CHEMICAL AND METABOLIC CHARACTERISTICS OF BRAIN TISSUE; ELECTRICAL IMPEDANCE CORRELATES

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The electrical activity of the brain recorded as the electroencephalogram (EEG) has offered a readily accessible parameter for measurement and has proved useful as a general index of physiological state (Berger, 1929; Brazier, 1961). The changes of patterning of the EEG with physiological state, as well as certain distinguishing features of the EEG in disease processes, have produced a substantial body of knowledge. However, this knowledge is based on scientifically uncertain ground, because the EEG is not easily quantifiable. As a measure of function or state, it can provide only circumstantial evidence. Although much new evidence has accumulated that indicates the genesis of the EEG in individual neuronal wave generators, the nature of their separate contributions to the ensemble or population characteristic recorded as the gross EEG remains only partly resolved (Elul, 1967; Adey, 1968).

This is not an unexpected result in view of what is known anatomically and histologically about the brain. The system, as an information processing organ, is comprised of a very large number of active elements, complexly interconnected, with dynamic and time varying interactions between the elements, and probably having non-repeating relationships as well. Although exceedingly complex, the functioning brain produces clearly definable behavior and in disease, produces classifiable symptoms.

In recent years, using high speed digital computing techniques with sophisticated statistical analysis methods, it has been shown that useful physiological indices are available in the EEG (Adey, 1966a; Walter, Rhodes, & Adey, 1967). These relationships in the component parts of the gross EEG which appear to yield information about brain function are not accessible through the usual avenues of clinical "EEG reading."

By the use of chronically implanted electrodes in animal studies and with the advent of surgical treatment for certain human neurological disorders, it has become possible to obtain the EEG from localized brain regions. Such studies have led to the establishment of patterns which characterize particular brain regions, and relations between brain regions, but have not established a set or sets of unique descriptors for the finer features of functional brain states. Animal studies in a learning situation have demonstrated that the EEG may become organized into rhythmical patterns with a high degree of order (Adey, 1966a; Elazar & Adey, 1967a & b). These studies implicate functional mechanisms which must re-direct the wave generating systems most probably at the expense of metabolic energy.

Biochemical studies of brain tissues as well as chemically manipulated electrophysiological studies in isolated neural tissues have long shown that this organ functions normally in a very finely balanced state. The constituents, from the single monovalent ion to the largest polyionic macromolecule function in a dynamic state which may be grossly disturbed by trace amounts of particular molecules and these disturbances can produce quite marked behavioral modifications (Adey, 1966b). It is logical then to seek a measurement method which would assess these dynamic properties directly.

Electrical Impedance of Tissue

One method which has long been used and recently reviewed by Aladjalova (1964) is simply to apply a known voltage (V) to a pair of electrodes which pass a known electric current (I) through the tissue

and see what the tissue has done to the current. The electrical impedance (Z) is defined by the effect of the tissue on the measuring current. This is usually given by the ratio:

$$Z = \frac{V}{I} \qquad (1)$$

Since the current will diffuse widely in passing through tissue, it is important to have an approximate idea of the physical nature of the system being observed both in terms of current spread volume and the constituents. These parameters will determine the way in which the tissue affects the impedance. Biological impedance measurement is therefore measured in a volume, and subject to the influence of all the components in the measured volume. In our studies impedance is used as an index of a physical property of the tissue; they are not determined solely for their relation to the intrinsic electrical activity of the brain.

With sufficiently large electrode separation, the whole head impedance may be observed (impedance rheography). With somewhat smaller volumes, but large enough to include arterioles, pulsations relating to blood flow may be observed (Birzis & Tachibana, 1965). The blood flow related impedance measurements have been used to study regional hemodynamics of the brain (Shalit, 1965) as well as blood volumes (Moskolenko, Cooper, Crow,& Walter, 1967). At the smallest extreme is the measurement of membrane impedance for single cells. Intermediate to these levels is a volume of tissue in which the impedance appears unaffected by blood volume. However, changes reflecting behavioral

state, physiological manipulations, and drug induced states may be found. It is at this tissue level that we have made impedance studies in the past several years (Adey, Kado, & Didio, 1962).

Since it is desirable to observe the impedance of cerebral tissues with the least possible disturbance, other than by insertion of the electrode, the electrodes and the measuring currents are kept small. The current is alternating at a frequency of 1 kHz to avoid cumulative polarization effects and its flow is measured as a steady state process. Furthermore, to be most useful, the measurements should be made in normal, performing animals.

The electrode is coaxial in construction with an outer conductor diameter of 0.5 mm and central conductor of 0.1 mm diameter extending approximately 1 mm beyond the end of the outer conductor. Both are made of stainless steel and insulated with epoxy varnish except at the tips where they are exposed for a distance of about 0.5 mm. The majority of the current passes through a roughly spherical volume of tissue approximately 1 mm in diameter as demonstrated with a model electrode in a homogeneous medium (Adey, Kado, Didio, & Schindler, 1963). Therefore, it is assumed that the impedances observed reflect the effects of the viable tissue surrounding the electrode tip within this small volume. A further assumption is that the complex interface impedance between the metal of the electrode and the tissue, due to many factors, is unaffected by the extremely small test current density (Schwann, 1963).

Measurement Methods in Small Volumes of Tissue

The measurement itself is made with a Wheatstone bridge circuit (Fig. 1A) which is used to balance the electrode impedance to zero

Fig. 1 about here

and to provide an unbalance voltage proportional to impedance changes. An excitation voltage of about 40 μV rms at 1.0 kHz is applied to the bridge which results in a current density at the exposed electrode surface of about 10^{-13} $A\mu^{-2}$. Since the voltage (V) remains approximately constant, the current (I) will vary with the impedance (Z) as shown in Eq. (1). It can be seen that the current cannot change over a very great range however, without very large impedance changes. A balance is obtained by adjusting resistors (R) and capacitors (C) which are combined in parallel in the known leg of the bridge. At balance, the values of resistance and capacitance in the bridge are the parallel equivalent of the impedance beyond the metal of the electrode. The resistance and capacitance are read directly from the switch positions in the bridge and are called the baseline values of R and C. The parallel connection of the R and C components results in the impedance Z being defined as shown in Eq. (3) which shows that a decrease in R and C could result in no Z change. Equation (2) shows that the capacitive reactance (X_c) varies immensely with capacitance so that a rise in capacitance results in a decreased impedance.

$$X_c = \frac{1}{\omega c} \tag{2}$$

and

$$Z = \frac{R}{\sqrt{1 + R^2\omega^2C^2}} \tag{3}$$

The exact equivalent circuit for the current path in tissue is not known; it is probably best approximated by the circuit shown in Fig. 1B. This configuration avoids the difficulty of explaining the conductivity

(R_p) which occurs at zero frequency. If only R_s and C_s are assumed, no current could flow for direct currents. No ambiguity of values can exist in the known elements of the bridge since only one combination of resistance and capacitance in parallel leg will yield the necessary impedance and the phase to balance the impedance of the electrode tip. The bridge provides the means for suppressing the large steady impedance (Z) so that small changes (ΔZ) (0.1 to 2.0 percent) may be detected as shown vectorialy in Fig. 1B. No effort is made to separate polarization impedance from tissue impedance since the bridge circuit balances a total impedance at the electrode tip.

