking the age into account (especially younger or older than 20 years) and the existence of severe non-epileptic diseases.

To understand the interaction between sleep and epilepsy some knowledge of the physiological and pathophysiological mechanisms of origin is required, in addition to the way by which different antiepileptics can affect these mechanisms. This mutual influence can be expressed both in a change of the epileptic EEG pictures and in the change of the polygraphic sleep patterns. It is therefore of importance to study both aspects in relation to each other. According our opinion the procedures mentioned would improve the diagnosis of epilepsy as well as the choice of treatment and guidance of the epileptic patients. In order to realize this it is required to complement the visual analysis by automatic methods of analysis of which a number of examples are mentioned in Addendum 1. It is therefore necessary to extend our investigations in the future in order to answer the following questions.

Question 1: Is there an antagonism between sharp vertex waves and K-complexes on the one hand or sleep spindles on the other hand? Is their mutual relationship predictive for the probability that epileptic EEG discharges occur and for the therapeutic effect of the medication given?
In our investigation we repetitively found that a normalization of the quantity of spindle activity is coincident with an improved regulation of epileptic and sleep abnormalities (Declerck et al., 1982a,b).

Question 2: To which degree are the changes in the sleep of epileptics useful as an additional parameter to better treat the epileptic and for the overall functioning of the patients?
During our investigations we found that an improved sleep pattern coincided with a better adjustment of the epilepsy, but also with a much better functioning of the patient. In addition we regularly found that due to the medication there were clear qualitative changes of the delta sleep.

Question 3: Is it possible to improve the quality of the 24-h ambulatory EEG recordings to such extent that they are suited for an automatic and quantitative analysis such that the gradation and fluctuation of the vigilance during day time can be determined precisely and in relation to the sleep?

## CHAPTER XII: SUMMARY

The present study dealt with the interactions between epilepsy, sleep and antiepileptics as based on clinical neurophysiological investigations.

In chapter I, the question discussed was whether a polygraphic sleep registration following one night total sleep deprivation (TSD) is a suitable method for the investigation of these interactions and what criteria needed to be fulfilled in order to optimalize such a recording.

In chapter II the findings from the literature are summarized and are divided into two parts. Part 1 treats the generally applied definitions of the EEG phenomena fitting with sleep and epilepsy and the criteria employed to classify the different forms of sleep and epilepsy. Part 2 surveys the different sleep methods which have been applied in order to register epileptic EEG phenomena and the sleep changes which may occur in epileptics in relation to the epilepsy and the intake of antiepileptics.

There exists an overall consensus that epileptic EEG abnormalities, of both the generalized and partial type, increase mostly during light N.REM 1-2 sleep. In contrast to REM sleep, during N.REM 1-2 sleep more polyspike wave formation occurs, and these show a greater anatomical spread. It is generally accepted that sleep is not affected by epileptic discharges except for the occurrence of some morphological changes. However, sleep can be affected by the prolonged intake of antiepileptics.

In chapter III questions are formulated which could not be answered by studying the literature. These questions are necessary to determine the advantages and disadvantages of sleep recordings following one night TSD. Our own investigations aimed at answering these questions.

Chapter IV describes materials and methods. The material consisted of more than 1500 polygraphic sleep recordings carried out during the period 1976-1981, in subjects which have or were suspected of having epilepsy. Of these 70 % are recorded following one night TSD each lasting 3-5 h and 30 % are recordings from the normal nocturnal sleep. All recordings were carried out with a 16- or 21-channel electroencephalograph of which minimally 12 channels were used for recording EEG potentials.

On the basis of the visual analysis, the sleep structure is represented in a hypnogram and underneath the following data are described: the quantitative composition and the qualitative aspects of the sleep; type, duration and quantity of epileptic abnormalities in relation to the kind and depth of sleep. Since 1979 the visual analysis of sleep is complemented by an automatic computerized sleep analysis and classification method.

Chapter V describes the extent of the confirmation of epilepsy achieved during sleep. In an unselected population of patients suspected of having epilepsy, the diagnostic gain reached 25 to 32 % on the basis of a sleep investigation as compared to a routine EEG investigation carried out during day time. This gain amounts up to 50 % for patients of whom, on a clinical basis, the diagnosis of epilepsy was very likely. Of the 395 patients which clinically very

probably had no epilepsy, in only 3 patients were specific epileptic EEG abnormalities observed during the sleep as opposed to 2 during a routine EEG investigation. Of the patients in whom clinical diagnosis of epilepsy was certain, specific epileptic EEG abnormalities were found in more than 84 % during sleep.

The percentage gain obtained by recording an all-night sleep is for the generalized epilepsy 6 % higher than during a sleep recording following one night TSD and equal for the partial epilepsy. In accordance with the literature most epileptic EEG abnormalities occur during N.REM 1-2 sleep and during the beginning of the sleep recording. Important is the finding that in about 13 % of the patients epileptic EEG abnormalities are only seen during the second sleep cycle, and in about 7 % only after a recording lasting more than 2 h. In addition, for a number of patients suffering from generalized epilepsy recording of deep N.REM 3-4 sleep is necessary.

Complementing the long term sleep recording following TSD which normally has at least two sleep cycles, with hyperventilation and/or intermittent light flashes, has only a very limited value. In addition, such investigations are burdensome for some of the patients.

The general conclusion is that the sleep recording of two sleep cycles following one night TSD are considered as optimal for the establishment of epileptic EEG phenomena.

Chapter VI deals with the quantitative changes of the composition of the first and second sleep cycle during the habitual nocturnal sleep in epileptics in comparison with a healthy control group. All patients have a longer cycle duration, due to more N.REM sleep, especially light N.REM 1-2 sleep. The differences are smallest for those patients which have epileptic EEG abnormalities during the sleep and which take antiepileptics. By adding benzodiazepine derivatives to the antiepileptics, N.REM 1-2 sleep increased. Depending on the type of epilepsy, only small differences were seen: more N.REM 1-2 sleep in the category with generalized forms of epilepsy, more REM sleep for the partial form of epilepsy and an increase of N.REM 1-2 as well as REM sleep when both forms of epilepsy co-exist.

In chapter VII the composition of the first and second sleep cycle following one night TSD in epileptics as compared to that of healthy subjects is described. The presence or absence of epileptic EEG abnormalities during sleep and the differences in sleep structure depending on whether antiepileptic medication is taken or whether antiepileptics are combined with benzodiazepine derivatives was investigated. The results show that during the first sleep cycle in epileptics as well as in healthy subjects the sleep deprivation effect dominates over other influences cited for the all-night sleep. The sleep pattern following TSD is affected in a stereotyped way: there is a shortening of the sleep latency and of the total duration of the first sleep cycle. This is due to a decrease in N.REM sleep in which there is a relatively increased deep N.REM 3-4 sleep as opposed to light N.REM 1-2 sleep. These effects almost disappear during the second cycle, which resembles in many aspects, the second sleep cycle of all-night sleep. In this chapter the importance of the age factor, especially the 20-year limit is stressed. The deprivation effect is more pronounced below the age of 20 years and this is further accentuated in patients taking benzodiazepine derivatives. Above the age of 20 years the deprivation effect is less pronounced, but is

complemented by a benzodiazepine effect which expresses itself by a lengthening of N.REM 1-2 sleep.

In chapter VIII it is described that the sleep composition of the first sleep cycle following one night TSD in epileptics treated with one or with maximally two antiepileptics, depended on the type of the antiepileptic medication taken. The effect of the deprivation is reinforced by the intake of carbamazepine and to a lesser extent by the intake of sodium valproate, but is neutralized by the intake of hydantoin derivatives. As compared to healthy subjects, the total cycle length of the first sleep cycle is prolonged by the intake of hydantoins and valproate derivatives. The prolongation seen after hydantoin derivatives is mainly due to an increase in light N.REM 1-2 sleep and with the intake of valproate, due to a smaller increase in light N.REM 1-2 sleep and a more pronounced increase of deep N.REM 3-4 sleep. We could also demonstrate that benzodiazepine derivatives given in combination with antiepileptics affect the composition of the first sleep cycle following TSD and that the kind and size of these changes depended on the benzodiazepine derivative taken. In addition, it is pointed out that the registered differences in the sleep composition as a consequence of the intake of antiepileptics or benzodiazepines are also dependent on the type and the intensity of the brain disturbances, responsible for the existence of epilepsy.

Chapter IX is composed of a series of investigations dealing with on the one hand the changes in the form of the epileptic EEG phenomena which may occur during the sleep and on the other hand the changes in the polygraphic sleep phenomena as a consequence of the epilepsy and its treatment. It is important to be aware of these changes as well as of their clinical significance in order to adequately interpret the epileptic EEG abnormalities during the sleep.

Further, we also show that certain changes seen during an all-night sleep recording in epileptics occur in a similar way, e.g. periods of apnea or even in a more pronounced way e.g. sharp K-complexes during the sleep following one night TSD. Certain changes which may be associated with the medication taken, such as a decrease in fast eye movements or muscle activity make these parameters less suitable as criteria to differentiate the kinds of sleep. This objection is most important when automatic sleep classifications are used.

In chapter X, 3 sleep procedures following one night TSD differs, according to the aim of the study. The first or simple procedure mainly serves for the diagnosis of epilepsy. The second or complex and more elaborate procedure is aimed at studying epilepsy, sleep and the influence of antiepileptics. Finally, the third or specific procedure denotes that it can be necessary to adapt the recording and analysis due to the aims of the investigation.

Chapter XI is the general discussion and consists of 3 parts. In the first part we discussed the physiological and pathophysiological regulatory mechanisms of sleep and epilepsy, by which we gain some insight into the way they may affect each other.

