HANDBOOK OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

EDITOR-IN-CHIEF A. REMOND

VOLUME 10

Direct, Cortical and Depth Evaluation of the Brain

EDITOR: C. AJMONE MARSAN

NINDS, National Institutes of Health, Bethesda, Md. (U.S.A.)

PART A

DC Potentials Recorded Directly from the Cortex

EDITOR: H. CASPERS

Institute of Physiology, University of Münster, Münster (F.R. Germany)

ELSEVIER

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International Federation of Societies for EEG and Clinical Neurophysiology

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

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

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

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

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

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PART A

DC POTENTIALS RECORDED DIRECTLY FROM THE CORTEX

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Preface

Part A of this Volume is concerned with DC potentials recorded directly from the cerebral cortex. In a short preface to this Part two points should be mentioned: (i) the problem of nomenclature and (ii) the scope of material presented.

(i) Up to now there is no general agreement on an appropriate denomination of this bioelectrical phenomenon. Besides *DC potentials*, terms such as *standing*, *steady* or *sustained potentials* and, most often, *slow potential changes (SP)* are being used. In one or more respects all of these labels seem unsatisfactory. Thus, the potential differences concerned may be steady or change slowly, but their fluctuations comprise high frequency components as well. Nevertheless, to avoid confusion a uniform nomenclature had to be used in this Part of the Handbook. Considering the variety of arguments against and in favour of each single name, it was concluded that the term *DC potentials*, derived from the application of *d*irect *c*oupled amplifiers, would be most unprejudiced. Therefore this term has been applied throughout the following sections, and it is recommended that this nomenclature be adopted in future publications.

(ii) The material presented in most sections of Part A is necessarily focussed on results of animal experiments. Findings obtained from scalp recordings in man (such as the contingent negative variations or the motor readiness potentials) have been mentioned, whenever applicable, but no detailed discussion of the results has been included. In such cases the interested reader is referred to the extensive list of references and to other Volumes of this Handbook.

H. Caspers

Section I. Introduction

A. HISTORY

The earliest observations of brain waves were DC studies. Richard Caton used Dubois Reymond's zinc sulphate non-polarizable electrodes directly connected to Thompson's reflecting galvanometer (Caton 1875). He observed the standing DC potential of the cortex as well as phasic fluctuations with movement, changes in level of consciousness, and the negative shifts occurring with death. He was able to obtain local responses from the motor and sensory area both in response to sensory stimulation in tactile, visual and auditory spheres and to motor acts. He also observed the DC shifts associated with seizure activity.

Caton's system reliably recorded slow changes, but could not follow faster frequencies. In an attempt to observe lower voltage and higher frequency potential changes, a great deal of energy was devoted to developing more powerful amplifiers. For technical ease, a low frequency ("high pass") filter was introduced in order to eliminate the drift in the base line inherent in early amplifier designs. It is thus an accident of technology that later studies ignored DC changes until the late 1930's when there was a brief flurry of renewed interest in slow changes in the central nervous system. Davis and coworkers (1939a, b) again using zinc sulphate electrodes, attempted to correlate DC changes with variation in depth of sleep. In 1941 Libet and Gerard published a study of steady potential fields and neuronal activity in the brain. In the mid-1940's the development of chopper stabilized amplifiers permitted Goldring and O'Leary in St. Louis and Wolfgang Köhler at Swarthmore to re-explore many classical problems with systems capable of recording DC changes, marking the opening of the modern era (Köhler *et al.* 1949, 1952, 1955a, b, 1957; Goldring *et al.* 1950).

B. DEFINITIONS

Many different terms such as steady potential, standing potential, slow potential, SP or DC have been used in reference to DC recording and DC changes. Operationally, a DC recording system can be defined as one which faithfully reproduces potential differences invariant over at least one minute. This definition is subject to a statement about noise level and drift in relation to the size of the potential differences being studied (see Section II for technical details).

Note that this is a definition of the recording system, separate from a definition of "DC changes" or "steady potentials" *per se*. The origin of the potential differences revealed by DC recording systems, and the cause of any changes in size that might be

observed, are empirical questions to be answered by appropriate experiments. Viewed in this light, DC changes are part of the general class of bioelectrical activity, occupying an extreme of the frequency spectrum and requiring special recording techniques to be observed.