In the balanced condition, the bridge provides a zero output signal to the high gain tuned amplifier (A) in Fig. 1A. However, as the tissue impedance changes by small amounts, an unbalance voltage will appear, proportional to the amount and direction of change in the impedance. The unbalance voltage appears as a single sine wave phase shifted from the bridge excitation voltage by the parallel equivalent circuit. An analysis of this unbalance voltage is given by Aladjalova (1964) and more recently reviewed for higher frequencies where the same principles apply (Smith, Weurker, & Frank, 1967). Where Aladjalova displayed the unbalance voltage on an oscilloscope and photographed a Lissajou pattern for subsequent measurement, Smith, et al. used identically the same sampling methods we have been applying.

Briefly stated, the unbalance voltage of the bridge may be shown to be equal to the vectorial addition of two sine waves. If the equivalent circuit at the electrode tip is a resistance and capacitance circuit only, the unbalance voltage may be expected to stay in one

quadrant only. Therefore, the unbalance voltage may be assumed to consist of only two components separated by 90^{o} in-phase. Figure 2A shows how voltages which are in phase (0^{o}) and precisely 90^{o} out of phase with the excitation voltage may be summed to equal the phase shifted unbalance voltage. It is possible to produce a phase shifted voltage of any amplitude and phase from 0^{o} to 90^{o} by combining the appropriate amplitudes of an in-phase and quadrature voltage with fixed phase.

Fig. 2 about here

Note that in Fig. 2A with two sine waves 90^{o} apart, when one is at its peak value, the other is passing through zero. The implication of this basic property is that if the unbalance voltage is sampled at the correct instant in time, an in-phase and quadrature component may be detected with respect to the excitation voltage. These voltages will be detected in a mutually exclusive fashion so that changes in amplitude of the components will result in independent changes, in the detected outputs.

This process is shown in Fig. 2B where the component sine waves are depicted separately. Actual detection is accomplished by two electronic switches which are turned on and off by 0.1 msec pulses separated by 250 μsec and synchronized by the same oscillator which drives the bridge. The 0^{o} and 90^{o} sine waves are sampled once in each cycle to obtain monophasic pulses. Sampling twice each cycle will result in twice the output but will require additional circuitry to obtain a unidirectional output. Thus two, one kHz pulse trains are produced where the pulse amplitudes are determined by the amplitudes of the component voltages at the time of sampling. The pulse trains

are smoothed to produce two continuous signals (Fig. 2C) which may be recorded by an ink writing instrument having sufficient sensitivity.

The method therefore yields two impedance measures. The baseline values of R and C are read from the adjustable bridge elements, and the continuous small perturbations in these impedances are written out by a pen writer. If the change in tissue impedance is so large as to drive the pen writer off scale, the bridge is rebalanced and the new baseline impedance is noted.

By floating the bridge circuit with isolation transformers, it has been possible to have the electrode located as far as 30 feet from the instrument. The cable capacitance must be balanced by fixed capacitors in the bridge (C_1, C_2, Fig. 1A) when the cable rms were long and had large capacitances. This capability makes remote impedance measurements possible both from chronically implanted, freely moving animals and from a patient recording room.

Fig. 3 about here

Measurements in Tissue

Studies have been made in both the acute and chronic preparations in animals and with chronically implanted electrodes in man (Porter, Adey, & Kado, 1965). The impedance responds rapidly to sensory stimuli in structures such as the hippocampus (Fig. 3). These are usually in the form of a sharp fall in the resistive component and an equally sharp rise in the capacitive component, followed by a slow return to the baseline level in both components. The term "fast" in these studies is usually in the range of 1 to 2 sec.

The magnitude of the shifts appear related to the intensity of stimulus. The example given in Fig. 3 is taken from a cat immobilized and placed in a stereotaxic instrument (Adey, Kado, & Walter, 1965). Relatively small shifts are produced with stimuli such as a loud clap (noise) and a very small response, when the observer passes in the field of view. However, with a paw squeeze applied only with the fingers, a shift off scale is elicited. On subsequent sightings of the observer a small shift followed by a much larger change is seen.

It is difficult to avoid the inference that the significance of the observer to the animal has been altered by the recent experience. The physiological response is a measure of an intrinsic change in cerebral tissue that differs from the brief neuroelectric response to an external stimulus. Of the regions studied, the hippocampus is by far the most responsive to all forms of stimuli.

Slow Impedance Changes

Impedance changes are not confined to transient effects. Altered physiological and behavioral states are accompanied by long term shifts which persist for the duration of the modified state. The effects of a barbiturate are different from those produced by a psychotomimetic drug. Figure 4, from an early study (Adey et al., 1962), shows an elevation of the resistance by about 10 percent and a return to near baseline in the course of an anesthetized state induced with pentobarbital (35 mg/Kg I.P.). By contrast, a psychotomimetic, cyclohexamine (2 mg/Kg I.P.) decreased resistance of about 5 percent over a period of 15 hrs.

Fig. 4 about here

These results are consistent with our other observations that somnolent states are associated with a rise in impedance and an excited or alerting state is accompanied by a fall in the impedance. The possiblity of a major contribution to these effects from altered blood volumes must be considered in a first evaluation of such findings. However, subsequent results have shown that the blood volume shifts appear to be an insignificant factor. This question has also been considered by van Harreveld and Ochs (1956) who found that approximately 10 percent increase in resistance may be produced by emptying of the cerebral vasculature. Since our studies do not involve such gross changes in blood volume it is reasonable to assume that the effects arise in other ways.