In the second part we discussed the results of our own investigations on the basis of these insights, and show how our results differ in certain aspects from the data in the literature. We also aim to explain the differences in the sleep structure of the first sleep

cycle following one night TSD depending on the type of antiepileptic medication taken, on the basis of their postulated mechanisms of action.

In the third part some of the important conditions of the TSD procedure which need to be fulfilled in order to achieve an optimal diagnostic gain are described. Further, some recommendations for further investigations are given.

The addenda contains a discussion of the automatic sleep stage classification (Add. 1) and the statistical method applied (Add. 2). Thereafter, follow a series of tables which contain supplementary data concerning differences in the composition of the first and second sleep cycle of the all-night sleep, the sleep following one night TSD (Add. 3) and finally, a list of all figures and tables is given (Add. 4).

## CHAPTER XIII: ADDENDA

Addendum 1: Experiences with automated sleep analysis.

Addendum 2: Statistical method.

Addendum 3: Tables with complementary data, corresponding with the simplified tables mentioned in the chapters VI, VII and VIII.

Addendum 4: List of tables and figures.

## ADDENDUM 1: EXPERIENCES WITH AUTOMATED SLEEP ANALYSIS

(W.L.J. Martens)*

### Add. 1.1. SLEEP CLASSIFICATION

The first (Wauquier et al., 1979) and the second method (Martens et al., 1981) of automated sleep analysis, as described previously (IV.2.2.) are based on an on-line procedure in which a set of parameters is extracted from the running EEG, and an off-line procedure, to classify the sleep, which is the same for both methods.

In the off-line procedure (Wauquier et al., 1979) the parameters are displayed over the whole registration time up to 8 hours. Then their validity is evaluated and a selection is made of those parameters which could be useful to classify sleep. Thereafter, 5 epochs are chosen visually as being representative examples of the various sleep stages for each individual patient. Finally the classification is carried out automatically by calculation of the "distances" of each consecutive epoch to the different sleep stages and labelling the epoch with the sleep stage.

The most relevant parameters appear to be: (1) the delta time-course for all the sleep stages, (2) the sleep spindle time-course of the N.REM 2 sleep, (3) the alpha time-course for the detection of awake periods and for discrimination between awake and REM sleep, (4) muscle activity to detect movement artefacts, and (5) the time-course of rapid eye movements.

Using the first method, there was a good agreement between the visually and the automatically scored hypnograms for the N.REM 2 and N.REM 4 (more than 90 %) and the REM sleep (more than 80 %), but the correlation was rather poor (less than 70 %) for the N.REM 1 and the N.REM 3 sleep stages. This can be caused by the fact that the criteria of Rechtschaffen and Kales are not completely covered by the parameters used for the automatic classification (e.g. sharp vertex waves and K-complexes are not estimated) and by the method of quantification based on power density spectra (one does not know in which percentage of time an EEG rhythm is present within a certain epoch). In the second method the agreement between the visual and the automated sleep classification could be improved by (1) a reduction of the variance of the different time courses of the parameters measured; (2) a compensation for the interaction of some parameters; (3) an appropriate recognition of artefacts and (4) an extension of the set of parameters.

### Add. 1.2. QUANTIFICATION OF THE PARAMETERS

In the on-line procedures of both methods the time signals are segmented into epochs of 30 seconds and power density spectrum analysis is carried out on the T4-C4 and the P4-O2 EEG derivations.

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In the first method an estimation of the activity of the various EEG rhythms is obtained by integration of the power density from 0.5 to 3.5 Hz, from 3.5 to 7.5 Hz, from 7.5 to 11.5 Hz and from 11.5 to 20.5 Hz. In the second method the integration of the power density is restricted to peaks, with as a result a reduced variance in the delta, theta and alpha time courses. Besides, by displaying the two frequencies of these rhythms where the power density is decreased to half the maximal power density of the peak, it is possible to get an impression not only of the peak frequency of the rhythms (or low frequency artefacts) but also of their time behaviour. A narrow "double" trace as shown in Figure IV.6. (IV.2.2.) corresponds to a stable rhythm within an epoch (e.g. a pure sine wave) while somewhat broadened tracings reflect stochastic variability. These tracings are only indicated if they exceed the visually determined levels.

In the first method sleep spindles are detected after a further segmentation of a 30-second epoch into time segments of 0.8 seconds, followed by spectral analysis and evaluation of the 11.25 to 15 Hz frequency band. In the second method a matched filter with adjustable peak frequency and bandwidth is calculated from the spectrum of each epoch and thereafter this filter is applied to the corresponding EEG signal. The resulting improvement of the signal to noise ratio facilitates detection of sleep spindles and calculation of their duration. Peak frequency and time duration of sleep spindles are also indicated as time courses. The bandwidth of the filter, matched to sleep spindles, appears to be about 1 Hz on average; as a result, detection is much less sensitive to disturbing activities compared to a more conventional approach considering the 11-15 Hz frequency band.

If sleep spindles have been detected, the corresponding part of the spectrum is set to zero; also the first harmonic of the alpha rhythm is removed from the spectrum and then the beta activity is estimated by integration of the power density from 11.5 to 25 Hz. As a result, the alpha, beta and sleep spindle time courses appear to have independent behaviour over time, which has beneficial effects for the sleep classification.

In the first method the mean amplitude of the EMG and EOG derivations are calculated for each epoch. In the second method, rapid eye movements are detected using a filter, matched to REM's and an inverse filter, to reduce the influence of EEG activity.

In Figure IV.6. (IV.2.2.) the various parameters show a rather smooth behaviour over time. This is caused by their more optimal quantification and by application of off-line smoothing to the various parameters. By this procedure ("Wiener" filtering, described by de Weerd and Martens, 1978), a slowly changing parameter is smoothed heavily and a quickly changing parameter only slightly. This leads to a better estimation of the various time course parameters by combining a maximal reduction of variance to a minimal distortion.

A future extension of the method will concentrate on quantification of phenomena such a sharp vertex waves, K-complexes and paroxysmal discharges. However, although all the refinements, as mentioned, will improve the agreement between the automatically and visually scored sleep classification, one may wonder if this is the only goal of the automated EEG analysis. In our department, the rough plot of the different parameters without classification are presented to the physician as a pre-screening. It can help him to interpret the EEG

in a more objective and faster way. Afterwards, with the visual analysis as a guide line, one can select from the parameter plot well-defined periods of neurophysiological stability as e.g. the N.REM 2 and 4 stage. The great number of objective measurements now allow valid statistics on these periods to be made and allow inter- as well as intra-individual comparisons (Declerck et al., 1982).

The author wishes to thank Dr. A. Wauquier, J.L. Verheyen, W.A.E. Van den Broeck and Dr. P.A.J. Janssen for getting the disposal of their software sleep analysing method.

## ADDENDUM 2: STATISTICAL METHOD (W.L.J. Martens)

### INTRODUCTION

In this study the aim was to get an idea of the sleep composition of various groups of patients showing different forms of epilepsy and/or medication. Therefore from the total patient group various subgroups were formed and the composition of their first and second sleep cycle was calculated. The only purpose of the statistics, as used in this study, was to indicate to what extent clear, clinically relevant findings could be relied upon in extrapolating the findings from a certain subgroup (a sample, e.g. 50 patients having partial epilepsy) to the corresponding population (all patients in the world having partial epilepsy). Therefore, so-called confidence intervals for the means were calculated; apart from the extrapolating power of such intervals they also can easily be compared to another in direct graphical representations (see e.g. Figure VI.16.), thus yielding a procedure of testing for significance of differences between sample means. Compared to the classical t-testing for significance of difference between two sample means (which is equivalent to testing, whether the confidence interval for the difference of two sample means includes zero and which therefore is focussed on the rejection of the hypothesis, that there is no difference) the comparison of the confidence intervals of two sample means will result into lower levels of significance, especially when these samples show different sizes and variances, which was often the case in this study.

### CRITERIA FOR A SLEEP CYCLE

In Figure Add. 2.1. histograms are shown of the minutes awake, N.REM 1-2, N.REM 3-4 and REM sleep of the first cycle after one night sleep deprivation as derived from the total patient group (n: 548) who showed an appropriate first cycle. A first sleep cycle was rejected if it contained:

> 60 minutes awake or
> 120 minutes N.REM 1-2 or
> 120 minutes N.REM 3-4 or
> 60 minutes REM sleep.

The second cycle was rejected according to the same criteria, or in case of an inappropriate first cycle.

### CONSTRUCTION AND USE OF CONFIDENCE INTERVALS FOR THE MEAN

By defining

$$\bar{x} = \frac{1}{n} \sum_{i=1}^{n} x_i = \frac{1}{n} \Sigma x$$

as the mean of a parameter x of a certain sample with size n (e.g. 50 patients having partial epilepsy), this $\bar{x}$ is an estimate of the true mean $\mu$ of the population (all patients in the world having partial epilepsy).

