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Research Report

Nonlinear Oscillation and Neuroelectric Phenomena I

EDMOND M. DEWAN

MICROWAVE PHYSICS LABORATORY PROJECT 5635

AIR FORCE CAMBRIDGE RESEARCH LABORATORIES, OFFICE OF AEROSPACE RESEARCH, UNITED STATES AIR FORCE, L.G. HANSCOM FIELD, MASS.

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Abstract

This is the first of a series of papers which treat both normal and epileptic electroencephalographic phenomena from a new point of view. Phenomena such as (1) spontaneity of normal discharges, (2) epileptic involvement of normal neurons, (3) epileptic hypersynchrony, (4) "exhaustion," and (5) normal and epileptic excitation and suppression effects are compared to phenomena of nonlinear oscillations such as (a) "soft" limit cycle behavior, (b) "hard" limit cycle behavior, (c) nonlinear entrainment effects, (d) oscillation hysteresis and Van der Pol oscillations, and (e) asynchronous excitation and quenching effects, respectively. This paper treats (1), (2), and (a), (b), leaving the remainder to future communications. The goal of this work is to lead toward a mathematical phenomenological scheme which shows relationships between seemingly diverse neuroelectric activity and to suggest new experiments which will increase our understanding of the brain mechanisms responsible for normal and abnormal activity.

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Nonlinear Oscillation and Neuroelectric Phenomena I

1. INTRODUCTION

The history of physics seems to indicate that it is essential to construct a mathematical phenomenological scheme before one can arrive at a quantitative physical theory. Such an intermediate scheme summarizes and interrelates what would otherwise be vast quantities of unconnected experimental data. In astronomy, Kepler discovered his three mathematical laws of motion which accurately summarized the data of Tycho Brahe before Newton could formulate his theory of universal gravitation. In atomic physics, the Balmer formula mathematically summarized much of the spectroscopic data before Bohr could formulate his theory of the atom. Bohr's theory was superseded by quantum mechanics which in turn rested on certain wave and particle models of optical phenomena and also on certain analogies between the behavior of matter and light. In special relativity, the so-called Lorentz transformations already existed as a phenomenological model for electromagnetic processes before Einstein re-derived them from a physical theory and showed their general and enormous implications not only in physics but in epistemology. This last example illustrates that the step from a phenomenological scheme to a physical theory is very significant. Finally, it might be

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1. INTRODUCTION

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mentioned that present day elementary particle physics is in the "phenomenological stage" and that there is tremendous striving both in experiment and in the construction of phenomenological schemes in the hope of eventually arriving at a physical theory.

A physical theory and its prerequisite* phenomenological scheme is also important in an investigation of the central nervous system. Obviously, the great complexity of this system forbids an exact mathematical description similar to Kepler's approach to astronomy. However, the history of physics is again helpful in that it suggests the possibility of considering a system at various phenomenological levels. One can temporarily (or even permanently, if necessary) ignore detailed microscopic events and mathematically describe and interrelate macroscopic observations. A specific example is that of thermodynamics. Here, macroscopic quantities, such as temperature, pressure, entropy, and enthalpy are defined in terms of macroscopic experiments and are related mathematically to one another. Microscopic processes are not considered and the so-called "equation of state" which defines the physical properties of a thermodynamic system must be derived entirely from experimental observation. Such a theory is very practical in addition to being useful for the next step toward a microscopic understanding. A microscopic theory constitutes a deeper phenomenological level and in a sense "explains" the former. The microscopic level of thermodynamics, which concerns molecules and atoms, is related to macroscopic thermodynamics by means of a statistical theory; hence, state variables such as pressure and temperature can be related to the average effects of enormous numbers of moving particles. Of course, the brain is exceedingly more complex than any inanimate thermodynamic system. Nevertheless, as will be shown, macroscopic electroencephalographic phenomena can be mathematically described in a way which displays unsuspected correlations in existing data and suggests new experiments.

There are at least three possible levels of phenomenology in the study of the nervous system: the macroscopic, the cellular, and the atomic-molecular. At this time one may strongly suspect that the so-called submicroscopic level (involving constituents and forces in the atomic nucleus) plays no part in neurology. At the cellular level data can be obtained by means of microelectrodes, and at the molecular level by means of electron microscopes. E. E. G. information, of course, represents macroscopic data. Although these levels will hopefully become related statistically, or in some other manner, and although there already exists data at all levels, it is fair to say that an almost purely macroscopic description may be sufficient to shed light upon important problems concerning the over-all organiza-

*Perhaps the need for phenomenological schemes is being reduced by the existence of large scale computers. An example of an approach based on the latter can be found in the work of B. FARLEY. [1]

tion properties and "cooperative phenomena" of the brain. Assuming this to be true and that such problems are crucially significant for any future interrelation between neorology and psychology, we shall devote most of our attention to macrosopic observations except for those cases where the cellular or microscopic information shows a discernible parallelism with the macroscopic information.

In physics, phenomenological schemes usually take the form of exact formulae or symmetry properties. The complexity of biological systems, however, does not always allow the luxury of such an exact approach. Therefore, of necessity, the goal of these papers is merely to compare qualitatively specific mathematical and neuroelectric phenomena and to arrive at a tentative but useful model with the hope that subsequent mathematical and experimental work will lead to a more general and quantitative phenomenological scheme. In other words, although the present scheme is useful for explaining important problems and for suggesting new experiments, it is to be regarded mainly as a demonstration that a mathematical, macroscopic phenomenological scheme (analogous to those in physics) which uses the theory of nonlinear oscillation* promises to be extremely useful in the investigation of the central nervous system.

2. THE PROBLEMS OF "SPONTANEITY" AND OF INITIATION AND SPREAD OF EPILEPTIC AFTERDISCHARGES IN NORMAL CELLS

In this paper, we shall consider problems of spontaneity and epileptic involvement of normal neurons and leave those of "exhaustion," "blocking," "suppression," and "excitation" phenomena for future publications. The mathematics needed will primarily involve so-called nonlinear characteristics and limit cycles. For the most part, these will be discussed at an elementary level so that a minimum of mathematical background will be necessary.

To illustrate the importance of the problems of spontaneity and spread of certain neuroelectric activity, let us consider what some authors have written. With regard to spontaneity, Grey Walter[2] emphasizes the paradoxical nature of the spontaneity of normal brain rhythms in the first part of the following quotation: "The word 'spontaneous'... introduces the most bewildering of the many unsolved problems in central neurobiology... Briefly, two inferences may be made when a state-determined system exhibits spontaneous oscillations: first, there must be some sort of reflexive, retroactive, or feedback pathway whereby two sets of variables can mutually influence one another; second, in the history of the system there must have occurred some event or events that initiated the oscillation... Since a

*The interested reader will find an elementary introduction to parts of the theory of nonlinear oscillations included throughout these papers.

spontaneous oscillation must have been initiated by some event, it may be considered as preserving the information that the event occurred."*

As we shall see, Walter's statements concerning history dependence do not hold true in the case of nonlinear systems! Although it is true that the behavior of linear systems must always depend on initial conditions and thus be, in a sense, history dependent, a nonlinear system can exhibit spontaneous oscillations which have not been initiated by a definite event. Indeed, they can be triggered by random thermal fluctuations and subsequently oscillate in a way entirely independent of the conditions or time of initiation. Thus, it will be shown that spontaneity is a well understood phenomenon which is exhibited by nonlinear systems and that, although we know very little about the causes of neuroelectric oscillations, their spontaneity as such should no longer be so bewildering.

Turning to the problem of initiation and spread of epileptic afterdischarges, Merlis[3] pointed out the present ignorance on this matter and stressed that new information would help greatly to understand epilepsy: "A cogent question and one which is misted in obscurity, concerns the mechanisms by which the normal neuron may become, through repetitive stimulation, at least temporarily epileptic. Put in another way, how are we to define the epileptogenic quality of synchronous bombardment? A better understanding of this phenomenon would do much to further our understanding of the basic mechanisms of the hyperexcitable or epileptic neuron."* An understanding of the latter would, in turn, be the key to an explanation of how epileptic seizure discharges can spread from foci of abnormal activity to other parts of the cortex which ordinarily exhibit only normal E. E. G. patterns.

Still another aspect of these problems is eloquently described by Penfield who analogizes between a glowing coal which can occasionally flare up and ignite the surrounding kindling and an epileptic focus which can occasionally produce discharges which spread to other parts of the brain. At the conclusion Penfield states: "...after a lapse of time a little coal begins to glow and to warm the area about it. Why? What lights the coal? In the answer to this question lies the secret of the cause of epilepsy."*[4] Thus, in addition to the problems of the spontaneity of normal oscillations and the spread and initiation of epileptic afterdischarges in normal cells, there is another phenomenon which Penfield considers to be one of the most important problems of epilepsy: the problem of the spontaneity of epileptic discharges in epileptic foci. Although this third problem involves the first two, its elucidation in terms of our phenomenological scheme will not be evident until Van der Pol oscillations and oscillation hysteresis are discussed and hence will be deferred to the sequel.

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*Words in quotes (") underlined by present author.

3. THE MATHEMATICS OF LIMIT CYCLE PHENOMENA WITH PHYSICAL EXAMPLES

From the point of view of cybernetics, it is evident that the brain is a nonlinear system; it should therefore not be surprising that, as will be shown, the theory of nonlinear oscillations is especially suitable for the problems under consideration. In the following pages we shall show that (a) nonlinear systems can oscillate spontaneously and in a manner independent of initial conditions and (b) more than one mode of self-sustained oscillation is sometimes possible; that is, a nonlinear oscillator can have several stable modes of cyclic behavior (in particular, it can have a small amplitude spontaneous oscillation and, in addition, can be excited into self-sustained, large amplitude oscillation if perturbed in a certain way).

