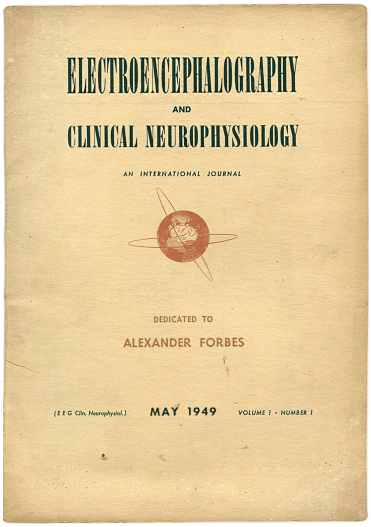
Centennial Anniversary of the Electroencephalogram (EEG)

July 1924 - 2024

An excerpt from the collection book

70th Anniversary of Clinical Neurophysiology Journal

by **Prof. Carlo Alberto Tassinari**



Dravet Italia
Associazione Italiana Sindrome di Dravet

www.dravet.it

crep
Centro Ricerca per le Epilessie in età Pediatrica

On the occasion of the ***100th anniversary of the Electroencephalogram (EEG)***, Prof. Carlo Alberto Tassinari is pleased to present an excerpt from a special publication: *the first volume of the* ***Electroencephalography and Clinical Neurophysiology Journal****,* graciously made available through open access by the publisher in honor of the *journal's 70th anniversary*.

This print edition has been made possible through the collaboration of Prof. Tassinari with C.R.E.P. (Center for Pediatric Epilepsy Research), Prof. Bernardo Dalla Bernardina and the Dravet Italia Onlus association.

We would like to take this opportunity to express our sincere gratitude to Prof. Paolo Rossini (Rome) and Prof. Gaetano Cantalupo (Verona) for their invaluable assistance with the editorial work of Prof. C.A. Tassinari.

70th Anniversary of Clinical Neurophysiology

We celebrate the 70th anniversary of Clinical Neurophysiology.

This Special Issue includes three Editorials that have been written on this occasion by the current Editor-in-Chief (Prof. Ulf Ziemann) and two clinical neurophysiologists, one electroencephalographer (Prof. Alberto Tassinari) and one electromyographer (Prof. Jun Kimura) who have been born in the 1930s and, therefore, have witnessed the course of the journal and the International Federation of Clinical Neurophysiology (IFCN) from almost the very beginning throughout the decades until now.

The remainder of this SI contains the full first volume, issues 1-4 of our journal, published in 1949.

The original name of the journal was "Electroencephalography and Clinical Neurophysiology", reflecting the dominance of EEG in clinical neurophysiology at that time.

You will see that many of the topics from 70 years ago are still timely today.

This illustrates nicely the longevity of fundamental research topics in clinical neurophysiology and their relevance throughout seven decades.

Several of the papers published in the first volume became milestone papers in our field. For instance, the paper by Moruzzi and Magoun (p. 455-473, http://www.sciencedirect.com/science/article/pii/0013469449902199) has revealed the fundamental role of the brainstem reticular formation on arousal reactions of the brain as monitored by changes in the EEG.

It is always worth looking back to the roots.
I wish you enjoyable reading.

Clinical Neurophysiology 130 (2019) 2255–2257

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Editorial

Seventy years of our journal

The grounds of our journal were laid on the occasion of the "founding meeting" of EEG researchers held in London, UK on July 14–16, 1947. Professor Herbert Jasper was appointed Editor and an Editorial Board was chosen to represent as many countries as possible. The official name of the new journal was "*Electroencephalography and Clinical Neurophysiology*", or abbreviated: "*The EEG Journal*". This reflected the dominance of EEG in the early days of the Federation (now called the International Federation of Clinical Neurophysiology, IFCN), which was founded during the 2nd International Congress in Paris, France on September 1–5, 1949. The liberal advice of W.T. Liberson of Hartford, USA during the 1947 founding meeting that the international journal "*. . .should not be concerned exclusively with electroencephalography, but be devoted to all the problems of experimental and clinical neurophysiology. . .many of us do not commit ourselves to the problems of the electrical activity of the brain alone, but carry on research in the fields of electromyography, electrodermography and electrodiagnosis of peripheral nervous diseases*" was largely ignored. Volume 1, Issues 1–4 of *Electroencephalography and Clinical Neurophysiology* appeared in 1949. This first volume contained 529 pages. Predominance of EEG topics in the first volume is obvious from its table of contents:

https://doi.org/10.1016/j.clinph.2019.10.006

Robert B. King, S.A. Trufant, W.P. Fuchs: A versatile apparatus providing immobilization of the head for electrophysiological studies: Accessory Equipment Described for Inserting Electrodes Into Subcortical Structures (p. 365–367)
Jerzy E. Rose, Clinton N. Woolsey: Organization of the mammalian thalamus and its relationships to the cerebral cortex (p. 391–404)
Herbert Jasper: Diffuse projection systems: The integrative action of the thalamic reticular system (p. 405–420)
George H. Bishop: Potential phenomena in thalamus and cortex (p. 421–436)
Robert A. Hayne, Louis Belinson, Frederic A. Gibbs: Electrical activity of subcortical areas in epilepsy (p. 437–445)
F. Bremer, V. Bonnet: An analysis of the sensory responses of the acoustic cortex (p. 447–449)
G. Moruzzi, H.W. Magoun: Brain stem reticular formation and activation of the EEG (p. 455–473)
W. Grey Walter: Coming to terms with brain waves (p. 474)
D.B. Lindsley, J.W. Bowden, H.W. Magoun: Effect upon the EEG of acute injury to the brain stem activating system (p. 475–486)
Grossman: Sensory stimulation during sleep: Observations on the EEG responses to auditory stimulation during sleep in patients with brain pathology (Preliminary Report) (p. 487–490)
Joseph A. Epstein, Margaret A. Lennox, Olga Noto: Electroencephalographic study of experimental cerebro-vascular occlusion (p. 491–502)
Erling Asmussen, Fritz Buchthal: A method for the rapid determination of the degree of forced breathing (p. 503–504)
Georg F. Henriksen, Chaskiel Grossman, Jerome K. Merlis: EEG observations in a case with thalamic syndrome (p. 503–507).

A closer look to the papers published in this first volume demonstrates, however, that *Electroencephalography and Clinical Neurophysiology* was much more multifaceted than just EEG research. It contains technical / methodological articles that are still forming areas of research today, such as streaming of electrophysiological data (see article by Breakell et al., p. 243–244), modeling of electrical fields in the individual brain induced by electrical brain stimulation (see article by Lorimer et al., p. 343–348), or automated analysis of EEG data (see article by Hoeffer et al., p. 357–363). This illustrates very nicely the longevity of fundamental research topics in clinical neurophysiology and their relevance throughout seven decades.

Several of the papers published in the first volume became milestone papers in our field. For instance, the paper by Moruzzi and Magoun (p. 455–473) has revealed the fundamental role of the brainstem reticular formation on arousal reactions of the brain as monitored by changes in the EEG. The paper has been cited 2181 times (Scopus) until now, a citation classic.

Many of the authors of the first volume took important roles in the later history of the Federation. For example, Herbert Jasper was the founding editor of The EEG Journal (1949–1961), and the first president of the federation (1949–1953), William Grey Walter was the organizer of the founding EEG meeting in (1947), the European Editor of the journal (until 1957) and the second president (1953–1957), Henri Gastaut was the third president (1957–1961), Mary A.B. Brazier was the fourth president (1961–1965) and Editor-in-Chief (1973–1984), Cosimo Ajmone-Marsan was the sixth president (1969–1973) and American Editor (1960–1969).

Another interesting observation is that several papers were published in French. It was only decided later, on the occasion of the International Congress in Brussels, Belgium in 1957 that all papers should be in English if possible.

Finally, it is absolutely worth reading the Editorial by W. Grey Walter: Coming to terms with brain waves (p. 474), in which he puts a strong stance on using clear nomenclature in clinical neurophysiology. He quoted Lewis Carol (Through the Looking Glass): "*When I use a word" Humpty Dumpty said in rather a scornful tone "it means just what I choose it to mean – neither more nor less". "The question is" said Alice "whether you can make words mean so many different things". "The question is" said Humpty Dumpty "which is to be master – that's all". And he concluded: "If we are not to be branded as Sorcerers, Vampires or Shamanists, we must decide which is to be master and try to make it possible to say just what we mean*". This is still also very true now, and its importance will be reflected in a glossary of terms in clinical neurophysiology, endorsed by the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) and the International Federation of Clinical Neurophysiology (IFCN) that will be published in *Muscle & Nerve* (the organ of the AANEM) and in *Clinical Neurophysiology* in 2020.

The development of our journal over the decades is very nicely summarized in two accompanying *Editorials* by Professor Carlo Alberto Tassinari from the perspective of an epileptologist and EEG researcher, and by Professor Jun Kimura (president of the federation 1990–1993) from the perspective of an EMG researcher. Both have been born in the 30ties and have witnessed the maturation of clinical neurophysiology from the early to the present days. The steadily increasing importance of other techniques than EEG led to the addition of two sections to the journal: "*Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*" in 1984, and "*Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control*" in 1995. Finally, this was all embraced under the new and still current name of the journal in 1999: "*Clinical Neurophysiology*". In 2016, the IFCN launched a second journal "*Clinical Neurophysiology Practice*". This is an open-access journal with a special focus on educational and practical studies while *Clinical Neurophysiology* aims now even more deliberately at publishing highest-quality research articles.

Our journal has now a wide scope, including all aspects of clinical neurophysiology in research: "*Clinical Neurophysiology is dedicated to publishing scholarly reports on the pathophysiology underlying diseases of the peripheral and central nervous system of humans. Reports on clinical trials that use neurophysiological measures as endpoints are encouraged, as are manuscripts on integrated neuroimaging of peripheral and central nervous function including, but not limited to, functional MRI, brain mapping, MEG, EEG, PET, ultrasound, and other neuroimaging modalities. Studies on normal human neurophysiology are welcome, if they are relevant to disease or clinical applications…Clinical Neurophysiology covers epilepsy, developmental clinical neurophysiology, psychophysiology and psychopathology, motor control and movement disorders, somatosensory disorders including pain, motor neuron diseases, neuromuscular diseases, neuropathies, sleep and disorders of consciousness, auditory and vestibular disorders, aging, Alzheimer's disease, other dementias, other psychiatric disorders, autonomic disorders, neural plasticity and recovery, intraoperative and ICU monitoring, and therapeutic clinical neurophysiology including non-invasive and invasive brain stimulation.*"

Currently, we are discussing several issues related to modern forms of publishing such as transforming *Clinical Neurophysiology* into an e-only journal, or moving from a subscription-based hybrid model to a full gold open access publication model, where all publications would become freely and immediately accessible. If set into action, these transformations will significantly affect authors the way they are publishing, readers the way they can access the content of the journal, and the publisher (Elsevier) and the federation with respect to their relations. However, no matter what will happen, I am confident that our journal will remain the premier

journal in its field as it has always been ever since its foundation 70 years ago.

This is a very good reason to celebrate. As the current Editor-in-Chief, I would like to thank all the people who have contributed to the ongoing success of our journal, in particular all the ad hoc reviewers, members of the Editorial Board, Associate Editors and the Editorial Officers and Journal Managers at Elsevier. As a particular contribution in celebrating the 70th anniversary, Elsevier has agreed to switch Volume 1, Issues 1–4 of our journal to open access. All articles of the first volume can be reached through:

https://www.sciencedirect.com/journal/electroencephalography-and-clinical-neurophysiology/vol/1/issue/1

Let me close this text by quoting Herbert H. Jasper, the founding Editor. He thought that scientific investigation and brain research "*. . .might be an excellent channel for the promotion of better international relations because so many of these problems are based on malignant mental attitudes that might respond to scientific studies of brain function as a detriment of social behavior. I feel strongly that modern neuroscience with all its advances during recent years should be used to apply knowledge and techniques to the understanding and prevention of such malignant mental attitudes that form the basis for so much conflict.*" While this might be an overoptimistic view, it articulates a self-conception of our journal: a globally interacting family of researchers and clinicians devoted to advancing our knowledge of the functions and dysfunctions of the human nervous system, one of the most intricate unresolved enigmas in science.

Ulf Ziemann
Department of Neurology & Stroke, and Hertie-Institute for Clinical Brain Research, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany
E-mail address: ulf.ziemann@uni-tuebingen.de

Available online 5 November 2019

Clinical Neurophysiology 130 (2019) 2258–2263

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Editorial

An electroencephalographer recalls the history of the Federation on the 70th anniversary of its journal, *Clinical Neurophysiology*

1. Introduction

The history of electroencephalogram (EEG) moves from Richard Caton (1842–1926), a physician practicing in Liverpool, who in 1875 presented his findings about electrical phenomena of the exposed cerebral hemispheres of experimental animals. Later the Polish physiologist Adolf Beck published an investigation of spontaneous electrical activity of the brain of rabbits and dogs, that included rhythmic oscillations altered by light; this was the first observation of brain waves. In 1912, Ukrainian physiologist Vladimir Vladimirovich Pravdich-Neminsky published the first EEG and the evoked potential in mammalians (Haas, 2003). In 1914, Napoleon Cybulski and Jelenska-Macieszyna photographed EEG recordings of experimentally induced seizures.

The modern history of Electroencephalography starts with the research of the German physiologist and psychiatrist Hans Berger (1873–1941) who recorded the first human EEG in 1924 and invented the term *electroencephalogram* (giving the device its name) (Berger, 1929). British scientists Edgar Douglas Adrian and Bryan Harold Cabot Matthews in 1934 first confirmed Berger's findings and further developed the EEG (Adrian and Matthews, 1934). In the following years, there was a *crescendo* of discoveries about the EEG. In 1934, Fisher and Lowenback first demonstrated epileptiform spikes. In 1935, Gibbs, Davis, and Lennox described interictal spike waves and the three cycles/s pattern of epileptic 'absence seizures', which began the field of clinical electroencephalography. Subsequently, in 1936 Gibbs and Jasper reported the interictal spike as the focal signature of epilepsy. The same year, the first EEG laboratory opened in US at Massachusetts General Hospital. Franklin Offner, at Northwestern University, developed a prototype of the EEG that incorporated a piezoelectric ink-writer called 'Crystograph'. In 1947, The American EEG Society was founded and the first International EEG congress was held.

In 1949 the first issue of the official Journal of the International Federation of Clinical Neurophysiology was published. It was the birth of *Electroencephalography & Clinical Neurophysiology*.

An electroencephalographer today can nicely recall the scientific journey of *Electroencephalography & Clinical Neurophysiology*, trying to highlight the insights stemming from the content of the first issues - see the enclosed **Index of Vol I - 1949** in the Editorial from Ulf Ziemann in this issue of *Clinical Neurophysiology* (Ziemann, 2019).

2. Part I – The electroencephalography: o*n waves and rhythms*

2.1. Alpha waves

The history of electroencephalogram was not an easy one since its first steps. Quoting from Jasper and Penfield (Jasper and Penfield, 1949) in a twenty years later tribute to Prof. H Berger: *"his sustained vision which carried him through on exemplary series of rigorously controlled systematic experiments on human subjects finally convinced skeptical scientists throughout the world of the validity and value of records of the electrical activity of the human brain*".

The "*sustained vision*" on alpha rhythm was confirmed by Adrian and Matthews (1934) whose work is summarized in a lively Editorial of Brain (Compston, 2010), from which we quote, in which is reported their "*combined satisfaction*" in demonstrating that the Berger rhythm is not an "artifact *"from pulsation of the vessels, activity of pilomotor muscles, tremor of the head or retinal potentials [. . .]The relationship between the Berger rhythm and vision is clear. Nothing abolishes the activity more easily than a visual stimulus, however uninteresting it may be. More specifically it is the recognition of pattern in the central visual field, or the attempt to perceive it, which interferes with the rhythm. Adrian and Matthews try various perturbations to show that the awareness of shape, not the level of illumination, most effectively stop the rhythms [. . .] responding to questions, mental arithmetic, tying and untying knots, hearing, or registering unexpected touch abolishes the potentials, although subjects may habituate to these intrusions; [. . .] Flicker is able to induce rhythms that can occur at a frequency of up to 25 cycle/s [. . .] Sitting in front of an opal bowl with his head covered by a black velvet curtain viewing a 30 watt bulb rotated by a gramophone motor, initially with his eyes closed and the stable 10 cycles/s Berger rhythm in place, Professor Adrian is exposed to the flickering light and 'responds' with a series of potential waves that are mostly synchronous with the flicker. Ideally, these need to be in the range of 10–20/s: at lower rates, the rhythms are unstable; and if too fast, they may halve or double by comparison with frequency of the visual stimulus*".

The 'Flickering' introduce us to the physiopathology of the complex domain of 'Photosensitive Epilepsies': (i) a variety of stimuli – characteristically related to frequency, pattern of stimulation, central vision, intensity of luminance; (ii) a number of etiologies, and (ii) different clinical manifestations (e.g. myoclonus, consciousness, etc) from papio-papio baboon (Killam et al., 1967) to man (Walter and Walter, 1949; Jeavons and Harding, 1975; Takahashi,2002; Duncan and Panayitopoulos,1996). Being *"evidence of the existence of a functional link between the circuits that*

https://doi.org/10.1016/j.clinph.2019.10.010

trigger the visual sensitivity phenomenon and those that generate the posterior alpha rhythm" (Vaudano et al., 2017).

"What causes the beat of these occipital neurons? Adrian and Matthews have already shown that the rhythmic activity observed from the water beetle eye in darkness breaks up when retinal stimulation is not uniform and of reduced brightness (and with all due modesty the Nobel Laureate points out that his own Berger rhythm is more or less identical to that of the water beetle)".

On a more general perspective we can wonder how "similar" waves or rhythms can be observed in extremely different conditions, in the same species: the alpha of the quiet and conscious Sir Adrian, with the eyes closed, and the alpha of a patient in a comatose or vegetative state with the eyes open. No doubts we will read the answer(s) in the next Centenary Editorial of the Journal.

2.2. Beta waves and the rhythm 'en arceau' (or Mu Rhythm)

Jasper and Penfield (1949) described rapid EEG rhythms*: "the beta rhythm (25 per* sec*) is characteristic of the electrical activity from the central region- is not affected by weak visual stimuli which blocked the alpha rhythm, [. . .] It was blocked by tactile stimulation to the contralateral side of the body [. . .] Blocking of the beta rhythm occurs, however only upon the initiation of movement and upon voluntary termination of a posture which the patient has assumed. It is not sustained during a maintained contraction such as clenching the fist, but blocking occurs at the beginning and cessation of the act. Sustained blocking occurs only with continuous consecutive movement or 'readiness to move' before the movement actually begins. These findings would be consistent with the suggestion that impulses reach the precentral gyrus at the beginning and at termination of a posture that is assumed voluntarily*".

Gastaut (Gastaut, 1952; Gastaut et al., 1952) described an 'arch-shaped' rhythm or "rhythm *en arceau*" (the mu-rhythm or 'wicked' rhythm) that was considered by its topography and reactivity as a '*dédoublement*' of beta activity: *"The somatotopic reactivity was precise: the mid rolandic arceau was blocked by hand mobilization, while a "superior – rolandic" (as recorded on vertex area) was blocked mainly by foot mobilization. Most interesting, thinking of performing a voluntary movement was effective to produce a reactivity of both beta and rhythm 'en arceau'*".