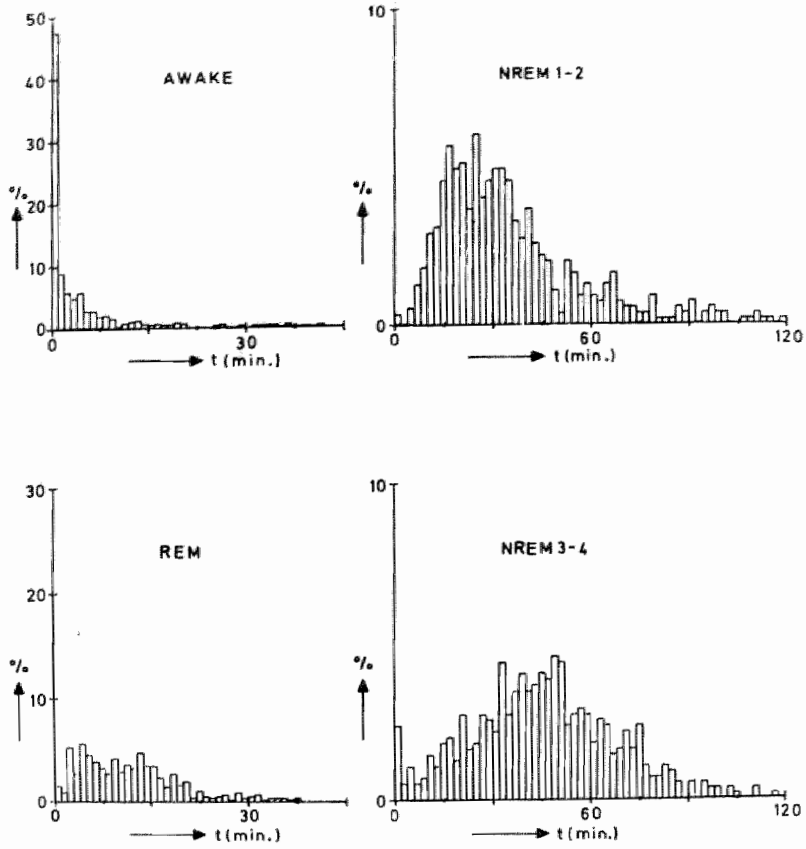


FIG. ADD. 2.1.
Histograms of minutes awake, N.REM 1-2, REM and N.REM 3-4 sleep of the first cycle after one night sleep deprivation of the total patient group (n: 548).

By defining:

$$s = \sqrt{\left\{\frac{1}{n-1} \sum (x - \bar{x})^2\right\}}$$

as the standard deviation of the parameter x of the sample, this s is an estimate of the true standard deviation $\sigma$ of the population.

Let us define:

$\upsilon = n - 1$

as the number of degrees of freedom of the sample.

By considering another sample, of course another $\bar{x}$ and s will be found; so $\bar{x}$ and s can be considered as stochastic variables. For the mean of the means of all possible samples it yields:

$$\mu_{\bar{x}} = \frac{1}{m} \Sigma \bar{x} = \mu$$

If the size n of the samples is not too small then for the standard deviation of the means of all samples it yields:

$$\sigma_{\bar{x}} = \frac{\sigma}{\sqrt{n}}$$

This $\sigma_{\bar{x}}$ is called the standard error of the mean (S.E.M.). If the distribution of the parameter x is about Gaussian, the means of the samples with size n appear to vary around the real mean $\mu$ according to a Gaussian distribution having a standard deviation $\sigma/\sqrt{n}$ (see Figure Add. 2.2.).

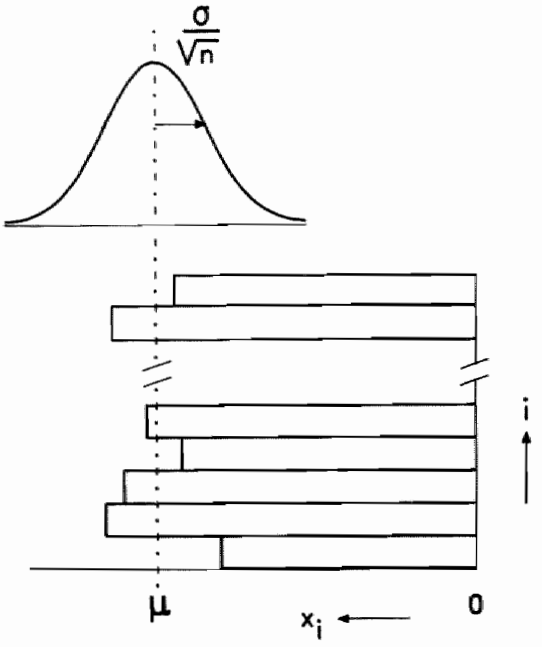


FIG. ADD. 2.2.
Distribution of the sample means with size n.

However, $\sigma$ is unknown mostly; now one can use the standard deviation, as measured from a sample, for an estimated S.E.M.

$$s_{\bar{x}} = \frac{s}{\sqrt{n}}$$

By subtraction of the mean and division by the estimated S.E.M., one arrives at the quantity:

$$t = \frac{\bar{x} - \mu}{s/\sqrt{n}}$$

which follows a so-called STUDENT-distribution with a number of n-1 degrees of freedom; the distribution is symmetrically around the mean $\mu_t$ with:

$\mu_t = 0$

and

$\sigma_t = \sqrt{\{\upsilon(\upsilon - 2)\}}$

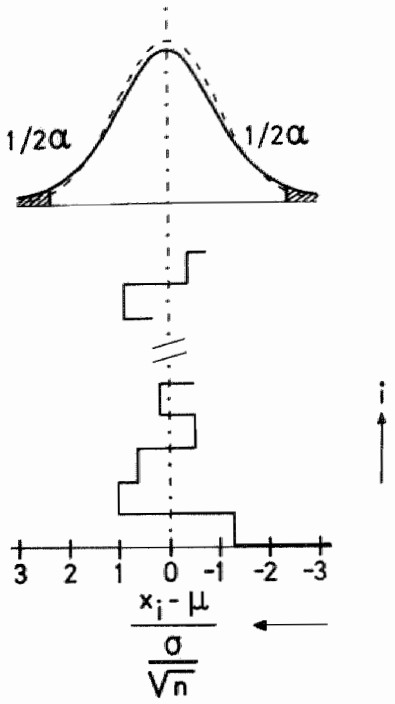


FIG. ADD. 2.3.
Distribution of normalized sample means with size 6.

In Figure Add. 2.3. the STUDENT-distribution is depicted for $\upsilon = 5$; the dashed line indicates a Gaussian distribution having zero mean and standard deviation 1. With an increasing number of degrees of freedom - so with increasing sample size - the STUDENT-distribution approximates the Gaussian.

The 1/2 α percentiles of both these distributions are listed in almost any statistical handbook.

Without exact knowledge of μ and σ of the population, one can construct a so-called (1 - α) x 100 % confidence interval for the mean of an ad random sample with size n by taking:

$$\bar{x} \pm t_{1/2\,\alpha} \frac{s}{\sqrt{n}}$$

This interval is determined by:

1. the sample mean $\bar{x}$
2. the sample standard deviation s
3. the sample size n
4. the $1/2\,\alpha$ percentile of a STUDENT-distribution with n-1 numbers of freedom
5. the required level of confidence (95 %, 99 %, etc.).

Apparently the confidence intervals are increasing with a higher level of confidence and decreasing with an increasing sample size. Considering confidence intervals for the means of several ad random samples from the population, the population mean $\mu$ will be within these intervals in an $(1-\alpha)$ x 100 % percentage.

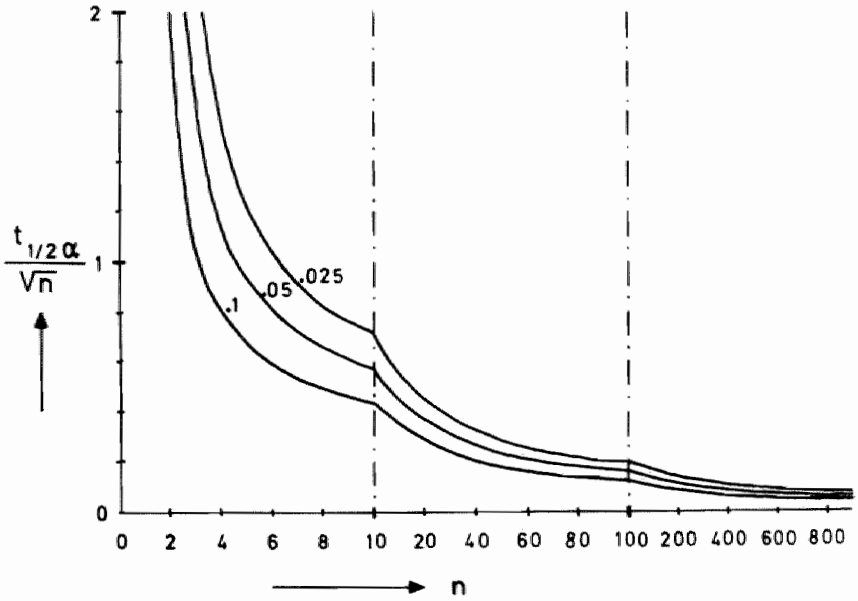


FIG. ADD. 2.4.
The quantity u as a function of the sample size n for $1/2\alpha$ = 0.1, 0.05 and 0.025.

In Figure Add. 2.4. the quantity

$$u = \frac{t_{1/2\,\alpha}}{\sqrt{n}}$$

is depicted for $1/2\alpha$ = 0.1, 0.05, and 0.025.

This quantity indicates, which portion of a measured standard deviation of a sample - having size n - has to be taken into account for the construction of the confidence interval around the measured mean of the sample.

Example

Suppose, sample 1 with size 5 has a mean $\bar{x}_1$ and standard deviation $s_1$ and another sample 2 with size 8 has a mean $\bar{x}_2$ and $s_2$. From Figure Add. 2.4. it follows for both 90 %, 95 % and 97.5 % one-sided confidence intervals:

| | 90 % | 95 % | 97.5 % |
|---|---|---|---|
| Sample 1 | $\bar{x}_1 \pm 0.68 \times s_1$ | $\bar{x}_1 \pm 0.94 \times s_1$ | $\bar{x}_1 \pm 1.24 \times s_1$ |
| Sample 2 | $\bar{x}_2 \pm 0.5 \times s_2$ | $\bar{x}_2 \pm 0.66 \times s_2$ | $\bar{x}_2 \pm 0.82 \times s_2$ |

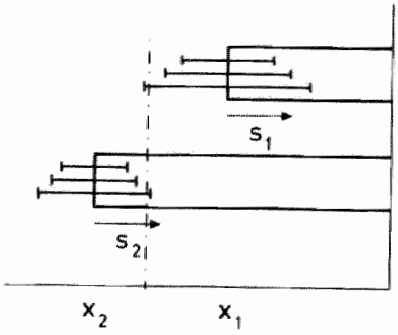


FIG. ADD. 2.5.
Two-sided confidence intervals for $\bar{x}_1$ and $\bar{x}_2$; $1/2\alpha$ = 0.1, 0.05 and 0.025.