Impedance Changes with Physiological Manipulation

Other factors require consideration. The expired CO_2 is increased with each stimulus in the lower trace of Fig. 3. The shifts in CO_2 are small but follow a time course similar to changes in impedance. If the impedance shift is causally related to the tissue CO_2 level, it should be possible to elicit the shifts by external manipulation of CO_2 levels.

A series of experiments were performed to test this hypothesis (Adey et al., 1965). A very large change in the respiratory CO_2 is necessary to elicit impedance shifts of the order obtained with physiological sensory stimuli. This result indicated that endogenous CO_2 production is far more influential than inhaling high levels of CO_2 in producing impedance changes, and supporting the hypothesis that the endogenous CO_2 shifts and the observed impedance changes may be produced

by a common metabolic mechanism. This inference is further supported by the finding shown in Fig. 5 where the hippocampus was studied incrementally (Adey et al., 1965). The responsiveness to exogenous CO_2 shifts is related to the nature of the tissue. It appears that regions with a high neuronal density are more susceptible to changes in CO_2 than fiber areas. Reverting again to the question of blood volume effects, the distribution of capillaries in neuropil is only 2 to 3 times greater than in white matter. Thus, if the impedance changes are reflecting changes in blood volume, one would expect to see changes also in white matter. Such responses are absent in Fig. 5. However, there still remains the possibility of a differential blood volume control mechanism in gray versus white matter.

Fig. 5 about here

In human studies (Porter et al., 1965) a lower baseline impedance and rapid response to changes in pCO_2 characterized the regions which also produced the spike-and-wave complexes in the electrical recording. Grant (1923) had shown that a glioma has about one half the resistance of normal cerebral tissue so that these results are not surprising, especially when it is considered that such pathological tissue may have abnormally high metabolic rates, and basically different metabolic paths in anaerobic processes (Elazar, Kado, & Adey, 1966).

Impedance Changes in Sleep

These perturbations in impedance do not appear closely related to the EEG except in the broad shifts such as the increased impedance in slow wave sleep and a decrease with the desynchronization on awakening.

Fig. 6 about here

This is illustrated in Fig. 6 which shows an all night study conducted on an implanted patient (Porter et al., 1965, unpublished results). The maximum impedance value recorded tends to remain the same for each period of stage III sleep but transient decreases with each awakening become progressively smaller. The impedance changes in the sleep phases and especially the diminution of the changes on awakening are similar in time course with the sweat rate changes in man reported by Satoh, Ogawa, & Takagi (1965) and opposite to the 17 hydroxicorticoid excretion reported by Mandell (1966).

In the sleeping cat, it was found that amygdaloid impedance changes did not follow cyclic changes in the EEG that are the usual concomitants of cyclic sleep mechanisms (Fig. 7). At the slow recording speed shown, individual waves cannot be identified but slow amplitude variations can be distinguished. At each period of low amplitude EEG activity, associated with paradoxical or rapid-eye-movement sleep, impedance rose slightly, even when the period of low amplitude activity was short. In the lower trace, the animal was awakened and the impedance fell slightly. Here, the amplitude of the EEG was of the same order as in spontaneous awakenings.

Fig. 7 about here

Impedance Changes and Learning

The method presented offers a new parameter which may be useful in assessing brain tissue in vivo. The electrical impedance of cerebral tissue appears to be a property related to the functional state of the tissue sensitively responding to small and innocuous manipulations which do not reliably manifest themselves by any other available technique. Impedance changes seen in learning studies

illustrate this point. Figure 8 shows impedance responses in the amygdala in a cat running in a T-maze situation. A drop in impedance can be seen to accompany the acquisition of the task and on reversal of the cue, the shift is re-established only when the animal re-learns the reversed task. These records are averaged over 40 trials in a particular run and display both the average impedance and one standard deviation about the mean. It can be seen that with cue reversal, increased variability accompanied loss of the shift during approach. These results would indicate that a type of reorganization was in progress, directly involving the physical properties of the tissue. In studies of such processes as learning or alerting, by chemical manipulation, the effects on the central nervous system may be very closely followed by this method. It would therefore, be most meaningful to know with some specificity, the mechanism or mechanisms which may be responsible for the impedance changes that we have seen.

Fig. 8 about here

Conclusion

At this time it appears highly unlikely that these results may be attributed to a single mechanism or functional state. There are too many possible pathways for the current to take and too many elements in each of these pathways to allow assignment of sole responsibility for these changes. Each one probably makes some contribution to the total impedance change. However, there are some known factors which are more likely than others. Of these, the extracellular space, having the lowest resistance to current flow is a prime candidate. Van Harreveld and Malhotra (1965) have used the impedance change with anoxia and fixation combined with a freeze drying technique to successfully

demonstrate the existence of a large interstitial space. Although these findings had not been supported by independent means, the assumption that the majority of the current flows through the extracellular space is probably valid. In this regard the statement by Cole in 1933 is still applicable. 'While we may then make any measurements that we wish at these two terminals...as long as the potential or current is kept sufficiently low...it must be remembered that there may well be more independent elements between these two terminals than there are independent measurements that we can make at the terminals." Where Cole referred to the system of cells, we extend the same thoughts to the complex system which exists in the interstitial space.

We are continuing our studies of the possible role in production of the impedance changes by the constituents in this space, which is clearly not only cerebrospinal fluid.

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Figure Legends

Fig. 1. Impedance measurement system.

A. Wheatstone bridge diagram with block representation of electronic system. C and R form the manually adjustable elements, C_1 and C_2 are used to balance cable capacitances, T_1 and T_2 are isolation transformers, R_1 and R_2 form a voltage divider to provide the microvolt bridge drive voltages through connections X-X. The bridge is connected to the electrode by means of two shielded cables. The bridge output is applied to the amplifier A through T_1.

B. Probable equivalent circuit seen by the electrode in tissue. R_s and C_s are series resistance and capacitance. R_p a parallel resistance would provide a current path at very low frequencies.

C. Vector representation of the complex impedance Z which is balanced to the origin by the bridge so that only the changes in impedance ΔZ appears at the input to the amplifier. ΔZ is composed of the resistance component ΔR and the capacitive component ΔC.

Fig. 2. Sine wave voltage phase relations and synchronous detection.

A. The sine wave signal Z shown in heavy broken line may be decomposed into two sine waves R and C phased 90° ($\frac{\pi}{2}$ radians) apart. The instantaneous values of R and C can be seen to be exactly represented on Z at the peaks.

