CONTRIBUTORS

Alajouanine, Th., Paris
Alano, J., Paris
Arfel, G., Paris
Baumgartner, G., Freiburg im Breisgau
Beaussart, M., Lille
Bonvallet, M., Paris
Brazier, M. A. B., Boston
Behrend, R. Ch., Köln-Merheim
Brierley, J. B., London
Buchtal, F., Copenhagan
Burch, N. R., Houston
Cahn, J., Paris
Carpi, A., Rome
Castaigne, P., Paris
Corday, E., Los Angeles
Creutzfeldt, O., Freiburg im Breisgau
Dell, P., Paris
Fernandez-Guardiola, A., Marseille
Fildisevski, P., Skopje
Fischer-Williams, M., London
Fischgold, H., Paris
Franks, W. R., Ottawa
Gastaut, H., Marseille
Goulon, M., Paris
Herold, M., Paris
Hugelin, G., Paris
Jouve, A., Marseille
Jung, R., Freiburg im Breisgau
Kugler, J., Munich
Laval, P., Marseille
Lechner, H., Graz
Lhermitte, F., Paris
Loeb, C., Genoa
Magnus, O., Wassenaar
Mathis, P., Paris
Mensikova, L., Plzen (Czechoslovakia)
Meyer, J. S., Detroit
Naquet, R. L., Marseille
Paillas, J. E., Marseille
Pampiglione, G., London
Pruvot, Ph., Lille
Puppel, H., Freiburg im Breisgau
Radermecker, J., Anvers.
Regis, H., Marseille
Remond, A., Paris
Roger, J., Marseille
Schneider, M., Cologne
Shev, E. E., San Francisco
Soussen, C., Paris
Spunda, C., Vienna
Storm van Leeuwen, Leiden
Terzian, H., Padua
Vigouroux, R., Marseille
Van der Drift, Wassenaar
Zanchetti, A., Siena
Zülch, K. J., Köln-Merheim

FOREWORD

THIS book is a record of the Colloquium held in Marseille by the Réunion Européene d'Information Electroencéphalographique from October 5 to October 9, 1959. The meeting was concerned with clinical neurophysiological, neuropathological and electroencephalographic studies of acute cerebral anoxia and hypoxia. For convenience in publishing this book, the title has been changed to "Cerebral Anoxia and the Electroencephalogram" since the editors believe that this title is brief and approximately describes the subject matter covered during the Symposium.

The Colloquium was conceived and organized through the genius of Professor Henri Gastaut and Doctor H. Fischgold. Dean Morin of the Faculté de Médecine of Marseille presided at the scientific presentations and permitted the magnificent new buildings of the Medical School at Marseille to be used.

The Colloquium was international from its conception and authorities on all aspects of the field of cerebral anoxia were present from all over the world. The roster of contributors included many famous names in the neurological sciences, several representing the second generation of scientists working in the field. The majority of papers were given in French, the rest in English, but all have been translated into English for publication in this monograph. For this reason the style of many papers has suffered. The editors have done their best to preserve high standards of writing throughout but a scientific communication is likely to be rendered inaccurate if many editorial changes are made for the sake of improved translation and the reader is therefore asked to forgive minor difficulties with style. To the Americans who were present, the ease with which all the Europeans spoke fluent French and English was impressive and caused us envy.

All those who attended the Colloquium were invited because of their interest in EEG and the problems of cerebral anoxia. The contributors represented every discipline interested in the subject including electroencephalographers, neurophysiologists, neuroanatomists, neuropathologists, internists, pediatricians, clinical neurologists, neurosurgeons, biochemists and neuropharmacologists. The papers indicate the vast importance of this subject to internal medicine, surgery, anaesthesiology, pediatrics, neurology and neurosurgery as well as to the neurophysiologist.

Throughout the presentation of the papers the discussion was brilliantly led by Dr. Gastaut and Dr. Fischgold who presided over the meeting. The Gallic intensity of the discussion was both stimulating and amusing. The editors have included little of the discussions, however, since the material is found in the substance of the papers and the general view of the discussants is summed up in the Conclusions of the Colloquium which may be found in the last chapter of the book written by Professor Gastaut with the assistance of Dr. Fischgold and myself. This record of the Colloquium presents the scientific data but unfortunately does not capture the charm, the Gallic wit and the rhetoric brilliance of our genial host, Professor Gastaut.