By comparing lower and upper bounds of the confidence intervals (Fig. Add. 2.5.) of the two samples at the same confidence level, it will be clear that in this case the conclusion is:
sample 2 has a larger mean than sample 1 at a significance level of at least 0.05 ($p < 0.05$).

Once the confidence intervals for the means of various samples, having various sizes, have been constructed at various levels of confidence, all these sample means can be compared one to another on various levels of significance.

We are very grateful to Dr. A. Clincke for his valuable advice and discussion.

## ADDENDUM 3: TABLES (bis) WITH COMPLEMENTARY DATA, CORRESPONDING TO THE SIMPLIFIED TABLES MENTIONED IN THE CHAPTERS VI, VII, AND VIII

TABLE VI.12. bis
Comparison of the sleep pattern of the first all night cycle: control group versus the different clinical groups (mean, standard deviation (SD), confidence intervals for the mean ($1/2\,\alpha = 0.05$, 0.025).

| Cy. 1 n | Total cycle | Time awake | Effective sleep time | N.REM sleep | REM sleep | N.REM 1-2 | N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| CO 9 | | | | | | | |
| mean | 85.5 | 7.7 | 77.8 | 70.4 | 7.4 | 39.2 | 31.2 |
| SD | 13.6 | 8.9 | 14.1 | 10.2 | 8.7 | 14.2 | 11.4 |
| 0.8 | ± 6.4 | ± 4.2 | ± 6.6 | ± 4.8 | ± 4.1 | ± 6.6 | ± 5.3 |
| 0.9 | ± 8.4 | ± 5.5 | ± 8.8 | ± 6.3 | ± 5.4 | ± 8.8 | ± 7.1 |
| 0.95 | ± 10.5 | ± 6.9 | ± 10.9 | ± 7.9 | ± 6.7 | ± 10.9 | ± 8.8 |
| | | | | N.REM/REM: 9.5 | | N.REM1-2/3-4:1.26 | |
| N.E.-A.E. 17 | | | | | | | |
| mean | 115.9 | 16.8 | 99.1 | 87.1 | 12.0 | 56.4 | 30.7 |
| SD | 32.7 | 19.3 | 33.6 | 29.3 | 7.8 | 25.4 | 24.1 |
| 0.8 | ± 10.6 | ± 6.3 | ± 10.9 | ± 9.5 | ± 2.5 | ± 8.2 | ± 7.8 |
| 0.9 | ± 13.9 | ± 8.2 | ± 14.2 | ± 12.2 | ± 3.3 | ± 10.7 | ± 10.2 |
| 0.95 | ± 16.9 | ± 9.9 | ± 17.3 | ± 15.1 | ± 4.0 | ± 13.1 | ± 12.4 |
| | | | | N.REM/REM: 7.3 | | N.REM1-2/3-4:1.84 | |
| N.E.+A.E. 19 | | | | | | | |
| mean | 94.5 | 9.5 | 85.0 | 72.8 | 12.2 | 43.8 | 29.0 |
| SD | 24.4 | 11.2 | 26.3 | 22.1 | 10.9 | 24.2 | 16.6 |
| 0.8 | ± 7.5 | ± 3.4 | ± 8.1 | ± 6.8 | ± 3.4 | ± 7.4 | ± 5.1 |
| 0.9 | ± 9.7 | ± 4.4 | ± 10.5 | ± 8.8 | ± 4.3 | ± 9.6 | ± 6.6 |
| 0.95 | ± 11.8 | ± 5.4 | ± 12.7 | ± 10.7 | ± 5.3 | ± 11.7 | ± 8.0 |
| | | | | N.REM/REM: 6.0 | | N.REM1-2/3-4:1.51 | |
| E.+A.E. 39 | | | | | | | |
| mean * | 107.8 | 7.3 | 100.5 | 89.8 | 10.7 | 45.8 | 44.0 |
| SD | 41.5 | 12.2 | 36.0 | 36.5 | 8.6 | 27.4 | 27.9 |
| 0.8 | ± 8.7 | ± 2.6 | ± 7.5 | ± 7.6 | ± 1.8 | ± 5.7 | ± 5.8 |
| 0.9 | ± 11.2 | ± 3.3 | ± 9.7 | ± 9.9 | ± 2.3 | ± 7.4 | ± 7.5 |
| 0.95 | ± 13.5 | ± 4.0 | ± 11.7 | ± 11.8 | ± 2.8 | ± 8.9 | ± 9.1 |
| | | | | N.REM/REM: 8.4 | | N.REM1-2/3-4:1.04 | |
| A.E.+B.D. 5 | | | | | | | |
| mean | 101.8 | 4.4 | 97.4 | 83.8 | 13.6 | 52.2 | 31.6 |
| SD | 31.5 | 2.9 | 31.4 | 27.9 | 9.0 | 14.3 | 17.5 |
| 0.8 | ± 21.5 | ± 2.0 | ± 21.5 | ± 19.1 | ± 6.2 | ± 9.8 | ± 12.0 |
| 0.9 | ± 30.0 | ± 2.8 | ± 29.9 | ± 26.6 | ± 8.6 | ± 13.6 | ± 16.7 |
| 0.95 | ± 39.1 | ± 3.6 | ± 39.0 | ± 34.7 | ± 11.3 | ± 17.8 | ± 21.7 |
| | | | | N.REM/REM: 6.2 | | N.REM1-2/3-4:1.65 | |

* These values correspond with Table VI.8.

TABLE VI.13.bis

Comparison of the second all-night cycle: control group versus different clinical groups (mean, standard deviation (SD), confidence intervals for the mean ($1/2\alpha$ = 0.05, 0.025).

| Cy. 2 n | Total cycle | Time awake | Effective sleep time | N.REM sleep | REM sleep | N.REM 1-2 | N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| CO 9 | | | | | | | |
| mean | 90.1 | 3.9 | 86.2 | 70.4 | 15.8 | 40.6 | 29.8 |
| SD | 17.35 | 4.3 | 15.2 | 12.3 | 6.6 | 14.6 | 14.1 |
| 0.8 | ± 8.1 | ± 2.0 | ± 7.1 | ± 5.8 | ± 3.1 | ± 6.8 | ± 6.6 |
| 0.9 | ± 10.8 | ± 2.7 | ± 9.4 | ± 7.6 | ± 4.1 | ± 9.1 | ± 8.8 |
| 0.95 | ± 13.4 | ± 3.3 | ± 11.7 | ± 9.5 | ± 5.1 | ± 11.3 | ± 10.9 |
| | | | | N.REM/REM: 4.5 | | N.REM1-2/3-4:1.36 | |
| N.E.-A.E. 16 | | | | | | | |
| mean | 106.6 | 10.6 | 96.0 | 76.1 | 19.9 | 47.7 | 28.4 |
| SD | 20.8 | 8.9 | 20.6 | 19.5 | 8.0 | 21.3 | 20.1 |
| 0.8 | ± 7.0 | ± 3.0 | ± 6.9 | ± 6.5 | ± 2.7 | ± 7.1 | ± 6.7 |
| 0.9 | ± 9.1 | ± 3.9 | ± 9.0 | ± 8.5 | ± 3.5 | ± 9.3 | ± 8.8 |
| 0.95 | ± 11.1 | ± 4.7 | ± 10.7 | ± 10.4 | ± 4.3 | ± 11.3 | ± 10.7 |
| | | | | N.REM/REM: 3.8 | | N.REM1-2/3-4:1.68 | |
| N.E.+A.E. 16 | | | | | | | |
| mean | 98.6 | 3.1 | 95.5 | 76.9 | 18.6 | 45.3 | 31.6 |
| SD | 18.9 | 3.7 | 19.2 | 14.6 | 10.8 | 21.7 | 22.4 |
| 0.8 | ± 6.3 | ± 1.3 | ± 6.5 | ± 4.9 | ± 3.6 | ± 7.3 | ± 7.5 |
| 0.9 | ± 8.3 | ± 1.6 | ± 8.4 | ± 6.4 | ± 4.7 | ± 9.5 | ± 9.8 |
| 0.95 | ± 10.1 | ± 2.0 | ± 10.2 | ± 7.8 | ± 5.8 | ± 11.6 | ± 11.9 |
| | | | | N.REM/REM: 4.1 | | N.REM1-2/3-4:1.43 | |
| E.+A.E. 37 | | | | | | | |
| mean * | 101.9 | 5.5 | 96.4 | 79.9 | 16.5 | 50.7 | 29.2 |
| SD | 36.6 | 8.0 | 376 | 34.8 | 11.7 | 25.7 | 21.4 |
| 0.8 | ± 7.9 | ± 1.7 | ± 8.0 | ± 7.5 | ± 2.5 | ± 5.5 | ± 4.6 |
| 0.9 | ± 10.2 | ± 2.2 | ± 10.4 | ± 9.7 | ± 3.3 | ± 7.1 | ± 5.9 |
| 0.95 | ± 12.2 | ± 2.7 | ± 12.5 | ± 11.6 | ± 3.9 | ± 8.6 | ± 7.1 |
| | | | | N.REM/REM: 4.8 | | N.REM1-2/3-4:1.74 | |
| A.E.+B.D. 5 | | | | | | | |
| mean | 92.8 | 9.0 | 83.8 | 73.8 | 10.0 | 51.8 | 22.0 |
| SD | 36.3 | 7.7 | 39.6 | 40.9 | 9.4 | 31.2 | 26.5 |
| 0.8 | ± 24.9 | ± 5.2 | ± 27.1 | ± 28.0 | ± 6.5 | ± 21.3 | ± 18.2 |
| 0.9 | ± 34.6 | ± 7.3 | ± 37.8 | ± 39.0 | ± 9.0 | ± 29.7 | ± 25.3 |
| 0.95 | ± 45.1 | ± 9.5 | ± 49.3 | ± 50.1 | ± 11.7 | ± 38.8 | ± 33.0 |
| | | | | N.REM/REM: 7.4 | | N.REM1-2/3-4:2.35 | |

* These values correspond with Table VI.9.