In a third article (Gastaut and Bert,1954) on "EEG changes during cinematographic presentation" it was clarified how the rhythm '*en arceau*': "*It also disappears when the subject identifies himself with an active person represented on the screen. This phenomenon is particularly interesting to study during a sequence of film showing a boxing match. A few seconds and at times, less than a second after the appearance of the boxers all type of rolandic activity disappears in spite of the fact that the subject seems completely relaxed and that there is no noticeable change of posture. The relation between the blocking of the 'arceau' rhythm and the image of boxers in action is unquestionable. In the middle of this particular film strip, the camera is suddenly turned from the ring to the spectators in the hall for a few seconds. In many subjects the rhythm 'en arceau' reappears during this short period and vanishes again as the boxers reappear on the screen. The motor characteristic of this identification is made obvious in a subject showing a bilateral rhythm 'en arceau' which is blocked only on the left hemisphere during the boxing match (it is with the right fist that one hits)*".

It was also demonstrated that mental motor action of the phantom limb in an amputee can block the contralateral rhythm '*en arceau*' (Gastaut et al. 1965).

Fifty years later there is a revival of mu rhythm: quoting from Avanzini et al. (2012):

"Although already mentioned by Gastaut (Gastaut et al., 1952) *the reactivity in mu rhythm to the observation of others' action remained for many years neglected. The discovery of mirror neurons, a set of motor neurons that discharge both during action execution and observation, determined a renewed interest in the cortical motor rhythms not only during action execution but also during action observation. A conceptual link between mu rhythm and the mirror neuron activity was first suggested by* Altschuler et al. (1997) *and later confirmed by other researchers. This proposal was based on the reactivity of both mu rhythm and mirror neurons in response to action observation and execution*".

The observation of motor acts determines a modulation of cortical rhythm analogous to that occurring during motor act execution. In particular the cortical motor system closely follows the velocity of the observed movements. This finding provides strong evidence of the presence in humans of a mechanism (mirror mechanism, Rizzolatti and Sinigaglia, 2016) mapping action observation on action execution motor programs. These data constitute the cornerstone of the modern Brain Computer Interface (BCI) techniques. The aim is to allow humans with motor disabilities to interact with the environment, by modulation of brain waves, i.e. electric signals, to control robotic arms (Babiloni et al., 1999) or even a 'full-body' exoskeleton Benabid et al., 2019).

2.3. The Delta waves and Sleep

M. Brazier (1949) introduces us to a third component of the EEG waves' family mainly occurring during physiological sleep: the Delta waves, at 1–4 c/sec, quite 'slow', as compared to waking alpha and beta rhythm. Quoting from Brazier: "*that slow potentials appear in the record when the subject is asleep was one of the first observations to be established in electroencephalography: and since Berger's original demonstration of this change, it has been plentifully confirmed by subsequent workers. . . The electrical activity of the brain during sleep is not the electrical concomitant of 'resting' cells, or of a quiescent brain, but the signal of activity in certain sub-cortical networks*".

We know actually that the EEG activity for most of normal sleep is characterized by a complex achitecture, physiologically composed by macro- and micro-structure - namely the Cyclic Alternating Pattern (Terzano et al., 1985), reflecting the relationship between other (fast) rhytms and slow wave activity (SWA). SWA corresponds, at a cellular level, to slow oscillations of membrane potentials of cortical neurons (Amzica and Steriade, 1998). The amount of EEG SWA is homeostatically regulated, showing an increment during wakefulness and returning to baseline during sleep (Borbély and Achermann, 2005). Slow wave sleep (SWS) has always been associated with restorative and recovery functions, but what these functions do really represent remains unclear. A hypothesis – the synaptic homeostasis hypothesis (Tononi and Cirelli, 2014) – suggests that a consequence of staying awake is a progressive increase in synaptic strength in many brain circuits. Sleep ensures synaptic homeostasis by promoting synaptic weakening/pruning after the increase of synaptic strength occurred during wakefulness. Recent studies in children with a high amount of paroxysmal activity during slow sleep (Cantalupo et al., 2019), failed to show changes of the slope of the SWA, which is a sensitive measure of cortical synaptic strength; in such children, the impaired synaptic homeostasis in the critical period of development may disrupt – often irreversibly – cognitive functions and behavior (Bölsterli et al., 2011; Rubboli et al., 2019; Halasz and Szucs, 2018).

2.4. A new language

With the end of World War II, electronic devices and human competences became available in EEG and neurophysiological lab-

oratories. The "Electroencephalography", now technically validated and scientifically recognized, became a relevant and trendy investigation in different clinical and neuroscientific domains: psychology, neurology, psychiatry, pharmacology, and in any condition susceptible or suspected to modify the brain function (see Niedermeyer's Electroencephalography). A wealth of new rhythms were observed from scalp electrodes, and carefully analyzed and 'validated' by subdural and intracerebral recordings in patients (mainly epileptic). The introduction of microprocessors and computers also allowed to average EEG signals triggered by an external stimulus giving then the opportunity to record Evoked Potentials to visual, acoustic, somatosensory stimuli (see Desmedt and Cheron, 1980; Rossini et al., 1987). The possibility to record EEG and stimuli on tape opened the door to analyze eventual potentials *preceding* a given event by 'back-averaging' a number of repetitive events; the Bereitschaft potentials preceding a movement as well as the cortical spike preceding a myoclonic jerk were, for the first time, recordable by back-averaging procedures (Shibasaki and Hallett, 2006; Pfurtscheller and Aranibar, 1978).

In the – how useful! – "Glossary of terms most commonly used by clinical electroencephalographers" (Chatrian et al., 1974), we find two variants of '*posterior 4 c/sec rhythm*'; six variants of the '*alpha rhythm*', six variants of '*spikes*', thirteen '*complexes*'. The new EEG findings were discussed for years, usually in lively and friendly moods, at times hotly, even in the cold surroundings of 'Alpine sky meeting' (Miletto, 1964):

"*Why* – claimed an astonished J. Stevens (USA) – *the '14-and-6 positive spikes' are considered so relevant and frequent in the US while are ignored in Europe? 'We never saw them' was the answer of Gastaut and Remond*"*!*

In turn, G. Walter stated of having "*never seen*" the 'rhythm *en arceau*' (the mu rhythm). In the same 'sky meeting' in a discussion on 'spike and waves without epilepsy', the soft spoken, well-mannered gentleman, Prof. Loiseau (Bordeaux) "*rose to protest with vehemence against the use of the term epileptic to describe a paroxysmal tracing*" (Miletto, 1964, page 345).

Unavoidable to reread the Grey Walter (1949) 'Commentaries' on *"Coming to terms with brain waves: the inevitable ambiguity of language is the joy of poets, the despair of scientist; [. . .] We need not to be afraid of naming phenomena we do not understand. It would be ludicrous to use 'alpha rhythm' to mean any activity at about 10c/sec, but equally absurd to have to write 'rhythmic oscillations of potential difference at 8–13c/sec, with an amplitude of 5–100 μv in the parietal occipital region, normally attenuated by opening of the eyes and/or mental alertness'. Perhaps we all know what we mean by alpha rhythm, but do we all mean the same things? And what about the others names, for some of which I must accept responsibility?*"

Indeed G. Walters was responsible for the naming of theta and delta waves.

It has been said: "*The confusion arises not from things but by the names we call them*".

3. Part II - Clinical electroencephalography

3.1. Epilepsy

It is not by chance that the first article of the first number of the first year of our Journal 'Electroenceph. Clin. Neurophysiol' is authored by W. Penfield (1949): 'Epileptic Manifestation of Cortical and subcortical Discharge'. It is a refreshing pleasure to quote verbatim the first sentences:

> *"The validity of the Jacksonian conception of an ictal ganglionic discharge has been verified by the clinical use of the electroencephalograph. But the disturbance of electrical rhythms of the brain during a seizure is only one of the manifestations of an attack. It does not tell the whole story of epilepsy. The clinical picture is also important and we must enquire into the pathological cause.*"

From Penfield there is an additional warning. *"The attempt to classify cases of epilepsy on electroencephalographic evidence alone tend to stop the study of a case before it is complete"*. H. Jasper (1949) a few pages later in the final comment of his article 'Electrical signs of epileptic discharge' furtherly comments: *"The clinical pattern of an epileptic seizure is not closely related to the form of associated EEG disturbance but rather to the functional area of the brain primarily involved and the functional characteristics of the neuronal circuits involved in the path of spread*".

There is an exception to these rules, i.e. an epileptic condition that can be diagnosed 'only' by the electroencephalographic recording of the seizure:

"Thanks to the pioneer work of Gibbs, Davis and Lennox (1935) an expert is now able to recognize a three per second rhythm as characteristic of idiopathic (essential genetic) epilepsy. Bursts of such rhythms accompany the minor lapses of consciousness which have been called petit mal".

How still fascinating the spike-and-wave discharge of 'Petit Mal', an imposing "*cathedral with pinnacles and arches*", so rhythmically repeated with a stereotyped common pattern and yet with so complex correlations, with regard to unitary cell discharges (Creutzfeldt, 1963), to spike morphology (Weir, 1965; Rubboli et al., 1995, 2006), to concomitant DC-shift (Goldring and O'Leary, 1957; Chatrian et al., 1968), and to motor manifestations (Speckmann and Elger, 1983; Stefan et al., 1982; Tassinari et al., 1998).

For years – up to now – and despite the contribution of experimental works (Gloor, 1979; Avanzini et al., 2000; Noebels et al., 2012) the issue is still complex (Loiseau and Cohadon, 1970; Duncan and Panayiotopoulos, 1995; Hirsch et al., 2006) even for the apparently simple "Petit Mal Absence".

3.1.1. Automatism and finger prints

"*The problem of epileptic automatisms is of great importance. . .They may follow any type of generalized convulsive seizure. . . but occur chiefly in seizures which arises in the temporal region, and also as the result of petit mal discharge and of anterior frontal region without major convulsion. Actually in all automatisms there is a paresis of a portion of the highest level of neural integration, and therefore all automatism may be said to be psychoparetic not psychomotor*" (Penfield, 1949).

It is implied in a Jacksonian perspective that the 'paresis' can lead to a 'release' of '*some physiological mechanisms involved in epileptic automatisms*', as discussed, in his Lennox Lecture by Jaspers (1964).

Along these lines, we proposed (Tassinari et al, 2009) that the 'physiological mechanisms' such as those occurring in 'alimentary or locomotor cursive automatisms' may be the stereotypical motor sequences generated by Central Pattern Generators. Central Pattern Generators (Grillner and Wallen, 1985) are functional neuronal aggregates present in spinal cord, pons and mesencephalon (see also Reticular Formation) and under control of cortical – mainly frontal – and subcortical – mainly putamen – structures. When this control becomes impaired the automatic, stereotyped, rhythmic motor sequences – or 'automatisms' – occur.

Significantly, Bancaud and Talairach (1991), in their report of a stereo-EEG investigations in 233 epileptic patients, stated: *"It would be very unusual to have two absolutely identical seizures in similar patients or even in the same patient. However, at least in the temporal lobe epilepsies, we have to admit – in a significant number of patients – an anatomo-electro-clinical profile strangely similar*

and extremely homogeneous as if a seizure event, in each subject, could be programmed as a fingerprint".

3.1.2. The Montreal-Marseille axis

Gastaut, with evident pleasure, often reminded us that he considered W. Penfield as one (the other being W. Lennox) of his teachers. The axis Montreal-Marseille was essentially lying on few basic common ideas:

1. There is an Idiopathic Epilepsy "*which would be due to an abnormality of cerebral physiology with a genetic background*". The prototype of such condition is the epilepsy with Petit Mal absences with the 3 c/sec. spike and waves (vide supra).
2. The others forms of Epilepsies should be defined on clinical ground first, then with the investigations relevant to define ictal and interictal EEG patterns, the etiologies and the involved brain areas. These information will constitute the backbone for the classification of seizures and epilepsies, 'personalized' according to the finalities of the various classifications and the specific interests and knowledges (medical or surgical therapy; genetic investigations; triggering mechanisms etc) (Gastaut and Broughton,1972; Gastaut and Tassinari, 1975).

In Gastaut's own word *"my approach (to Epilepsy) was to be based on the three disciplines in which I had been trained: clinical neurology, electroencephalography and neuropathology*". Gastaut used all his knowledges to produce clinical neurophysiology. In 1952 he wrote: *"It now seems necessary to go beyond the static conditions of EEG recording, as performed with eyes closed, to try and study the bioelectrical modifications in conditions as close as possible to those of life itself, i.e. with the eyes opened, in front of diverse and changing situation*" (in this way he discovered the lambda waves and the rhythm '*en arceau*'; vide supra).

Gastaut was very curious on the limit of impatience at times: late on the night, on his way home, he would appear in the EEG lab with his wife Yvette, both elegantly dressed, asking: *"Did you record the seizures? the enuresis? the apnoeas?*" If so he would stay, looking at the 'polygraphic records'.

Polygraphic recording became indeed one of the legacies of the Marseille School (Broughton edr., 1982) and of its disciples. The polygraphic recordings in different domains of neurosciences further document and expand what has been suspected or collected on clinical ground (is it a myoclonus or a spasm? has the patient sleep apnea and of which type? is there ictal bradycardia or tachycardia? etc) or by previous EEG recordings. Consequently, various parameters are associated with the EEG recording, to simultaneously evaluate muscular activity, vegetative functions, respiration, eye movements or degree of performance/responsiveness, etc; tailoring each polygraphic study to the specific clinical problem that the researcher/clinician is investigating.

The need of establishing and maintaining – as much as possible – a continuous link with the clinical aspects was one of the efforts of Gastaut, primarily a clinician, as Secretary, President, and Past President of the Federation.

An important albeit difficult balance, though, and a not new problem. In the 1962 Editorial of the journal, pag. 604, we read a complaint: too few 'clinical' papers [..]? The answer was "*To those who say that the Journal is insufficiently clinical it is only possible to replay that the remedy is in their hands […]*".

Over the years, other neurophysiological techniques have been developed and implemented in the clinical evaluation, joining electroencephalography in the diagnostic armamentarium of the clinician/researcher. Appropriately, in a more general perspective *"to foster and disseminate information on all aspects of Neurophysiology, we have changed […] the name of the Journal to "Clinical Neurophysiology" to represent all fields of human physiology and pathophysiology*" (Celesia and Rossini, 1999).

3.2. Brain Stem Reticular Formation and Behaviors

The reactivity of the above-described rhythms requires a functional interplay to connect the different rhythmogenic areas and networks. This function is that of the 'Brain Stem Reticular Formation', as described by Moruzzi and Magoun in Vol. I n.1 of the EEG Journal, 1949 (Moruzzi and Magoun, 1949).

The Reticular Formation (RF) is a neuronal network in the central part of neuroaxis, elongated from inferior bulbar pontine region to posterior hypothalamus. As by Magoun (1958) we can think of the RF as a transactional center acting as an integrator and modulator of other systems in relation also to its own internal excitability, in turn depending of peripheral afferences, humoral and metabolic conditions and signals and on reciprocal interplay in the cortex.

Quoting from Moruzzi and Magoun (1949) the RF stimulation *"evokes changes in the EEG consisting in the abolition of synchronized discharges and introduction of low voltage fast activity in its place. The effect of Reticular Stimulation is strikingly like Berger's alpha wave blockade or any arousal reaction… The EEG modifications reflect the transition from sleep to wakefulness or from relaxation to alertness*". It became thus possible to correlate (a) the EEG rhythms reactivity with the processes of attention, habituation and plasticity, and of sleep and arousals: that is the basis of behavior (Jouvet, 1963); and concomitantly (b) to correlate the clinical manifestations with the motor and autonomic events.

In this context, it became rewarding to have chronic experimentations, allowing to compare the behaviors in animal and in man in wakefulness and sleep in a more appropriate ethological approach (Jouvet, 1978; Hess, 1944; Moruzzi, 1969).

At times, the clinical conditions could offer the initial cue for experimental investigations: the eye movements during the dreaming of the students in the Dement and Kleitman (1957) sleep laboratory were the first clinical observations leading subsequently to experimental definition of a 'new' stage of sleep, paradoxical or REM (Hobson et al., 1974; Jouvet and Michel, 1960).

Understandably disorders of the RF, "*the modulator or transactional system*" attuning vigilance, muscular and vegetative activities can occur during sleep-to-wakefulness transition.

It is matter – during slow sleep – of the parasomnias (e.g. pavor nocturnus, enuresis, somnambulism), rightly considered as 'arousal disorders' (Broughton, 1968), or it is matter of REM-related sleep events: violent behaviors, sleep paralysis, cataplectic attacks, and narcoleptic episodes, examples of brain-body 'dissociated' behavioral disorders (Plazzi et al., 2011; Schenck et al., 1997).

4. Unending conclusions

If Hans Berger were with us now, trying to evaluate the scientific accomplishments stemming from his *Elektrenkephalogramm*, would he be satisfied? It is certainly so, but not completely in some respect. Quoting from his last paper (Berger, 1938): *"My preferred interest was the psychophysiology […] and the connection between cerebral processes and the psychic manifestations*". In this respect he himself considered the Electroencephalogram somewhat disappointing. We can speculate, 70 years later, how the mirror neuron system (Rizzolatti and Sinigaglia, 2016) can offer a partial answer to Berger psychophysiology; even if, in the last decades, a rich scientific production has focused on 'Event Related potentials' and to those brain waves (e.g. the P300) which are mainly produced by a cognitive/psychological process. In recent years neuroscientists started to explore 'brain connectivity' as the cornerstone for better

understanding neuropsychiatric diseases and normal brain functions. Within this frame advanced mathematical analysis of EEG signals (e.g. via graph theory) are progressively opening new avenues for a better interpretation of the working brain, of its dynamics as well as of its network organization in the healthy and disease conditions (Rossini et al., 2019). However, Berger went on, quoting Mosso (1883): *"As far as we apply instruments to evaluate the human brain functions, we should hope to understand the physical basis of consciousness. And even if do not reach satisfactory results we are on the right track"* (as quoted by Fischgold et al., 1963).

Along this track, neuroscientists from all over the world went in a seventy year old journey as by testimonial evidence of our International Journal*: Clinical Neurophysiology.*

On perusal of our Journal I got the feeling that the people on the Mosso track became progressively a family, a family of friends in a common *Bergerian* pursuit: how *"cerebral processes became psychic manifestations?"* Neuroscientists, as novel untiring Hermes, are striving for data collection and interpretation, in an unremitting hermeneutic endeavor, *"a continuous tension between the will of listening and the will of conjecture"* (Ricoeur, 1965).

Declaration of Competing Interest

None.

References

Adrian ED, Matthews BHC. The Berger rhythm: potential changes from the occipital lobes in man. Brain 1934;57:355–85.

Altschuler EL, Vankov A, Wang V, Ramachandran VS, Pineda JA. Person see, person do: human cortical electrophysiological correlates of monkey see monkey do cells. 27th Annual Meeting of the Society for Neuroscience. New Orleans, LA. In: Poster session; 1997.

Avanzini P, Fabbri-Destro M, Dalla Volta R, Daprati E, Rizzolatti G, Cantalupo G. The dynamics of sensorimotor cortical oscillations during the observation of hand movements: an EEG study. Plos One 2012;7:e 37534.

Amzica F, Steriade M. Electrophysiological correlates of sleep delta waves. Electroenceph Clin Neurophysiol 1998;107:69–83.