Crucial to the understanding of such behavior is the concept of "limit cycles." Before investigating these in detail, however, it is useful to consider some of their qualitative properties. Limit cycles describe oscillatory behavior and can be classified into three categories: stable, unstable, and indifferent or neutral.

A stable limit cycle corresponds to an oscillation which, if perturbed a small amount by some external agent, will return to its original mode of oscillation after a certain lapse of time. That is, a stable limit cycle refers to a situation quite analogous to "stable equilibrium" in which a system will return to its equilibrium configuration after being slightly disturbed. (A linear system cannot possess a stable limit cycle.) In contrast, an unstable limit cycle corresponds to an oscillation which, if perturbed an arbitrarily small amount, will never return to its initial so-called "equilibrium" configuration. Instead, it will continue to alter until it reaches a stable limit cycle or, if none exists, it will continue to alter indefinitely. This is analogous to "unstable equilibrium." In the neutral limit cycle, the behavior is neither stable nor unstable but depends only on initial conditions. The latter corresponds to the situation contemplated by Walter and, because of its total dependence upon initial events, can be considered to preserve information concerning them.

Finally, stable limit cycles can be classified into two categories: the so-called "soft" and "hard" limit cycles. A soft limit cycle refers to an oscillation which is unstable in the "off" configuration and hence will spontaneously build up if perturbed by an arbitrarily small amount. The amplitude increases until it reaches a stable state of oscillation; that is, the stable limit cycle. On the other hand, a hard limit cycle refers to an oscillation which is stable in the "off" configuration and which will remain so until it is perturbed or "kicked" into a cyclic mode. An effective perturbation must be greater than a certain amount; if it is not, the system will merely re-establish the off configuration. In other words, such an oscillator will not oscillate unless it is kicked with a sufficiently strong influence, but once thus started, will continue indefinitely in a way that does not contain information regarding the initial conditions (other than the fact that at one time there had been an adequate stimulus). In general, no stable limit cycle contains a "memory."

For clarification, let us consider physical examples of soft and hard limit cycle phenomena. Following the examples, we shall consider their mathematical descriptions. The mathematical aspects are to be considered the main basis for the phenomenological scheme we are seeking; however, one can gain some understanding merely by having an understanding of the underlying physical concepts.

3.1 Physical Examples of Limit Cycle Oscillation

3.1.1 SOFT OSCILLATIONS

3.1.1.1 Frictionless Watch

A clock is usually regarded as an example of a hard oscillator because, in general, it must be jolted or excited before oscillation can occur. However, we can consider a "frictionless" watch or a watch which, if fully wound, has effectively no friction. In this case, the watch can start to oscillate spontaneously and hence its oscillation can be classified as "soft."

3.1.1.2 Electronic Oscillator Circuit

An oscillator circuit generally consists of a nonlinear device such as a tube or transistor and a means to couple output to input (feedback): for example, Fig. 1. When the circuit parameters have appropriate values (this will be amplified in the mathematical section), the plate voltage will spontaneously oscillate. Such oscillators (or others based on essentially the same principles) obviously play a large role in technology.

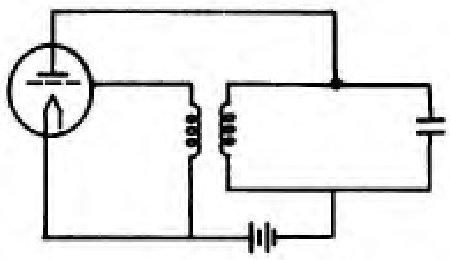

Figure 1. Van der Pol Tuned Plate Oscillator

3.1.1.3 Musical Instruments

In addition to electronic organs which use the above type of oscillator circuits, there are many mechanical self-sustained oscillators among the musical instruments. For example, the organ pipe becomes a soft oscillator when air blows across the edge of the lip located at its "foot." An "edge tone" is generated by the flow of wind across a thin partition. This edge tone is caused by an interaction involving (nonlinear) turbulence; it subsequently drives and is in turn "locked" into resonance or "entrained"[5] by the resonant column of air in the pipe. Other wind instruments work on similar principles. The violin is another interesting example; when the bow passes over the string, the string becomes very unstable and spontaneously oscillates. Here the nonlinear interaction involves a difference between the values of static and dynamic friction.[6]

In all of the above cases, the oscillations occur spontaneously simply because the "off" state is very unstable. Next, let us consider the case in which this state is stable: namely, the case of hard oscillation.

3.1.2 HARD OSCILLATIONS

The classic example of a hard oscillation, as mentioned previously, is that of a pendulum clock with friction.[7] In this case, the pendulum must be displaced beyond a certain amount before the so-called escapement mechanism can drive it into self-sustained oscillation. Another example is the circuit in Fig. 1 with the parameters (the bias on the tube) arranged so that there is no oscillation unless an externally supplied voltage is applied to the grid. Still another example is an electric motor having a large amount of static friction and a low amount of dynamic friction and which can rotate in a stable manner only after it has received an initial push to get it started.

Finally, there is the familiar example of a gasoline engine which must have either an electric starter or a hand crank to initiate self-sustained oscillations. However, as will be shown, this example is more complicated than the ones given previously and cannot be considered a "hard" oscillator in terms of the usual mathematical definition given in section 3.2. On the other hand, this example has important properties and is discussed in the section on inertial nonlinearities.

3.1.3 "INDIFFERENT" OSCILLATIONS

An oscillation corresponding to a neutral limit cycle is similar to hard oscillations in the sense that it must be externally initiated. An example is the frictionless pendulum. Once started, it oscillates indefinitely. The analogy to hard oscillation breaks down when one realizes that the amplitude depends completely on the initial displacement and velocity, whereas in the case of a clock, the amplitude becomes the <u>same</u> for <u>all</u> initial adequate conditions. The frictionless pendulum thus "remembers" its initial conditions and, if not frictionless, the amplitude at any time will "remember" information concerning the <u>initial</u> time. This is the example contemplated by Grey Walter, and such "memory" properties are shared by all <u>linear</u> oscillators.

3.2 Mathematical Description of Limit Cycle Oscillation

Perhaps the most important concept needed for a mathematical understanding of limit cycles is that of damping (negative as well as positive). To illustrate* the

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*For most readers this treatment may seem too elementary at the start, but certain obvious details are included for the sake of completeness so that readers with a limited mathematical background will be able to grasp the essential arguments.

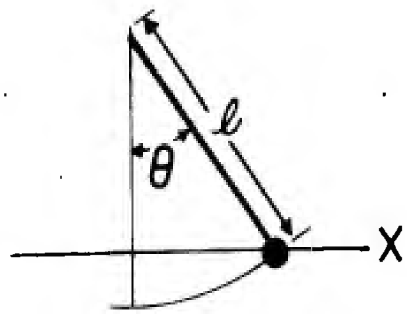

Figure 2. Freely Hanging Pendulum on a Rigid Support

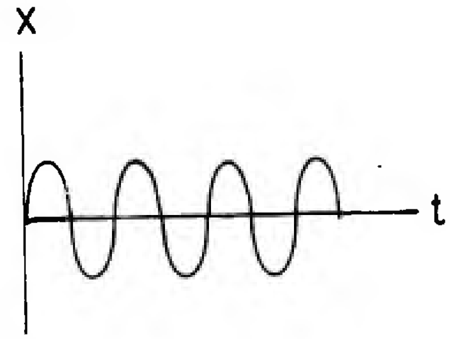

Figure 3. Displacement of a Swinging Pendulum as a Function of Time

meaning of damping with regard to oscillatory motion, consider a swinging frictionless pendulum hanging from a rigid support (see Fig. 2). Fig. 3 illustrates the motion of the pendulum as it oscillates in time. Such oscillation (for a small deflection angle) is called simple harmonic motion and is described by:

$$\ddot{x} + \left(\frac{g}{\ell}\right) x = 0 , \tag{1}$$

where x is the deflection,
g is the acceleration of gravity,
ℓ is the length of the pendulum, and
$\ddot{x}$ is the acceleration of the bob in the x direction. *

In general, the differential equation for simple harmonic motion is

$$\ddot{x} + kx = 0 , \tag{2}$$

where k is a measure of the force which causes the object to return to $x = 0$; that is, $F = -kx$. In other words, k refers to the "spring constant" in the case of a mass hanging on a spring and oscillating without friction (Fig. 4). When friction is present, there will be damping forces proportional to the velocity. The motion is then described by a differential equation of the form

$$\ddot{x} + b\dot{x} + kx = 0 , \tag{3}$$

where $\dot{x}$ is the velocity and b is a positive constant.

* See any elementary physics book.

If the system is initially displaced from equilibrium, x_0, by an amount $\bar{x}$, its oscillations are described by Fig. 5 which shows damped oscillations. [8]

Next, consider the hypothetical case (not realizable in practice) where the damping constant is negative. The equation is then

$$\ddot{x} - b\dot{x} + kx = 0 \qquad (4)$$

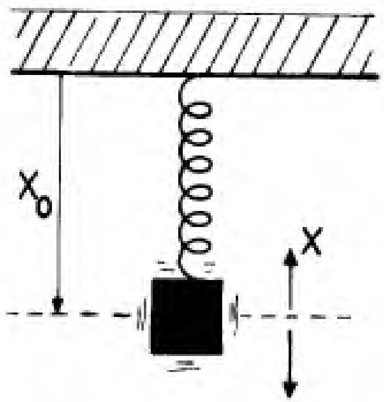

Figure 4. Mechanical Oscillator Consisting of a Spring and a Mass in a Gravitational Field

and its solution is shown in Fig. 6. Such "damping" is a form of so-called "negative damping." In this case, there is spontaneous oscillation starting with essentially zero amplitude and building up to arbitrarily large values.