The Colloquium was a great success and was generally thought to be among the best of the series. It is hoped that this book will present to the reader contributions on a scientific subject that has only recently been examined in detail by the neurophysiologist and electroencephalographer. It is believed that this book, at the time of publication at least, offers the reader more information on all aspects of ischemic and hypoxic hypoxia of the brain than is obtainable in any other publication and much of what is published here includes recent or new work (e.g. the recording of single neuronal activity during hypoxia and the use of hypoxia as an activation technique in electroencephalography). The order of presentation of the material has been preserved exactly as the contributions were given and a title and author index is given at the beginning of this book. A subject index is not provided and if information on some aspect of cerebral anoxia is desired, it is suggested that the papers relevant to the subject be read in their entirety.

The Editors wish to express their gratitude to the following: Mrs. Kathleen Borushko, Neurology Department Secretary, Wayne State University College of Medicine for typing many of the manuscripts, Mr. Charles Pickard, Medical Photographer, Wayne State University, for preparing many of the illustrations and Dr. Mariella Fischer-Williams of the London Hospital for translating many of the French papers.

JOHN STIRLING MEYER, M.D.

CONTENTS

CEREBRAL ANOXIA AND THE ELECTROENCEPHALOGRAM

The Proceedings of the Marseille Colloquium, sponsored by the Reunion Europeénne d'Information Eleectroéncéphalographique, and organized by Professor H. Gastaut and Dr. H. Fischgold.

Edited by

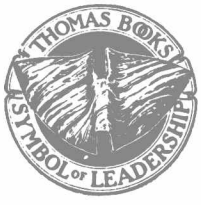
HENRI GASTAUT, M.D.

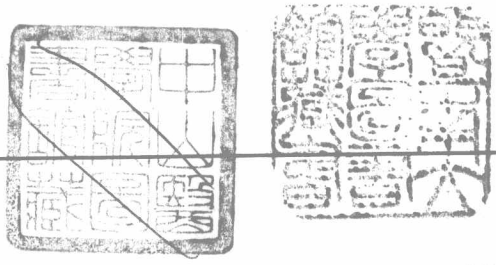
Professor and Director
Laboratories of Neurobiology
Faculté de Médecine, Institut National d'Hygiène
Marseille, France

And

JOHN STIRLING MEYER, B.S., M.Sc., M.D., C.M.

Professor and Chairman
Department of Neurology
Wayne State University, College of Medicine
Detroit, Michigan





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Physiological Studies of Hypoxia and Anoxia in Animals

Chapter I

MICROPHYSIOLOGY OF CORTICAL NEURONES IN ACUTE ANOXIA AND IN RETINAL ISCHEMIA*

GUENTER BAUMGARTNER, OTTO CREUTZFELDT AND RICHARD JUNG
Abteilung für Klinische Neurophysiologie der Universität Freiburg/Br. Germany

IN contrast to the vast literature on anoxic alterations of brain waves there are very few papers studying cortical neuronal activity during and after anoxia. The first reports on neuronal discharges contained only a few remarks on the effects of anoxia (23, 29, 39). They remarked that single neuronal discharges disappear usually before the macrorhythms of the cortex (29, 39) and described neuronal burst discharges in the second period of anoxia and in the postanoxic phase (23). However, systematic studies were lacking until the work of Creutzfeldt, Kasamatsu and Vaz Ferreira (8) describing in detail the anoxic alterations of cortical neurones in the cat encéphale isolé preparation. These authors found 4 characteristic periods with certain correlations between neuronal discharge and brain waves during and after anoxia.

In the following investigations, these early results were supplemented by a study of spontaneous and evoked potentials during hypoxia, by comparative neuronal recordings in cerveau and encéphale isolé cats, by a more detailed study of the postanoxic phase, and by experiments on retinal anoxia. The aim of these investigations was to elucidate further the influence of the lower reticular system on cortical neuronal activity and on anoxic activation, suggested by the experiments of Dell and collaborators (20).

In the following, we shall treat first the relation between cortical neurone activity and brain waves during the various anoxic periods and during postanoxic recovery in cats with intact and with severed connections from the lower brain stem. Then we shall discuss the evoked neuronal responses in anoxic conditions and describe the anoxic deafferentation of the visual cortex following retinal ischemia and how this differs in encéphale and cerveau isolé cats. Finally, we shall discuss some observations on synaptic transmission during anoxia and their relation to anoxic alterations of the membrane potentials of neurones, postulated in 1953 (23) and now demonstrated by Kolmodin's and Skoglund's intracellular recordings from cells of the spinal cord (26).