Avanzini G, Panzica F, de Curtis M. The role of the thalamus in vigilance and epileptogenic mechanisms. Clin Neurophysiol 2000;111(Suppl 2):S19–26.

Babiloni C, Carducci F, Cincotti F, Rossini PM, Neuper C, Pfurtscheller G, et al. Human movement-related potentials vs desynchronization of EEG alpha rhythm: a high-resolution EEG study. Neuroimage 1999;10(6):658–65.

Bancaud J, Talairach J. Sémiologie clinique des crises du lobe temporal (méthodologie et investigations SEEG de 233 malades). In: Bancaud J, Talairach J, editors. Crises épileptiques et épilepsies du lobe temporal. Cours de perfectionnement en épileptologie. Paris: Sanofi; 1991. p. 5–110.

Benabid Alim Louis, Costecalde Thomas, Eliseyev Andrey, Charvet Guillaume, Verney Alexandre, Karakas Serpil, Foerster Michael, Lambert Aurélien, Morinière Boris, Abroug Neil, Schaeffer Marie-Caroline, Moly Alexandre, Sauter-Starace Fabien, Ratel David, Moro Cecile, Torres-Martinez Napoleon, Langar Lilia, Oddoux Manuela, Polosan Mircea, Pezzani Stephane, Auboiroux Vincent, Aksenova Tetiana, Mestais Corinne, Chabardes Stephan. An exoskeleton controlled by an epidural wireless brain–machine interface in a tetraplegic patient: a proof-of-concept demonstration. The Lancet Neurol 2019;18(12):1112–22. https://doi.org/10.1016/S1474-4422(19)30321-7.

Berger H. Das Elektrenkephalogramm des Menschen. Nova Acta Leopoldina, Halle (Saale) 1938;6:173–309.

Berger H. Über das Elektrenkephalogramm des Menschen. Archiv für Psychiatrie und Nervenkrankheiten. 1929;87:527–70.

Bölsterli BK, Schmitt B, Bast T, Critelli H, Heinzle J, Jenni OJ, et al. Impaired slow wave sleep downscaling in Encephalopathy with Status Epilepticus during sleep (ESES). Clin Neurophysiol 2011;122:1779–87.

Borbély Alexander A, Achermann Peter. Sleep homeostasis and models of sleep regulation. In: Principles and Practice of Sleep Medicine. Elsevier; 2005. p. 405–17. https://doi.org/10.1016/B0-72-160797-7/50040-9.

Brazier MAB. The electrical fields at the surface of the head during sleep. EEG Clin Neurophysiol 1949;1:195–204.

Broughton R. Sleep Disorders: disorders of arousal? Science 1968;159:1070–8.

Broughton RJ (editor). Henri Gastaut and the Marseilles school's contribution to the neurosciences. Electroenceph Clin Neurophysiol 1982, Suppl. 35.

Cantalupo G, Pavlidis E, Beniczky S, Avanzini P, Gardella E, Larsson PG. Quantitative EEG analysis in Encephalopathy related to Status Epilepticus during slow Sleep. Epileptic Disord 2019;21:31–40.

Celesia GG, Rossini PM. Editorial. 50th anniversary of Electroencephalography and Clinical Neurophysiology. Clin Neurophysiol 1999;1:110.

Chatrian GE, Bergamini L, Dondey M, Klass DW. Lennox – Buchtal M. and Petersen I. A glossary of terms most commonly used by clinical electroencephalographers. Electroenceph Clin Neurophysiol 1974;37:538–48.

Chatrian GE, Somasundaram M, Tassinari CA. DC changes recorded transcranially during "typical" three per second spike and wave discharges in man. Epilepsia 1968;9:185–209.

Compston A. The Berger rhythm: potential changes from the occipital lobes in man, by E.D. Adrian and B.H.C. Matthews (From the Physiological Laboratory, Cambridge). Brain 1934: 57; 355–385.. Brain 2010;133(1):3–6. https://doi.org/10.1093/brain/awp324.

Creutzfeldt O. Activité neuronique du système nerveux central de quelques aspects de l'activité neuronique unitaire corticale et de ses rapports avec l'électroencéphalogramme. In: Fishgold, editor. Problèmes de base en èlecroencéphalographie. Masson, Paris. p. 34–60.

Dement W, Kleitman N. Cyclic variations in EEG during sleep and their relation to eye movement, body motility and dreaming. Electroenceph Clin Neurophysiol 1957;9:673–90.

Desmedt JE, Cheron G. Somatosensory evoked potentials to finger stimulation in healthy octogenarians and in young adults: wave forms, scalp topography and transit times of parietal and frontal components. Electroencephalogr Clin Neurophysiol 1980;50:404–25.

Duncan JS, Panayiotopoulos CP, editors. Typical Absences and related epileptic syndromes. Churchill CE; 1995.

Duncan JS, Panayiotopoulos CP, editors. Eyelid Myoclonia with Absences. London: J. Libbey; 1996.

Fischgold H, Dreyfus-Brisac C, Pruvot P. Problemes de base en Electroencephalographie. Paris: Masson; 1963.

Gastaut H, Tassinari CA, editors. Clinical EEG-Epilepsies. Handbook of Electroenceph and Clin Neurophysiol.

Gastaut H. Etude électrocorticographique de la réactivité des rythmes rolandiques. Rev Neurol 1952;87:176–82.

Gastaut H, Bert J. EEG changes during cinemotographic presentation. Electroenceph Clin Neurophysiol 1954;6:443–4.

Gastaut H, Broughton R. Epileptic Seizures: Clinical and Electrographic Features, Diagnosis and Treatment. Springfield, IL: Charles C. Thomas; 1972.

Gastaut H, Terzian H, Gastaut Y. Etude d'une activité électroencéphalographique méconnue: "le rhythmse rolandique en arceau". Marseille Med 1952;89:296–310.

Gloor P. Generalized epilepsy with spike and wave discharge: a reinterpretation of its electrographic and clinical manifestations. Epilepsia 1979;20:571–88.

Goldring S, O'Leary JL, Cortical DC. changes incident to midline thalamic stimulation. Electroencephalogr Clin Neurophysiol 1957;9:577–84.

Grillner S, Wallen P. Central Pattern Generators for locomotion with special reference to vertebrates. Ann Rev Neurosci 1985;8:233–61.

Haas LF. Hans Berger (1873–1941), Richard Caton (1842–1926), and electroencephalography. J Neurol Neurosurg Psychiatry 2003;74:9.

Halasz P, Szucs A. Sleep, Epilepsies, and Cognitive Impairment. 1st ed. ISBN: 9780128125793. Academic Press. 2018.

Hirsch E. et al., editors. Generalized seizures: from clinical phenomenology to underlying systems and networks. J. Libbey. Progress in Epileptic Disorders, Vol. 2; 2006.

Hess WR. Das Schlafsyndrom als Folge chienzephaler Reizung. Helvetica Physiologica et Pharmacologica Acta 1944;2:305–44.

Hobson JA, McCarley RW, Pivik RT, Freedman R. Selective firing by cat pontine brain stem neurons in desynchronized sleep. J Neurophysiol 1974;37(3):497–511.

Jasper H, Penfield W. Electrocorticograms in man: Effect of voluntary movement upon the electricalo activity of the precentral gyrus. Archiv Fur Psychiat Zeitsh Neurol 1949;183:163–74.

Jasper HH. Some physiological mechanisms involved in epileptic automatisms. Epilepsia 1964;23:1–20.

Jeavons PH, Harding GFA. Photosensitive Epilepsy. Heinemann, London: Clinics in Develop. Medicine; 1975.

Jouvet M. Le sommeil paradoxal est—il responsable d'une programmation génétique du cerveau? C R Soc Biol (Paris) 1978;172:9–32.

Jouvet M. Formation réticulaire et comportement. In: Fischgold H, Dreyfus-Brisac C, Pruvot P, editors. Problemes de base en Electroencephalographie. Paris: Masson; 1963.

Jouvet M, Michel F. Déclenchement de la phase paradoxale du sommeil par stimulation du tronc cérébral chez le chat intact mésencéphalique chronique. C. R. Soc. Biol. (Paris) 1960;154:636–41.

Killam KF, Killam EK, Naquet R. An animal model of light sensitive epilepsy. Electroenceph Clin Neurophysiol 1967;22:497–513.

Loiseau P, Cohadon F. Le petit mal et ses frontiers. Paris: Masson; 1970.

Magoun HW. The waking brain. Springfield, IL: Thomas; 1958.

Miletto G. EEG Alpine Sky Meeting. Electroenceph Clin Neurophysiol 1964;17:342–9.

Moruzzi G. Sleep and instinctive behavior. Archives Italiennes de Biologie 1969;107:175–216.

Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1949;1:455–73.

Mosso A. La paura. A. Treves, Milano; 1883.

Niedermeyer's Electroencephalography: Basic Principles, Clinical Applications, and Related Fields (7 ed.) Schomer DL and Lopes da Silva FH. Oxford University Press; 2017.

Noebels Jeffrey, Avoli Massimo, Rogawski Michael, Olsen Richard, Delgado-Escueta Antonio, editors. Jasper's Basic Mechanisms of the Epilepsies. Oxford University Press; 2012.
Penfield W. Epileptic manifestatios of cortical and supracortical discharge. Electroenceph Clin Neurophysiol 1949;1:3–10.
Pfurtscheller G, Aranibar A. Occipital rhythmic activity within the alpha band during conditioned externally paced movement. Electroencephalogr Clin Neurophysiol 1978;45:226–35.
Ricoeur P. De l'interprétation. Essai sur Freud. Le Seuil, 1965.
Plazzi G, Pizza F, Palaia V, Franceschini C, Poli F, Moghadam KK, et al. Complex movement disorders at disease onset in childhood narcolepsy with cataplexy. Brain 2011;134:3477–89.
Rizzolatti G, Sinigaglia C. The mirror mechanism. A basic principle of brain function. Nat Rev Neurosci 2016;17:757–65.
Rossini PM, Di Iorio R, Bentivoglio M, Bertini G, Ferreri F, Gerloff C, et al. Methods for analysis of brain connectivity: An IFCN-sponsored review. Clin Neurophysiol 2019;130:1833–58.
Rossini PM, Gigli GL, Marciani MG, Zarola F, Caramia M. Non-invasive evaluation of input-output characteristics of sensorimotor cerebral areas in healthy humans. Electroencephalogr Clin Neurophysiol 1987;68:88–100.
Rubboli G, Mai R, Meletti S, Francione S, Cardinale F, Tassi L, et al. Negative myoclonus induced by cortical electrical stimulation in epileptic patients. Brain 2006;129:65–81.
Rubboli G, Parmeggiani L, Tassinari CA. Frontal inhibitory spike component associated with epileptic negative myoclonus. Electroencephalogr Clin Neurophysiol 1995;95:201–5.
Rubboli G, Huber R, Tononi G, Tassinari CA. Encephalopathy related to Status Epilepticus during slow Sleep: a link with sleep homeostasis? Epileptic Disord 2019;21:62–70.
Schenck CH, Boyd JL, Mahowald MW. A parasomnia overlap disorder involving sleep walking, sleep terrors and REM sleep behaviour disorder in 33 polysomnographically confirmed cases. Sleep 1997;20:972–81.
Shibasaki H, Hallett M. What is the Bereitschaftspotential? Clin Neurophysiol 2006;117:2341–56.
Speckmann E-J, Elger CE. Epilepsy and motor system. Baltimore: Urban & Schwarzenberg; 1983.
Stefan H, Burr W, Hildenbrand K, Penin H. Basic temporal structure of absence symptoms. In: Akimoto A, Kazamatsuri H, Seino M, War A, editors. Advances in epileptology: XIII the Epilepsy International Symposium. New York, NY: Raven Press. p. 55–60.
Takahashi T. Photosensitive epilepsy. Igaku –Sohn Tokyo 2002.
Tassinari CA, Rubboli G, Shibasaki H. Neurophysiology of positive and negative myoclonus. Electroencephalogr Clin Neurophysiol 1998;107:181–95.
Tassinari CA, Cantalupo G, Hogl B, Cortelli P, Tassi L, Francione S, et al. Neuroethologic approach to frontolimbic seizures and parasomnias: the same central pattern generators for the some behaviours. Rev Neurol 2009;165:762–8.
Terzano MG, Mancia D, Salati MR, Costani G, Decembrino A, Parrino L. The cyclic alternating pattern as a physiologic component of normal NREM sleep. Sleep 1985;8:137–45.
Tononi G, Cirelli C. Sleep and the price of plasticity from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 2014;81:12–34.
Vaudano AE, Ruggieri A, Avanzini P, Gessaroli G, Cantalupo G, Coppola A, et al. Photosensitive epilepsy is associated with reduced inhibition of alpha rhythm generating networks. Brain 2017;140:981–97.
Walter VI, Walter WG. The central effects of rhythmic sensory stimulation. Electroenceph Clin Neurophysiol 1949;1:57–86.
Walter WG. Commentary – Coming to terms with Brain Waves. Electroenceph Clin Neurophysiol 1949;1:474.
Weir B. The morphology of the spike-wave complex. Electroencephalogr Clin Neurophysiol 1965;19:284–90.
Ziemann Ulf. Seventy years of our journal. Clin Neurophysiol 2019;130:2255–7.

Carlo Alberto Tassinari *
Università degli Studi di Bologna, Italy

Centro Ricerca per le Epilessie in età Pediatrica (CREP), Verona, Italy
* *Address: via S. Isaia, 55, 40123 Bologna, Italy.*
E-mail address: carloalbertotassinari@gmail.com
Accepted 25 October 2019

Available online 9 November 2019

Clinical Neurophysiology 130 (2019) 2264–2267

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Editorial

An electromyographer recalls the history of the Federation on the 70th anniversary of its journal, *Clinical Neurophysiology*

To celebrate this historical occasion, Dr. Ulf Ziemann, the Editor-in-Chief, asked me if I would contribute an editorial as an old timer who has witnessed some of the early days of our Federation. He instructed me to describe the historical events related to the development of electromyography (EMG) for study of the peripheral nerve and muscle in the scope of scientific activities of the Federation, which initially exclusively dealt with the study of electroencephalography (EEG) to assess cerebral function. I understand Dr. Tassinari will review the more traditional accounts for the progress of the Federation primarily as an EEG organization (see his article in the same issue of *Clinical Neurophysiology*). As I accepted the kind offer, thousands of thoughts crossed my mind, some of which I will list below. I know one should avoid starting a paper with an apology, which instantaneously weakens the position. This notwithstanding, I admit that the article, by necessity, describes a very private recollection only in the context of the Federation activities and may have overlooked some personalities and historical events crucial to the development of EMG. For such unintentional omissions, I can only claim my ignorance and hope others more knowledgeable would be willing to fill in the void created in this review.

The first volume of our journal, *EEG and Clinical Neurophysiology* (EEG Journal), was published in 1949, two years after the founding meeting in London of the International Congress of EEG (EEG Congress) in 1947, when Professor Edgar D. Adrian, the President of the UK EEG Society, suggested the formation of a World EEG Organization and the founding of an International Journal. Herbert H. Jasper of Montreal, the first President of the *International Federation of Societies for Electroencephalography and Clinical Neurophysiology* (IFSECN), was appointed as the founding Editor (1949–1961) for the forthcoming journal. Dr. W.T. Liberson of Hartford, CT, USA, already voiced a more liberal view. He argued that the Federation and the journal should deal with all the fields of clinical neurophysiology, including EMG, rather than exclusively devoted to EEG. This advice, falling on deaf ears, gained no support during the early days. He told me all about the ordeal much later in the late1980s, when we worked together in selecting the Muscle & Nerve as the official journal of the American Association of Electromyography and Electrodiagnosis (AAEE).

I came to the US as a Fulbright scholar in 1962 for residency training at the University of Iowa, a distinguished neurology program, which celebrates its 100th anniversary under the chairmanship of Dr. George Richerson this year as the third oldest Neurology Department in the US. I then had my first contact with electrophysiology as an EEG fellow in the Psychopathic Hospital with Dr. John Knott, who had already established one of the first EEG laboratories in the country. Herbert Jasper, who studied psychology in Iowa before his medical education, worked with John Knott, who also earned PhD in the same field. The 1983 Wave Length book, authored by W. A. Cobb of London, the second Editor-in Chief (1962–1973), mentions that John Knott prepared the Society Proceedings to help Herbert Jasper launch the EEG journal in February 1949.

In 1969, I moved to the University of Manitoba, Canada to work with Dr. Michael Saunders, who served as a member of the Rules Committee for Mary A. Brazier of Los Angeles (1961–1965), the 4th President of the IFSECN. She was preceded in this capacity by Herbert H. Jasper (1949–1953), W. Grey Walter of Bristol (1953–1957) and Henry Gastaut of Marseilles (1957–1961). Her administration proposed three distinguished electromyographers to form the EMG Commission to look after EMG interests in this primarily EEG oriented organization: Fritz Buchthal of Copenhagen, Denmark as the founding Chairman, Irena Hausmanova of Warsaw, Poland, and Ed Lambert of Rochester, MN, USA, as the members. Under the 5th President, Antoine Remond of Paris (1965–1969), Dr. Saunders served as the first Member-at-Large and first Chairman of the Rules Committee. He also worked for the Journal as a member of the Editorial Board, helping W.A. Cobb; Ed Lambert looked after EMG matters as the second Chairman of the EMG Commission after Fritz Buchthal.

The 3rd International Congress of EMG (EMG Congress) took place in Glasgow, Scotland, UK (1967) following the 1st and 2nd Congresses in Pavia, Italy (1961) and Copenhagen, Denmark (1963). When the American EEG Society hosted the 7th EEG Congress in San Diego in 1969 under the presidency of Herbert Jasper, Ed Lambert attended to EMG interests, representing AAEE. A change in the By-Laws allowed admission of two societies from the same country. Taking advantage of this new rule, AAEE, an EMG organization, joined the IFSECN as the second member society from the US. This event reflected a new thought in the minds of Executive Committee (ExCo) members realizing that the Federation should have more than EEG alone.

As for the journal, H.H. Jasper concluded a contract with Elsevier in September 1960. The IFSECN apparently had serious differences with Elsevier around 1970, when the publisher wished to draw up a new contract. Feeling uneasy, Peter Kellaway resigned at the end of 1971 and Mary Brazier took on the task of American Editor. Despite the initial concern over the new contract, the income from the Journal rose to a new high during the next Fiscal Period and Elsevier offered to include in each number a two-page insert as

https://doi.org/10.1016/j.clinph.2019.10.005

"News and Notes" to improve communication with member societies. Dr. Cosimo Ajmone Marsan of Bethesda (1969–1973) was elected as President. Fritz Buchthal, founding Chairman of the EMG Commission in the previous decade, returned for an encore service in that same role.

Following the AAEE lead, the Belgian Society of EMG and Clinical Neurophysiology applied successfully for a membership as the second society of the country in 1971, the year the 4th EMG Congress took place in Brussels. The IFSECN, for the first time, played an active role in its organization. This stood in sharp contrast to the three prior EMG Congresses which received very limited input from the strongly EEG oriented Federation. The three volume treatise that John Desmedt edited as the Convener, assembling most of the topics discussed in the Congress, appeared in 1973 under the name of "New Developments in Electromyography and Clinical Neurophysiology". I believe, and many of my neurophysiology colleagues agree, that this masterpiece propelled the field of EMG to a much higher level, defining the role of clinical neurophysiology as a practical tool. Inspired by this development, I asked Dr. Thoru Yamada to join us as Director of EEG laboratories, which allowed me to concentrate in my chosen field.