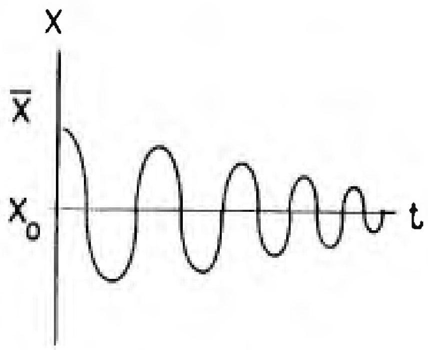

Figure 5. Positively Damped Oscillation

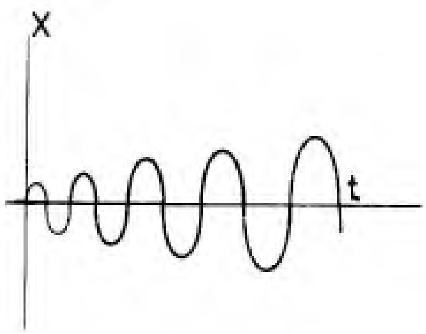

Figure 6. Negatively Damped Oscillation

Physical systems exist which display negative damping; however, instead of being constant as in the hypothetical case above, the damping usually depends on amplitude and/or velocity. In this way, the damping coefficient corresponding to b can change sign so as to limit the amplitude build-up to finite values. An example of an equation exhibiting this feature* is

$$\ddot{x} - \mu\dot{x}(1 - x^2) + x = 0 . \qquad (5)$$

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* For perhaps the most excellent first introduction to nonlinear phenomena, the reader is referred to F. H. CLAUSER. [9]

This equation* describes the behavior of a "feedback" oscillator (Van der Pol) such as the one shown in Fig. 1. The presence of negative damping in the region where $x < 1$ is physically due to the fact that energy is fed into the system. The feedback or self-regulatory aspect of the circuit is responsible for the injection of energy at the proper time so as to maintain oscillation (like pushing a child on a swing). Notice that when $x > 1$, the sign of the damping term changes from negative to positive. This, of course, limits the build-up of amplitude which becomes stabilized about a certain value. For values of $x < 1$, the oscillations tend to build up due to negative damping while for values of $x > 1$, they tend to be damped out. Thus, there exists a stable amplitude of oscillation and it is called a "stable limit cycle". Such limit cycles are clearly independent of initial conditions. Since the damping is negative at $x = 0$, Eq. (5) describes soft oscillation.

Another way to visualize limit cycles is to consider so-called "phase diagrams." An example of such diagrams is shown in Fig. 7 which corresponds to the motion of a simple harmonic oscillator such as the frictionless pendulum. x is the displacement as before, while p is the momentum or velocity (that is, the phase diagram shows the trajectory in "phase space" in the sense that this term is used in statistical mechanics). In this diagram we see that at the maximum value of $|x|$ (at the extreme points of the motion), the velocity of the pendulum is zero; while at the midpoints of the swings (where $x = 0$), the velocity is at its maximum. The phase plane motion of the pendulum is clockwise and elliptical. Readers unfamiliar with phase diagrams[12] would gain much insight by visualizing the phase plane and physical motion in the above simple example and then correlating them.

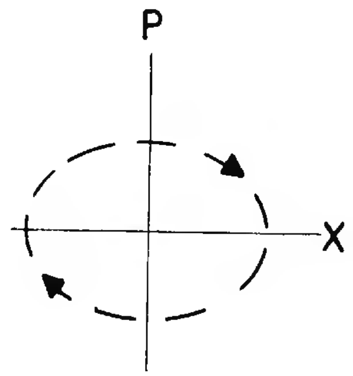

Figure 7. Phase Diagram for Simple Harmonic Motion

Next, let us consider phase trajectories of negatively and positively damped systems. Fig. 8 shows a case of positive damping with gradual decrease in amplitude until the point $x = 0$ is asymptotically reached. Fig. 9 shows the effect of negative damping resulting in a build-up from $x = 0$.

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*For an elementary derivation, see A. A. KHARKEVICH[10] or MINORSKY.[11]

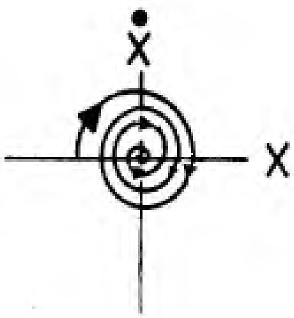

Figure 8. Phase Diagram for Positively Damped Oscillation

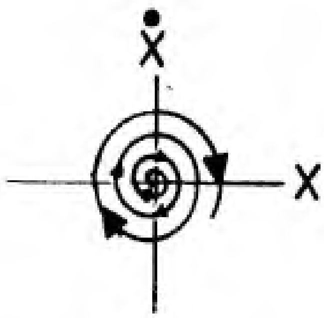

Figure 9. Phase Diagram for Negatively Damped Oscillation

Finally, Fig. 10 shows a stable limit cycle and from this it is clear that the system is independent of initial conditions in that <u>any</u> initial condition results in a stable oscillation.

Until now, only soft self-sustained oscillations have been discussed. Let us next consider hard oscillations where the damping factor is positive for small amplitudes but is negative in some region of larger amplitude as in the following equation (see Fig. 11):

$$\ddot{x} + (\alpha - \beta x^2 + \delta x^4)\dot{x} + x = 0, \tag{6}$$

where $\alpha > 0$, $\beta > 0$, $\delta > 0$.

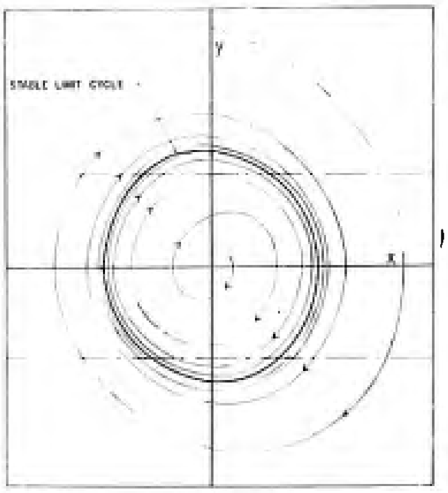

Figure 10. Phase Diagram for a Stable Limit Cycle

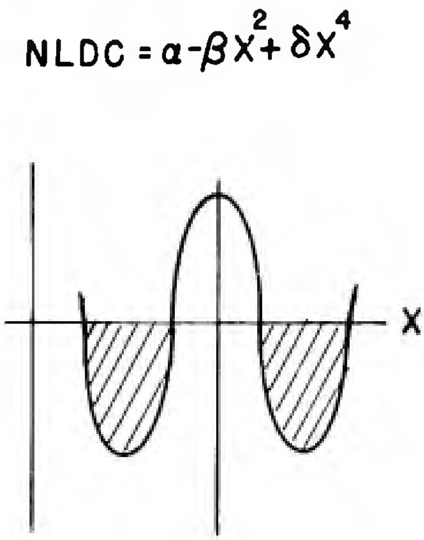

Figure 11. Nonlinear Damping Coefficient for a Hard Oscillator

In this case we see that there would be no spontaneous excitation from $x = 0$, but if a disturbance caused the displacement to exceed a certain "threshold," a spontaneous oscillation would become possible because of the negative damping region.* The phase trajectories for this case are shown in Fig. 12. Two stable forms of behavior are shown in this figure: one is the state of rest and the other is the limit cycle shown schematically as the outer heavy circle. The dotted circle represents an unstable limit cycle. Trajectories starting with displacement and momenta on the inner side of the limit cycle spiral in toward the origin while those starting on the outer side spiral outward toward the stable limit cycle. Finally, those trajectories which start outside the stable limit cycle encounter more positive damping and hence tend to spiral into the limit cycle just as in the soft case. Again we see how initial conditions have very little to do with the ultimate behavior of the system other than determining which of the two stable modes will be in effect.

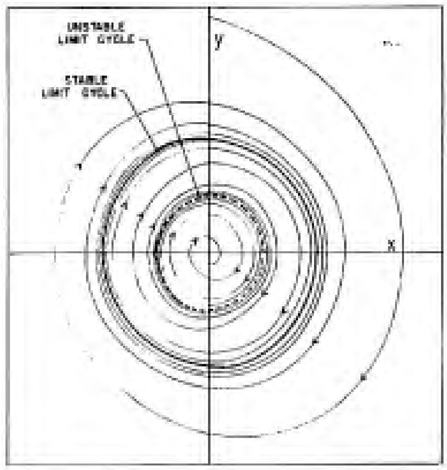

Figure 12. Phase Diagram for a Hard Oscillation

Next, let us consider an instructive situation where there are two limit cycles, one soft, the other hard. Consider the case where the nonlinear damping coefficient (NLDC) consists of a sixth order polynomial

$$\ddot{x} + (-a + bx^2 - cx^4 - gx^6)\,\dot{x} + x = 0\,, \tag{7}$$

where all constants are positive. The form of the NLDC is shown in Fig. 13 where one can see that there are two (shaded) regions where it is negative. The negative region around the origin would cause soft oscillation while that at greater displacement would cause an additional hard mode as shown in Fig. 14. In other words, such a system would spontaneously oscillate in one mode but, if sufficiently jolted in some way, would go into an entirely different mode with larger amplitude and different frequency. As we shall see, such behavior is not very unlike that of excitation of epileptic macroscopic afterdischarges in normal cortex.