Even transient phenomena may be clarified by DC recording. The term "DC changes" is not synonymous with "slow swings" but refers to technique of recording. See Section VII.A for an illustration of where DC recording clarified a situation in which rapid transients play a prominent role.

As already mentioned above a variety of terms has been used in literature. To avoid confusion the terms "DC recordings", "DC shifts" or "DC changes" will be used throughout this work.

Section II. Recording Techniques

A. RECORDING SYSTEMS

An ideal recording system would faithfully reproduce a square wave of instantaneous rise time and infinite duration. In practice, for a variety of factors, all amplifiers have a limit to both their high and low frequency responses. The problems are more serious at the low frequency end of the spectrum. Not only may the system be unable to amplify, or even to pass, very slow changes, but artefactual extraneous slow swings of the base line may interfere with faithful recording.

Amplifiers specifically designed to record slow changes are commonly called "DC". Not so long ago this literally would have meant "direct coupled", because only direct coupled amplifiers (*i.e.*, without a capacitor introduced between stages) could pass slow events. The coupling capacitor was introduced in "AC" amplifiers (technically called r-c for resistance capacitance coupling) by the electronic engineer to achieve two goals: to block out large voltage slow swings of the base line and to avoid ever increasing voltages on the grids of the tubes of succeeding stages (so-called brute force amplification). Nowadays "DC" amplification may be achieved in a variety of ways.

(a) *Carrier amplifiers.* With a technique similar to that used in frequency modulated radio transmission, it is possible to use the bioelectric voltage to change the frequency of a carrier signal. The carrier is chosen to be in a convenient frequency range for conventional amplification. The frequency of the carrier signal then varies with the size of the bioelectric voltage. The signal is decoded and presented to a galvanometer with a voltage directly proportional to that modulating the carrier. Carrier amplifiers are commonly used for DC recording from strain gauges, but most do not have sufficient sensitivity to be used for small bioelectrical signals.

(b) *Chopper stabilized amplifiers.* Instead of modulating a carrier signal, the signal itself may be broken into small bits by use of a pair of contacts on a vibrating reed (a mechanical chopper). These bits are easily amplified by conventional capacity coupled techniques. The amplified signal is led to another set of contacts on the same reed. These amplified bits are placed back into a DC form with, however, a series of very fast transients superimposed. Since most pen writers are incapable of responding to such very rapid transients, the machine in effect writes out the very slow changes which were initially sought. Chopper stabilized amplifiers are commonly used for recording low-voltage DC bioelectrical changes but of necessity have a very poor high frequency response which, at best, can be 50 per cent of the chopper frequency (Fig. 1).

(c) *Direct coupled amplifiers.* The advent of transistors, many of which have good

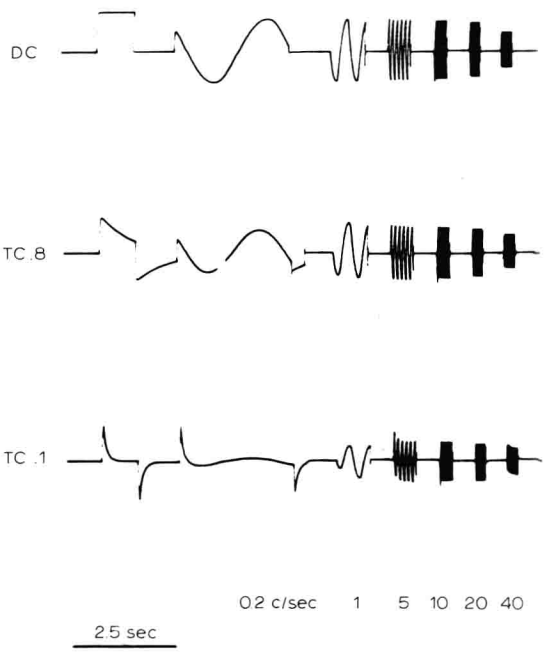

Fig. 1. Effect of amplifier characteristics on the reproduction of square waves. This figure was obtained by using three identical chopper stabilized amplifiers with capacitors introduced to limit the time constant in two of them. The value of the time constant is given to the left. Note the attenuation of high frequencies in this type of amplifier which has an effective chopping rate of 120 c/sec. When operating in a DC mode, the square wave, which has a duration of approximately 1 sec, is faithfully reproduced. Reducing the time constant distorts the square wave response proportionately. Distortion is produced not only by the limitation of low frequency response but also by phase shift introduced by the capacitor.