The 8th EEG Congress was held in 1973 under the Presidency of Henri Gastaut. William A Cobb (1973–1977) was elected as president. Marry A.B. Brazier (1973–1984) took over the job of Editor-in-Chief and Pierre Buser of Paris became the European Editor. Professor A. Struppler from Munich became Chairman of the EMG Commission.

The 5th EMG Congress, organized by AAEE, took place in Rochester, MN, USA in 1975. Despite considerable anxiety expressed by the members of the Organizing Committee for the usual lack of communication from Ed Lambert, serving as the President, the meeting was well attended. They provided very personal hospitality, each Mayo Clinic EMG staff member inviting a group of attendees to their homes for meals. I had the good fortune of having Jasper and Cindy Daube as my host. We discussed, among other things, how we should tie the AAEE to the IFSECN to further develop EMG in the US and globally. Jasper promoted EMG vigorously, working as the Secretary-Treasurer of AAEE, the post I inherited shortly thereafter.

The EEG journal was receiving a progressively increasing number of submissions, which made publication delay inevitable with an unacceptable backlog of papers despite a high rejection rate. The problem was resolved near the end of the Fiscal Period by a return to small print and the use of extra pages. The 9th EEG Congress, held in Amsterdam in conjunction with the 11th World Congress of Neurology (WCN), elected Robert Naquet of Marseilles (1977–1981) as President. John Desmedt became the Chairman of the EMG Commission.

In June 1979, the Swedish Society held the 6th EMG Congress in Stockholm. Erik Stalberg, a close friend of mine, was helping K.E. Hagbarth, the Convener. J. E. Desmedt represented the Federation as Chairman of the Organizing Committee. Despite the initial concern about the opposing personalities of the Convener and Chairman, the congress went well, drawing over 600 attendees. On a personal note, Junko, my wife, and I, exhausted after a long flight, took a nap on arrival. Seeing bright daylight on awakening, we thought we had overslept. Fearing that I was about to miss my presentation scheduled for 5:00 PM, we rushed to the hotel lobby asking for a taxi and the clerk told us it was 3:00 AM, not 3:00 PM. I visited Uppsala a number of times since, always remembering this embarrassing experience very fondly.

With the news that the World Federation of Neurology would hold the 12th WCN in Japan, the IFSECN immediately accepted the bit to hold the 10th EEG Congress in Kyoto in 1981. Professor Naquet and the members of ExCo wondered in amazement why Japanese appointed such a huge local organizing committee of some 150 members. They had no knowledge of the traditional practice in Japan to round up as many names as possible in the honor role, the trend I inherited when we later organized the EMG Congress in the same venue in 1995. The ExCo members praised not only the scientific presentations but also the ladies' programs as one of the best, contributing to the value of the meeting. Since then, Japanese organizers consider an international meeting a big success if the accompanying persons' programs go well. In passing, I should mention that the success of this joint venture prompted another similar arrangement later in Vancouver between the 15th WCN and 13th EEG Congress, which Andy Eisen of Vancouver and I had the honor to help organize in 1993.

To celebrate the 30th anniversary of the journal in 1979, the February number came out in a pale green cover, containing a brief history by Brazier and Cobb entitled "Thirty years." Hans van Duijn, working in Amsterdam close to the Elsevier office, replaced Peirre Buser, who, after 6 years of distinction, resigned as European Editor. R. J. Ellingson (1981–1985) was elected as President and Mary Brazier was reappointed as Editor-in-Chief. The 7th EMG Congress took place in Munich in 1983 with A. Struppler as the Convener. J.E. Desmedt, as the Chairman of EMG Commission, represented the Federation in the Organizing Committee. In 1984, Marry Brazier, after 11 years of yeoman work, relinquished the post of Editor-in-Chief to Hans van Duijin (1984–1987) conveniently placed in Amsterdam for daily contact with the desk Editor at Elsevier.

W.A. Cobb, serving the IFSECN as the Publication Editor, edited "Recommendations for Practice of Clinical Neurophysiology", and authored, "Wave Length" in 1983. With about 3000 subscriptions, the journal had consolidated its position in the competitive field of neuroscience publications. The 11th EEG Congress was held in London in August 1985 with A.M. Halliday as the Convener. Although the meeting offered a very good scientific and educational program, financial issues developed because of the unexpectedly high cost for the use of Barbican as a venue, the problem unresolved until the next Fiscal Period, when John E. Desmedt (1985–1989) served as President and Stephane Metral from Paris, as Chairman of the EMG commission.

The 8th EMG Congress was held in Sorrento, Italy in May, 1987 at the invitation of the Italian Society of EEG and EMG, celebrating the 40th anniversary of the founding Federation meeting in 1947. Giuseppe "Peppino" Caruso served as Convener and John E. Desmedt represented the Federation as President. Coinciding with the start of the conference, Italian railroad workers went on strike, which shut down all transportation serving Rome and Sorento. As a result, a group of us were stranded in Milan and, to my great regret, I could not deliver a scheduled talk. When I finally arrived at the Congress hall, I was warmly greeted at the entrance by Convener Caruso himself who stated "we were all worried about you" in his concerned and personal way, saying nothing about the missed session. I still remember my ordeal and the lesson I learned from Peppino on how to handle invited speakers who have failed to show up for their assigned role.

The 12th EEG Congress was held in Rio de Janeiro, Brazil in January 1990, summertime in the southern hemisphere. The Brazilian Society of Clinical Neurophysiology served as the host society with Gilson E. Goncalves e Sila as Convener and Joao Nobrega as Treasurer. John E. Desmedt represented the IFSECN as the President. The Council, in a historical move, voted to disband the EMG Commission, which, formed at the first EMG Congress in 1961, continued its work to promote EMG in the EEG oriented Federation for three decades under the chairmanships of Fritz Buchthal (1961 and 1969), Edward H. Lambert (1965), Albrecht Struppler (1973), John E. Desmedt (1977 and 1981) and Stephane Metral (1985). This decision clearly signaled the recognition of EMG as a core discipline equal to EEG. Reflecting this sentiment, the Nominations

Rules were also altered to guarantee fair representation of the EEG and EMG disciplines in the ExCo composition.

With the realization that the IFSECN's focus had now expanded well beyond EEG itself, the 1990 General Assembly in Rio de Janeiro voted in favor of changing the name of the Federation to *International Federation of Clinical Neurophysiology* (IFCN), a forward step to indicate that we should encompass all disciplines of clinical neurophysiology. The name change signaled the new era of the organization which now recognized equal importance of EEG and EMG, reflecting the unity of clinical electrophysiology. For the first time, the Federation, under the new name IFCN, represented all disciplines of our fields. The Council also approved ExCo proposal to amend the by-law on Other International Meetings to state: "In addition to the International Congress of EEG and Clinical Neurophysiology, the IFCN organizes an International Congress of EMG and Clinical Neurophysiology and may organize or sponsor other interim meetings on any topic related to clinical neurophysiology". The main quadrennial convention called EEG Congress now dealt with a broader representation of techniques, including EMG materials. Similarly, the midterm convention, known as the EMG Congress, encompassed a wider scope of clinical neurophysiology, a trend already noticeable at the 1987 EMG Congress in Sorrento.

The name of the journal, *Electroencephalography and Clinical Neurophysiology*, remained unchanged until the end of that decade to preserve the high impact factor linked to the well-established name. Hans van Duijn, Editor-in-Chief, and Mary A.B Brazier, Western Hemisphere Editor, both expressed their wish to step down from their duties for personal reasons. Timothy Pedley (1987) from New York, appointed as Western Hemisphere Editor, resigned after several months and was succeeded by Gastone Celesia from Chicago (1988–1999). Francois Mauguière from Lyon (1987–1995) was appointed as Editor for the European Office. For the first time, both Editors served with the title, Editors-in-Chief, and a full vote each in the ExCo. The journal expanded to include a six-issue volume each year dedicated to *EMG and Motor Control* following the procedure four years earlier of adding a six-issue volume named *Evoked Potentials*. Both separate volumes were published in parallel with the main journal, which had two six-issue volumes. Therefore, the journal reached four volumes and 24 issues each year. The journal achieved the highest impact factor in the categories of clinical neurophysiology.

A group of EMGers, trying to further consolidate the trend to establish EMG as an equally important discipline as EEG in clinical practice, suggested that I run for the Office of the next President. Needless to say, I had no guarantee to win against internationally prominent opponents, who mostly represented EEG. At the end it became a contest between the two disciplines involving traditionally strong EEG and newly emerging EMG. I felt all along that I had a slight edge as a candidate nominated from Japan, which had never had a post in the ExCo despite early participation and contribution to the affairs of the Federation. Thus, I found myself in the right place at the right moment to win the race despite my inexperience. It was a triumphant moment, for sure, although I had considerable anxiety on how to handle this added responsibility as I had just accepted the offer to return to my alma mater as Chair of Neurology and relocated the Editorial Office of the *Muscle & Nerve* from Iowa to Kyoto.

Political tensions in the near East worsened and war broke out in Kuwait and Iraq in February and March, 1991 threatening the 9th EMG Congress in Jerusalem originally scheduled for June 1991. Israel found itself under air attack. When the hostility ceased and an uneasy truce declared, the political outlook continued to raise concern for further provocative actions against Israel. The Organizing Committee of International Congress (OCIC) and Israel Society of Clinical Neurophysiology represented by Dr. A. Gilai as the Convener considered and reconsidered various options on many occasions. The discussions remained congenial although we found it difficult to secure a mutually agreeable plan. In the end, I recommended to postpone the meeting to 1992 as a compromise, a plan eventually supported by both sides. When the Congress finally took place in the following year, more than 500 physicians and scientists participated in the meeting from all corners of the world. This attendance clearly exceeded the originally anticipated size, although smaller than the typical EMG Congress. The meeting had strong scientific and social programs, which included the Kugelberg Lecture delivered by Arthur K. Asbury on "Polyneuropathies of the Millennium" and the Adrian Lecture, by John Newson-Davis on "New Concepts in Neuromuscular Disorders".

We had the OCIC meeting in Kyoto, July 1993 when John Desmedt, Immediate Past President, and Carl Lücking, President Elect, found something resembling a gavel in a small antique shop near Kiyomizu Temple. Dr. Hiroshi Shibasaki, who later served as the Federation Secretary and President, told us that this wooden piece called "Nyoi-bo", described in a Japanese folk story, belonged to an ape warrior who helped a Chinese priest seeking the Buddhist Bible. The Saiyuhki, "a tale of a venture to the West", written in ancient China, proposes the belief that, Nyoi-bo, a magic bar, helps one accomplishes the esteemed goal for the benefit of all mankind. The Nyoi-bo was handed over to me as the 11th President (1990–1993) during the OCIC session in Kyoto with the intention that this instrument would serve from that point forward as the ceremonial gavel for the president to use during the delegate meeting. Given its tradition, it also symbolizes, as a sign of hope, that the president and the Federation will achieve the objective during each term.

Andrew and Kathy Eisen, residents in Vancouver, handled much of the difficult and often controversial issues with finesse for the 13th EEG Congress in September, 1993. Because of a major delay of their flight from Tokyo, the Japanese contingent barely made the Opening Ceremony which took place at the historic beautifully restored Orpheum Theatre. My wife and I were amongst them. Andy sent a limousine to pick us up and we came straight to the "Opening" in a T-shirt and jeans. I wanted to "show up" rather than "dress up" to pay our respect and gratitude to the local organizers who spent countless hours preparing for the occasion. From my vantage point, the meeting offered one of the best scientific and social events we have ever experienced.

At the Vancouver General Assembly in 1993, I presented the Nyoi-bo for the first time as a ceremonial gavel to Carl Lücking of Freiburg (1993–1997), the incoming President, wishing him and the new ExCo success in the coming four years in what they hoped to accomplish for the course of IFCN. Since then, each succeeding President has received the Nyoi-bo from the outgoing President at the end of the quadrennial General Assembly as a ceremonial token of their authority in the office and wish for good fortune throughout their term of office. Thus, Nyoi-bo has found its way to Presidents Marc Nuwer from Los Angles (1997–2001), Franciois Mauguière from Lyon (2001–2006), Hiroshi Shibasaki from Kyoto (2006–2010), Paolo Rossini from Rome (2010–2014), Mark Hallett from Bethesda (2014–2018), and Walter Paulus from Göttingen (2018–2022).

I had the privilege of serving on the Organizing Committee for the 10th EMG Congress in Kyoto, Japan as the Convener and Immediate Past President of IFCN in 1995. Carl Lücking represented the Federation as the new President. Nobuo Yanagisawa served as Secretary, Koki Shimoji, as Treasurer and Hiroshi Shibasaki, as Chair of the Program Committee. Ichiro Akiguchi, Ryuji Kaji and Nobuo Kohara ran as the Secretariat instead of a professional congress organizer to reduce the cost as we anticipated difficulty in fund raising for three adverse factors we experienced: strong Japanese currency, reaching 80 yen per 1 US dollar, an incident of under-

ground sarin poisoning and a major quake with epicenter in Kobe located only 60 km from the conference venue. Despite such concern, the congress went well drawing over 1500 participants, considered a record high at that time. The scientific program covered not only EMG but also EEG and other disciplines of clinical neurophysiology. Stephen Waxman presented the Adrian lecture on "Ion Channels and Nerve Conduction". K.E. Hagbarth discussed "Muscle Spindle and Fusimotor System" for the Kugelberg lecture.

The 14th EEG Congress held in Florence, Italy in 1997 with Roberto Zappoli as the Convener celebrated the 50th anniversary since the 1947 founding meeting in London. The ExCo referred to the 1999 Conference that Zdenek Ambler organized in Prague, Czech Republic as the 11th EMG Congress for the last time. Since then, EEG and EMG Congresses were combined into a unified International Congress of Clinical Neurophysiology (ICCN). For the record, I wish to enumerate the subsequent conventions held under this new designation, listing the name of the convener, venue and year for each: Carlos Medina, Buenos Aires, Argentina, 2001; Mark Hallett, San Francisco, CA USA, 2003; Jonathan Cole, Edinburgh, Scotland UK, 2006; Hiroshi Shibasaki, Kobe, Japan, 2010; Otto Witte, Berlin, Germany, 2014 and Marc R. Nuwer, Washington, DC, 2018.

The field of clinical neurophysiology has undergone marked changes backed by many technical advances in the past several decades. It is now obsolete to separate neurophysiology, the IFCN Congresses or ExCo officers on the basis of EEG and EMG as clinical neurophysiology has expanded to include several other sub-specialties such as transcranial magnetic stimulation and intraoperative monitoring. The time has come to integrate all these techniques under a large umbrella of clinical neurophysiology so that we can take advantage of various subdisciplines, as needed, in conducting clinical evaluations. We have also experienced a major gain in molecular biology and imaging techniques applicable to the disorders commonly seen in electrophysiologic laboratories. I believe that all these methods compliment rather than compete in the evaluation of our patients

In retrospect, it was my good fortune to have had a very early contact with EEG as the only electrophysiologic technique useful in clinical evaluation in the early 1960 s and have witnessed first-hand how EMG has developed slowly but steadily to match the EEG in its scope towards the end of 20st century. This was followed in the 21st century by somewhat explosive advance of various other electrophysiology techniques, which are closely interrelated, making divisions into subdisciplines difficult and irrelevant. I wish to conclude my treatise with the observation that a wider scope of clinical neurophysiology, reflecting technical advance, now encompasses much more than traditional EEG and EMG with no clear division among different fields. Clinical neurophysiology remains an important tool to understand and diagnose common disorders of the nerve and muscle as the only discipline to evaluate their function and dysfunction. To keep pace with the rapid advances of the related fields, we should always disseminate the latest advances in clinical neurophysiology as they apply to clinical assessment of neurological patients.

Our journal has played a crucial role in keeping clinical neurophysiologists up to date as the emphasis changes from time to time to satisfy the needs of the readership. An electronic version of the EEG Journal became available in 1996. The journal marked its 50th Anniversary in 1999 and changed its name to *Clinical Neurophysiology*. A new cover went into effect at the same time. When Francois Mauguière resigned in1995, Paolo Rossini (1995–2003) took over the position of European Editor-in-Chief. Gastone Celesia retired at the end of 1999 and Mark Hallett (2000–2008) replaced him as American Editor-in-Chief. The ExCo, after lengthy discussion of pros and cons, decided to return to the previous policy of a single Editor-in-Chief. When Paolo Rossini stepped down in 2003, Mark Hallett continued as the sole Editor-in-Chief until 2008, when David Burke (2008–2015) replaced him. Ulf Ziemann of Tübingen serves as the current Editor-in-Chief since 2016. The IFCN launched, on line, a new Open Access journal, *Clinical Neurophysiology Practice*, in 2016 with David Burke as the founding Editor-in-Chief.

I credit the exceptional growth of the Federation in great part to the scores of member leaders who have served as Editors-in-Chief of the journal. They have given us enormous amount of volunteer time to disseminate information vital to the progress of our disciplines. As we celebrate the 70th anniversary, I wish to congratulate the past and current Editors-in-Chief and their Editorial teams for a job well done and wish them the best for continued success for the benefit of us all. I also want to thank Marc R. Nuwer and Carl Lücking for their time and effort for contributing "Wave Length and Action Potential: History of the International Federation of Clinical Neurophysiology" (Supplements to Clinical Neurophysiology, Volume 61, 2010). I recommend this volume highly to readers with an interest in historical accounts of IFCN or *Clinical Neurophysiology*.

Respectfully submitted,
Jun Kimura, MD
Professor Emeritus
Department of Neurology
University of Iowa Health Care
Iowa City IA, USA
Professor Emeritus
Kyoto University School of Medicine
Kyoto, Japan

Jun Kimura
University of Iowa Health Care, Iowa City, IA, USA
E-mail address: jun-kimura@uiowa.edu
Accepted 21 October 2019

Available online 5 November 2019

Volume 1

Issues 1–4 of Electroencephalography and Clinical Neurophysiology appeared in 1949.

This first volume contained 529 pages. Predominance of EEG topics in the first volume is obvious from its table of contents:

COMMUNICATIONS

BRAIN STEM RETICULAR FORMATION AND ACTIVATION OF THE EEG [1]

G. MORUZZI, M.D. [2] and H. W. MAGOUN, M.D.
Department of Anatomy, Northwestern University Medical School

Transitions from sleep to wakefulness, or from the less extreme states of relaxation and drowsiness to alertness and attention, are all characterized by an apparent breaking up of the synchronization of discharge of elements of the cerebral cortex, an alteration marked in the EEG by the replacement of high-voltage slow waves with low-voltage fast activity. The magnitude of the electrical change parallels the degree of transition, and that most commonly observed in clinical electroencephalography is a minimal one, consisting of an alpha-wave blockade during attention to visual stimulation. Such activation of the EEG may be produced by any type of afferent stimulus that arouses the subject to alertness, or it may be centrally generated, but the basic processes underlying it, like those involved in waking from sleep, have remained obscure.

Recent experimental findings which may contribute to this subject have stemmed from the observation that EEG changes seemingly identical with those in the physiological arousal reactions can be produced by direct stimulation of the reticular formation of the brain stem. The following account describes such features of the response and its excitable substrate as have been determined, provides an analysis of changes in cortical and thalamic activity associated with it, and explores the relations of this reticular activating system to the arousal reaction to natural stimuli. Alterations produced by acute lesions in this system are presented in a succeeding paper. The effects of chronic lesions within it are under investigation.