*A full discussion of this type of behavior will be found in APPLETON and VAN der POL.[13]

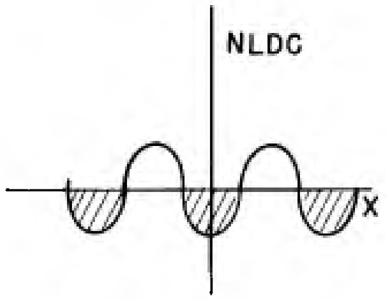

Figure 13. Nonlinear Damping Coefficient for a Double Oscillator with a Soft and Hard Mode

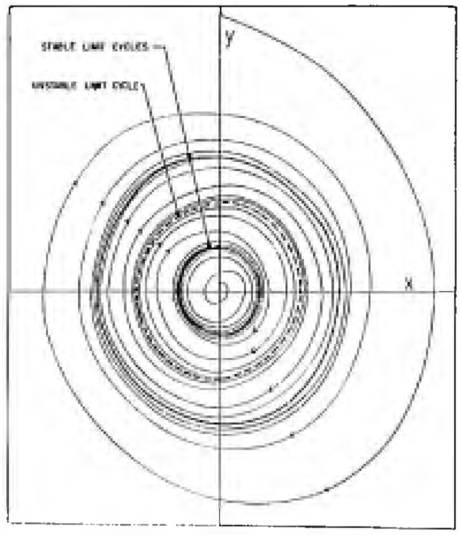

Figure 14. Phase Diagram for a Double Oscillation with a Soft and Hard Mode

4. INITIATION AND SPREAD OF AFTERDISCHARGES

4.1 Definition of "Afterdischarge"

Because the term "afterdischarge" is used quite loosely in literature, it is necessary to define precisely what meaning is intended in this paper. In the first place, we shall not refer to the type of "evoked potentials" which, although caused by and outlasting a certain external stimulus, are not epileptic in nature. Such evoked potentials consist of "ringing" phase-locked rhythms seeming to act as a reverberating memory which preserves the significance of the stimulus.[14] It is also apparently what Wiener considers[15] in his discussion of the normal activity of the "nonlinear oscillations" exhibited in E. E. G. *. Thus, in this paper, we shall discuss only discharges which come under the following definition: "... the epileptiform discharges of neurons following strong tetanic electrical stimulation which persist long after the cessation of stimulation."[16]

Afterdischarges of this type fall into three classes:[17] repetitious firings of single units (cells) which are self-maintained; persistent local afterdischarges

* Wiener observed that in the case of non-epileptic evoked potentials, the amplitude and frequency are related to one another, and he cites this as evidence that cortical oscillations are nonlinear. He goes on to describe "entrainment" effects in the alpha rhythm; this will be discussed in the sequel.

involving a domain of neurons (having a volume of about one cubic cm of cortex);[18] and long chain reverberating neuronal circuits connecting widely separated structures. The first two types will be discussed below while the third will be postponed until the phenomena of nonlinear entrainment and "petit mal" are discussed.

4.2 Initiation of Local and Unit Afterdischarges

4.2.1 LOCAL AFTERDISCHARGE

4.2.1.1 Parameters of Stimulus Efficacy

The electrical stimulation which is used to induce a local epileptic afterdischarge in the cortex (henceforth, the abbreviation AD will be used to mean epileptiform afterdischarge) usually consists of a train of rectangular pulses administered by means of an electrode directly to the cortex. Experiments indicate that the following parameters are relevant for determining whether or not a particular stimulation will be efficacious:* pulse width (PW), pulse repetition frequency (PRF), pulse amplitude (PA), and pulse train duration (PTD). Fig. 15 shows the relation between minimum effective PA and PW upon PRF when PTD is constant.** One should notice here that up to a certain point an increase of PW results in the lowering of minimum effective PA for a given PRF. Fig. 16*** shows how minimum effective PA decreases as PRF is increased when PTD and PW are held constant. This curve shows a relation which is of crucial importance: for PRF there is a region between

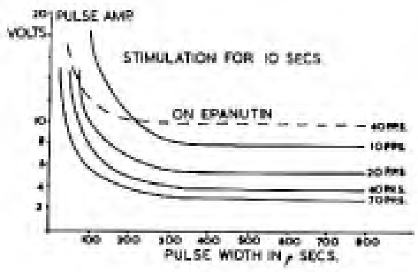

Figure 15. Amplitude-Duration Curves Showing Excitability Characteristics

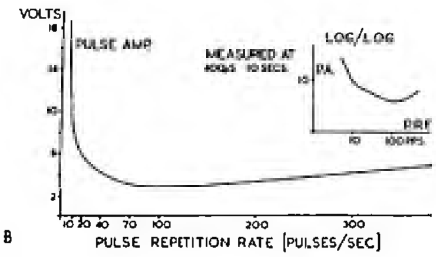

Figure 16. Variation of Threshold with Pulse Repetition Frequency (inset) Log/Log Scale Showing Negative Slope of 1:3 for Constant Energy Requirement

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*Here we follow GREY WALTER (op. cit.) where he stimulates the human visual cortex with a pair of fine electrodes (2 square mm area) separated by 8 mm.

**Fig. 15 is taken from GREY WALTER: op. cit., p. 229, Fig. 7-1A

***Fig. 16 is taken from Ibid., p. 229, Fig. 7-1B

10 to 100 cps (approximately) where the product of PRF and the square of PA (the square of the voltage) is constant.[19] Such a square law suggests, as Grey Walter points out,[20] that there is a constant energy requirement in the production of AD's. Another notable feature is that this requirement fails at very low PRF in that a single isolated pulse, even if it is quite powerful, is incapable of eliciting an AD. *

4.2.1.2 Evolution of the Initiation Stage of Local Afterdischarges

In Figs. 17A-G** we see the cortical response (detected by means of single electrodes near the site of stimulation and by using the skull as a "ground" to complete the circuits) changes during the application of an effective stimulation. Fig. 17A shows the spontaneous activity before stimulation and Fig. 17B, the initial negative pulse output of the cortex in response to the stimulation. Notice that there is a gradual decrease in response until it reaches essentially zero (as seen in Fig. 17C).

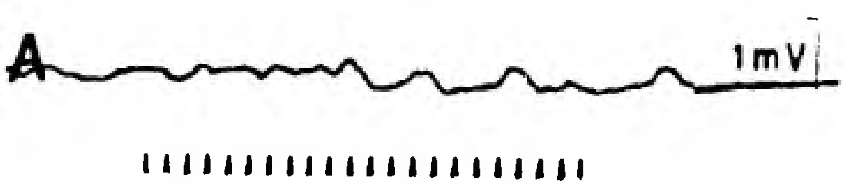

Figure 17A. Spontaneous Resting Activity. Marks indicate 20 ms intervals, voltage scale at right

Figure 17B. First Stage in which Response to Stimulation Involves a Negative Pulse which Decreases with Stimulation Time

*BURNS: Journ. Physiol., 112, 156 (1951) was able to induce AD's from single shocks, but, as BONNET and BREMER (Journ. Physiol., Paris, 1956) have pointed out, this seems to be an effect of the anesthesia used by Burns.

**BONNET, BREMMER: op. cit.: Here the AD's are induced by means of electrodes 1-2 mm apart placed on the suprasylvan gyrus of a cat brain which is, in some sense, electrically isolated from the rest of the cat's body (a "preparation" known as "encephale isolé"). In these experiments, the AD's are not significantly disturbed by stimulae coming from the cat's receptors or from subcortical influences, the latter being assured by the choice of site.

Figure 17C. Cortical Inertia Stage

Figure 17D. Positive Response Stage with Increasingly Delayed Response and Evolution to Alternation Stage

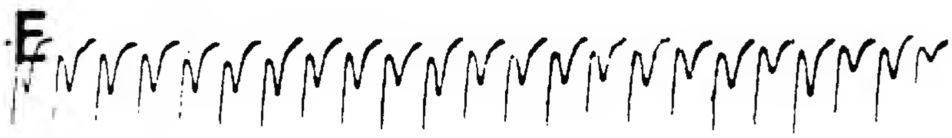

Figure 17E. Alternation Stage

Figure 17F. End of Stimulation Followed by Start of AD

This phenomenon of unresponsiveness has been called "cortical inertia."[21] Next, there suddenly appears a positive pulse (Fig. 17D) which occurs with an increasing delay with respect to the stimulation pulse. This process continues (Fig. 17E) until an alternation occurs, seen at the end of Fig. 17E and more obviously at the beginning of Fig. 17F. When the alternation reaches this stage there invariably follows,