TABLE VII.12. bis
Comparison of the sleep pattern of the first sleep deprivation cycle: control group versus the different clinical groups of patients between 20 and 40 years old (mean, standard deviation (SD), confidence intervals for the mean ($1/2\alpha$ = 0.05, 0.025).

| Cy. 1 n | Total cycle | Time awake | Effective sleep time | N.REM sleep | REM sleep | N.REM 1-2 | N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| CO 15 | | | | | | | |
| mean | 77.1 | 5.1 | 72.0 | 63.3 | 8.7 | 28.5 | 34.8 |
| SD | 15.2 | 7.3 | 18.1 | 16.0 | 6.5 | 11.3 | 18.6 |
| 0.8 | ± 5.3 | ± 2.5 | ± 6.3 | ± 5.5 | ± 2.3 | ± 3.9 | ± 6.5 |
| 0.9 | ± 6.9 | ± 3.3 | ± 8.2 | ± 7.3 | ± 3.0 | ± 5.2 | ± 8.5 |
| 0.95 | ± 8.4 | ± 4.1 | ± 10.0 | ± 8.5 | ± 3.6 | ± 6.3 | ± 10.3 |
| | | | | N.REM/REM: 7.3 | | N.REM1-2/3-4:0.82 | |
| N.E.-A.E. 48 | | | | | | | |
| mean | 94.7 | 5.2 | 89.5 | 77.2 | 12.3 | 34.5 | 42.7 |
| SD | 32.2 | 7.6 | 30.0 | 26.2 | 10.2 | 19.8 | 20.6 |
| 0.8 | ± 6.1 | ± 1.5 | ± 5.6 | ± 4.9 | ± 1.9 | ± 3.7 | ± 3.9 |
| 0.9 | ± 7.8 | ± 1.9 | ± 7.3 | ± 6.4 | ± 2.5 | ± 4.8 | ± 5.0 |
| 0.95 | ± 9.4 | ± 2.2 | ± 8.7 | ± 7.6 | ± 3.0 | ± 5.8 | ± 6.0 |
| | | | | N.REM/REM: 6.3 | | N.REM1-2/3-4:0.81 | |
| N.E.+A.E. 49 | | | | | | | |
| mean | 97.2 | 4.0 | 93.2 | 82.5 | 10.7 | 39.6 | 42.9 |
| SD | 28.2 | 6.5 | 25.7 | 25.5 | 11.8 | 20.7 | 20.7 |
| 0.8 | ± 5.2 | ± 1.2 | ± 4.8 | ± 4.7 | ± 2.2 | ± 3.9 | ± 3.9 |
| 0.9 | ± 6.8 | ± 1.6 | ± 6.2 | ± 6.1 | ± 2.8 | ± 5.0 | ± 5.0 |
| 0.95 | ± 8.1 | ± 1.9 | ± 7.4 | ± 7.3 | ± 3.4 | ± 6.0 | ± 6.0 |
| | | | | N.REM/REM: 7.7 | | N.REM1-2/3-4:0.92 | |
| E.+A.E. 94 | | | | | | | |
| mean * | 92.7 | 5.4 | 87.3 | 76.5 | 10.8 | 33.4 | 43.1 |
| SD | 29.0 | 10.5 | 25.0 | 24.5 | 10.8 | 19.3 | 20.8 |
| 0.8 | ± 3.9 | ± 1.4 | ± 3.4 | ± 3.3 | ± 1.5 | ± 2.6 | ± 2.8 |
| 0.9 | ± 5.0 | ± 1.8 | ± 4.3 | ± 4.2 | ± 1.9 | ± 3.3 | ± 3.6 |
| 0.95 | ± 6.0 | ± 2.2 | ± 5.1 | ± 5.0 | ± 2.2 | ± 4.0 | ± 4.3 |
| | | | | N.REM/REM: 7.1 | | N.REM1-2/3-4:0.77 | |
| A.E.+B.D. 11 | | | | | | | |
| mean | 108.6 | 3.5 | 105.1 | 99.9 | 5.2 | 65.1 | 34.8 |
| SD | 27.1 | 5.3 | 23.9 | 24.7 | 6.4 | 29.7 | 26.5 |
| 0.8 | ± 11.2 | ± 2.2 | ± 9.9 | ± 10.2 | ± 2.6 | ± 123 | ± 10.9 |
| 0.9 | ± 14.8 | ± 2.9 | ± 13.1 | ± 13.5 | ± 3.5 | ± 16.2 | ± 14.5 |
| 0.95 | ± 18.2 | ± 3.5 | ± 16.1 | ± 16.6 | ± 4.3 | ± 19.9 | ± 17.8 |
| | | | | N.REM/REM: 19.2 | | N.REM1-2/3-4:1.87 | |

* These values correspond with Table VII.8. (S).

TABLE VII.13. bis

Comparison of the sleep pattern of the second sleep deprivation cycle: control group versus the different clinical groups in patients between 20 and 40 years old (mean, standard deviation (SD), confidence intervals for the mean ($1/2\alpha = 0.05, 0.025$).

| Cy. 2 n | Total cycle | Time awake | Effective sleep time | N.REM sleep | REM sleep | N.REM 1-2 | N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| CO 14 | | | | | | | |
| mean | 84.4 | 2.8 | 81.6 | 69.2 | 12.4 | 38.8 | 30.4 |
| SD | 26.1 | 3.0 | 24.5 | 18.5 | 10.7 | 21.1 | 11.5 |
| 0.8 | ± 9.4 | ± 1.1 | ± 8.8 | ± 6.7 | ± 3.9 | ± 7.6 | ± 4.2 |
| 0.9 | ± 12.4 | ± 1.4 | ± 11.6 | ± 8.8 | ± 5.1 | ± 10.0 | ± 5.4 |
| 0.95 | ± 15.1 | ± 1.7 | ± 14.1 | ± 10.7 | ± 6.2 | ± 12.2 | ± 6.6 |
| | | | | N.REM/REM: 5.6 | | N.REM1-2/3-4:1.28 | |
| N.E.-A.E. 44 | | | | | | | |
| mean | 80.9 | 5.4 | 75.5 | 61.8 | 13.7 | 35.5 | 26.3 |
| SD | 25.3 | 5.8 | 26.7 | 20.6 | 12.9 | 16.4 | 17.8 |
| 0.8 | ± 5.0 | ± 1.2 | ± 5.2 | ± 4.1 | ± 2.5 | ± 3.2 | ± 3.5 |
| 0.9 | ± 6.4 | ± 1.5 | ± 6.8 | ± 5.2 | ± 3.3 | ± 4.2 | ± 4.5 |
| 0.95 | ± 7.7 | ± 1.8 | ± 8.1 | ± 6.3 | ± 3.9 | ± 5.0 | ± 5.4 |
| | | | | N.REM/REM: 4.5 | | N.REM1-2/3-4:1.35 | |
| N.E.+A.E. 43 | | | | | | | |
| mean | 91.0 | 5.4 | 85.6 | 74.6 | 11.0 | 39.3 | 35.3 |
| SD | 22.6 | 6.7 | 23.0 | 18.2 | 9.7 | 17.3 | 18.5 |
| 0.8 | ± 4.5 | ± 1.3 | ± 4.6 | ± 3.6 | ± 1.9 | ± 3.4 | ± 3.7 |
| 0.9 | ± 5.8 | ± 1.7 | ± 5.9 | ± 4.7 | ± 2.5 | ± 4.4 | ± 4.7 |
| 0.95 | ± 7.0 | ± 2.1 | ± 7.1 | ± 5.6 | ± 3.0 | ± 5.4 | ± 5.7 |
| | | | | N.REM/REM: 6.8 | | N.REM1-2/3-4:1.11 | |
| E.+A.E. 83 | | | | | | | |
| mean * | 87.6 | 7.0 | 80.6 | 70.1 | 10.5 | 35.9 | 34.2 |
| SD | 21.3 | 11.0 | 23.2 | 20.7 | 10.6 | 16.8 | 19.5 |
| 0.8 | ± 3.0 | ± 1.6 | ± 3.3 | ± 2.9 | ± 1.5 | ± 2.4 | ± 2.8 |
| 0.9 | ± 3.9 | ± 2.0 | ± 4.2 | ± 3.8 | ± 2.0 | ± 3.1 | ± 3.6 |
| 0.95 | ± 4.7 | ± 2.4 | ± 5.1 | ± 4.5 | ± 2.3 | ± 3.7 | ± 4.3 |
| | | | | N.REM/REM: 6.7 | | N.REM1-2/3-4:1.05 | |
| A.E.+B.D. 8 | | | | | | | |
| mean | 79.0 | 5.2 | 73.8 | 65.0 | 8.8 | 34.1 | 30.9 |
| SD | 23.5 | 6.6 | 26.5 | 24.9 | 8.0 | 18.4 | 27.4 |
| 0.8 | ± 11.7 | ± 3.3 | ± 13.2 | ± 12.4 | ± 4.0 | ± 9.2 | ± 13.7 |
| 0.9 | ± 15.7 | ± 4.4 | ± 17.7 | ± 16.7 | ± 5.3 | ± 12.3 | ± 18.3 |
| 0.95 | ± 19.6 | ± 5.5 | ± 22.1 | ± 20.8 | ± 6.7 | ± 15.3 | ± 22.9 |
| | | | | N.REM/REM: 7.4 | | N.REM1-2/3-4:1.10 | |

* These values correspond with Table VII.9. (S).