METHODS

The experiments were performed in cats under chloralosane anesthesia (35-50 mgm./K, intraperitoneally) or in the "encéphale isolé" of Bremer, prepared under ether, with exposure margins infiltrated with procaine. Ephedrine was administered intravenously immediately after transection of the cord at C 1. At least an hour elapsed after ether was discontinued before work was begun.

Concentric bipolar electrodes, oriented with the Horsley-Clarke technique, were used for stimulation of, or pickup from, the brain stem. Condenser discharges from a Goodwin stimulator were employed routinely. Lesions were made surgically or electrolytically, and their positions, together with those of electrode placements, were verified histologically.

Potentials were recorded with a Grass model III amplifier and inkwriter. Some cortical records were taken directly from the pial surface, but usually as much of the brain case as possible was left intact, and most cortical pickups were between two screw electrodes, 5-10 mm. apart, inserted through burr holes in the calvarium until their tips rested on the dura overlying functional areas. With bipolar leads and by grounding the scalp, stimulus artifacts were negligible. Other technical details are given in the legends.

[1] Aided by a grant from the National Institute of Mental Health, U. S. Public Health Service.

[2] University of Pisa, Italy. Visiting Professor of Neurology, supported by the Rockefeller Foundation.

RESULTS

The response to reticular stimulation consisted of cessation of synchronized discharge in the EEG and its replacement with low-voltage fast activity. The intensity of the alteration varied with the degree of background synchrony present. Conspicuous effects were thus observed against the high-voltage slow waves of chloralosane anesthesia (fig. 1 C, D), while a fully activated EEG was not further affected (fig. 2A). Responses were seen to best advantage when the unanesthetized brain exhibited some relaxation (fig. 2 B and C) or when light chloralosane anesthesia had induced synchronization without greatly impairing neural excitability (fig. 1 A and B). With deeper chloralosane, slow waves were blocked, but low-voltage fast activity was not elicited (fig. 1 C and D).

The response was a generalized one, being observed in the sensory-motor cortex

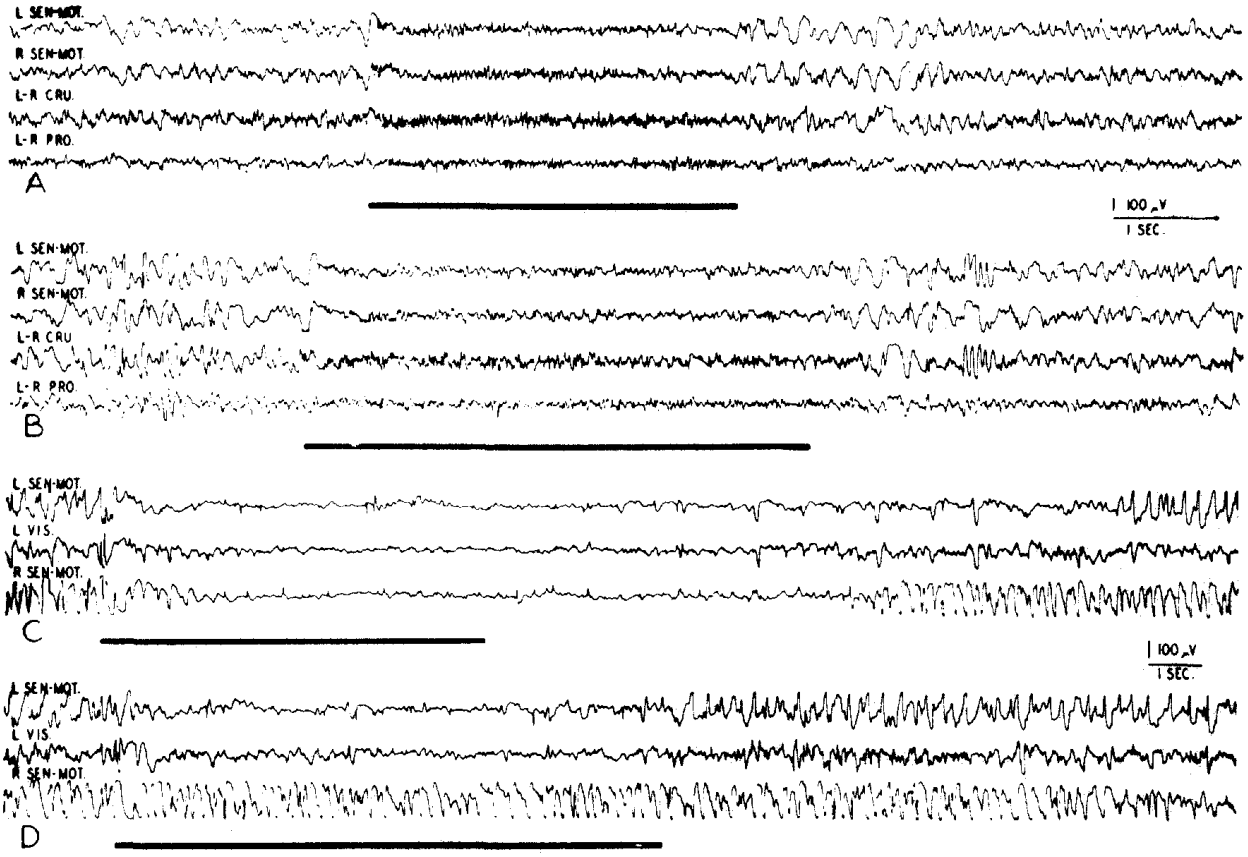


Fig. 1

Effect of stimulation of the brain stem reticular form ion upon electro-cortical activity of chloralosane preparations.

A and B. "Encéphale isolé" with 7 mgm. chloralosane/K. Replacement of high voltage slow waves, present in A and more pronounced in B, with low voltage fast activity during left bulbo-reticular stimulation (1.5 V, 300/sec.).

C. Intact cat with 50 mg. chloralosane/K. Left bulbo-reticular stimulation (3 V, 300/sec.) blocks chloralosane waves bilaterally, but more rapidly and for a longer time in the ipsilateral cortex. Note that low voltage fast activity does not appear.

D. Like C, but frequency of reticular stimulation reduced to 100/sec. Effect limited to ipsilateral cortex and doesn't outlast stimulus.

In all records, the origin of activity in different channels is given at the left: L. SEN. MOT. signifies left sensory-motor cortex; L.-R. CRU., left to right cruciate gyrus; L.-R. PRO., left to right gyrus proreus; L. VIS., left visual area; L. AUD., left auditory area; L. THAL., left thalamus. The period of bulbar stimulation is marked by a heavy line beneath the record. Calibration and time are stated.

(fig. 1), where it was often most pronounced, and in the visual (fig. 1 C) and auditory (fig. 2 B, C) cortical areas as well. With minimal reticular stimulation, alterations were best obtained in the ipsilateral hemisphere and were sometimes limited to it (fig. 1 D).

The response was readily obtained with low intensities of reticular stimulation; voltages of 1-3 being usually employed. Brief shocks, with a falling phase of 1 msec. were used routinely and were as effective as longer lasting ones. Stimulus frequencies of 50/sec. were the lowest at which definite alterations could be elicited and the response was considerably improved by increasing frequencies up to 300/sec., which were regularly utilized. Thus the EEG response to reticular excitation was best obtained with low voltage, high frequency stimulation.

These responses were not secondary to any peripheral effects of brain stem stimulation. By direct test they were independent of changes in respiration, blood pressure and heart rate. They occurred in the isolated brain after full atropinization and curarization. As will be seen, they were unquestionably mediated by neural connections between the reticular formation and the cerebral hemisphere.

The distribution of the excitable area is projected upon a reconstruction of the midsagittal plane in figure 3, and includes the central core of the brain stem, extending from the bulbar reticular formation forward through the pontile and mesencephalic tegmentum into the caudal diencephalon. At the

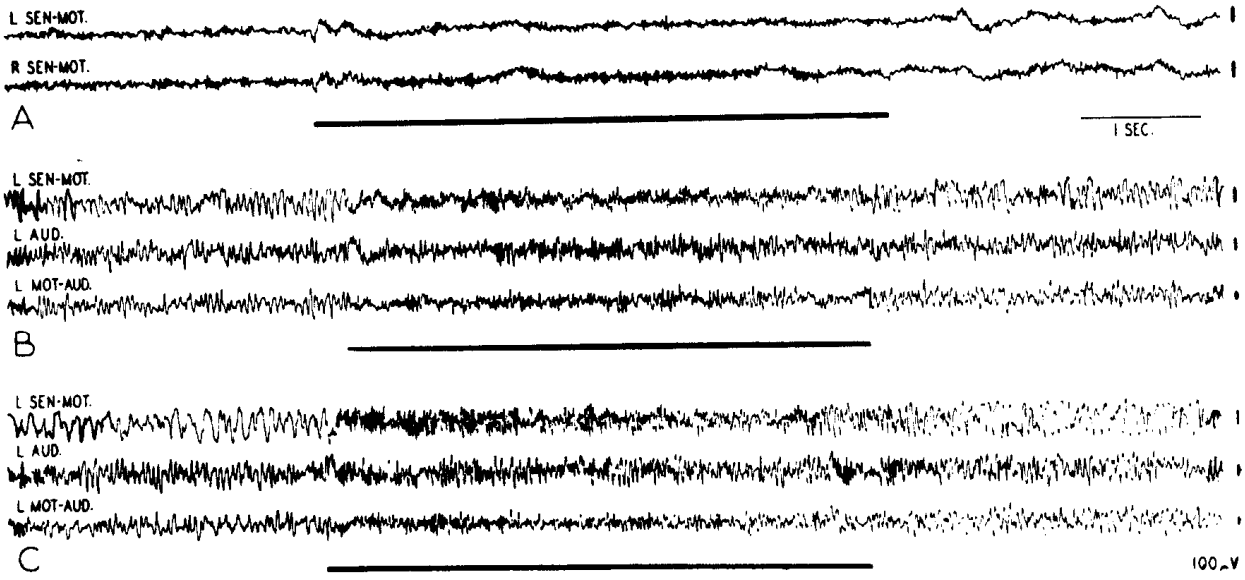


Fig. 2

Effect of reticular stimulation on electro-cortical activity of the unanesthetized "encéphale isolé". A-C. Left bulbo-reticular stimulation (3 V, 300/sec.) is without effect upon the fully activated cortex (A), but evokes characteristic low voltage fast activity when spontaneous synchrony is present (B and C).

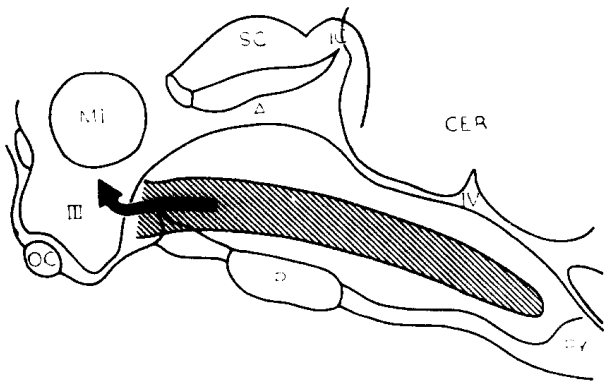


Fig. 3

Reconstruction of midsagittal plane of cat's brain stem upon which is projected, with cross-lining, the distribution of the ascending reticular activating system.

Abbreviations are as follows: A, aqueduct; CER, cerebellum; IC, interior colliculus; MI, massa intermedia; OC, optic chiasma; P, pons; PY, pyramidal crossing; SC, superior colliculus; III, third ventricle; IV, fourth ventricle.

bulbar level, excitable points were distributed in the ventromedial reticular formation and the area of their distribution coincided with that from which suppression of motor activity (Magoun and Rhines, 1946) could be elicited (fig. 4A). Exploration of the overlying cerebellum has revealed excitable central grey and extending in a paramedian position beneath it (fig. 4B). In the caudal diencephalon, effective points were located near the midline in the dorsal hypothalamus and subthalamus (fig. 4C). From this region, the excitable system is evidently distributed to the overlying thalamus, through

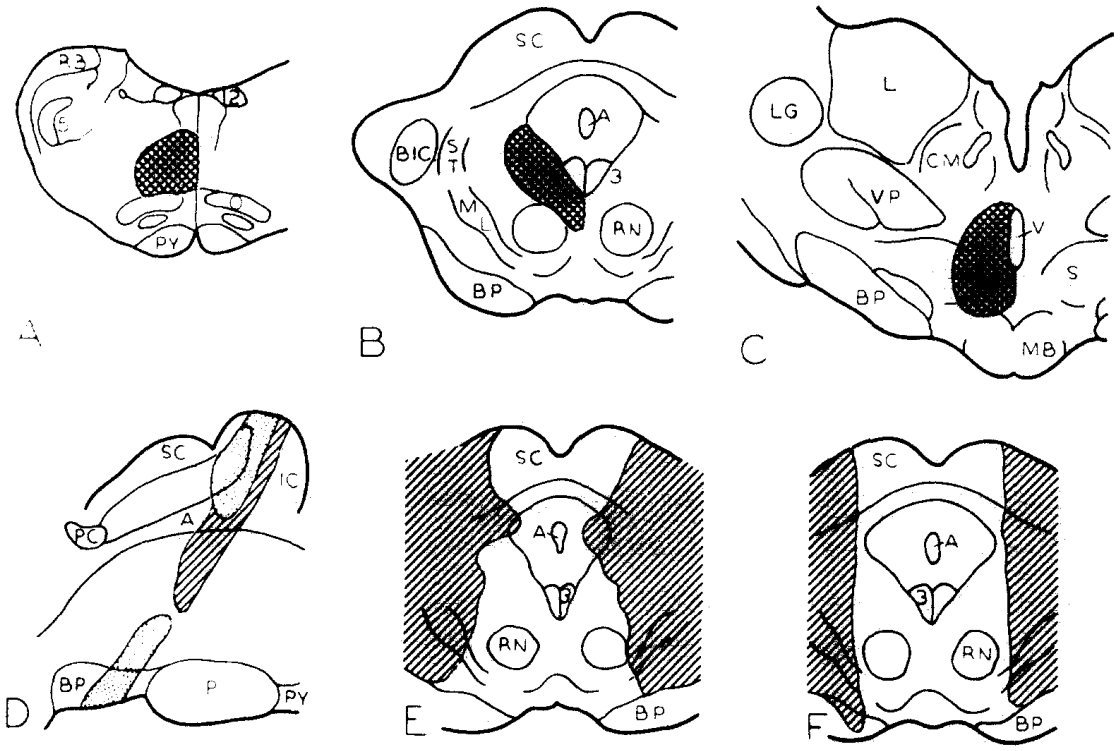


Fig. 4

A-C. Transverse sections through bulbar (A), mesencephalic (B) and caudal diencephalic (C) levels, with cross-lining indicating the area from which reticular responses were elicited with lowest voltage and without complications from exciting other ascending or descending neural connections.

D. Reconstruction of midsagittal plane of the midbrain upon which is projected, with stipple, the position of tectal and peduncular lesions which failed to block the EEG response to bulbo-reticular stimulation. Cross-lining marks the position of a tegmental lesion which abolished this response to bulbar stimulation.

E, F. Transverse sections through the midbrain of two cats, showing the extent of lesions which interrupted the medial and lateral lemnisci and spinothalamic tracts, but which failed to impair the EEG response to bulbo-reticular stimulation.

Abbreviations are as follows: A, aqueduct; BIC, brachium of inferior colliculus; BP, basis pedunculi; CM, centre médian; IC, inferior colliculus; L, lateral thalamic nucleus; LG, lateral geniculate body; MB, mammillary body; ML, medial lemniscus; O, inferior olive; P, pons; PY, pyramid; RB, restiform body; S, subthalamus; SC, superior colliculus; ST, spino-thalamic tract; VP, posterior part of ventral thalamic nucleus; 3, oculomotor nucleus; 5, spinal fifth tract and nucleus; 12, hypoglossal nucleus.

points in its fastigial nuclei, the responses possibly being mediated by connections of the roof nuclei with the brain stem reticular formation (Snider, Magoun and McCulloch, 1949). In the midbrain, responses were obtained from the tegmentum bordering the which its effects are exerted upon the cortex, and some data bearing on its thalamic mediation will be given later.

The distribution of this ascending system within the midbrain was studied further by observing the effect of lesions here upon the

EEG response to bulbo-reticular stimulation. Such responses were unimpaired following sections of the cerebral peduncles or tectum, but were blocked by injury to the mesencephalic tegmentum (fig. 4D). Typical cortical responses to bulbo-reticular stimulation were still obtained after bilateral destruction of all laterally placed mesencephalic structures, including the medial and lateral lemnisci and the spinothalamic tracts (fig. 4 E, F), leaving intact only the paramedian region from which responses were obtained on direct stimulation (fig. 4B).

(fig. 4 D). Furthermore, single shock stimuli to effective reticular sites did not evoke antidromic potentials in the sensory-motor cortex (fig. 5 C and E) (fig. 10 A), nor did direct stimulation of the bulbar pyramid reproduce the EEG response to reticular stimulation.

A cortico-bulbo-reticular path from area 4-S is distributed to the excitable reticular area of the lower brain stem (fig. 4 A) (McCulloch, Graf and Magoun, 1946), but it is similarly impossible to attribute the EEG responses to its antidromic stimulation.

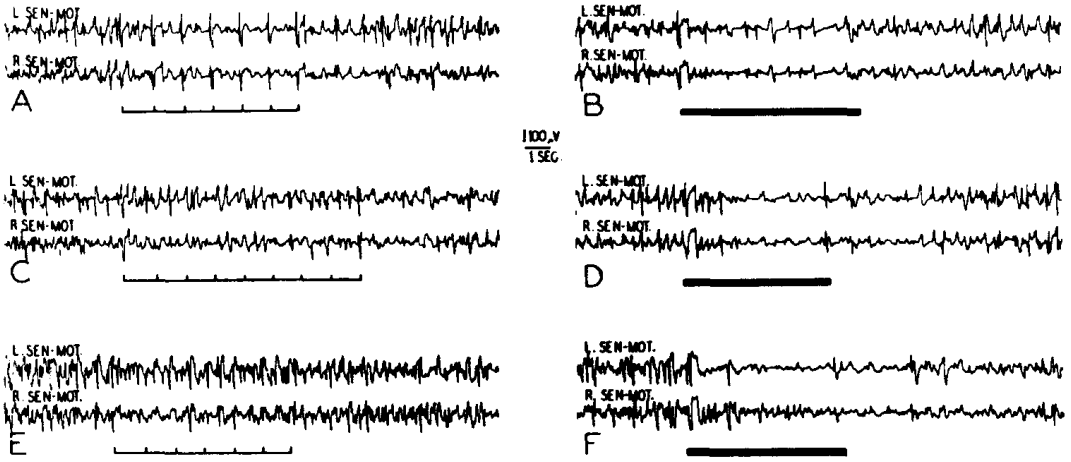


Fig. 5

Comparison of the effects of stimulating the right posterior column (A, B) and the left reticular activating system at bulbar (C, D) and midbrain (E, F) levels, under full chloralosane anesthesia. Stimulus frequency is 1/sec. in left records (A, C, E) and 300/sec. in right records (B, D, F); intensity is 3 V throughout.