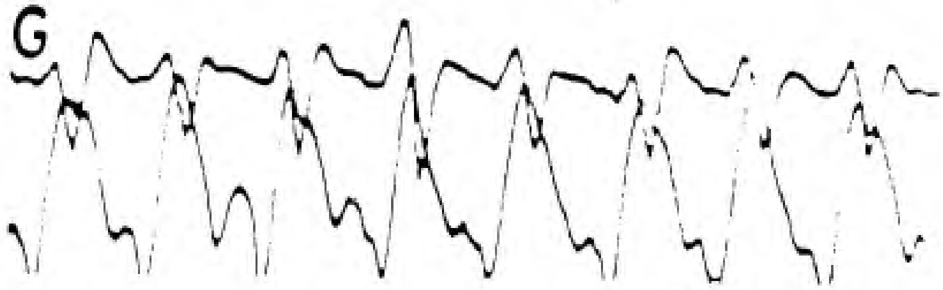

Figure 17G. More Advanced Stage of AD

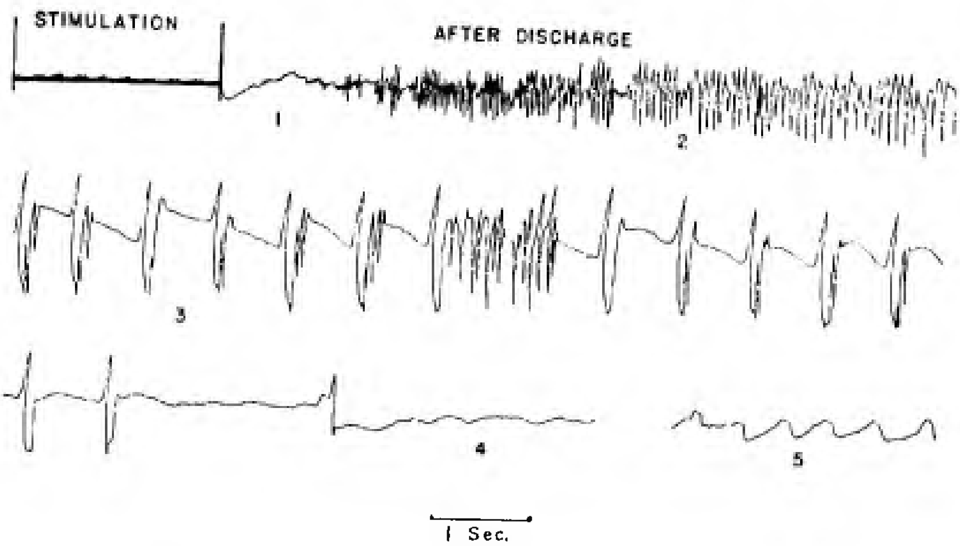

Figure 17H. An Overall View of the Evolution of the AD

after a brief period of latency, the gradual build-up of an AD (Fig. 17G). At its height and under certain circumstances[22] the AD voltage can exceed normal voltages by a factor of 10. It is important to notice that the alternation is both a <u>necessary</u> <u>and</u> <u>sufficient</u> <u>condition</u> for epileptic activation and that such activation has a definite "all or none" quality.

The subsequent evolution of the AD, shown in Fig. 17H, will be discussed in the sequel where oscillacion hysteresis and Van der Pol oscillations will be described.

4.2.2 UNIT AFTERDISCHARGES

4.2.2.1 Parameters of Efficacy

The meaning of the word "afterdischarge" as applied to single cortical cell units is obscured by the fact that normal unit activity can involve repetitive self-sustained discharge. We shall therefore define[23] "afterdischarge" in this case to refer only to long duration, high frequency discharges such as those initiated by means of strong, repetitive electrical stimulation. The stimulation used to provoke these discharges is essentially the same in all respects as that used to provoke local AD's.

As for the "parameters of efficacy," Gerin*[24] has demonstrated that they are essentially the same as they were in the case of local AD's: namely, PRF, PTD, and "strength," the latter being a composite of PA and PW. Unfortunately, it appears that the "constant energy" requirement found in local AD's has not yet been demonstrated in the case of the unit.

4.2.2.2 Evolution of the Initiation of Unit Afterdischarges [25]

If the "parameters of efficacy" are set at such low levels so as to be very weak, then the stimulation can cause no unit response at all. As these parameters are increased, then the following sequence takes place: (1) a single spike appears with each pulse, (2) a burst of spikes appears with each stimulation, (3) if an AD is to follow, the response bursts decrease in amplitude until they vanish (see Fig. 18). This vanishing of the spikes is a sufficient condition for producing AD's. The necessary amount of spike amplitude decrease has apparently not yet been ascertained. After the vanishing there is a latency from a fraction of a second to several seconds following which the AD occurs. The duration of this latency depends somewhat upon the time that the stimulation is turned off, the longer latency time corresponding to the longer stimulation time (Fig. 18).[26]

It should be noted here that the vanishing of unit spikes is quite analogous to the "cortical inertia" observed in local AD's and that in both cases a latency is involved. Also, in both cases the AD is definitely an "all or none" phenomenon. One difference between the microscopic and macroscopic AD's, however, is that in the latter case, the amplitude of the AD far exceeds that of the normal resting level, whereas in the unit case, the AD never exceeds the resting spike amplitude.

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*In the experiments about to be described, the stimulus had the following characteristics: (a) square waves were used, (b) space between electrodes was 1 mm (like Bonnet and Bremer but unlike Grey Walter who used 8 mm spacing), (c) stimulation was applied to the suprasylvian gyrus (like Bonnet). In contrast, the pickup electrode was 1 mm away from the stimulated area as opposed to 5 mm in Bonnet's case, and its cross section size was only 2μ so that it could presumably measure the electrical activity of a single unit.

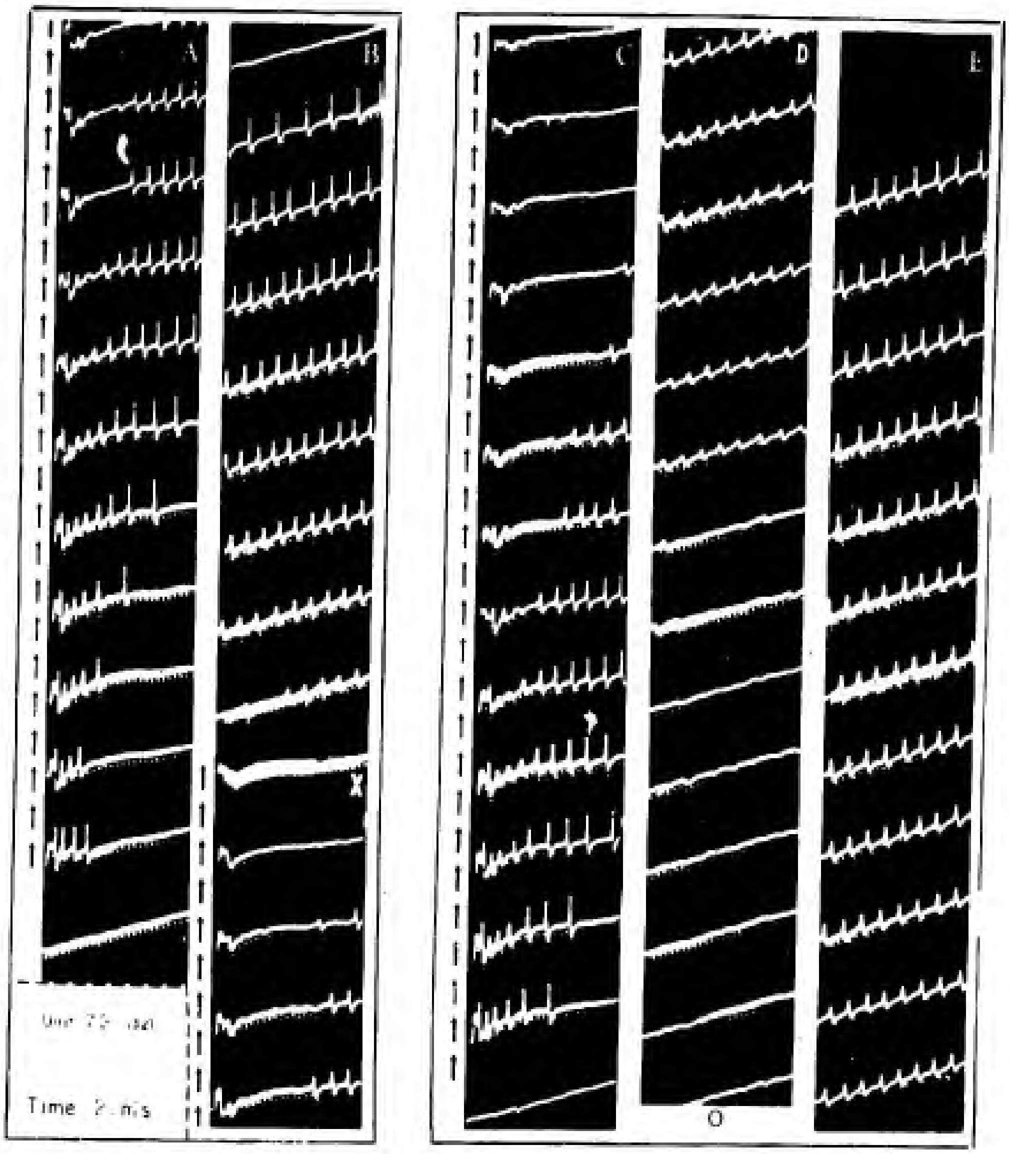

Figure 18. Initiation of Afterdischarges. A, B, C, show the typical repetitive bursts with their peculiar size evolution (see text). The silent phase is much shorter in B (where pulses stop when spikes disappear in X) than in C (where the stimulation is continued 1 sec later). There is an interval of 3 sec.between C and D (at 0). Parameters of stimulation: 8 V, 20 sec., 2. 5 msec pulse duration. Records read from bottom to top. Note progressive amplitude increase in the course of the afterdischarge (B, D, E).

5. THE MATHEMATICS OF INERTIAL NONLINEARITIES* WITH LIMIT CYCLES

In the preceeding paragraphs, we have seen that at both the macroscopic and microscopic levels the brain is capable of generating oscillations falling into two classes: normal and epileptic. On both levels, the abnormal activity is (at least in its initial stages) of a higher frequency than the normal. At the macroscopic level, epileptic voltages can be far greater than normal; at the unit level, although amplitudes do not exceed normal values, the epileptic activity is far more self-sustained than normal activity. This situation is somewhat analogous to the phenomenon of limit cycles, the epileptic activity corresponding to a sort of "hard" oscillation. This analogy, although extremely suggestive, fails in two important aspects: (a) the limit cycle analogy does not take into account that PA and PRF obey a PRF $(PA)^2$ "constant energy law" for the case of local AD's (and presumably also for unit AD's), and (b) it also does not explain why a single pulse cannot evoke an AD.** In addition, it also does not explain such things as the "latent period." To remedy this situation, we again turn to the mathematics of nonlinear phenomena and consider a more sophisticated approach.