B. The two component sinewaves (0° and 90°) are shown separated and sampled at the peaks (ruled segments). The sampling pulses occur with a 250 μsec interval and have a duration of 100 μsec.

With the sampling occurring at the peak, the alternate sine wave is being sampled at an instant when equal negative and positive portions appear. Thus, the output of the switch when averaged, contains only the mean of the peak value.

In actual operation only the sine wave Z is sampled by two switches which are gated at the times shown. The exponentially filtered outputs of the two switches provide the steady state values of the two components.

C. The outputs of the switches are shown recorded with a pen write while the resistance value was being changed ± 100 ohms around a baseline of 15.98 kilohms and the capacitance changes ± 0.05 kilopicofarads around a baseline value of 3.35 kilo-picofarads. The separation of the two components is clearly evident beyond the switching artifacts produced by the infinite resistance between switch contacts in R.

Fig. 3. Transient impedance responses.

Simultaneous records of hippocampal resistive impedance (R.D. HIPP. RES.), expressed in kilohms, and reactive impedance (R.D. HIPP. CAP.), expressed in kilopicofarads. These tracings show effects of auditory, visual and somatic stimuli. A small transient increase in expired CO_2 accompanies each stimulus.

Fig. 4. Prolonged impedance changes.

A. Change in impedance in left dorsal hippocampus in the course of nembutol anesthesia (30 mg/Kg) and subsequent recovery. Transient drop is shown 55 min after injection of drug during painful squeeze to skin of back.

B. Impedance changes in same left dorsal hippocampus leads from same animal as in A during action of hallucinogenic cyclohexamine drug (CL-400, n-ethyl-1-phenyl-cyclohexamine monochloride, 2 mg/Kg). The drug induced a long lasting drop in impedance, in contrast to the effects of nembutol (Adey, Kado, & Didio, 1962).

Fig. 5. Differential sensitivity.

Repeated exposure to brief episodes of hypercapnea, with impedance changes at successively deeper levels in the hippocampus. Little change was discerned with the electrode tip located near the alvear surface (A). Records B, C, D and E were obtained in successive steps 300, 200, 100 and 200μ, respectively below the previous CO_2 challenge. Maximal changes occurred in the dendritic layers of the pyramidal cells (Adey, Kado, & Walter, 1965).

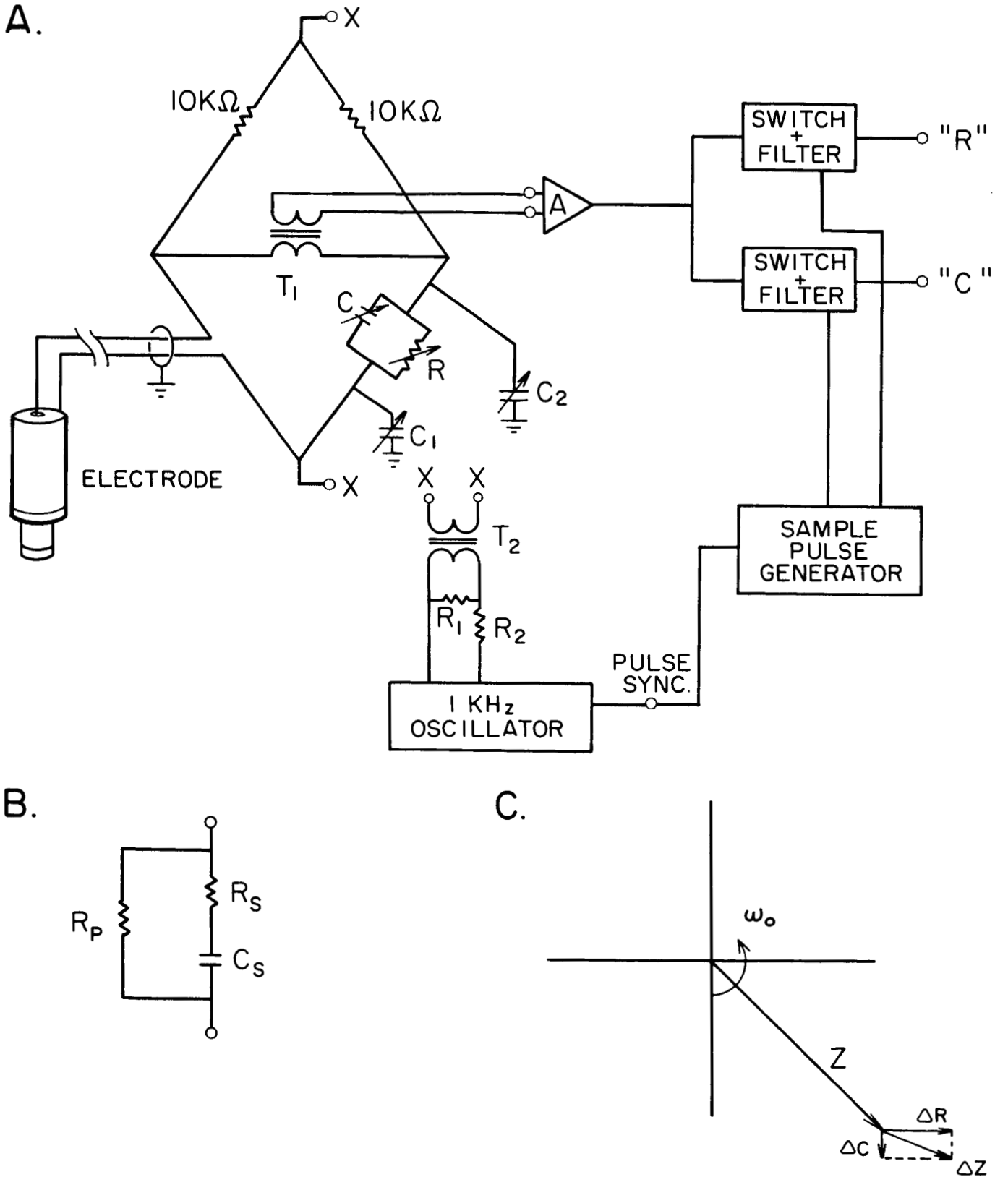
Fig. 6. Human hippocampal impedance in different levels of sleep. Record from a patient with implant in the left posterior Pes hippocampus. The impedance changes with such awakenings become smaller with progression through the night. The levels of sleep are indicated on the upper graph with two REM periods, the first occurring about 12:45 AM and the second at about 2:30 AM. No remarkable changes in impedance are associated with this state except that the second REM period is accompanied by a gradual decrease in impedance.