DC characteristics, permitted the design of quite stable and very sensitive direct coupled amplifiers. There are frequently many stages with feedback circuits employed to improve stability. Such amplifiers can have a much better high frequency response than either the carrier or chopper stabilized amplifiers. However, there remains the practical limitation that the wider the frequency range, the greater the background noise.

B. TIME CONSTANT

Electroencephalographers are familiar with the term "time constant" and with the switch on their machine which varies its value and thus alters the low frequency response of the amplifier (Fig. 1). Changing the time constant control actually changes the size of the first coupling capacitor of the machine. Frequently the time constant will be shortened to block-out slow swings which are not of interest, for example sweat artefacts. The first capacitor may be introduced between the electrode input and the first stage. There is, however, another capacitor even earlier in the system. This is the capacitor created at the boundary between the electrode and the preparation (see below).

C. ELECTRODES

The interface between the metal of the recording electrode and the salts of tissue fluid forms a capacitor. It can affect the characteristics of the recording system by limiting the size of the time constant, and may severely attenuate slow changes. In addition, the difference in concentration of electrolytes can serve as a battery, introducing a source of electromotive force (EMF) and other possible types of artefact. For recording DC changes, therefore, one must carefully choose the type of electrode (Fig. 2).

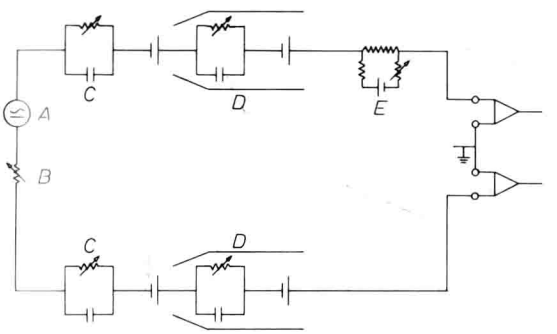

Fig. 2. Scheme of some of the electrical characteristics of the preparation and recording circuits in DC recording. *A*: EMF generated by the neural tissue. *B*: changes in impedance within the neural tissue. *C*: electrode-tissue interface which has EMF, capacitive and resistive components. *D*: similar components lying within the physical structure of the non-polarizable electrode itself. *E*: a bucking circuit to adjust for standing potentials in the circuit. Alterations at any one of these points, as well as changes in power supply voltages of the amplifier, will produce a change in the DC base line. Generally, only alterations produced by *A* are considered real DC shifts.

For DC recording it is best to avoid (a) any extraneous current generated within the electrode or at the electrode-subject interface, and (b) any capacitance effect at the electrode-subject interface which will tend to offer greater resistance to low frequencies. The type of electrode best suited for DC recording is the so-called non-polarizable electrode (see the next paragraph and Section II. D on DC artefacts of biological origin). For further details the interested reader should consult Feder (1963a, b) and Cooper *et al.* (1969).

(a) *Non-polarizable electrodes.* An electrode is non-polarizable if, when connected to an outside EMF of equal but opposite sign, no chemical reaction occurs within it. This implies that all electrodes are miniature batteries (which they are) and that for ideal conditions there must be unhindered ionic exchange. These conditions are best met by using a metal in a solution of its own salt. For biological work Zn:$ZnCl_2$, Hg:HgCl and Ag:AgCl have proven best. Other types of electrode commonly used in neurophysiology (pure silver, stainless steel, tungsten, platinum) are generally not satisfactory for DC recording. Electrodes made of these pure metals all polarize easily and form high-pass filters.

(b) *Fabrication.* The larger the surface area, in general, the more stable the electrode. By appropriate techniques surface area can be increased without increasing overall

size. Design, therefore, is of importance, and many of the technical problems have been overcome. Electrodes satisfactory for DC recording can be made in many shapes and sizes and can also be used for chronical implantation (Brown 1934; O'Connel *et al.* 1960a, b; Gumnit and Grossman 1961; Rowland 1961; Wurtz 1965; Bord and Philipp 1970).

(c) *Electrode potentials.* Since all electrodes are miniature batteries, the inherent EMF is a factor of major importance. If very long duration changes are to be observed, the EMF must not vary. For this reason it is best to work with selected pairs of electrodes of identical EMF. The pairs may be brought into equilibrium if stored in a salt solution with the leads connected to form a complete circuit. With properly constructed electrodes, a potential difference of approximately 100 μV between members of a pair can usually be obtained.