5.1 Physical Examples of Inertial Nonlinearities

An inertial nonlinearity is that type of nonlinearity which depends upon the average or other "cumulative" value of the dependent variable over a certain period. As we shall see, such nonlinearities have an important bearing on our problem. To familiarize the reader with this concept, we next consider physical examples.

5.1.1 GASOLINE ENGINE

The following properties of a gasoline engine are analogous to AD's: (a) there is a sort of hard limit cycle which cannot be initiated unless the motor has been externally forced to oscillate several times with a certain rapidity, (b) a single revolution is, in general, not sufficient. These properties depend partly on the fact that rotation of the engine is responsible for the supply of gasoline in the combustion chambers (available energy). Unfortunately, this analogy is complicated by the need for angular momentum in the starting process of an engine; hence, we next turn to a better analogy concerning electronic circuits.

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*See N. MINORSKY: op. cit, Ch. 25, KHARKEVICH, op. cit., uses the term "delay nonlinearity" instead of "inertial nonlinearity."

**This fact is no longer true when the subject is under the influence of chloroform or metrazol. That is, under the latter conditions, single shocks can be effective. See BONNET and BREMER: op. cit. and GREY WALTER: op. cit.

5.1.2 THERMISTOR CIRCUIT

A thermistor is a device which has a temperature-dependent resistance, and the temperature in turn depends upon the square of its average current. For current frequencies with periods much smaller than times involved in temperature changes, one can see that the average current can reach a steady value. Since such devices for certain values of average currents can have negative resistances (for example, the electric arc), they can be used to cause self-sustained oscillations.

If we imagine a case where a thermistor exhibits a negative resistance only when the average current is above a certain level, then we have a situation like the gasoline engine in that the circuit will not spontaneously oscillate until it has been externally driven for a length of time.

The behavior of systems with inertial nonlinearities is governed by a nonlinear integrodifferential equation. Generally, this type of equation is impossible to solve; hence, we are quite fortunate that the needed information can be extracted from the equation with little difficulty.

5.2 Mathematical Description of Inertial Nonlinearities

To tie the following general mathematical treatment to the above physical examples, let us begin by considering a definite illustration of inertial nonlinearity. For generality we shall consider the case where the usual and inertial nonlinearity exist side by side. Such a case is a Van der Pol oscillator circuit with a thermistor element of resistance r' as shown in Fig. 19. Letting R be the total resistance in the circuit and S be the transconductance of the tube, we have[27]

$$\ddot{x} - \mu (nS - R)\dot{x} + x = 0, \qquad (8)$$

where n is a constant and μ is small. The question now arises as to how the dependence of R upon the current x can be taken into account since it depends not only upon the instantaneous values of x but also upon some sort of average value.

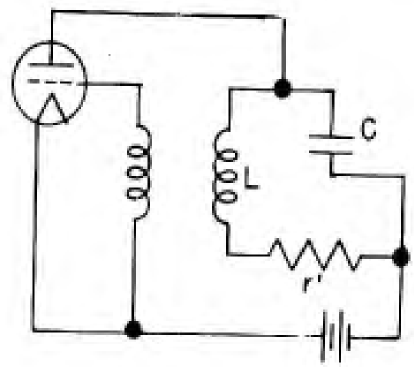

Figure 19. Van der Pol Oscillator with Thermistor in the Tuned Circuit

As pointed out by Minorsky[28], when the differential equation for the temperature of a resistance is solved, the solution has two parts: one is a constant proportional to x^2, the square of the amplitude of the current, and the other is oscillatory. In the limit where there is a long time lag between the change of x and the consequent temperature changes, the oscillatory part becomes negligible and the temperature simply is proportional to x_0^2, which in turn is proportional to the mean square value of the current. Thus, R can be taken as a function of x_0^2. Approximating R by a polynomial, we then have[29]

$$S = 1 - x^2 ,$$

$$R = R_0 + b_1 x_0^2 + b_3 x_0^6 + b_5 x_0^{10} \quad . \tag{9}$$

Letting $1 \cdot R_0 \equiv A$, we obtain

$$\ddot{x} - \mu \, [A - (x^2 + b_1 x_0^2 + b_3 x_0^6 + b_5 x_0^{10})] \, \dot{x} + x = 0 \, . \tag{10}$$

The important fact about this equation is that the NLDC depends on both the instantaneous value of x and the average of x_0^2.[30] The following treatment will hold for the more general case:

$$\ddot{x} - \mu f (x, \, x_0^2) \dot{x} + x = 0 \, , \tag{11}$$

where $\mu f (x, \, x_0^2)$ is a general NLDC with the desired properties.

The stroboscopic method (to be discussed next) makes use of the transformation to polar coordinates in phase space:

$$\rho = x^2 + \dot{x}^2, \quad \tan \psi = \frac{y}{x} \, ,$$

$$x = \sqrt{\rho} \, \cos \psi, \text{ and } y = \sqrt{\rho} \, \sin \psi, \tag{12}$$

where $y = \dot{x}$. The physical meaning of ρ and ψ is best illustrated by the case of the simple harmonic oscillator (S. H. O.) $\ddot{x} + x = 0$. Here

$$\frac{d\rho}{dt} = 0 \, , \quad \frac{d\psi}{dt} = -1 \, , \tag{13}$$

and the motion in the phase plane traces out a circle of constant radius at a constant angular speed equal to unity. Notice that the expression "ρ equals a constant" corresponds to energy conservation (when x and $\dot{x}$ are regarded as position and velocity of an oscillator).

If this transformation is performed on Eq. (11) we obtain

$$\frac{d\rho}{dt} = - \, 2\mu \, y^2 \, f = -2\mu\rho \sin \psi \, f \, (\sqrt{\rho} \, \cos \psi, \, \rho_0) \, , \tag{14}$$

where we have used the identity

$$\frac{1}{2}\ \frac{d\rho}{dt} = x\dot{x} + y\dot{y}\ . \tag{15}$$

This equation shows the connection between the rate of change of ρ and the NLDC (f). Notice that x_0^2 becomes ρ_0.

5.2.1 THE STROBOSCOPIC METHOD [31]

In the following discussion, we shall assume that the parameter μ is much less than one so that, to the zeroth-order approximation in a perturbation series, the oscillation is simple harmonic. In addition, we shall be concerned with the motion in phase space as it would appear under the illumination of a stroboscope tuned to the frequency of the approximate S.H.O. For example, if an exact S.H.O. were examined in this way, one would "see" a stationary point (ρ, ψ). Looking at the motion of a system spiralling in to an equilibrium rest point (a positively damped oscillation), one would see a continuous decrease in ρ at constant ψ (assuming no change in frequency). On the other hand, if the NLDC tended to perturb the frequency from the S.H.O. approximation value, then a stroboscopic change would be seen in ψ. Obviously, the stroboscopic motion in the phase plane would allow one to determine whether or not a system can exhibit stable limit cycle oscillations* or stable equilibrium behavior. As will be shown, when the equations of motion are transformed into stroboscopic equations of motion, the latter are often much simpler to treat than the former and indeed seem to be the only analytical way of treating inertial nonlinearities.

Let us now turn to the mathematics of the stroboscopic method. Suppose the equation of motion is given by

$$\ddot{x} + \mu f\,(x,\ \dot{x})\ \dot{x} + x = 0. \tag{16}$$

This second order differential equation can be transformed into two first order equations by defining $y \equiv \dot{x}$:

$$\dot{x} = X(x,\ y,\ t)\ \ ,\quad \dot{y} = Y\ (x,\ y,\ t)\ \ . \tag{17}$$

---

*In the case where ρ = a constant and $\frac{dx}{dt}$ = constant, one would have a stable oscillation. To perceive it as being stationary, one would merely re-adjust the frequency of the stroboscope (the mathematical method of doing this is merely to introduce a constant speed rotation transformation).

Transforming these into polar coordinates and using the identities

$$\frac{1}{2}\ \frac{d\rho}{dt} = x\dot{x} + y\dot{y} \quad \text{and} \quad x\dot{y} - y\dot{x} = \rho\,\frac{d\psi}{dt}\ , \tag{18}$$

one obtains the forms

$$\frac{d\rho}{dt} = F\,(\rho,\ \psi,\ t) \text{ and } \frac{d\psi}{dt} = G\,(\rho,\ \psi,\ t)\ . \tag{19}$$

Since μ is very small, the motion must be nearly S. H. O., and hence F and G can be assumed to have a period almost equal to 2π. From Eq. (13) we see that for a S. H. O., $F = 0$ and $G = -1$; thus, for nearly harmonic motion one has

$$\frac{d\rho}{dt} = \mu\,h\,(\rho,\ \psi,\ t) \text{ and } \frac{d\psi}{dt} = -1 + \mu\,g\,(\rho,\ \psi,\ t)\ , \tag{20}$$

where one re-obtains the S. H. O. equations when $\mu = 0$. Using perturbation expansions in powers of μ,[32]

$$\rho\,(t) = \rho_0\,(t) + \mu\,\rho_1\,(t) + \mu^2\,\rho_2\,(t) + \ldots \text{ and}$$

$$\psi\,(t) = \psi_0\,(t) + \mu\,\psi_1\,(t) + \mu^2\,\psi_2(t) + \ldots\ . \tag{21}$$