TABLE VIII.7. bis
Composition of the first cycle after one night sleep deprivation of sleep patterns without epileptic EEG phenomena in patients treated with one or two antiepileptic drugs (mean, standard deviation (SD), confidence intervals for the mean ($1/2\alpha = 0.05, 0.025$).

| Cy. 1 n | Total cycle | Time awake | Effective sleep time | N.REM sleep | REM sleep | N.REM 1-2 | N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| CO 15 | | | | | | | |
| mean | 77.1 | 5.1 | 72.0 | 63.3 | 8.7 | 28.5 | 34.8 |
| SD | 15.2 | 7.3 | 18.1 | 16.0 | 6.5 | 11.3 | 18.6 |
| 0.8 | ± 5.3 | ± 2.5 | ± 6.3 | ± 5.5 | ± 2.3 | ± 3.9 | ± 6.5 |
| 0.9 | ± 6.9 | ± 3.3 | ± 8.2 | ± 7.3 | ± 3.0 | ± 5.2 | ± 8.5 |
| 0.95 | ± 8.4 | ± 4.1 | ± 10.0 | ± 8.5 | ± 3.6 | ± 6.3 | ± 10.3 |
| | | | | N.REM/REM: 7.3 | | N.REM1-2/3-4:0.82 | |
| Sod.V. 19 | | | | | | | |
| mean | 100.5 | 4.1 | 96.4 | 84.9 | 11.5 | 32.6 | 52.3 |
| SD | 21.2 | 4.7 | 19.4 | 17.6 | 11.4 | 17.0 | 20.0 |
| 0.8 | ± 6.5 | ± 1.4 | ± 5.9 | ± 5.4 | ± 3.5 | ± 5.2 | ± 6.1 |
| 0.9 | ± 8.4 | ± 1.9 | ± 7.7 | ± 7.0 | ± 4.5 | ± 6.8 | ± 8.0 |
| 0.95 | ± 10.2 | ± 2.3 | ± 9.4 | ± 8.5 | ± 5.5 | ± 8.2 | ± 9.7 |
| | | | | N.REM/REM: 7.4 | | N.REM1-2/3-4:0.62 | |
| Carb. 32 | | | | | | | |
| mean | 81.9 | 2.0 | 79.9 | 69.3 | 10.6 | 24.8 | 44.5 |
| SD | 18.6 | 4.6 | 18.8 | 18.3 | 7.7 | 14.6 | 18.2 |
| 0.8 | ± 4.3 | ± 1.1 | ± 4.3 | ± 4.3 | ± 1.8 | ± 3.4 | ± 4.2 |
| 0.9 | ± 5.6 | ± 1.4 | ± 5.6 | ± 5.5 | ± 2.3 | ± 4.4 | ± 5.5 |
| 0.95 | ± 6.7 | ± 1.7 | ± 6.8 | ± 6.6 | ± 2.8 | ± 5.3 | ± 6.6 |
| | | | | N.REM/REM: 6.5 | | N.REM1-2/3-4:0.56 | |
| D.P.H. 11 | | | | | | | |
| mean | 96.9 | 9.0 | 87.9 | 84.0 | 3.9 | 48.4 | 35.6 |
| SD | 37.8 | 13.2 | 30.3 | 30.4 | 5.3 | 24.8 | 19.7 |
| 0.8 | ± 15.6 | ± 5.5 | ± 12.5 | ± 12.6 | ± 2.2 | ± 10.2 | ± 8.1 |
| 0.9 | ± 20.6 | ± 7.2 | ± 16.5 | ± 16.6 | ± 2.9 | ± 13.5 | ± 10.8 |
| 0.95 | ± 25.4 | ± 8.9 | ± 20.4 | ± 20.4 | ± 3.5 | ± 16.6 | ± 13.2 |
| | | | | N.REM/REM: 21.5 | | N.REM1-2/3-4:1.36 | |

TABLE VIII.7. bis (continued).

| Cy. 1 n | Total cycle | Time awake | Effective sleep time | N.REM sleep | REM sleep | N.REM 1-2 | N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| Carb.+ Sod.V. 11 | | | | | | | |
| mean | 89.4 | 1.0 | 88.4 | 78.1 | 10.3 | 23.9 | 54.2 |
| SD | 20.6 | 2.5 | 20.3 | 19.2 | 7.1 | 23.4 | 18.3 |
| 0.8 | ± 8.5 | ± 1.0 | ± 8.4 | ± 7.9 | ± 2.9 | ± 9.7 | ± 7.6 |
| 0.9 | ± 11.2 | ± 1.4 | ± 11.1 | ± 10.5 | ± 3.9 | ± 12.8 | ± 10.0 |
| 0.95 | ± 13.8 | ± 1.7 | ± 13.6 | ± 12.9 | ± 4.8 | ± 15.7 | ± 12.3 |
| | | | | N.REM/REM: 7.6 | | N.REM1-2/3-4:0.44 | |
| Carb.+ D.P.H. 13 | | | | | | | |
| mean | 102.3 | 3.9 | 98.4 | 87.7 | 10.7 | 38.2 | 49.5 |
| SD | 34.5 | 7.6 | 31.2 | 31.3 | 8.0 | 23.8 | 18.2 |
| 0.8 | ± 13.0 | ± 2.9 | ± 11.8 | ± 11.8 | ± 3.0 | ± 9.0 | ± 6.9 |
| 0.9 | ± 17.0 | ± 3.8 | ± 15.4 | ± 15.5 | ± 3.9 | ± 11.7 | ± 9.0 |
| 0.95 | ± 20.8 | ± 4.6 | ± 18.8 | ± 18.9 | ± 4.8 | ± 14.4 | ± 11.0 |
| | | | | N.REM/REM: 8.2 | | N.REM1-2/3-4:0.77 | |

TABLE VIII.8. bis
Composition of the first cycle after one night sleep deprivation of sleep patterns with epileptic EEG phenomena in patients treated with one or two antiepileptic drugs (mean, standard deviation (SD), confidence intervals for the mean ($1/2\alpha = 0.05, 0.025$).

| Cy. 1 n | Total cycle | Time awake | Effective sleep time | N.REM sleep | REM sleep | N.REM 1-2 | N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| CO 15 | | | | | | | |
| mean | 77.1 | 5.1 | 72.0 | 63.3 | 8.7 | 28.5 | 34.8 |
| SD | 15.2 | 7.3 | 18.1 | 16.0 | 6.5 | 11.3 | 18.6 |
| 0.8 | ± 5.3 | ± 2.5 | ± 6.3 | ± 5.5 | ± 2.3 | ± 3.9 | ± 6.5 |
| 0.9 | ± 6.9 | ± 3.3 | ± 8.2 | ± 7.3 | ± 3.0 | ± 5.2 | ± 8.5 |
| 0.95 | ± 8.4 | ± 4.1 | ± 10.0 | ± 8.5 | ± 3.6 | ± 6.3 | ± 10.3 |
| | | | | N.REM/REM: 7.3 | | N.REM1-2/3-4:0.82 | |
| Sod.V. 25 | | | | | | | |
| mean | 86.6 | 2.1 | 84.5 | 75.7 | 8.8 | 31.6 | 44.1 |
| SD | 18.8 | 2.8 | 17.9 | 16.6 | 9.7 | 18.2 | 18.4 |
| 0.8 | ± 5.0 | ± 0.8 | ± 4.8 | ± 4.4 | ± 2.6 | ± 4.8 | ± 4.9 |
| 0.9 | ± 6.4 | ± 1.0 | ± 6.2 | ± 5.7 | ± 3.3 | ± 6.2 | ± 6.3 |
| 0.95 | ± 7.8 | ± 1.2 | ± 7.4 | ± 6.9 | ± 4.0 | ± 7.5 | ± 7.6 |
| | | | | N.REM/REM: 8.6 | | N.REM1-2/3-4:0.72 | |
| Carb. 34 | | | | | | | |
| mean | 78.8 | 2.9 | 75.9 | 64.6 | 11.3 | 21.4 | 43.2 |
| SD | 19.5 | 8.0 | 18.0 | 18.2 | 12.0 | 9.1 | 19.8 |
| 0.8 | ± 4.4 | ± 1.8 | ± 4.0 | ± 4.1 | ± 2.7 | ± 2.1 | ± 4.5 |
| 0.9 | ± 5.7 | ± 2.4 | ± 5.2 | ± 5.3 | ± 3.5 | ± 2.7 | ± 5.8 |
| 0.95 | ± 6.8 | ± 2.8 | ± 6.3 | ± 6.4 | ± 4.2 | ± 3.2 | ± 6.9 |
| | | | | N.REM/REM: 5.7 | | N.REM1-2/3-4:0.49 | |
| D.P.H. 11 | | | | | | | |
| mean | 86.9 | 5.0 | 81.9 | 72.0 | 9.9 | 31.9 | 40.1 |
| SD | 36.5 | 7.8 | 38.9 | 33.9 | 8.9 | 18.7 | 27.7 |
| 0.8 | ± 15.1 | ± 3.2 | ± 16.1 | ± 14.0 | ± 3.7 | ± 7.8 | ± 11.5 |
| 0.9 | ± 20.0 | ± 4.3 | ± 21.2 | ± 18.5 | ± 4.9 | ± 10.2 | ± 15.2 |
| 0.95 | ± 24.6 | ± 5.2 | ± 26.2 | ± 22.8 | ± 6.0 | ± 12.6 | ± 18.7 |
| | | | | N.REM/REM: 7.3 | | N.REM1-2/3-4:0.79 | |