Fig. 7. Anomalous impedance cycling.

Resistive (L. AMYG (R)) and reactive (L. AMYG (C)) amygdaloid impedance changes in sleep (A) and behavioral arousal (B). Recurrent episodes of paradoxical sleep, characterized by low amplitude EEG records, showed a rise in resistive impedance and a slight decrease in capacitance. Arousal records, however, showed reduced resistance and slightly increased capacitance. Abbreviations: L.M.H. and R.M.H., left and right hippocampus; L.V.C., left visual cortex (Adey, Kado, & Walter, 1965).

Fig. 8. Impedance in alerting, orienting and discrimination.

Calculation of means and variability in hippocampal impedance over 5 day periods at various levels of training. In each graph, the middle trace indicates the mean, with upper and lower traces showing one standard deviation from the mean. Calibrations indicate 50 picofarads with mean baseline at 11.1 kilopicofarads throughout the training meaneuvers; and 100 ohms against a mean baseline of 16 kilohms for the same period. Variability was low at 100 percent performance (A) increase substantially immediately after cue reversal (B), but decreased again after retraining (C). The fast decrease accompanying the approach period is diminished at the time of cue reversal and restablished with training to the reversed paradigm (Adey, Kado, McIlwain & Walter, 1966).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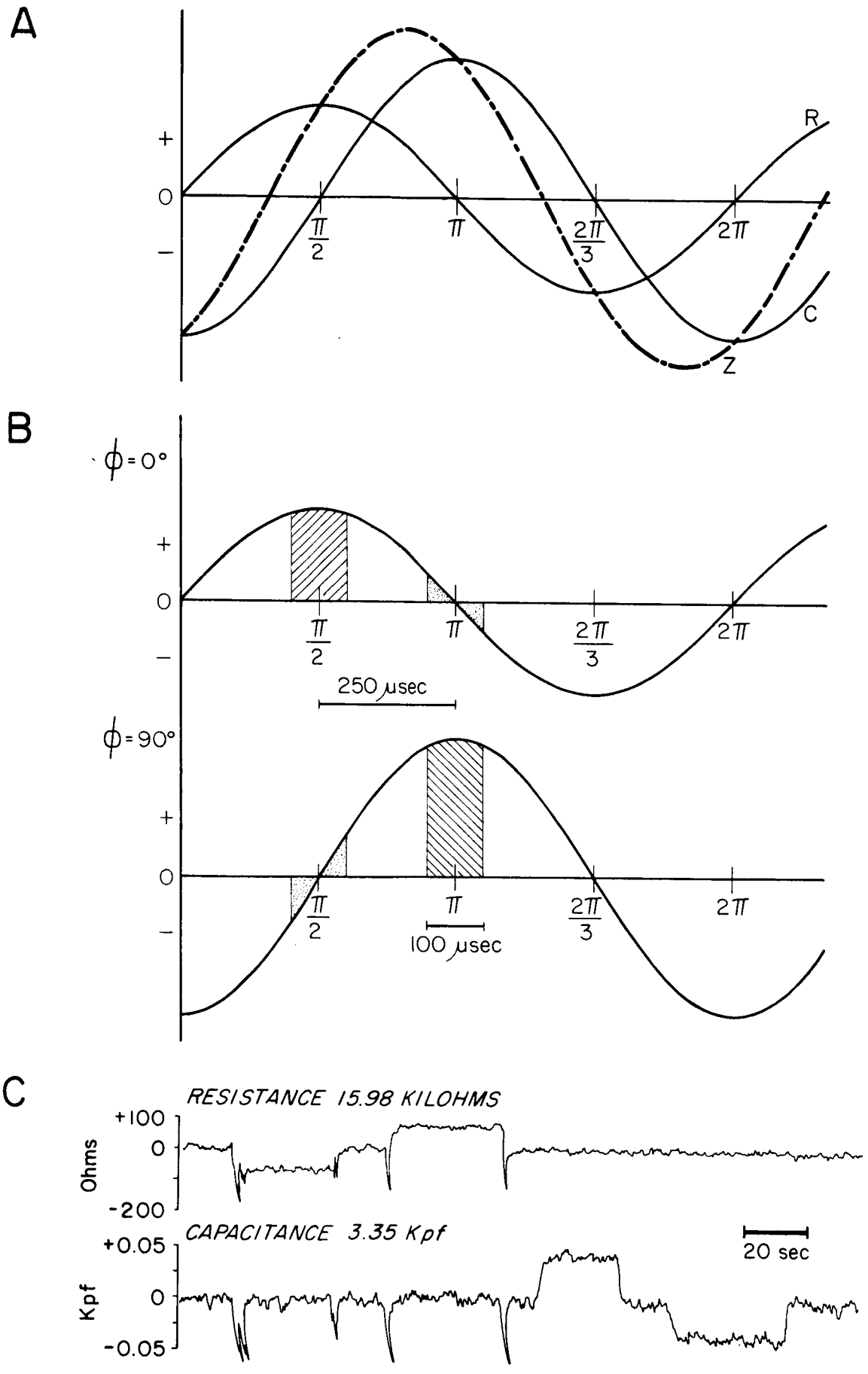
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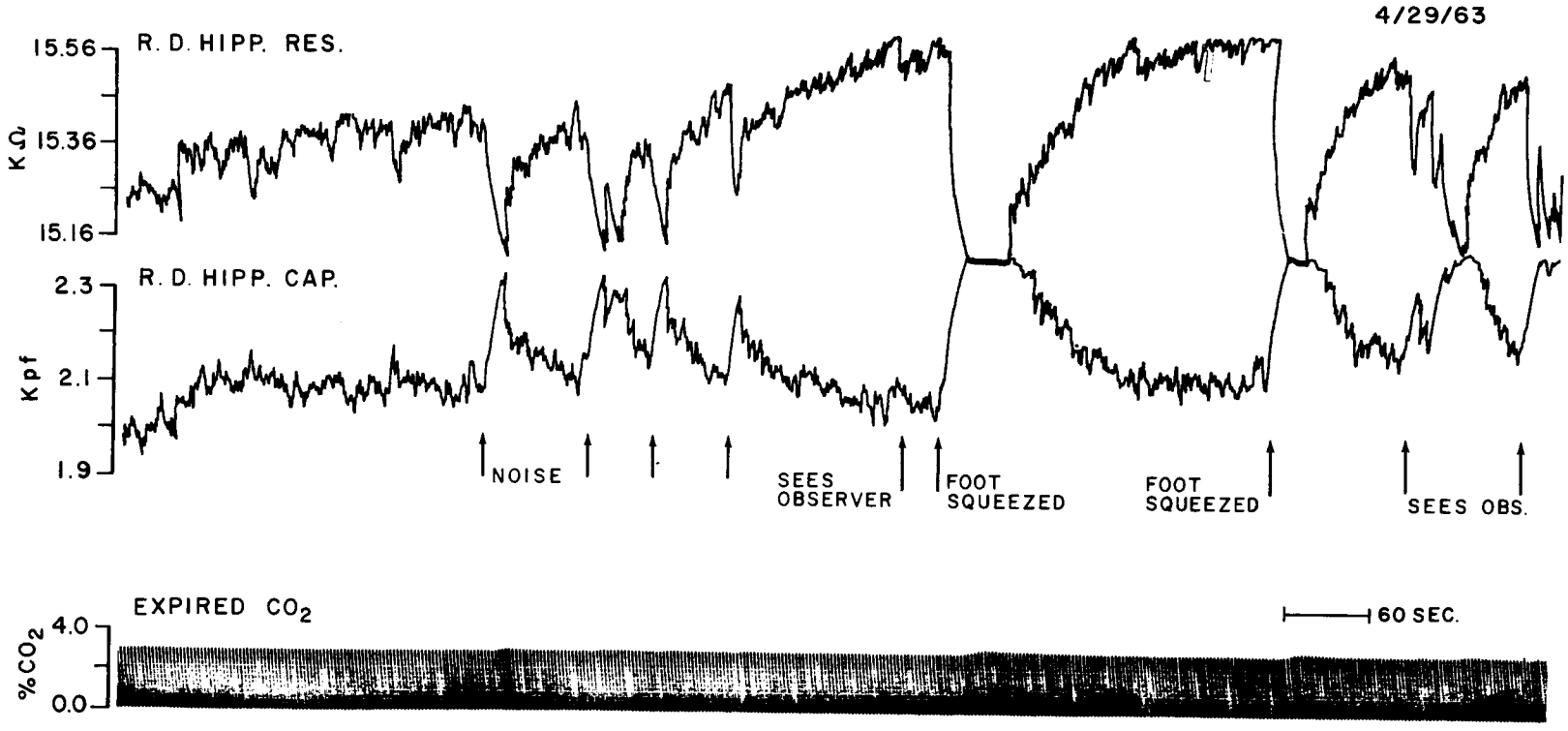
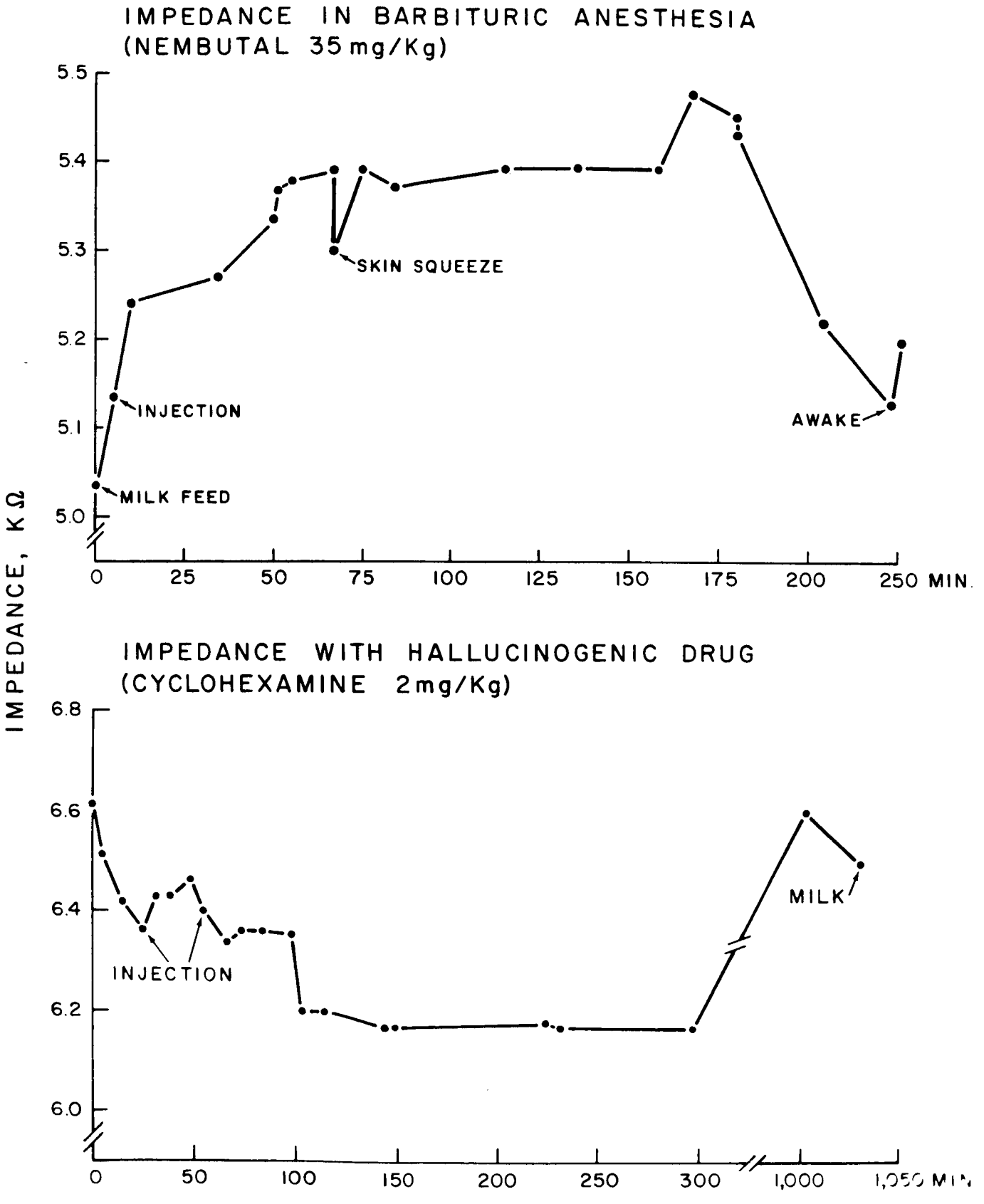
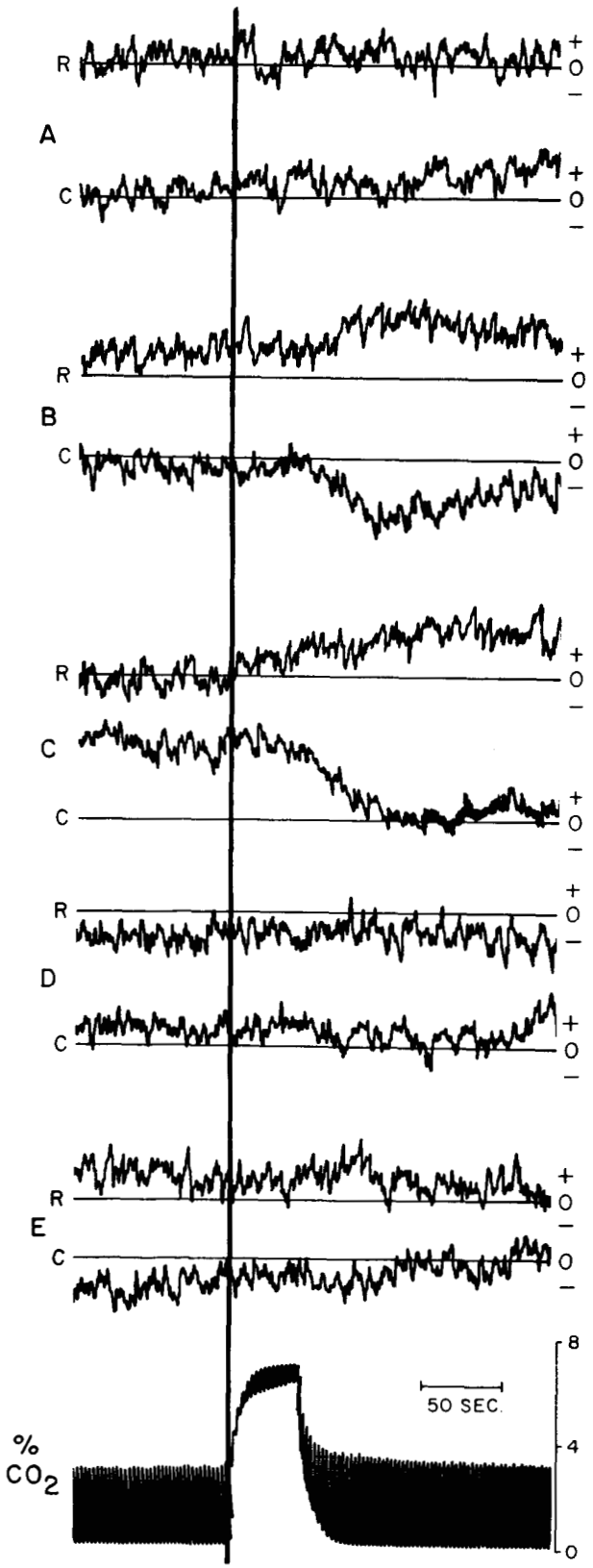
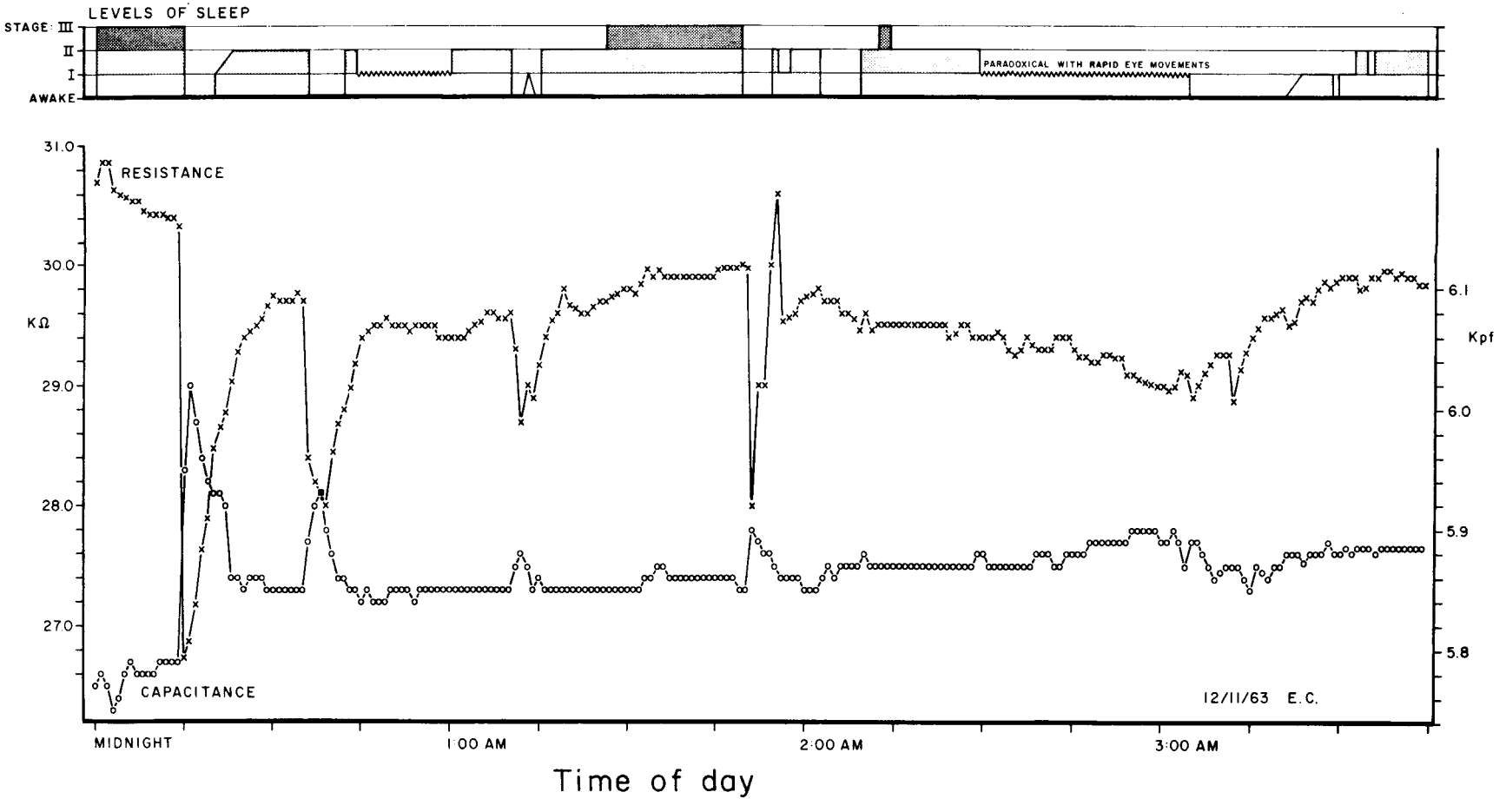
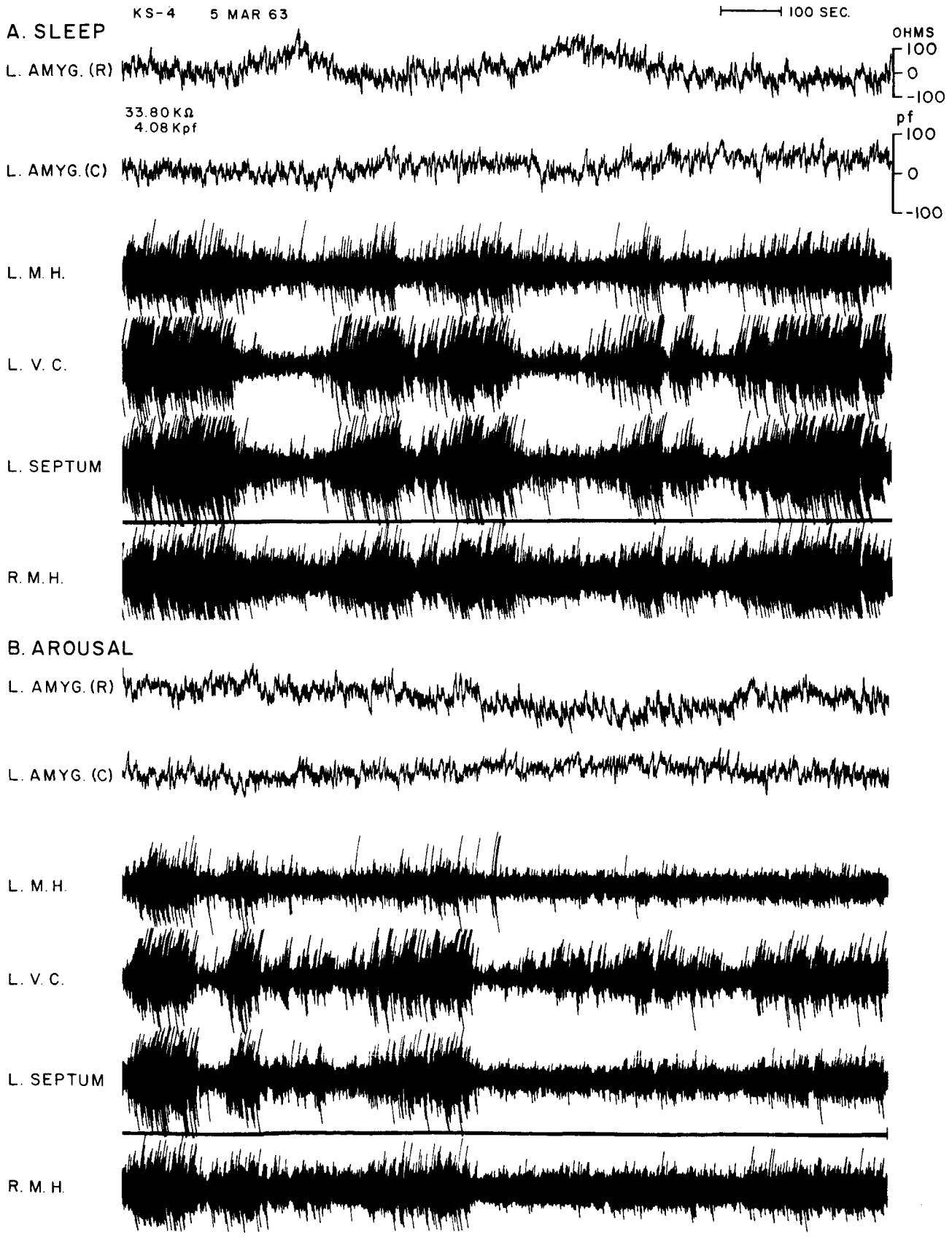