We obtain for the zeroth-order terms

$$\rho_0\,(t) = \rho_0 \quad \text{and} \quad \psi_0\,(t) = \phi_0 - t\ ; \tag{22}$$

that is, the same values as for the S. H. O. The next approximation gives

$$\rho\,(t) = \rho_0 + \mu\,\rho_1\,(t) \text{ and } \psi\,(t) = (\phi_0 - t) + \mu\,\psi_1\,(t)\ , \tag{23}$$

where

$$\rho_1\,(t) = \int_0^t h\,(\rho_0,\ \psi_0,\ t)\,dt \tag{24}$$

and

$$\psi_1\,(t) = \int_0^t g\,(\rho_0,\ \psi_0,\ t)\,dt\ . \tag{25}$$

Using these relations, we can construct our mathematical stroboscope by letting $t = 2\pi$ (that is, letting the time jump from 0 to 2π) and determining

$$\rho_1(2\pi) = K(\rho_0, \phi_0), \quad \psi_1(2\pi) = L(\rho_0, \psi_0), \tag{26}$$

where K and L are defined as ρ_1 and ψ_1 at $t = 2\pi$. Thus,

$$\rho(2\pi) = \rho_0 + \mu K(\rho_0, \phi_0) \quad ,$$

$$\psi(2\pi) = \phi_0 - 2\pi + \mu L(\rho_0, \phi_0) . \tag{27}$$

Letting

$$\rho(2\pi) - \rho_0 \equiv \Delta\rho , \quad \psi - \phi_0 + 2\pi \equiv \Delta\phi , \tag{28}$$

we can write

$$\Delta\rho = \mu K(\rho_0, \phi_0), \quad \Delta\phi = \mu L(\rho_0, \phi_0) . \tag{29}$$

Notice that $\Delta\rho$ is the change of ρ in the time 2π (that is, the time corresponding to "flashes" of the stroboscope) and that $\Delta\phi$ is a similar change of ϕ. If this is continued in an iterative manner, one can obtain the equations of motion of the "stroboscopic image." To do this we define $\Delta\tau \equiv \mu$.* This gives

$$\frac{\Delta\rho}{\Delta\tau} = K(\rho_0, \phi_0) \text{ and } \frac{\Delta\phi}{\Delta\tau} = L(\rho_0, \phi_0) , \tag{30}$$

where τ can be considered as a sort of synthetic time which describes the motion of the stroboscopic image. Now, since μ is very small, 2π is a short time compared to the duration of changes of ρ and the "phase" of ψ . We can therefore pass to the limit and obtain the stroboscopic equations

$$\frac{d\rho}{d\tau} = K(\rho, \phi) \ , \ \frac{d\phi}{dt} = L(\rho, \phi) . \tag{31}$$

The limit cycles and equilibrium points will therefore correspond to

$$\frac{d\rho}{d\tau} = K(\rho, \phi) = 0 \ \text{ and } \ \frac{d\phi}{dt} = L(\rho, \phi) = 0. \tag{32}$$

*Since the integrations for ρ_1 and ψ_1 usually have a factor 2π, one usually uses $\Delta\tau \equiv 2\pi\mu$ in practical applications.

Returning to the original equation (Eq. 16) and obtaining the stroboscopic equation for ρ, we get

$$\frac{d\rho}{d\tau} = -\rho_0 \mathcal{F}(\rho_0) \equiv \Phi(\rho_0) , \tag{33}$$

where $\mathcal{F}$ involves an integral of the NLDC over ψ (for one period) and ρ_0 corresponds to the magnitude of ρ (proportional to its average) over an entire cycle (a virtue of crucial importance for the analysis of inertial nonlinearities).

The stability of the limit cycles and equilibrium points can be determined as follows: Let Fig. 20 represent $\Phi(\rho)$ graphically. Since $\Phi(\rho) = d\rho/dt$, ρ will tend to become larger when $\Phi(\rho)$ is positive and vice versa. As can be seen by the arrows in the figure, stationary points $\bar{A}$ and $\bar{C}$ are stable whereas $\bar{B}$ is an unstable point. From the figure we therefore see that the mathematical condition for stability is given by $d\Phi(\rho) / d\rho < 0$.

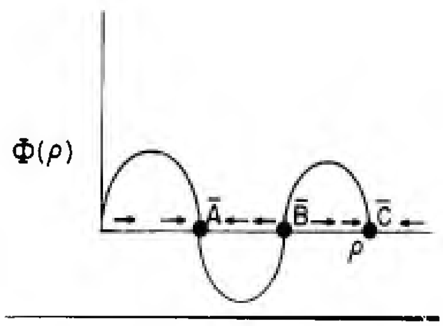

Figure 20. $\Phi(\rho)$ vs. ρ for an Oscillator with Two Stable Limit Cycles, an Unstable Limit Cycle, and an Unstable Equilibrium Point

As a simple illustrative example, let us consider the Van der Pol equation (Eq. 5) from the stroboscopic point of view. Here $f(x, \dot{x}) \equiv 1 - x^2$ and it can be shown[33] that $\Phi(\rho) = \rho(1 - \rho/4)$. It is clear from Fig. 21 that $\rho = 0$ is an unstable equilibrium point and that $\rho = 4$ is stable; hence, $x_{max} = 2$ is the amplitude of a stable limit cycle. The connection between $\Phi(\rho)$ and the NLDC (cf. Eq. 14) should be noted.

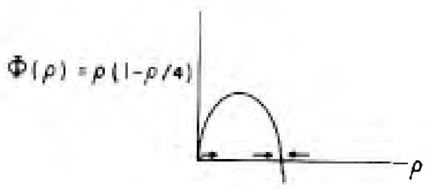

Figure 21. $\Phi(\rho)$ vs. ρ for Van der Pol Oscillator

5.2.2 MATHEMATICAL TREATMENT OF INERTIAL NONLINEARITIES

Returning to Eq. (10) and applying the stroboscopic transformation, we obtain[34]

$$\Phi(\rho_0) = \rho_0 \quad [A - (\frac{1}{4}\rho_0 + b_1\rho_0 + b_3\rho_0^3 + b_5\rho_0^5)] \quad . \tag{34}$$

There are several things to notice here: (a) there is a relationship between the NLDC and $\Phi(\rho_0)$ as pointed out above; (b) a factor $\frac{1}{4}$ results from the integration of x^2 over a cycle; and (c) $\Phi(\rho_0)$ depends solely upon the amplitude, x_0^2, and hence, the difficulty presented by the original equation is removed. Assuming A, b_1, and b_5 are positive and $b_3 < 0$, one can obtain a curve of the form shown in Fig. 19. It is clear that the tube contributes to a soft limit cycle at $\rho = \overline{A}$ and that the nonlinear resistor, if driven at sufficiently high amplitudes, will cause a sort of stable limit cycle when the average value of ρ reaches the value E. Of course, such a "limit cycle" differs from the type considered in Section 3 in that it involves averages rather than instantaneous values of the displacement in the NLDC.*

6. PHENOMENOLOGICAL EXPLANATION OF AFTERDISCHARGE INITIATION

We have seen in the previous physical examples and in the mathematical illustration, situations in which a certain type of self-sustained oscillation can be initiated only by driving the oscillator for a duration of time sufficient to cause the average value of ρ** to reach a certain value. In particular, we have considered Eq. (10) which has a soft limit cycle and a hard inertial limit cycle. The behavior of this equation is analogous to macroscopic neuronal behavior in that normal activity is spontaneous (soft) while epileptic activity can be induced by repetitive stimulation. Although this sort of behavior is analogous to that associated with AD initiation, one additional refinement is needed if Grey Walter's "constant energy" requirement is to be adequately represented in the scheme. This consists of replacing ρ in the inertial nonlinearity by $\int_{t-T}^{t} \rho(t)\, dt$ where T is a given time interval of integration relating to physical properties of neurons. Details of the quantitative connection are to be found in Sec. 6.1.

To mathematically incorporate this form of history dependence, one need only to substitute $\overline{\rho}_0$, defined by $\overline{\rho}_0 \equiv \int_{t-T}^{t} \rho(t)\, dt$, into the above formalism. Of course, ρ is essentially constant in neighborhoods sufficiently close to the point where $\Phi(\rho) = d\rho/dt = 0$; therefore, $\int_{t-T}^{t} \rho(t)\, dt$ can be replaced by $\rho_0 T$ (where ρ_0 is the value at the equilibrium point). The determination of the stationary point now consists of solving $\Phi(\rho_0 T) = 0$ instead of the previous equation $\Phi(\rho_0) = 0$. As

*This property of inertial nonlinearity (i.e., the fact that NLDC is constant over a period) gives rise to much smoother wave forms than can be obtained by means of tube circuits with time-dependent NLDC; hence, thermistor circuits are used in technology when very pure sine waves are needed. Of course, the equation for such circuits would resemble Eq. (10) without the x term in the NLDC.

**In the case of the S.H.O., ρ is essentially the energy while in the thermistor case, it is proportional to the power.

for the stability determination, this consists merely of ascertaining the sign of $d\Phi(\overline{\rho}_0 T)/d\overline{\rho}_0$ since we can again use the fact that $\overline{\rho}_0$ can be considered constant at the point of interest.

In what follows we shall employ the preceding mathematical approaches to formulate a tentative partial phenomenological scheme which explains and links together the main features of the initiation of AD at both the microscopic and cellular levels. Although this scheme may seem somewhat arbitrary when considered with respect to AD initiation alone, we shall show later that it has increasingly greater value as more of the other aspects of AD are considered. The high degree of analogy between unit and macroscopic activity makes it necessary to treat them together in the next sections.

6.1 The Constant Energy Requirement

As mentioned previously, Grey Walter has shown that a certain minimum energy is needed to start a local AD and that such an amount is relatively constant at frequencies from approximately 10 cps to 100 cps. Also, Gerin found that the "parameters of efficacy" are essentially the same for unit AD's as they are for local epileptic activity. This, of course, suggests that it is possible that the constant energy requirement also holds at the unit level and should therefore be checked experimentally.* For the sake of discussion, we shall assume this to be the case.