TABLE VIII.8. bis (continued)

| Cy. 1 n | Total cycle | Time awake | Effective sleep time | N.REM sleep | REM sleep | N.REM 1-2 | N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| Carb. + Sod. V. 36 | | | | | | | |
| mean | 86.0 | 1.8 | 84.2 | 71.7 | 12.5 | 22.6 | 49.1 |
| SD | 21.8 | 2.8 | 21.7 | 16.2 | 14.7 | 11.8 | 18.9 |
| 0.8 | ± 4.7 | ± 0.6 | ± 4.7 | ± 3.5 | ± 3.2 | ± 2.6 | ± 4.1 |
| 0.9 | ± 6.1 | ± 0.8 | ± 6.1 | ± 4.6 | ± 4.2 | ± 3.3 | ± 5.3 |
| 0.95 | ± 7.4 | ± 0.9 | ± 7.4 | ± 5.5 | ± 5.0 | ± 4.0 | ± 6.4 |
| | | | | N.REM/REM: 5.7 | | N.REM1-2/3-4:0.46 | |
| Carb. + D.P.H. 31 | | | | | | | |
| mean | 88.6 | 4.7 | 83.9 | 74.5 | 9.4 | 37.3 | 37.2 |
| SD | 25.1 | 7.1 | 21.4 | 22.4 | 6.9 | 23.3 | 15.7 |
| 0.8 | ± 5.9 | ± 1.7 | ± 50 | ± 5.3 | ± 1.6 | ± 5.5 | ± 3.7 |
| 0.9 | ± 7.7 | ± 2.2 | ± 6.5 | ± 6.9 | ± 2.1 | ± 7.1 | ± 4.8 |
| 0.95 | ± 9.2 | ± 2.6 | ± 7.8 | ± 8.2 | ± 2.5 | ± 8.6 | ± 5.8 |
| | | | | N.REM/REM: 7.9 | | N.REM1-2/3-4:1.00 | |

TABLE VIII.9. bis

Composition of the first cycle after one night sleep deprivation in patients treated with antiepileptic drugs in combination with chlorazepate (Chlor.) or clonazepam (clon.), (mean, standard deviation (SD), confidence intervals for the mean [1/2α = 0.05, 0.025).

| Cy. 1 n | Total cycle | Time awake | Effective sleep time | N.REM sleep | REM sleep | N.REM 1-2 | N.REM 3-4 |
|---|---|---|---|---|---|---|---|
| A.E. + Chlor. 15 | | | | | | | |
| mean | 101.0 | 0.9 | 100.1 | 94.2 | 5.9 | 43.9 | 50.3 |
| SD | 24.1 | 1.8 | 23.2 | 24.1 | 7.9 | 25.1 | 25.4 |
| 0.8 | ± 8.3 | ± 0.6 | ± 8.0 | ± 8.3 | ± 2.7 | ± 8.7 | ± 8.8 |
| 0.9 | ± 11.0 | ± 0.8 | ± 10.6 | ± 10.9 | ± 3.6 | ± 11.4 | ± 11.6 |
| 0.95 | ± 13.3 | ± 1.0 | ± 12.8 | ± 13.3 | ± 4.4 | ± 13.9 | ± 14.0 |
| | | | | N.REM/REM: 16.0 | | REM 1-2/3-4: 0.87 | |
| A.E. + clon. 14 | | | | | | | |
| mean | 108.6 | 4.4 | 104.2 | 96.2 | 8.0 | 59.6 | 36.6 |
| SD | 33.3 | 7.5 | 27.0 | 30.2 | 8.4 | 28.7 | 29.1 |
| 0.8 | ± 12.0 | ± 2.7 | ± 9.7 | ± 10.9 | ± 3.0 | ± 10.4 | ± 10.5 |
| 0.9 | ± 15.8 | ± 3.6 | ± 12.8 | ± 14.3 | ± 4.0 | ± 13.6 | ± 13.8 |
| 0.95 | ± 19.2 | ± 4.4 | ± 15.6 | ± 17.4 | ± 4.9 | ± 16.5 | ± 16.8 |
| | | | | N.REM/REM: 12.0 | | REM 1-2/3-4: 1.63 | |

## ADDENDUM 4: LIST OF TABLES AND FIGURES

## SAMENVATTING

Dit proefschrift behandelt de interacties tussen epilepsie, slaap en anti-epileptica, gebaseerd op klinisch neurofysiologisch onderzoek.

In hoofdstuk I komt de vraag aan de orde of polygrafische slaapregistratie na 1 nacht totale slaapdeprivatie (TSD) een geschikte methode is voor onderzoek van deze interakties en aan welke voorwaarden die dan moet voldoen.

In hoofdstuk II zijn de literatuurgegevens samengevat en opgesplitst in twee delen.

In het eerste deel werden de algemeen geldende definities vermeld om EEG fenomenen, passend bij slaap en epilepsie, te beschrijven alsmede de criteria die worden gehanteerd om de verschillende soorten slaap en epilepsie te classificeren.

In het tweede deel wordt een overzicht gegeven van de verschillende slaapmethoden die toegepast worden om epileptische EEG verschijnselen te registreren en de slaapveranderingen die kunnen optreden bij de epilepsie ten gevolge van de epilepsie of de inname van anti-epileptica. Er bestaat een algemene consensus over het feit dat de epileptische EEG verschijnselen, zowel van het gegeneraliseerde als van het partiële type, het meest toenemen tijdens de oppervlakkige N.REM 1-2 slaap, een slaap die ook aanleiding geeft tot meer polypiekvorming en spreiding van de epileptische EEG verschijnselen, dit in tegenstelling tot de REM slaap. Algemeen wordt aangenomen dat de slaap niet wezenlijk wordt beïnvloed door het optreden van epileptische EEG ontladingen, met uitzondering van het optreden van enkele morfologische veranderingen, maar dat de slaap wel gewijzigd kan worden door langdurige inname van anti-epileptica.

In hoofdstuk III worden de vragen geformuleerd die aan de hand van literatuurstudie onvoldoende beantwoord konden worden, antwoorden nodig om de voor- en nadelen van de slaapregistratie na 1 nacht TSD methode te bepalen. Met behulp van eigen onderzoek is geprobeerd deze vragen te beantwoorden.

In hoofdstuk IV wordt dieper op het gebruikte materiaal en de methoden ingegaan. Het materiaal bestond uit ruim 1500 polygrafische slaapregistraties die in de periode 1976-1981 werden verricht bij personen met of verdacht van epilepsie. Hierin is 70 % opgenomen na 1 nacht TSD, met een registratieduur van 3 tot 5 uur en 30 % tijdens de gewone nachtelijke slaap. Alle opnamen werden verricht met een 16- of 21-kanaals elektroencephalograaf waarvan minimaal 12 kanalen werden gebruikt voor het registreren van EEG potentialen.

Na visuele beoordeling werd de samenstelling van de slaap weergegeven in een hypnogram, met daaronder vermelding van de kwantitatieve samenstelling en de kwalitatieve aspecten van de slaap en tevens van de soort, duur en hoeveelheid epileptische EEG afwijkingen in relatie tot de slaapsoort en diepte. Sinds 1979 werd de visuele analyse aangevuld met een automatische slaapanalyse en classificatie.

In hoofdstuk V wordt de registratie van epileptische EEG fenomenen tijdens de slaap besproken. In een aselecte populatie van patiënten, verdacht van epilepsie wordt in vergelijking met de routine en de diagnostische EEG onderzoekingen overdag een diagnostische winst van 25 % tot 32 % geboekt. Deze winst loopt op tot ca. 50 % voor de patiënten bij wie op klinische gronden epilepsie zeer waarschijnlijk

is. Slechts bij 3 van de 395 patiënten, klinisch zeer waarschijnlijk zonder epilepsie, werden tijdens de slaap specifieke epileptische EEG afwijkingen vastgesteld in vergelijking met 2 personen tijdens het routine EEG onderzoek overdag. Het aantal patiënten met specifieke epileptische EEG afwijkingen tijdens de slaap was ruim 84 % bij patiënten bij wie de klinische diagnose van epilepsie als zeker werd beschouwd. Het percentage winst verkregen door registratie van slaap gedurende een hele nacht is voor gegeneraliseerde epilepsie 6 % hoger dan tijdens de slaap na TSD en voor partiële epilepsie gelijk. Conform de literatuur werden de meeste epileptische EEG verschijnselen tijdens de N.REM 1-2 slaap en tijdens de beginperiode van de slaapregistratie gezien. Belangrijk is echter de bevinding dat bij ca. 13 % de epileptische EEG afwijkingen slechts aanwezig waren tijdens de 2e slaapcyclus en bij ca. 7 % enkel na een registratieduur van meer dan 2 uur. Daarenboven is voor een aantal patiënten met gegeneraliseerde epilepsie de aanwezigheid van diepe N.REM 3-4 slaap noodzakelijk.

Bij het uitvoeren van langdurige slaapregistraties na TSD, met gemiddeld 2 slaapcyclussen, heeft het completeren van het onderzoek met hyperventilatie en/of intermitterend lichtflitsen slechts een beperkte waarde en vormt voor de patiënt een extra belasting.

De algemene conclusie luidt dat na 1 nacht TSD, een slaapregistratie van 2 slaapcylussen als optimaal beschouwd kan worden voor het registreren van epileptische EEG fenomenen.