Single shock stimuli to the posterior column evoke sensory potentials in the cortex (A), not elicited by similar reticular stimulation (C, E). High frequency stimulation of the posterior column causes some desynchronization of the EEG (B), but more pronounced effects are induced by reticular stimulation (D, F).

A series of ascending reticular relays is presumed to constitute the structural substrate of this brain stem activating system. That responses are not attributable to the antidromic excitation of corticifugal paths, nor to the dromic stimulation of known afferent paths, bordering the reticular area, is indicated by a variety of data.

As regards the pyramidal tract, movements referable to its excitation never accompanied EEG responses to reticular stimulation, and the latter were still obtained from the bulbar level after section of the fibers of this tract in the basis pedunculi This path accompanies the pyramidal tract in the basis pedunculi (McCulloch, Graf and Magoun, 1946) section of which, as noted, left reticular responses unimpaired. The absence of antidromic potentials in the sensory-motor cortex, on single shock stimuli to the bulbar reticular formation (fig. 5 C; 10 A), might be explained by the small size of the suppressor areas in the cat (Garol, 1942), but a more likely possibility is that the unmyelinated terminals of this extrapyramidal path were never excited with the low intensities of reticular stimulation employed in the present experiments. Reticular

responses elicited from brain stem levels cephalad to the bulb are, moreover, impossible to explain on the basis of antidromic stimulation of this extrapyramidal pathway.

It is equivalently impossible to ascribe reticular responses to the dromic activation of known afferent pathways ascending to the cortex through the brain stem. The medial lemniscus is adjacent to the excitable reticular area through much of its course, and high frequency stimulation of the lemniscal system, like that of the sciatic nerve (Gellhorn, 1947), exerts a desynchronizing influence upon the EEG (fig. 5 B). This influence is not as pronounced as that of the reticular formation and higher voltages of stimulation are required to induce it than those which yield primary and secondary cortical sensory responses.

Three lines of evidence clearly show, however, that the desynchronizing influence of the reticular formation cannot be attributed to activation of the lemniscal system, either through physical spread of stimulating current, or by antidromic excitation of possible lemniscal collaterals to the brain stem reticular formation. First, single shock stimuli to excitable reticular points at bulbar (fig. 5 C) or midbrain (fig. 5 E) levels never evoked potentials in the sensory-motor cortex, as was invariably the case when such shocks were applied to the lemniscal system (fig. 5 A), and this simple control was routinely applied throughout the work. Second, the distribution of the excitable reticular area was distinct from that of the course of the medial lemniscus through the brain stem (fig. 4, A-C). Third and finally, EEG responses to bulbar stimulation were unaffected by mesencephalic lesions which bilaterally interrupted the medial and lateral lemnisci and the spino-thalamic tracts (fig. 4 E, F).

Elimination of these possibilities and the distribution of excitable points through the brain stem both indicate that this response is mediated by a paramedian system of ascending reticular connections. Single shock stimuli to effective bulbar sites do not evoke potentials at effective midbrain or diencephalic sites, however, suggesting that a number of relays are present and that the synapses involved are iterative in nature.

Having now described the desynchronization of the EEG induced by brain stem stimulation and presented evidence that this alteration results from exciting a system of reticular relays ascending to the diencephalon, attention may next be directed to the effect of reticular stimulation upon types of evoked activity in the cortex.

Effect upon evoked sensory potentials. In the chloralosane cat, a single afferent volley, initiated either by natural stimuli or by shocks to the sciatic nerve or posterior column, evokes primary and secondary [1] cortical potentials and sensory "after-discharge" succeeding them. The secondary response and after-discharge occur generally in the cortex and are readily observed in the EEG. During stimulation of the brain stem reticular formation, such secondary responses continued to be evoked by afferent volleys, usually without alteration (fig. 6 A), but sometimes with reduction of amplitude and simplification of potential form, particularly in cortical areas outside the sensori-motor region (fig. 8 B). Following conclusion of reticular stimulation, transient enhancement of the secondary response was occasionally observed (fig. 6 B).

The succeeding high-voltage slow waves, called sensory after-discharge, were invariably abolished during reticular stimulation (fig. 6 A-C). In full anesthesia, the cortical record then became flat between secondary responses (fig. 6 A, B), while, if anesthesia was light, low-voltage fast activity was present in these intervals (fig. 6 C). The abolition of sensory after-discharge might thus be simply another manifestation of the desynchronization of the EEG induced by brain stem stimulation.

[1] These "secondary potentials" resemble those of Forbes and Morison (1939) recorded, in deep barbiturate anesthesia, in and also outside of the somatic receiving area and disappearing when the frequency of afferent stimuli rose above 5/sec. Since under chloralosane anesthesia, they are associated with pyramidal discharge they correspond to the "efferent waves" of Adrian (1941).

Such sensory after-discharge was not impaired, however, during cortical desynchronization induced by high frequency stimulation of the sciatic nerve (fig. 8 D). desynchronization resulting from reticular stimulation (fig. 5 B, D, F) opposed simultaneous discharge of a sufficient number of interneurons connecting the sensory with

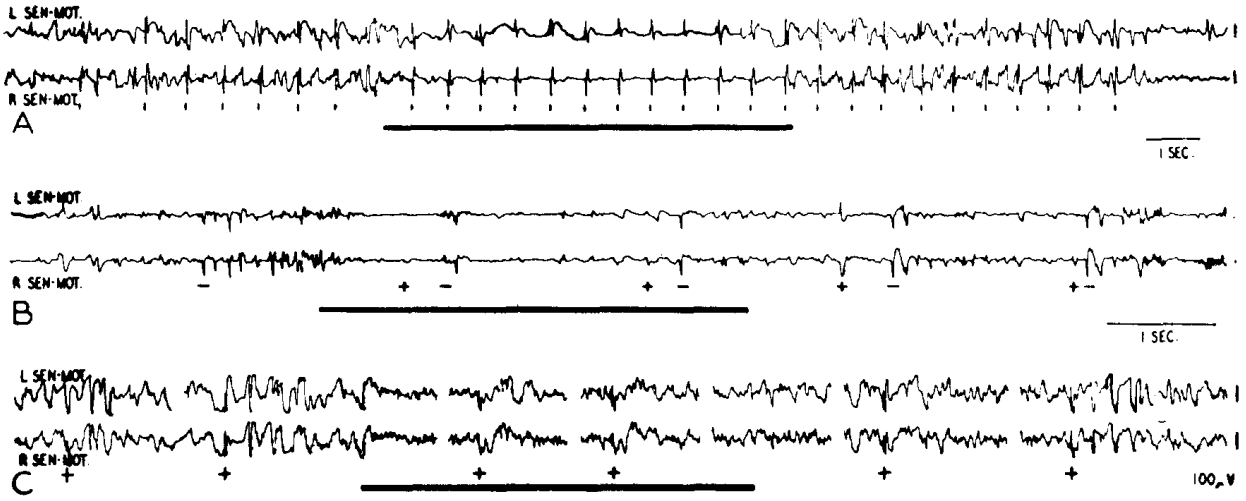


Fig. 6

Effect of reticular stimulation upon cortical sensory responses.
A. Tapping skin of ankle. B. Make and break shocks to the sciatic nerve, under full chloralosane anesthesia as in A. C. Single shocks to the upper end of the posterior column, in "encéphale isolé" with 7 mgm. chloralosane/K. In each instance the evoked sensory spike is unaffected, while consequent after-discharge is abolished. Note low voltage fast activity during reticular stimulation in C, with minimal anesthesia, and its absence in A and B, with full anesthesia.

Effect upon evoked pyramidal discharge. In the chloralosane cat, afferent volleys arriving at the cortex there evoke pyramidal discharges which are responsible for the jerky movements characteristic of this anesthesia (Adrian and Moruzzi, 1939). Although afferent volleys continued to reach the cortex during stimulation of the brain stem reticular formation, such pyramidal discharge, recorded from the basis pedunculi, was reduced or abolished (fig. 7 A) and contraction of leg muscles, induced by it, disappeared (fig. 7 B; 8 F). This disappearance of movement was not attributable to spinal inhibition, for reflexly induced contraction of the same muscles was not affected by such midbrain stimulation (fig. 8 G). The movements induced by this pyramidal discharge were not reduced during desynchronization of cortical electrical activity by high-frequency sciatic stimulation (fig. 8 E), and the facilitation observed might have been due to spinal alterations. Whether the more pronounced cortical

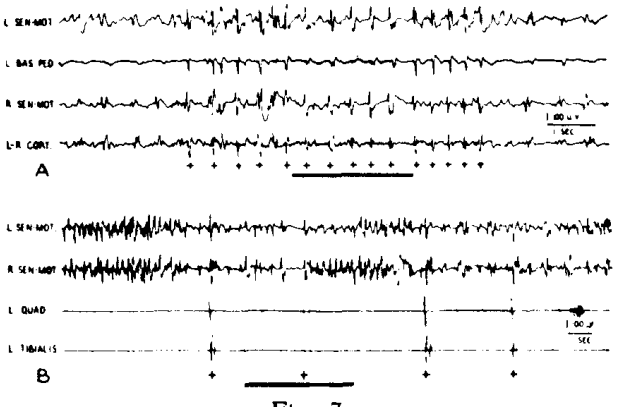


Fig. 7

Effect of reticular stimulation on pyramidal discharges and chloralosane jerks.
A. Break shocks to sciatic nerve cause sensory cortical responses and corresponding pyramidal discharge, recorded from the basis pedunculi (channel 2). The latter and sensory after-discharge are almost abolished by bulbo-reticular stimulation (3 V, 300/sec.), which leaves cortical sensory spikes unaffected. B. Break shocks to sciatic nerve cause chloralosane jerks, recorded in myograms of the quadriceps and tibialis (channels 3 and 4). Movement was abolished during stimulation of the midbrain tegmentum (3 V, 300/sec.), although cortical sensory potentials were still elicited. Such midbrain stimulation had no effect on spinal reflexes.

the motor cortex to prevent threshold activation of the cells of origin of the pyramidal tract, or whether these cells were somehow rendered incapable of being excited by afferent cortical volleys, during brain stem stimulation, remains unsettled.

tion of the diffuse thalamic projection system consists of a series of high-voltage slow waves, one for each shock, which recruit to a maximum during the initial period of stimulation (figs. 10, 11, 12, 13) (Morison and Dempsey, 1942; Dempsey and Morison,

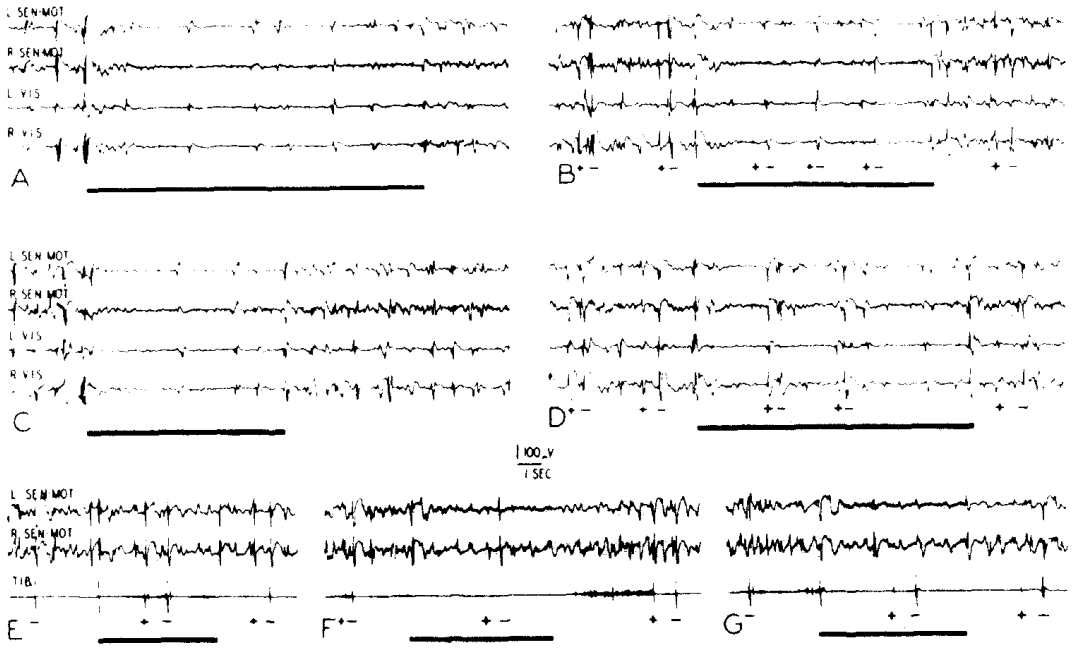


Fig. 8

Comparison of effect of reticular and sensory stimulation upon spontaneous and evoked electro-cortical activity.

A, C. Abolition of chloralosane waves during (A) bulbo-reticular stimulation (2 V, 300/sec.) and (C) sciatic nerve stimulation (3 V, 300/sec.).

B, D. Sensory cortical potentials evoked by make and break shocks to sciatic nerve are reduced by bulbo-reticular stimulation at 2 V, 300/sec. (B), but not by stimulation of the contralateral sciatic nerve at 3 V, 300/sec. (D).

E, F. Chloralosane jerks evoked by break shocks to the sciatic nerve, and recorded in myograms of the tibialis anticus, were augmented (E) by contralateral sciatic nerve stimulation (3 V, 300/sec.) and abolished (F) by stimulation of the midbrain tegmentum (3 V, 300/sec.). Such midbrain stimulation did not influence tibialis contraction in the ipsilateral flexor reflex (G).

Effect upon cortical strychnine spikes. The recurring spikes produced by local strychninization of the sensori-motor cortex were not prevented by exciting the brain stem reticular formation, nor was conduction of this discharge to the opposite cortex interfered with (fig. 9 B). Synchronized convulsive waves in a cortical fit, induced by supramaximal stimulation of the motor cortex, were similarly unaffected by bulbo-reticular stimulation.

Effect upon recruiting response. The cortical response to low frequency stimula-

1942; Jasper and Droogleever-Fortuyn, 1946; Jasper, 1949). These waves may be confined to the ipsilateral hemisphere, but are usually present, though smaller, contralaterally as well. Depending upon the site of thalamic stimulation, they may be distributed anteriorly, posteriorly, or generally in the cortex.

In the unanesthetized "encéphale isolé", such a recruiting response, in both sensori-motor cortices and the ipsilateral auditory area (fig. 10 D), was either abolished or greatly reduced in all regions during intercurrent

bulbo-reticular stimulation and recruited again upon its cessation (fig. 10, E, F). Exciting the rostral end of the reticular system in the subthalamus had a similar effect (fig. 11 E). Another instance is shown in figure 9 A, in which case, strychnine was then applied locally to the cortex. The recruiting response was transiently abolished following strychnine spikes interspersed in its course, suggesting that identical cortical neurons were involved in these two activities

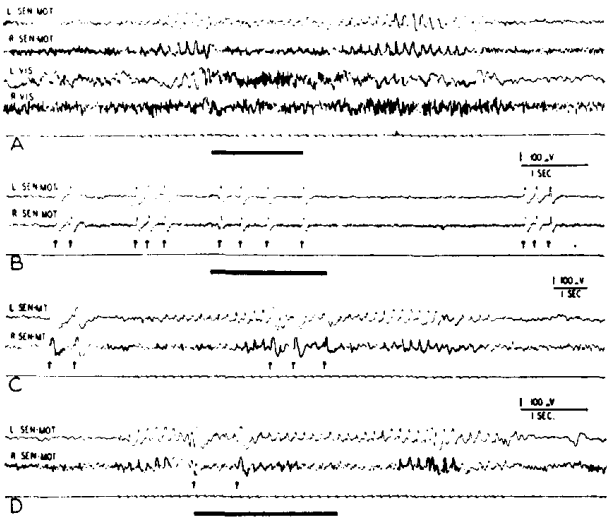


Fig. 9

Effect of reticular stimulation upon recruiting response and cortical strychnine spikes.

A. Recruiting response to left thalamic stimulation (5 V, 7.5/sec.) in "encéphale isolé," abolished by left bulbo-reticular stimulation (2 V, 300/sec.).

B. Strychnine spikes in both sensory-motor areas, induced by local application of strychnine to left motor cortex, were not decreased by left bulbo-reticular stimulation (2 V, 300/sec.).

C. Decrease of recruiting response (evoked as in A), following interspersed strychnine spikes.

D. Recruiting response (evoked as in A) markedly decreased by left bulbo-reticular stimulation (2 V, 300/sec.) which did not affect strychnine spikes.

(fig. 9 C). Subsequent repetition of reticular stimulation again opposed the recruiting response without, as noted above, altering the spikes induced by strychnine (fig. 9 D). It should be noted that low frequency stimulation of the ascending reticular system, even in the subthalamus, did not itself induce a recruiting response (figs. 10 B; 11 D).

Of the different types of evoked cortical activity upon which the effect of reticular stimulation was tested, certain ones, then, secondary sensory responses and strychnine spikes, exhibited little or no alteration, while others, sensory after-discharge and recruiting responses, were abolished. Of the two types of transcortical conduction observed, that from the sensory to the motor cortex, underlying the pyramidal discharge to afferent volleys under chloralosane anesthesia, was blocked, while the other, from a strychninized area of the cortex to the opposite cortex, was unaffected. It is not at present possible to decide whether any common factors underly these similarities and differences.

Thalamic mediation of response. The generalized distribution of the alteration in the EEG induced by reticular stimulation has implications for the manner of its mediation by the thalamus. It seems likely that the reticular formation could exert its influence upon all parts of the cortex either by acting generally upon the thalamus or by influencing its diffuse projection system alone. At present, each possibility appears relevant, for there is indication both that the diffuse projection system is involved and that the reticular influence may not operate exclusively through it.