METHODS

Neuronal discharges were recorded extracellularly by micropipets of the Ling-Gerard type with tips of 0, 5-3 u diameter from the cat's cortex in Bremer's preparations (4) "encéphale isolé" and "cerveau isolé." The microelectrodes were

* This work was supported by a grant from the Deutsche Forschungsgemeinschaft.

introduced into the cortex through holes of a window closing the skull to prevent cortical pulsation. Simultaneously, the EEG was recorded through the same window electrocorticographically from the pial surface. In the following, these surface records are called "EEG."

Artificial respiration was used throughout to prevent hypoxic hyperventilation and alterations of CO_2 content of the blood. Therefore, the cerveau isolé cats were curarized to attain the same conditions of regular artificial respiration as in the encéphale isolé.

The artificial respiration was achieved by an open system with intermittent pressure respiration and small ventilation volume to minimize respiratory pulsation of the cortex. In the early series of pure anoxia (1956/57), no oxygen was added to the air before N_2-respiration. In the later series of hypoxia, preanoxic respiration was made with a mixture of O_2 and air to decrease the ventilation volume. Therefore the preanoxic O_2-reserve in tissue, blood and dead space was larger in the second series of incomplete anoxia than in the first 50 neurones reported in 1956/57 (8).

Evoked activity of the neurones of the visual cortex was recorded under normal and anoxic conditions during application of light stimuli or optic nerve stimuli.

Illumination of the eyes was applied by diffuse white light of 500 Lux and brief light flashes (0.3 msec., 12000 Lux). The optic nerve was stimulated electrically by square wave impulses of less than 0.1 msec. duration.

Anoxia was achieved by giving pure N_2 instead of air by artificial respiration. When cortical electrical activity had disappeared (generally 1 minute following N_2) oxygen was supplied in the form of fresh air. In the later experiments, an admixture of O_2 (20-50%) was employed for revival. Incomplete anoxia and *hypoxia* were induced by changing oxygenated air (20-50% O_2) to a mixture 1% or 8% O_2 in N_2. Retinal anoxia was achieved by *intraocular pressure ischemia* (Method of Bornschein (6)). Ringer saline with heparine was injected through the sclera into the anterior ocular space until all blood retinal supply was occluded (pressures between 150-400 mm Hg). Intraocular pressure was relieved by the same needle after 1 to 1.5 minutes.

Material: A total population of *192 neurones* was recorded before and during anoxia, but only 49 neurones were recordable again during the postanoxic periods.

In 25 *encéphale isolé* cats, *125 neurones* were studied in anoxia and hypoxia.

For the study of spontaneous neuronal activity in pure anoxia, the old material of Creutzfeldt and collaborators was used (50 neurones in 12 cats) see part A-1. In a new series, another 29 neurones of the visual cortex in 8 cats were recorded. In this series, only hypoxia was employed (parts A2 and B).

In 4 *cerveau isolé cats,* the anoxic and postanoxic activity of another *30 neurones* following suprapontine transection was studied (part A II). Two of these cats were prepared first as encéphale isolé by cervical transection, then as cerveau isolé by suprapontine transection. In these preparations, the cerebellum was removed to permit free access to the quadrigeminals before the first recording to minimize the side effects of the pontine section.

In further *37 neurones* of the visual cortex, the changes of activity following

retinal ischemia were compared in encéphale isolé and cerveau isolé preparations(see part C and Fig. 7).

Elsewhere we have given detailed descriptions of the various response types of visual neurones to light stimuli (22, 24) (type A, B, C, D, E), to thalamic stimuli (1) (type I, II, III, IV, V) and to electrical stimuli of the optic nerve (15, 17) (type 1, 2, 3, 4). These various neuronal response types (from which Figure 3 shows an A-neurone, Figures 4 and 5 a B-neurone, Figure 7 B and D-neurones, Figure 8 an E-neurone and Figures 6, 9, and 10 the type 2 response following optic nerve stimuli) did not disclose essential differences during systemic anoxia. However, the corresponding neurones may show a somewhat different behavior and survival time during retinal ischemia (21).

RESULTS

A. Spontaneous Neuronal Discharges During Systemic Anoxia and Hypoxia

I. Encéphale Isolé Preparations

One hundred and six cortical neurones were recorded in the absence of sensory stimulation. Essentially the same anoxic alterations occurred in 63 neurones of the motor cortex and 43 neurones of the visual cortex.