Hoofdstuk VI behandelt de kwantitatieve veranderingen in slaapsamenstelling van de 1e en 2e slaapcyclus tijdens de gewone nachtelijke slaap bij epileptici in vergelijking met een controlegroep gezonden. Alle patiënten hebben een langere cyclusduur, te wijten aan meer N.REM slaap vooral van de oppervlakkige N.REM 1-2 slaap. De verschillen zijn het kleinst bij de patiënten met epileptische EEG afwijkingen tijdens de slaap en met inname van anti-epileptica. Bij toevoeging van benzodiazepine derivaten aan de anti-epileptica ziet men een toename van de N.REM 1-2 slaap. Afhankelijk van het type epilepsie zijn er slechts lichte verschillen, bestaande uit: meer N.REM 1-2 slaap bij de gegeneraliseerde vormen van epilepsie, meer REM slaap bij de partiële vormen en vooral meer N.REM 1-2 als N.REM slaap bij epilepsie met zowel gegeneraliseerde als partiële aanvallen.

In hoofdstuk VII wordt, naar analogie van de doorslaapregistratie, aangegeven hoe de slaapsamenstelling van de 1e en 2e slaapcyclus na een nacht slaapdeprivatie bij epileptici verschilt van die bij gezonden. Bij epileptici blijkt de slaapsamenstelling minder afhankelijk te zijn van het wel of niet aanwezig zijn van epileptische afwijkingen dan het wel of niet innemen van anti-epileptica, hetzij alleen, hetzij in kombinatie met benzodiazepine derivaten.

Onze resultaten tonen aan dat tijdens de 1e cyclus zowel bij gezonden als bij patiënten het slaapdeprivatie-effect overweegt boven andere invloeden zoals geciteerd bij de doorslaap.

Ten gevolge van de slaaponthouding wordt het slaappatroon op stereotype wijze beïnvloed, en wel door een verkorting van de inslaaptijd en van de totale 1e cyclusduur. Dit is te wijten aan een afname van de N.REM slaap. Binnen de N.REM slaap is er verhoudingsgewijze meer diepe dan oppervlakkige N.REM slaap. Deze effecten zijn nagenoeg verdwenen tijdens de 2e cyclus die daardoor in vele opzichten grote gelijkenis vertoont met de 2e doorslaapcyclus.

In dit hoofdstuk wordt gewezen op het belang van de leeftijd en met name de leeftijdsgrens van 20 jaar. Onder de 20 jaar is het deprivatie-effekt sterker dan daarboven, en wordt nog geaccentueerd door benzodiazepine derivaten. Boven de 20 jaar wordt het deprivatie-effekt gecompleteerd met een benzodiazepine effekt, waardoor nog sterkere verlenging van de cyclusduur optreedt.

In hoofdstuk VIII wordt aangetoond dat de samenstelling van de le slaapcyclus na 1 nacht TSD, bij epileptici die slechts met 1 anti-epilepticum of een combinatie van 2 anti-epileptica worden behandeld, verschilt per type anti-epilepticum. Het deprivatie-effekt wordt versterkt bij inname van carbamazepine en in iets mindere mate door inname van natriumvalproaat, maar daarentegen geneutraliseerd bij toediening van hydantoine derivaten. In vergelijking met de slaap bij gezonde proefpersonen is de totale le cyclusduur verlengd bij inname van hydantoine of valproaat derivaten. Die verlenging is bij de hydantoine derivaten vooral te wijten aan meer oppervlakkige N.REM 1-2 slaap en bij valproaat aan geringe vermeerdering van de oppervlakkige N.REM 1-2 en iets sterkere toename van de diepe N.REM 3-4 slaap.

Ook kon worden aangetoond dat benzodiazepine derivaten, gegeven in combinatie met anti-epileptica, conform hun werkingsprofiel, de samenstelling van de le slaapcyclus na 1 nacht TSD wijzigen. De soort en grootte van de wijziging verschilt per benzodiazepine derivaat.

Tevens wordt erop gewezen dat de geregistreerde verschillen in slaapsamenstelling per soort anti-epilepticum of benzodiazepine derivaat mede afhankelijk kunnen zijn van de soort en ernst van hersenfunctiestoornis die voor het optreden van epilepsie verantwoordelijk is.

Hoofdstuk IX bestaat uit een reeks evaluatieonderzoeken waarbij vooral de aspectveranderingen worden belicht die enerzijds de epileptische EEG afwijkingen kunnen ondergaan ten gevolge van de slaap en anderzijds de polygrafische slaapfenomenen ten gevolge van de epilepsie met de hiervoor ingestelde behandeling. Voor een goede interpretatie van de epileptische EEG afwijkingen tijdens de slaap moet men van die veranderingen op de hoogte zijn alsmede van hun klinische betekenis.

Zowel tijdens de doorslaap als tijdens de slaap na TSD hebben epileptici geen abnormaal lange apnoeperioden. Wel zijn er meer scherpe K-complexen dan bij de controlepersonen en na TSD nog meer dan tijdens de nachtelijke slaap. Sommige veranderingen, zoals de afname van snelle oogbewegingen of niveau van spieractiviteit, veranderingen die kunnen samenhangen met de ingenomen medicatie, maken deze parameters minder bruikbaar als criteria om de slaapsoorten van elkaar te onderscheiden. Dit bezwaar is vooral van belang bij het gebruik van automatische slaapanalyse en classificatie.

In hoofdstuk X worden 3 slaapprocedures voorgesteld die na 1 nacht TSD, afhankelijk van de beoogde doelstelling, bij voorkeur worden toegepast. De le of eenvoudige procedure richt zich hoofdzakelijk op de epilepsiediagnostiek.

De 2e of complexe en meer uitvoerige procedure richt zich zowel op bestudering van de epilepsie als slaap en beïnvloeding van elk van beide door anti-epileptica.

De 3e of gerichte procedure geeft aan dat het noodzakelijk kan zijn de registratie en de verwerkingswijzen aan te passen aan de

indicatiestelling van het onderzoek.

Hoofdstuk XI of de bespreking omvat 3 onderdelen. In het 1e deel worden de fysiologische en pathofysiologische regulatie en ontstaansmechanismen van slaap en epilepsie besproken, waardoor enig inzicht wordt verkregen van de wijze waarop deze elkaar kunnen beïnvloeden.

In het 2e deel worden aan de hand van deze inzichten de bevindingen van eigen onderzoek besproken en wordt aangegeven waardoor onze resultaten in bepaalde opzichten verschillen van de literatuurgegevens. Ook wordt getracht de verschillen in slaapsamenstelling van de 1e slaapcyclus na 1 nacht TSD per anti-epilepticum te verklaren uit de wijze waarop dit de hersenen beïnvloedt.

In een 3e en laatste deel worden enkele van de belangrijkste voorwaarden benoemd waaraan de TSD procedure moet voldoen om een zo hoog mogelijk diagnostisch rendement te verkrijgen alsook enkele aanbevelingen voor verder onderzoek.

De addenda bevat een bespreking van de toegepaste automatische slaapclassificaties (Add. 1) en de gebruikte statistische methoden (Add. 2). Daarop volgt een reeks tabellen met aanvullende gegevens betreffende verschillen in samenstelling van de 1e en 2e slaapcyclus tijdens de nachtelijke slaap en de slaap na 1 nacht TSD (Add. 3) en het laatste addendum bevat een lijst met alle geciteerde tabellen en figuren (Add. 4).

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## CURRICULUM VITAE

August Declerck werd geboren op 20.11.1933 te Westkerke (België) en volgde van 1946 - 1952 de middelbare schoolopleiding aan het O.L. Vrouwen-college te Oostende.

Hij studeerde geneeskunde aan de Universiteit te Leuven en behaalde zijn artsexamen in juli 1959.

Van december 1959 tot februari 1961 was hij in militaire dienst en werkzaam op de afdeling Interne Geneeskunde van het Militair Hospitaal te Oostende.

Van april 1961 tot mei 1963 deed hij algemene huisartsengeneeskunde.

Op 1 mei begon zijn opleiding tot zenuwarts waarvan 1 jaar psychiatrie te Kortrijk (hoofd Dr. J. van Laere) en 3 jaar neurologie op de afdeling neurologie van het Academisch Ziekenhuis te Leuven (hoofd Prof. P. van Gehuchten, opgevolgd door Prof. R. van den Bergh).

In het kader van zijn opleiding tot zenuwarts was hij in 1966-1967 gedurende 6 maanden werkzaam op de afdeling neurologie van het Wilhelmina Gasthuis te Amsterdam (hoofd Prof. Dr. D. Biemond).

In 1967 volgde zijn benoeming tot adjunct kliniekhoofd van de afdeling neurologie van het Academisch Ziekenhuis te Leuven, een funktie die hij heeft vervuld tot oktober 1970. In deze periode had hij speciale interesse voor de kinderneurologie.

Van oktober 1970 tot februari 1972 was hij als zenuwarts gevestigd te Oostende.

Van februari 1972 tot april 1975 was hij full-time werkzaam op de afdeling electroencephalografie en klinische neurofysiologie van het St. Antoniusziekenhuis te Utrecht (hoofd Dr. A.J.R. Simons). Tevens heeft hij veel aandacht besteed aan de bestudering van het centrale "mu-ritme" in het electroencephalogram.

Sinds april 1975 is hij full-time werkzaam in het epilepsiecentrum "Kempenhaeghe" te Heeze als hoofd van de afdeling electroencephalografie en klinische neurofysiologie. Hij heeft veel onderzoek verricht naar het belang van slaaponderzoek voor het diagnostiseren van epilepsie en voor het bepalen van de invloed van antiepileptica, en naar de diagnostische waarde van de evoked potential methode bij epileptici. Samen met zijn medewerkers worden die onderzoekingen gekontinueerd maar worden nu aangevuld met de betudering van de mogelijkheden voor langdurige (24-48 uurs) ambulante EEG registraties in kombinatie met automatische verwerking.

ERRATA

| | | |
|---|---|---|
| Page 7 | : | 1/12 (1/2) |
| " 25 | : | uninterrupted (interrupted) |
| " 27 | : | sleep (recording) |
| " 120 | : | transition (activation) |
| " 122 | : | state (stage) |
| " 132 | : | question 3: and medication? |