Evidence for the mediation of the reticular effect by the diffuse thalamic projection system is presented in figure 12. The low-frequency stimulation of a portion of this system, on one side of the midline, induced recruiting responses not only in both cortices but in a corresponding region of the opposite thalamus as well (fig. 12 A). This evoked intra-thalamic activity was then abolished during intercurrent bulbo-reticular stimulation and returned again upon its cessation (fig. 12 B, C), thus demonstrating a reticular influence upon the diffuse projection system at the thalamic level. It is uncertain whether the corresponding cortical changes were secondary to those in the thalamus in these instances, however, for though cortical recruiting responses were greatly reduced, small cortical waves were still present dur-

ing reticular stimulation at a time when all synchronized activity was absent from the record of this thalamic sample (fig. 12 B, D: compare left cortical and thalamic channels). This same preparation was next lightly anesthetized with chloralosane, with the development of characteristic high-voltage slow waves both in the cortex and subcor-

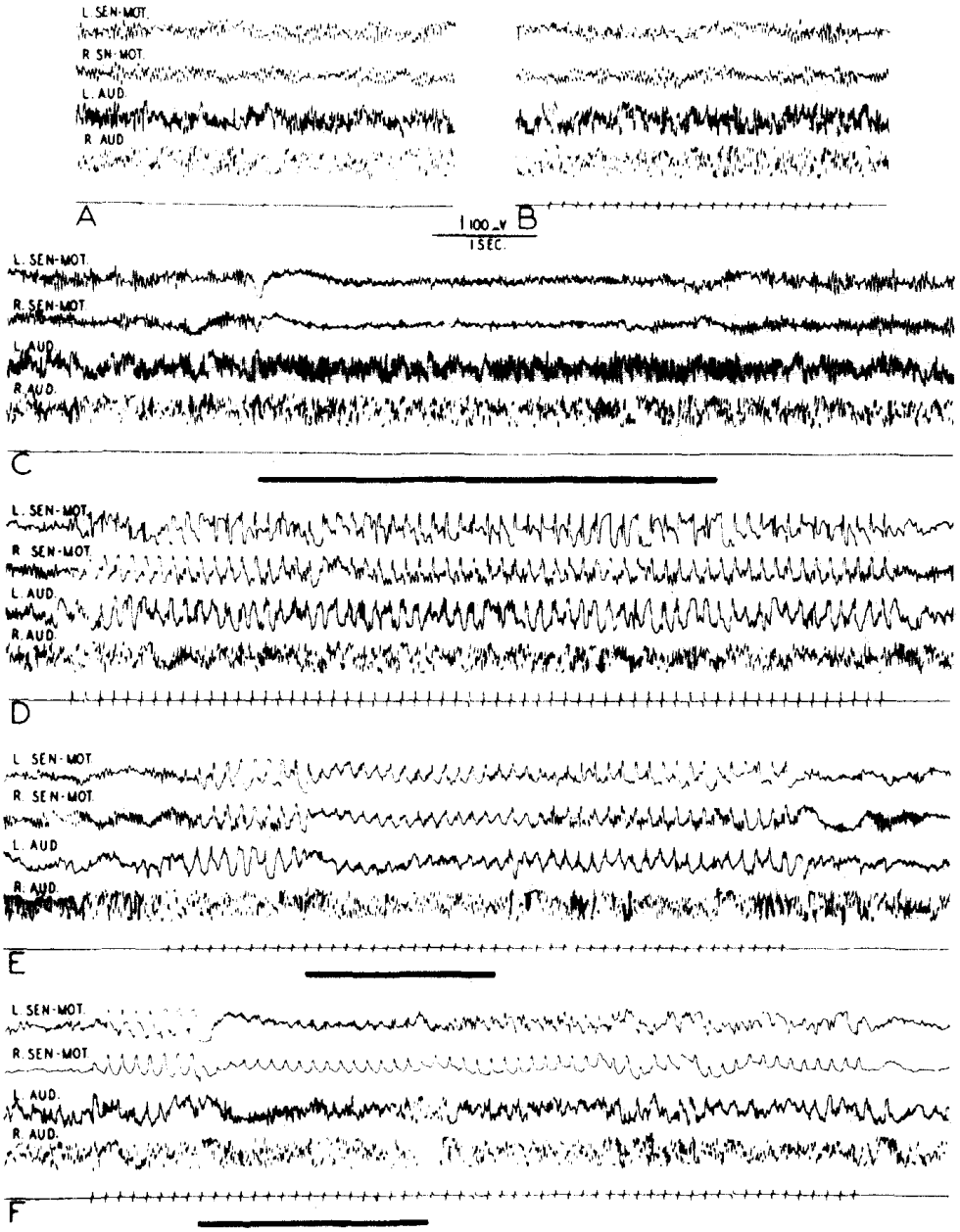


Fig. 10

Effect of reticular stimulation upon recruiting response. Left bulbo-reticular stimulation at 3 V in "encéphale isolé".

A. Single shocks to bulb do not evoke cortical potentials.
B. Bulbar stimulation at 7.5/sec. does not evoke recruiting response.
C. Bulbar stimulation at 300/sec. activates EEG.
D. Recruiting response evoked by left thalamic stimulation (5 V, 7.5/sec.).
E. Recruiting response to left thalamic stimulation reduced or abolished by left bulbar stimulation (3 V, 300/sec.).
F. Recruiting response to right thalamic stimulation reduced or abolished by left bulbar stimulation (3 V, 300/sec.).

tically, within and between components of the diffuse thalamic projection system. Bulboreticular stimulation then desynchronized this activity as effectively in the electrothalamogram as in the EEG (fig. 12 D, E).

Further indication that the reticular influence may be mediated by the diffuse thalamic projection system is provided by

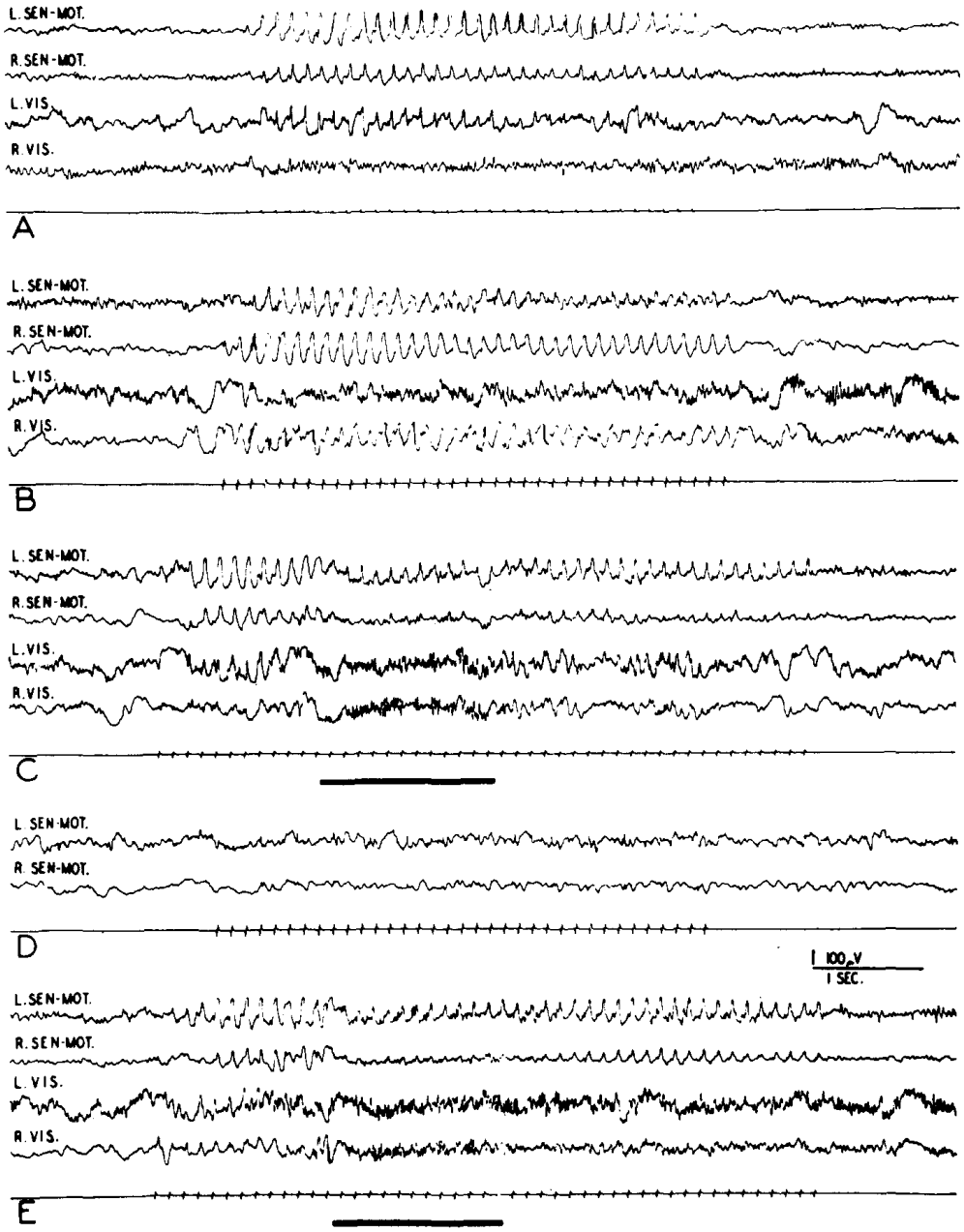


Fig. 11

Reproduction of reticular response by high frequency stimulation of diffuse thalamic projection system.

A and B. Recruiting responses induced by left (A) and right (B) thalamic stimulation (5 V, 7.5/sec.) in "encéphale isolé".

C. Recruiting response to left thalamic stimulation reduced or abolished by stimulating the same right thalamic site as in B, but with 5 V, 300/sec.

D. Right electrode lowered into subthalamus, the stimulation of which with 5 V, 7.5/sec. fails to induce a recruiting response.

E. Subthalamic stimulation, with 5 V, 300/sec., reduces or abolishes the recruiting response to left thalamic stimulation.

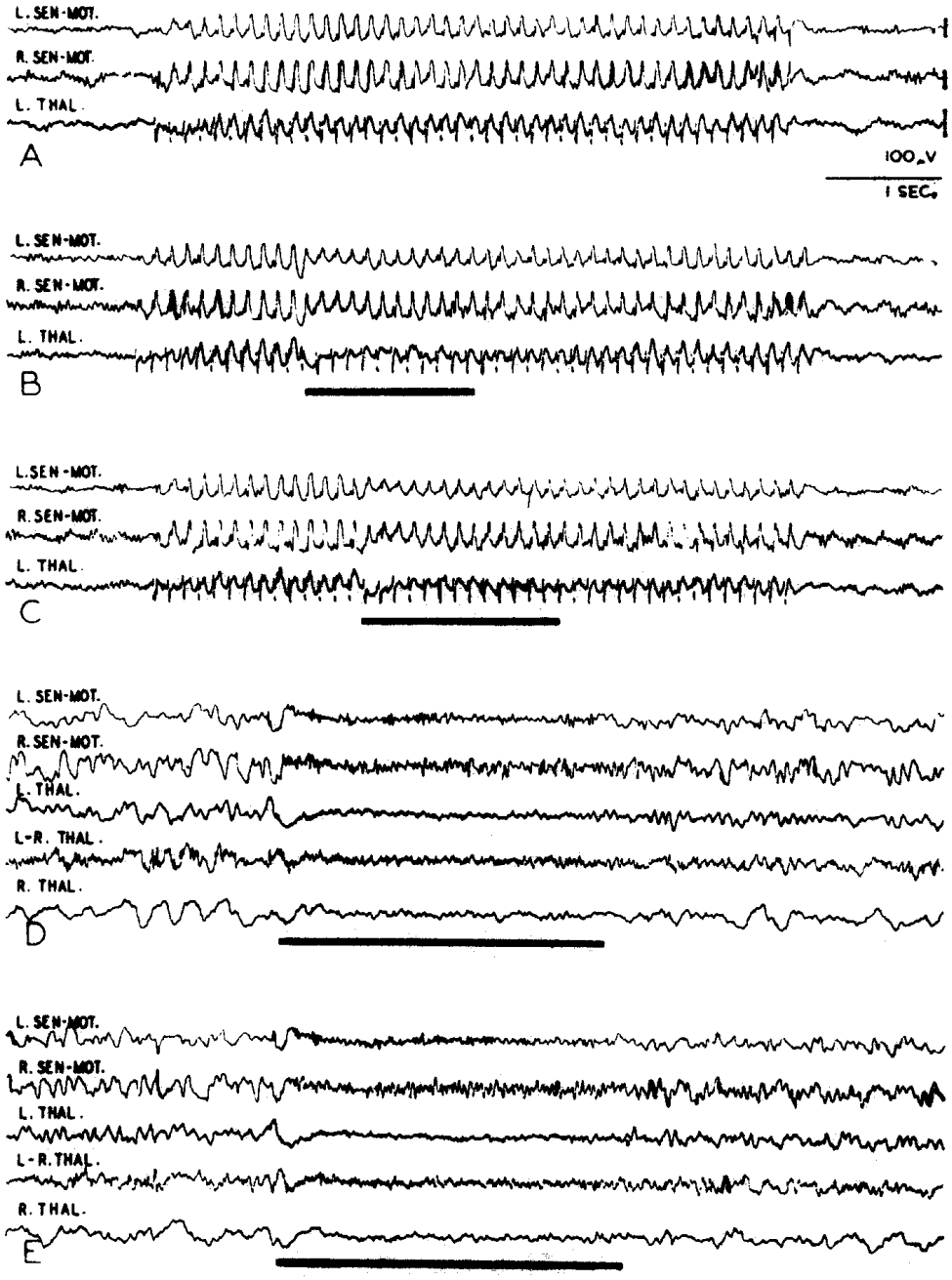


Fig. 12

Effect of reticular stimulation upon electrothalamogram of diffuse projection system. A-C. Unanesthetized "encéphale isolé".

A. Recruiting response to right thalamic stimulation (8 V, 7.5/sec.) is recorded both from cortex and from and between thalamic sites yielding recruiting responses or response on stimulation.

B, C. Recruiting response in cortex and left thalamus, evoked by right thalamic stim ulation as in A, is reduced or abolished during left bulbo-reticular stimulation (3 V, 300/sec.).

D, E. Same preparation with 7 mgm. chloralosane/K. Chloralosane waves recorded from cortex and from left thalamic site (channel 3), which itself yielded a recruiting stimulation, are abolished in all areas and replaced by low voltage fast activity during left bulbo-reticular stimulation (2 V, 300/sec.).

comparing its effect upon the EEG with that of direct, intra-thalamic stimulation of this system. Recruiting responses were obtained by successively stimulating portions of the diffuse system in the left (fig. 11 A) and right (fig. 11 B) sides of the thalamus. The stimulation has the same effect upon the electrogram of its thalamic components that it does upon the EEG, and this influence upon the EEG can be reproduced by the direct high-frequency stimulation of this system within the thalamus.

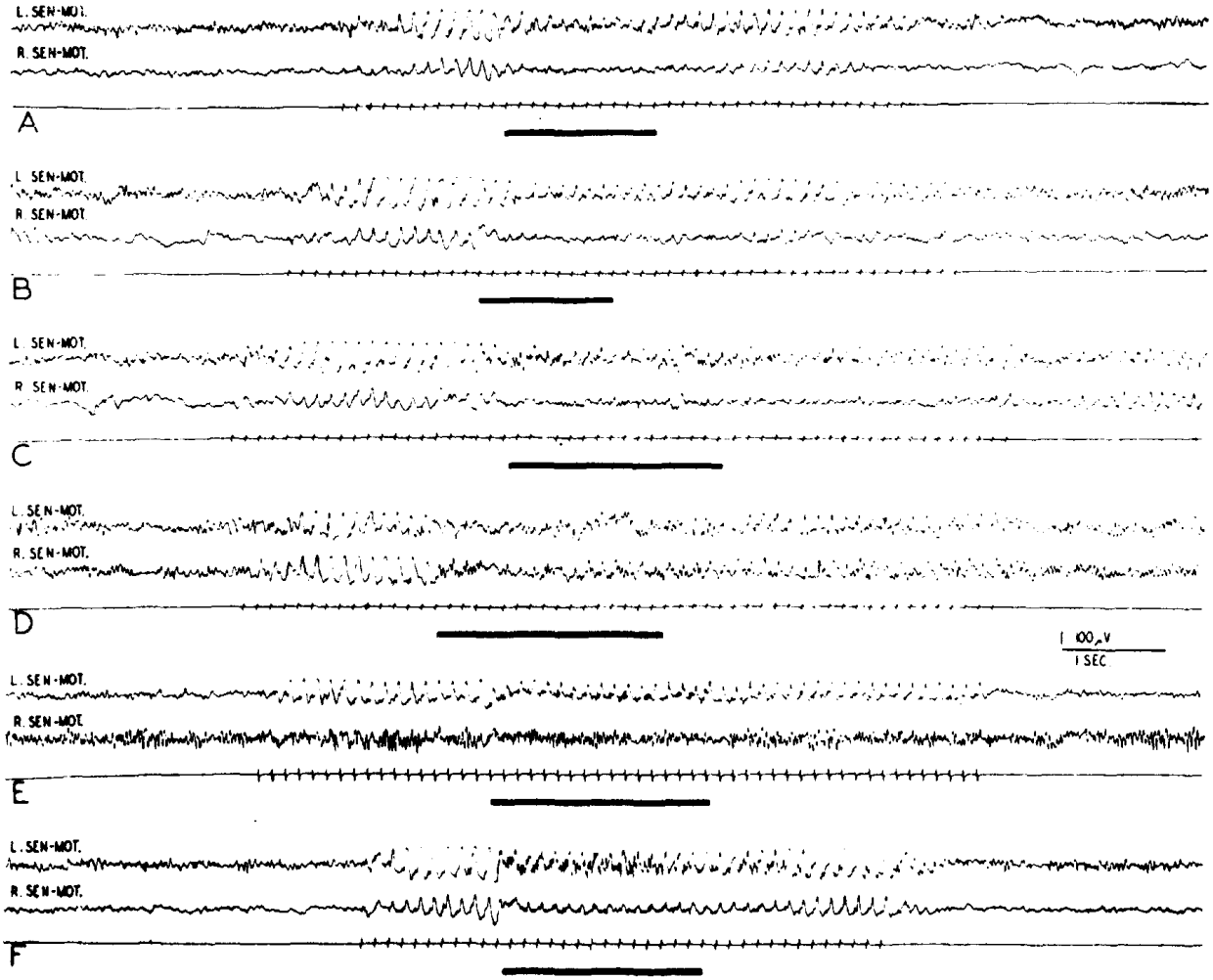


Fig. 13

Abolition of recruiting responses by sensory and reticular stimulation.
Recruiting responses, evoked by left thalamic stimulation (5 V, 300/sec.) in an "encéphale isolé", identically reduced or abolished by loud whistling (A), blowing air on head (B), rubbing nose (C), blowing air on eyes (D), stimulating the right posterior column at 2 V, 300/sec. (E), and stimulating the left bulbar reticular formation at 2 V, 300/sec. (F).

recruiting response to left thalamic stimulation was then repeated and intercurrent stimulation of the same right thalamic site at 300/sec. abolished it as effectively (fig. 11 C) as did subsequent stimulation of the rostral end of the reticular system in the subthalamus (fig. 11 E). As regards the diffuse thalamic projection system, then, reticular

Similar desynchronization, both of spontaneous activity and of the recruiting response has been observed, however, to result from high frequency stimulation of the discretely projecting, posterior part of the ventral thalamic nucleus, and the effect was generalized in the cortex. It remains for further study to determine whether such re-

sponses were mediated by direct cortical projections or, as seems more likely, through other subcortical systems.

After ipsilateral destruction of the intralaminar thalamic region, bulbo-reticular stimulation still desynchronized the EEG bilaterally and as markedly as in initial controls. After extending the lesion until the massa intermedia and intralaminar regions of the thalamus were destroyed bilaterally, bulbar stimulation still seemed to have some effect upon the EEG, but cortical activity was then so reduced that it was difficult to draw conclusions concerning the significance of the results. These findings only serve to introduce the problem of thalamic mediation of the lower brain stem influence upon the EEG, and much added study will be necessary to clarify this subject.

The reticular effect and arousal reactions. In the acute study of arousal reactions, anesthesia cannot be employed, for its major action is to block them, nor is the unanesthetized "encéphale isolé" suitable, for its EEG is typically activated and only rarely exhibits spontaneous synchrony. In the latter preparation, however, recruiting responses sometimes provide a background of cortical activity upon which the arousal effect of natural stimuli can be tested. Figure 13 shows a series of such instances, in which the high-voltage slow waves of the recruiting response were abolished and replaced by low-voltage fast activity, during loud whistling (A), rubbing the nose (B), and blowing air on the head (C) and eyes (D). Indistinguishable from these changes to natural stimuli, except for somewhat faster low-voltage activity, were those produced by electrical stimulation of the posterior column (E) and bulbar reticular formation (F).