In the *preanoxic control period,* the spontaneous discharge frequency was rather variable, sometimes periodically changing between 1 and 10 per sec. In many experiments the frequency was lower than the average 10 per sec. discharge normally found in cortical neurones of encéphale isolé preparations. This lower spontaneous discharge may partly have been a symptom of slight depression, following repeated anoxic periods during the series of experiments.

1. Pure Anoxia (N_2 respiration): Following N_2 respiration, the EEG, recorded as electrocorticogram from the pial surface, and the neuronal discharges showed the following *four periods,* described earlier by Creutzfeldt and coworkers (8) and more or less associated in time with the anoxic alterations of single neurones (see Fig. 1).

First Period (Free Interval): Duration 10-20 sec. This first period corresponds to the latent period following the onset of N_2 respiration (störungsfreies Intervall, Strughold and coworkers 18). The *EEG* continues as before anoxia with irregular fast waves interspersed by trains of alpha-waves (8-12 per sec.) typical of the encéphale isolé cat. Alpha waves may become a little more prominent but no slow waves appear.

Single neurones continue their discharge at the same more or less irregular frequency as before anoxia. Sometimes the grouping of discharges was somewhat more marked if the neurones discharged periodically with pauses before anoxia, but the mean discharge frequency remained essentially the same: averaging 4.5 per sec.

Second Period (Activation Period): Duration 10-20 sec. Between the 10th and 20th seconds following onset of N_2 respiration, the *EEG* pattern is changed to an arousal type. Fast waves of 15-40 per sec. become more prominent in frequency and amplitude and alpha waves from 8-10 per sec. disappear. In a few experiments, the last part of the activation period shows an alpha-activation of 7-10

per sec. instead of the fast EEG waves. *Single neurones* are mostly accelerated during this activation period. They show either a slightly higher frequency with occasional grouping and more regular discharges and cease abruptly at the end of the activation period, or the units discharge more regularly and faster to about the double or triple of the previous frequency (Fig. 1C) and then continue more irregularly and at lower rate during the next delta period. About half of the neurones already cease to discharge during the activation period, the other half ceases later in the third period. During the inconstant alpha activation at the end of the activation period, the neurones discharge in rather regular frequency around 10 per sec., beating in phase with the alpha waves.

Third Period (Delta Period): Duration 1-5 sec. The third period shows slow rhythms in the *EEG* between 1 and 5 per sec. This period is rather short in pure anoxia in contrast to hypoxia and cannot be seen clearly in about half of the experiments. *Singles neurones* have either ceased discharging before this period, or if they continue their discharges, change to irregular bursts. These bursts consist of 2-5 spikes appearing in short succession of 5-20 msec. duration, separated by longer pauses of more than 200 msec. The bursts become progressively shorter and the pauses longer. Some neurones show no bursts but only single discharges with progressively longer intervals. If several neurones are recorded from the same microelectrode or from 2 microelectrodes in close neighborhood, a tendency to abnormal synchronization is apparent. The synchronized neuronal bursts occur mostly together with certain phases of the slow waves.

Fourth Period (Null Period): Duration Until Respiration Is Restored and Recovery Starts. Complete electrical silence of EEG and neuronal activity. In some cats, the first part of the null period shows some very small regular fast waves (40-60 per sec. 10 uV) lasting 5-10 sec. before complete silence occurs. Sometimes these fast waves are already seen during the delta period. Usually the onset of the null period determining the survival time of the EEG appeared between 20 and 45 sec. following N_2-respiration. The duration depends upon the continuation of the anoxia.

Average values of survival times were 36 ± 1.7 sec. for EEG and 29 ± 1.53 sec. for single neurones. Only half of the neurones were still active in the third period and none showed spontaneous discharges beyond the onset of the fourth null period (Fig. 2). Evoked neuronal discharges, however, could be elicited also during the first part of the fourth (null) period (see part B).

Anoxic convulsions may occur during the delta or null period without convulsive brain waves or neuronal discharges in the cerebral cortex (Fig. 1d). Apparently only brain-stem and spinal neurones are able to discharge rapidly during this late anoxic period.

2. Hypoxia (N_2 respiration with admixtures of O_2): *a) Incomplete Anoxia (N_2 with 1-2% O_2).* In a second series of experiments, less pure N_2 was given, containing about 1% O_2, and before anoxia, O_2 was added to the respired air, thus increasing the O_2 reserve of brain and other tissues. In principle, similar results were obtained. The four stages of anoxic periods described above occurred in the same sequence as previously, but they lasted considerably longer and showed