(d) *Reference point.* Even when the investigator looks only at transient changes the electrical activity under the "reference" electrode must be taken into account. The confusion introduced by the "hot ear" in clinical EEG or by the spread of electroretinogram (ERG) are classic examples of the inherent dangers. In DC studies, where longer lasting phasic and tonic changes are to be observed, the location of the reference electrode can be still more critical. The standing potential across the blood brain barrier can vary in size and must be evaluated when the reference electrode is outside the CNS. Even if the reference electrode is within the CNS, changes in ionic concentration must be considered. These factors have importance in additon to the familiar problems of controlling for bioelectric signals under the electrode, muscle potentials, ERG, etc.

D. DC ARTEFACTS OF BIOLOGICAL ORIGIN

It is a truism to state that all of the physiochemical processes associated with life are also associated with changes in electrical potential. A moment of reflection on the implications of this statement helps one to understand why the investigator applying DC recording techniques to neural processes must always keep other basic physical and chemical considerations in mind. The potential changes associated with life processes are often very large and even very subtile changes can generate potentials in the voltage range of those commonly investigated. For example, a DC shift of 200 μV can represent a change of only one part in 1000 in the concentration of sodium chloride between two electrodes.

Some of the processes that can contribute to slowly changing potentials are:

(a) *Redox or oxidation-reduction potentials.* This potential difference develops between two inert electrodes releasing (oxidation) or capturing (reduction) electrons. Such reactions are carried out in every part of the body at all times during basic oxygen metabolism, but are by no means limited to oxygen pathways.

(b) *Liquid junction concentration or diffusion potentials.* This potential change develops between solutions of a different concentration of the same ion or of two different ions. If one portion of neural tissue is intensely excited and releases a large amount of potassium, a potential will develop between this point and a distant

reference. Also, if ions leak from the recording electrode, a diffusion potential develops.

(c) *Donnan or membrane potentials.* The potential difference develops across a membrane which does not conduct electricity or which is only permeable to one class of ions when that membrane is in a solution containing ions. Contaminated pores in recording electrodes can produce this situation.

(d) *Phase boundary potentials.* If certain semiconducting substances (alkaloids or hormones) are placed in an aqueous solution, incomplete mixing may occur and a potential develop across the boundary.

(e) *Streaming or electrokinetic potentials.* The potential difference is developed between two otherwise identical solutions which are in relative motion with one another. For example, there is a potential difference between the center and the edge in a rapidly flowing stream of blood in an artery.

(f) *Polarization potentials.* This is one of the most common causes of artefact in neurophysiological recording. The potential difference develops between two dissimilar metals (or between two pieces of the same alloy) in an aqueous ionic solution, a situation commonly arising with conventional metallic electrodes (consult Bates 1963 and Feder 1963a).

The equations describing these situations all contain elements which are responsive to changes in temperature and other physical factors. Practically speaking, not only the physical movement of the electrodes but movements of the tissue, injuries to membranes, temperature changes in the room as well as temperature changes of the animal, alterations in blood pressure and flow, of pH, tissue impedance, metabolism, etc., can all affect recordings.

Section III. DC shifts released by direct and afferent stimulation

If DC recording is used, virtually every stimulus-bound cortical activity is seen to be accompanied by a change in cortical steady potentials (DC shift). Before the advent of intracellular recording these shifts were viewed as after-effects (or after-effect summations) of the initial, briefer, evoked cortical potentials (Goldring and O'Leary 1951a, b). The after-effects were considered analogous to after-effects and/or after-potentials of peripheral nerve. However, the analogy did not imply that CNS after-effects had excitability significance, as do after-potentials of peripheral nerve.

More recently, intracellular studies have shown that excitatory and inhibitory post-synaptic potentials are a more plausible source of DC shifts (Pollen 1964; Sugaya *et al.* 1964). Synaptic potentials endure for many milliseconds, respond in a graded manner to progressively increasing intensities of stimulation and summate to produce sustained changes in membrane potential. Also, glia in leech and amphibia (Kuffler *et al.* 1964, 1966a) and "idle" or "unresponsive" cells in cat cerebral cortex (Karahashi and Goldring 1966) undergo a transient slow depolarization (SD) during various kinds of CNS activation. Like synaptic potentials, SDs are graded responses and summate. Evidence accumulated to date indicates that "unresponsive" cells are probably glia. Hereafter, we refer to them as presumed glial cells.