Such abolition of recruiting responses by natural or bulbar stimulation was observed only when the frequency and intensity of thalamic stimulation yielding the recruiting response was just above threshold, and in some cases reticular stimulation could still abolish the recruiting response at a time when natural stimuli were ineffective. Because of these and other difficulties in securing stable testing conditions, attempted repetition of arousing natural stimuli after differential interruption of ascending sensory and reticular paths in the anterior brain stem was abandoned in favor of chronic preparations.

DISCUSSION

The evidence given above points to the presence in the brain stem of a system of ascending reticular relays, whose direct stimulation activates or desynchronizes the EEG, replacing high-voltage slow waves with low-voltage fast activity. This effect is exerted generally upon the cortex and is mediated, in part, at least, by the diffuse thalamic projection system. Portions of this activating system, chiefly its representation in the basal diencephalon, have previously been identified.

In the pioneer studies of Morison and his associates, in which the foundation for so much current work upon the EEG was laid, hypothalamic, subthalamic and medial thalamic excitation was found, in 1943, to suppress intermittent Dial bursts without affecting other types of cortical activity, such as responses to sensory stimulation (Morison, Finley and Lothrop, 1943; Dempsey and Morison, 1943). The effect was considered to be inhibitory in nature and was attributed to the excitation of afferent pathways simply passing through this region.

Two years later, Murphy and Gellhorn (1945) found this suppression of Dial bursts, on hypothalamic stimulation, to be accompanied by dispersal of strychnine spikes and by prolonged increase in the frequency and amplitude of low-voltage, background, electro-cortical activity. They pointed out that these latter alterations were excitatory or facilitatory in nature, and attributed the disappearance of bursts to an associated lessened degree of synchrony of firing of cortical neurons, rather than to inhibition. Connections from the hypothalamus to the dorsomedial and intralaminar thalamic region, and thence to cortex, were suggested to provide the channels by way of which these effects were produced and, though the study

was undertaken principally to elucidate hypothalamic facilitation of the motor cortex, the generalized distribution of the EEG changes was emphasized.

More recently still, Jasper and his associates (1948) observed a generalized acceleration of spontaneous electrocortical activity, simulating an arousal or waking reaction, from stimulation of the periaqueductal portion of the midbrain, the posterior hypothalamus and the massa intermedia of the thalamus; and Ward (1949) obtained a prolonged generalized increase in both voltage and frequency of the EEG following stimulation of the bulbar reticular formation.

While interpretation of these findings has been varied, their basic similarity can leave little doubt that each of these investigators has dealt with manifestations of the same system as that described above. The present work thus confirms, extends and interrelates these earlier contributions and, from the mass of observations brought to bear upon it, the existence of this brain stem activating system now seems firmly established.

In discussing the general significance of these findings for electroencephalography, attention should certainly be focussed upon the arousal reaction. The breaking up of synchronous cortical discharge by afferent stimulation, first observed by Berger (1930) as alpha blockade on opening the lids, and since found to be a common response to any type of afferent stimulation, is currently attributed to the desynchronizing action of afferent volleys arriving directly at the receiving areas of the cerebral cortex (Adrian and Matthews, 1931; Adrian, 1947; Bremer, 1938, 1944; Walter and Walter, 1949). A number of relevant observations are difficult to explain on this basis, however.

More than a decade ago, Ectors (1936) and Rheinberger and Jasper (1932) observed that serially repeated stimulation soon failed to induce activation, though afferent volleys presumably continued to reach the cortex, and it was noted that, in order to be effective in this regard such stimuli must arouse the subject to alertness or attention. In addition, when an activation pattern was so induced, it was by no means confined to the receiving area of the afferent system stimulated (see also Bremer, 1943), nor did it appear first in this area and radiate from it. Whether somatic, auditory or, to a lesser extent, visual stimulation was employed, when an arousal reaction was evoked, it appeared simultaneously in all parts of the cortex and often continued for considerable periods in it after afferent stimulation had ceased.

More recently, Monnier's (1949) analysis of the sequence of EEG events induced by visual stimulation in man has shown that alpha blockade is not initiated for a considerable period after the electrocortical changes evoked by the afferent volley are completed, and its prolonged latency might more easily be explained by invoking a subsidiary mechanism than by accounting for it through direct cortical action. Furthermore, the generalized arousal reaction to vestibular stimulation has been shown by Gerebtzoff (1940) to be still elicitable after ablation of the cortical receiving area for this afferent system.

In the present experiments, typical EEG arousal reactions have been reproduced by stimulating the brain stem reticular formation, without exciting classical sensory paths. Crucial evidence that the reticular formation is involved in the arousal reaction to natural stimuli may not yet be obtained but, in addition to being suggested by the data at hand, such a possibility might offer an explanation for the failure of afferent stimuli to evoke arousal from somnolence, lethargy or coma, resulting from injury to the upper brain stem, which left the major sensory paths to the cortex intact (Ingram, Barris and Ranson, 1936; Ranson, 1939; Magoun, 1948). A conception of the arousal reaction in which collaterals from sensory paths first activated the brain stem reticular formation and exerted their influence upon cortical electrical activity indirectly through it, seems a logical postulate from all these observations, and was, in fact, proposed as long ago as 1940 by Gerebtzoff to account

for his observations to which reference was made above.

The proposed participation of the brain stem activating system in the arousal reaction, if established, might represent an aspect of its function concerned with alerting the cortex to abrupt and more or less pronounced alterations in the external environment. It may next be proposed that the presence of a steady background of less intense activity within this cephalically directed brain stem system, contributed to either by liminal inflows from peripheral receptors or preserved intrinsically, may be an important factor contributing to the maintenance of the waking state, and that absence of such activity in it may predispose to sleep.

Bremer's fundamental discovery (1935, 1938) that the EEG of the unanesthetized cerebrum, isolated from the rest of the nervous system by mesencephalic transection, resembled that of an intact brain in natural sleep or under barbiturate anesthesia, led him to the conclusion that sleep is the result of deafferentation of the cerebral cortex. Afferent impulses from olfactory and visual receptors are still accessible to such a "cerveau isolé", and more recent work has indicated that sleep changes in the EEG are best produced by basal diencephalic injury (Lindsley, Bowden and Magoun, 1949). But putting these qualifications aside, it should be pointed out that at the time Bremer's discovery was made, classical sensory paths were the only known connections ascending through the midbrain, to the interruption of which the ensuing sleep changes in the "cerveau isolé" could be attributed. The present identification of a second, parallel system of ascending reticular relays, whose direct stimulation induces EEG changes characteristic of wakefulness, now raises a possible alternative interpretation of Bremer's observations, for the obvious question arises: is the production of sleep in the cerebrum, following mesencephalic transection, to be attributed to deafferentation in the strict sense, or to the elimination of the waking influence of the ascending reticular activating system? Two lines of evidence favor this latter possibility.

As regards barbiturate sleep, Forbes et al (1949) have recently pointed out that the ready conduction of afferent impulses to the cortex under deep barbiturate anesthesia is inconsistent with the view that the sleep-inducing properties of these drugs depend upon functional deafferentiation.[1] Conversely, it has been found in the present study that under barbiturate anesthesia, bulboreticular stimulation is much less effective in activating the EEG than in a chloralosane or unanesthetized preparation. The fact that hypothalamic stimulation is effective under such anesthesia (Morison, Finley and Lothrop, 1943; Murphy and Gellhorn, 1945; Jasper, Hunter and Knighton, 1948) suggests that the blocking of reticular relays within the brain stem may be involved in the production of sleep by barbiturates.

As regards sleep induced by rostral brain stem injury, prolonged somnolence has followed chronic lesions in the basal diencephalon and anterior midbrain which did not involve afferent pathways to the cortex, but which were placed medial and ventral to them in the region of distribution of the ascending reticular activating system (Ingram, Barris and Ranson, 1936; Ranson, 1939), and similar results have followed injury to this region from tumors (Fulton and Bailey, 1929) or encephalitis (von Economo, 1918; Richter and Traut, 1940) in man.

Though somnolence was incontestable, EEG studies were not undertaken in the animals or patients to which reference is made, but more recently Ingram, Knott and Wheatley (1949) have studied alterations in the EEG following chronic, experimental hypothalamic lesions, and the results of acute basal diencephalic and lower brain stem destruction are reported in the succeeding paper (Lindsley, Bowden and Ma-

[1] This argument would appear to apply only to the conduction of a single afferent volley. W. H. Marshall (*J. Neurophysiol.*, **1941**, *4*: 25-43) has observed impairment of conduction of repeated afferent volleys to the cortex under nembutal anesthesia, due to great prolongation of thalamic recovery time.

goun, 1949). In the latter investigation, sleep changes in the EEG, identical with those of barbiturate anesthesia, resulted from basal diencephalic and anterior midbrain lesions which spared sensory pathways to the cortex, but interrupted the rostral distribution of the ascending reticular activating system. Conversely, extensive deafferentiation of the cortex, by section of ascending pathways in the lateral portion of each side of the midbrain, together with bilateral interruption of the optic and olfactory tracts, failed to induce such alterations.

The conception of sleep as a functional deafferentation of the cerebrum is not opposed by this evidence if the term "deafferentation" is broadened to include interruption of the ascending influence of the brain stem reticular activating system, the contribution of which to wakefulness now seems more important than that conducted to the cortex over classical sensory paths.

SUMMARY

1. Stimulation of the reticular formation of the brain stem evokes changes in the EEG, consisting of abolition of synchronized discharge and introduction of low voltage fast activity in its place, which are not mediated by any of the known ascending or descending paths that traverse the brain stem. The alteration is a generalized one but is most pronounced in the ipsilateral hemisphere and, sometimes, in its anterior part.

2. This response can be elicited by stimulating the medial bulbar reticular formation, pontile and midbrain tegmentum, and dorsal hypothalamus and subthalamus. The bulbar effect is due to ascending impulses relayed through these more cephalic structures. The excitable substrate possesses a low threshold and responds best to high frequencies of stimulation.

3. Some background synchrony of electrocortical activity is requisite for manifestation of the response. In the "encephale isolé", reticular stimulation has no additional effect upon the fully activated EEG. With synchrony, in spontaneous drowsiness or light chloralosane anesthesia, the effect of reticular stimulation is strikingly like Berger's alpha wave blockade, or any arousal reaction. In full chloralosane anesthesia, high voltage slow waves are blocked but no increase in lower amplitude, fast activity occurs. With barbiturate anesthesia, the reticular response is difficult to elicit or is abolished.

4. In the chloralosane preparation, the secondary cortical response evoked by a sensory volley is generally unaffected by reticular stimulation. Consequent sensory after-discharge is abolished, however, as is pyramidal tract discharge and jerky movements referable to it. Outside the sensory receiving area, secondary responses themselves may be reduced or prevented.

5. The convulsive spikes produced by local strychnine and those of a fit following supramaximal cortical excitation, are not decreased by stimulating the reticular formation.

6. The cortical recruiting response induced by low frequency stimulation of the diffuse thalamic projection system is reduced or abolished by reticular stimulation.

7. There is some indication that the cortical effect of reticular stimulation may be mediated by this diffuse thalamic projection system, for synchronized activity within it is similarly prevented by reticular excitation, and direct high frequency stimulation of this system, within the thalamus, reproduces the reticular response. It is possible, however, that other mechanisms may be involved in its mediation.

8. The reticular response and the arousal reaction to natural stimuli have been compared in the "encéphale isolé", in which EEG synchrony was present during spontaneous relaxation or was produced by recruiting mechanisms, and the two appear identical.

9. The possibility that the cortical arousal reaction to natural stimuli is mediated by collaterals of afferent pathways to the brain stem reticular formation, and thence through the ascending reticular activating system, rather than by intra-cortical spread follow-

ing the arrival of afferent impulses at the sensory receiving areas of the cortex, is under investigation.

10. The possibility is considered that a background of maintained activity within this ascending brain stem activating system may account for wakefulness, while reduction of its activity either naturally, by barbiturates, or by experimental injury and disease, may respectively precipitate normal sleep, contribute to anesthesia or produce pathological somnolence.

CONCLUSIONS

Experiments on cats have identified a cephalically directed brain stem system, the stimulation of which desynchronizes and activates the EEG, replacing high-voltage slow waves with low-voltage fast activity.

This system is distributed through the central core of the brain stem and appears to comprise a series of reticular relays ascending to the basal diencephalon. Its effects are exerted generally upon the cortex and are mediated, in part, at least, by the diffuse thalamic projection system.

Possible implication of this system in the arousal reaction to afferent stimulation and in the maintenance of wakefulness is discussed.

REFERENCES

ADRIAN, E. D. Afferent discharges to the cerebral cortex from peripheral sense organs. *J. Physiol.*, **1941**. *100*: 159-191.

ADRIAN, E. D. The physical background of perception. Oxford, The Clarendon Press, **1947**. 95 pp.

ADRIAN, E. D. and MATTHEWS, B. H. C. The interpretation of potential waves in the cortex. *J. Physiol.*, **1934**. *81*: 440-471.

ADRIAN, E. D. and MATTHEWS, B. H. C. The Berger rhythm: potential changes from the occipital lobes in man. *Brain*, **1934**, *57*: 355-385.

ADRIAN, E. D. and MORUZZI, G. Impulses in the pyramidal tract. *J. Physiol.*, **1939**, *97*: 153-199.

BERGER, H. Uber das Elektrenkephalogramm des Menschen. II. *J. Physiol. Neurol.*, **1930**, *40*: 160-179.

BREMER, F. Cerveau isolé et physiologie du sommeil. *C. R. Soc. Biol., Paris*, **1935**, *118*: 1235-1242.

BREMER, F. L'activité cérébrale et le problème physiologique du sommeil. *Boll. Soc. It. Biol. Sp.*, **1938**, *13*: 271-290.

BREMER, F. L'activité électrique de l'écorce cérébrale. Paris, Hermann, **1938**.

BREMER, F. Etude oscillographique des réponses sensorielles de l'aire acoustique corticale chez le chat. *Arch. Internat. Physiol.*, **1943**, *53*: 53-103.

BREMER, F. Aspect théorique de l'électro-encéphalographie. *Arch. Néerl. Physiol.*, **1944-47**, *28*: 481-482.

DEMPSEY, E. W. and MORISON, R. S. The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. *Amer. J. Physiol.*, **1942**, *135*: 293-300.

DEMPSEY, E. W. and MORISON, R. S. The electrical activity of a thalamocortical relay system. *Amer. J. Physiol.*, **1943**, *138*: 283-298.

ECONOMO, C. von. Die Encephalitis Lethargica. Wien, Deuticke, **1918**.

ECTORS, L. Etude de l'activité électrique du cortex cérébral chez le lapin non narcotisé ni curarisé. *Arch. Internat. Physiol.*, **1936**, *43*: 267-298.

FORBES, A., BATTISTA, A. F., CHATFIELD, P. O. and GARCIA, I. P. Refractory phase in cerebral mechanisms. *EEG Clin. Neurophysiol.*, **1949**, *1*: 141-193.

FORBES, A. and MORISON, B. R. Cortical responses to sensory stimulation under deep barbiturate narcosis. *J. Neurophysiol.*, **1939**, *2*: 112-128.

FULTON, J. F. and BAILEY, P. Tumors in the region of the third ventricle: their diagnosis and relation to pathological sleep. *J. nerv. ment. Dis.*, **1929**, *69*: 1-25, 145-164, 261-272.

GAROL, H. W. The functional organization of the sensory cortex of the cat. *J. Neuropath. Exp. Neur.*, **1942**, *1*: 320-329.

GELLHORN, E. Effect of afferent impulses on cortical suppressor areas. *J. Neurophysiol.*, **1947**, *10*: 125-132.

GEREBTZOFF, M. A. Recherches sur la projection corticale du labyrinthe. I. Des effets de la stimulation labyrinthique sur l'activité électrique de l'écorce cérébrale. *Arch. Internat. Physiol.*, **1940**, *50*: 59-99.

HUNTER, J. and JASPER, H. Reactions of unanesthetized animals to thalamic stimulation. *Trans. Amer. Neur. Ass.*, **1948**, *73*: 171-172.

INGRAM, W. R., BARRIS, R. W. and RANSON, S. W. Catalepsy, an experimental study. *Arch. Neurol. Psychiat.*, Chicago, **1936**, *35*: 1175-1197.

INGRAM, W. R., KNOTT, J. R. and WHEATLEY, M. D. Electroencephalograms of cats with hypothalamic lesions — III. Meeting Amer. EEG Society, **1949**.

JASPER, H. H. and DROOGLEEVER-FORTUYN, J. Experimental studies on the functional anatomy of petit mal epilepsy. *Res. Publ. Ass. nerv. ment. Dis.*, **1947**, *26*: 272-298.

JASPER, H., HUNTER, J. and KNIGHTON, R. Experimental studies of thalamocortical systems. *Trans. Amer. Neur. Ass.*, **1948**, *73*: 210-212.

LINDSLEY, D. B., BOWDEN, J. and MAGOUN, H. W. Effect upon the EEG of acute injury to the brain stem activating system. *EEG Clin. Neurophysiol.*, **1949**, *1*: 475-486.

MAGOUN, H. W. Coma following midbrain lesions in the monkey. *Anat. Rec.*, **1948**, *100*: 120.

MAGOUN, H. W. and RHINES, R. An inhibitory mechanism in the bulbar reticular formation. *J. Neurophysiol.*, **1946** *9*: 165-171.

MCCULLOCH, W. S., GRAF, C. and MAGOUN, H. W. A cortico-bulbo-reticular pathway from area 4-S. *J. Neurophysiol.*, **1946**, *9*: 127-132.

MONNIER, M. Retinal time, retino-cortical time and motor reaction time in man. III. Meeting Amer. EEG Society, **1949**.

MORISON, R. S. and DEMPSEY, E. W. A study of thalamocortical relations. *Amer. J. Physiol.*, **1942**, *135*: 281-292.

MORISON, R. S., FINLEY, K. H. and LOTHROP, G. N. Influence of basal forebrain areas on the electrocorticogram. *Amer. J. Physiol.*, **1943**, *139*: 410-416.

MURPHY, J. P. and GELLHORN, E. The influence of hypothalamic stimulation on cortically induced movements and on action potentials of the cortex. *J. Neurophysiol.*, **1945**, *8*: 339-364.

RANSON, S. W. Somnolence caused by hypothalamic lesions in the monkey. *Arch. Neurol. Psychiat.*, Chicago, **1939**, *41*: 1-23.

RHEINBERGER, M. B. and JASPER, H. H. Electrical activity of the cerebral cortex in the unanesthetized cat. *Amer. J. Physiol.*, **1937**, *119*: 186-196.

RICHTER, R. B. and TRAUT, E. F. Chronic encephalitis. Pathological report of a case with protracted somnolence. *Arch. Neurol. Psychiat.*, Chicago, **1940**, *44*: 848-866.

SNIDER, R. S., MAGOUN, H. W. and MCCULLOCH, W. S. A suppressor cerebello-bulbo-reticular pathway from anterior lobe and paramedian lobules. *Fed. Proc.*, **1947**, *6*: 207.

WALTER, W. G. and WALTER, V. J. The electrical activity of the brain. *Ann. Rev. Physiol.*, **1949**, *11*: 199-230.

WARD, A. A. The relationship between the bulbar-reticular suppressor region and the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 120.

Reference: MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.