IMPEDANCE IN BARBITURIC ANESTHESIA
(NEMBUTAL 35 mg/Kg)
IMPEDANCE, KΩ
5.5
5.4
5.3
5.2
5.1
5.0
INJECTION
SKIN SQUEEZE
AWAKE
MILK FEED
0
25
50
75
100
125
150
175
200
250 MIN.
IMPEDANCE WITH HALLUCINOGENIC DRUG
(CYCLOHEXAMINE 2mg/Kg)
6.8
6.6
6.4
6.2
6.0
INJECTION
MILK
0
50
100
150
200
250
300
1,000
1,050 MIN.


R
+
0
−
A
C
+
0
−
R
+
0
−
B
C
+
0
−
R
+
0
−
C
C
+
0
−
R
+
0
−
D
C
+
0
−
R
+
0
−
E
C
0
−
50 SEC.
8
4
0
% CO2


LEVELS OF SLEEP
STAGE: III
II
I
AWAKE
PARADOXICAL WITH RAPID EYE MOVEMENTS
31.0
30.0
29.0
28.0
27.0
KΩ
RESISTANCE
CAPACITANCE
6.1
6.0
5.9
5.8
Kpf
12/11/63 E.C.
MIDNIGHT
1:00 AM
2:00 AM
3:00 AM
Time of day


KS-4 5 MAR 63
100 SEC.
A. SLEEP
OHMS
100
0
-100
L. AMYG. (R)
33.80 KΩ
4.08 Kpf
pf
100
0
-100
L. AMYG. (C)
L. M. H.
L. V. C.
L. SEPTUM
R. M. H.
B. AROUSAL
L. AMYG. (R)
L. AMYG. (C)
L. M. H.
L. V. C.
L. SEPTUM
R. M. H.

DORSAL HIPPOCAMPUS - CAT KAM 2