Thus, there are at least three kinds of membrane changes whose temporal and summating qualities are capable of producing cortical DC shifts. Each has a different function, and the distribution of current flow which each generates differs from that of the other. For example, incident to an afferent volley, excitatory post-synaptic potentials (EPSPs) occurring in apical dendrites produce a surface negative change while those arising in the soma result in surface positivity. By contrast, inhibitory post-synaptic potentials (IPSPs) occurring at the soma produce surface negativity. Current flow created by SD in presumed glial cells does not distribute itself along a dipole, as is the case for neurons, and it always produces surface negativity regardless of where it occurs in cortical depth (see below). When one considers that these three different kinds of membrane changes can occur simultaneously and that any surface potential is the algebraic summation of some or all of them, the difficulty in assigning functional significance to cortical DC shifts becomes obvious.

In this Section we review the various kinds of stimulus-bound cortical DC shifts and then describe experiments that deal with those shifts in which it has been possible to gather evidence for a membrane origin.

A. STIMULUS-BOUND DC SHIFTS

(a) *Sensory evoked potentials.* Polarity and duration of DC changes vary with the kind of stimulation (electrical *vs.* physiological), kind and depth of anesthesia and state of alertness in unanesthetized preparations. In acute experiments in which the spinal cord was sectioned at C-5 and the animals studied without anesthesia, the slow potential change (then called after-effects of the primary visual evoked response) was usually positive, but could be negative or diphasic (Goldring and O'Leary 1951a, b). A briefer negative potential (220–300 msec duration) intervenes between the primary response and the positivity; it is probably identical to the slow negativity of the direct cortical and recruiting response (see below). With progressively deeper stages of pentobarbital anesthesia, positivity alone comes to characterize the DC record. The positivity starts earlier and earlier, the 200–300 msec negative potential disappearing (Pearlman *et al.* 1960) (Fig. 3). When the DC shift was negative or diphasic, the negative change either followed the positivity or appeared alone with a latency equal to the duration of the positive potential. It had a longer duration than did the positivity (circa 1 sec), and was associated with low voltage fast activity in the electrocorticogram (ECoG).

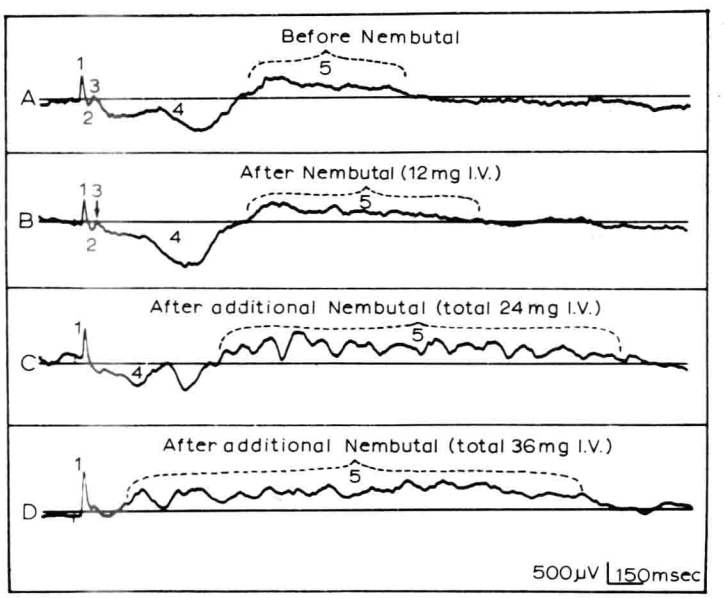

Fig. 3. Effect of deepening pentobarbital (Nembutal) anesthesia on visual response evoked by flash stimulation of the retina. 1, 2 and 3, components of primary evoked potential; 4, slow negativity; 5, positivity (previously called positive after-effect). Positive is up. (From Pearlman *et al.* 1960)

With repetitive stimulation (25–30/sec), a negative DC shift is the usual case in the unanesthetized animal, amplitude and duration of the negative shift depending upon the background ECoG activity. If the trace was already activated, negativity persisted only during the period of stimulation. However, if elicited during periods of