The constant energy requirement suggests that electrical stimulation can alter the integrated value of a parameter (proportional to energy received over a time duration, T) which can in turn alter the NLDC of the oscillation. When this parameter (ρ in Eq. 34) reaches a critical value, a stable limit cycle becomes possible. In the case of a local AD, the epileptic oscillations can be regarded as corresponding to a limit cycle which (after build-up to full amplitude) is characterized by a voltage far exceeding that of normal activity. On the other hand, in the case of microscopic epileptic activity, the amplitude is almost never greater than normal, and its characteristic is the long duration of self-sustained oscillations. Heretofore, the long duration of the AD has been essentially unexplainable.

We can now make quantitative connection with experimental data. The energy absorbed by the phenomenological oscillator is proportional to $(PA)^2$ times the number of effective pulses (PRF)(T), (where T is the time of integration in the inertial nonlinearity) times the width of each pulse, and the constant energy requirement becomes

$$(PA)^2\,(PRF)\,(T)\,(PW) = \text{CONST}\,. \tag{35}$$

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*Notice that energy constraints are usually found at both the microscopic and macroscopic levels (e.g., thermodynamics and statistical mechanics). I was reminded of this circumstance by E. P. Gross in a general discussion of phenomenological theories.

Since each PA of the stimulation is the same, Eq. (35) simply states that $\int_{t-T}^{t} \rho(t)\,dt$ equals a <u>certain</u> <u>value</u> if an AD is to be caused; that is, the term ρ is to be identified* with $(PA)^2$ and the terms (PRF), (T), and (PW) are related to the integration over time so that

$$\int_{t-T}^{t} \rho(t)\,dt = (PA)^2\,(PRF)\,(PW)\,(T)\,. \tag{36}$$

When the value of this integral reaches a certain critical point, the AD oscillation starts. In our model we assume that this critical value corresponds to a stable point of $\Phi(\rho)$ which gives rise to a hard limit cycle of the inertial nonlinearity. The value of T can be immediately obtained from Fig. 22[35] which relates $(PA)^2$, PRF, and PTD. This is done by noticing where the $(PA)^2$ value "levels off" with respect to PTD; that is, where a further increase in PTD no longer lowers $(PA)^2$. This value of PTD must be equal to T since only pulses in this range are integrated into the effective integrated energy, ρ. From the figure we see that $T \approx 7$ sec; thus in $\int_{t-T}^{t} \rho(t)\,dt$, the integration time at the inertial nonlinearity is about seven seconds.

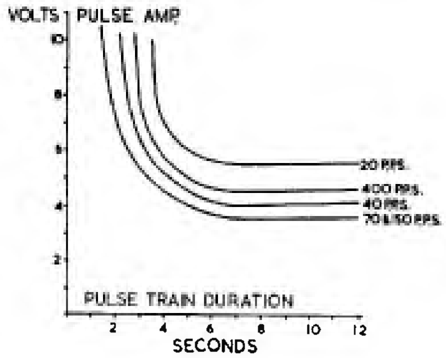

Fig. 22. Variation of Threshold with PTD; PRF as Parameter

Another important point concerns the PW. From Fig. 15 we see that an increase of PW beyond 350 μsec does not increase its effectiveness. This implies that we have an inertial nonlinearity within an inertial nonlinearity and that the PW is integrated over a time $\tau = 350\ \mu$sec. We thus have the following approximate relation between the data and the value $\int_{t-T}^{t} \rho(t)\,dt$:

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*Strictly speaking, ρ is not constant but decreases during the period of stimulation due to cortical inertia. To take this into account, one would have to take a sum $\Sigma_i (PA)^2 k_i\,(PW)$ where i goes from 1 to (PRF) (T) and where k_i is the ratio of the response (ρ) to the applied voltage (PA). However, this complication need not enter our calculations at this point since the actual numerical value of ρ is not yet needed. On the other hand, if additional inertial nonlinearities enter (for example, Eq. 34 and 35) which involve a different period of integration, call it T', then the factor k_i must definitely be taken into account since it would then have <u>qualitative</u> experimental meaning: namely, interrupted stimulation experiments would enable one to get relationships between k_i, T, and T'. In the following, however, we shall assume T = T' and this complication will therefore be at least temporarily avoided (cf. sec. 6.2).

$$\int_{t-T}^{t} \rho(t)\,dt = (\mathrm{PRF})\,(\mathrm{PA})^2\,(\mathrm{T})\,(\tau)\,(\mathrm{W}) \quad , \tag{37}$$

where the

$$\mathrm{W} = \begin{cases} \dfrac{(\mathrm{PW})}{\tau} \text{ for PW } < \tau \\ \\ 1 \text{ for PW } \geq \tau \quad . \end{cases} \tag{38}$$

W is the effective pulse duration per unit time which when multiplied by τ gives the effective pulse duration.

Considered from the point of view of our model, Fig. 15 reveals a very interesting effect of a certain anticonvulsant drug known as epanutin. Most striking about this curve is the increase of $(\mathrm{PA})^2$ needed for a given frequency, but one should also notice that τ has altered from 350 μsec. to 250 μsec., a fact which may account in large measure for the drug's effectiveness! We see that any drug which lowers T or τ (other factors held constant) generally will have anticonvulsant properties.

6.2 Cortical Inertia

Another phenomenon which occurs at both the unit and cortical levels is a stage during stimulation when the oscillation cannot be driven. This unresponsive state or "cortical inertia"* occurs on both levels immediately after a stage in which the amplitude of the driven response goes steadily down to zero. But here the similarity between the two levels ends, for in the case of the unit, the attainment of the zero amplitude stage is the sufficient condition for AD, whereas in the macroscopic case, it is necessary but <u>not</u> sufficient. Let us assume that this inertia at the macroscopic level is caused directly by inertia at the unit level. This assumption could be tested by measuring the time it takes both levels to reach the inertial stage. If this would occur earlier at the macroscopic level, then the difference in times might be explained by masking of unit activity through noise and lack of synchronization.** If experiments show both times to be equal, then the difference in the necessary and sufficient conditions might have to involve unit synchronization. In any case, the steady decline of amplitude at both levels, involving as it does a cumulative effect, would be explained by an inertial nonlinearity of some sort.

We shall now discuss the microscopic and macroscopic cases separately.

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*The use of this term in this context has, of course, no direct semantic connection with "inertial nonlinearity."

**This will be discussed in the sequel when nonlinear entrainment effects are examined.

6.2.1 MICROSCOPIC LEVEL

A mathematical model of the phenomena associated with the initiation of AD's at the unit level is complicated by the fact that the unit response to stimulation consists of bursts of repetitive relaxation oscillations*. Such oscillations correspond mathematically to the case of very large μ rather than the situation where $\mu \ll 1$. For this reason, the previous mathematical discussion is not helpful at this point, and hence, further discussion must be postponed until the topic of relaxation oscillations is treated.

The model to be described later, however, makes two predictions: (a) the necessary and sufficient condition for unit AD's is that the amplitude of the response must be driven to zero. Gerin has established the sufficiency of this condition and suggests that variation of PTD could be used to find the necessary condition, (b) the integration time, T, of the inertial nonlinearity responsible for eventual self-sustained oscillation is the same as the time T' in the mechanism causing cortical inertia. To experimentally test the latter, one would make use of interrupted stimulation. Each interval of stimulation would be arranged so that it is inadequate, yet these intervals would be spaced close enough in time to allow the occurrence of a cumulative effect. If $T = T'$, then the necessary and sufficient conditions for AD would occur for a unique response amplitude, whereas if $T \neq T'$, this amplitude could be varied by altering the length of the stimulation and rest intervals.

6.2.2 MACROSCOPIC LEVEL

As we have seen, the initiation of AD's at this level differ from the unit level in that the response to electrical stimulation involves neither spontaneity (bursts) nor relaxation oscillation. The explanation of the cortical inertia can therefore be related to previous mathematical arguments. For example, consider the following equation:

$$\left[A \int_{t-T'}^{t} g(\rho)\, dt \right] \ddot{x} + f\left(x, \int_{t-T}^{t} q\,(\rho)\, dt \right) + \left[B \int_{t-T'}^{t} g\,(\rho)\, dt \right] x = 0. \tag{39}$$

Here the "spring constant" and "mass" involve the same inertial nonlinearity so that the amplitude of the response will go down (without altering natural frequency) as the integrals become larger. Notice that, as written, T' need not equal the integrating time for the NLDC and we leave the determination of this equality, if it exists, to interrupted stimulation experiments similar to those described for the unit case. Notice, however, that since it seems likely that cortical inertia might

*Relaxation oscillations are those waveforms which contain sudden transitions. In this case, the waves consist of a series of spikes (see GERIN: op. cit.)

be a direct result of unit unresponsiveness; and since the model for the latter implies $T = T'$, we are led to expect that $T = T'$ also at the macroscopic level.

6.3 Latent Period

Another stage of initiation common to both levels of activity is the latent period between the cessation of stimulation and the onset of the AD. In this period there is very little activity at the local level and none at the unit level. As in the case of cortical inertia, it is natural to suppose that latency at the unit level is the basis for latency at the macroscopic level. Again, careful simultaneous measurements of the times involved at both levels could check this supposition. One would expect that the start of the latency stage at the macro-level would definitely commence before the unit level latency, and that generally, AD would commence at the unit level before it does at the macroscopic level.

6.3.1 MICROSCOPIC LEVEL

Let us assume that the latency effect is due to an inertial nonlinearity and that the same mechanism is responsible for an AD. One would expect then that stimulation, up to but not beyond the point where both necessary and sufficient conditions are met for initiation of AD, would be followed by zero latency time and that stimulation beyond this point would tend to increase the latency time.* Gerin's results are consistent with these expectations in the sense that if stimulation is stopped at almost the exact point of zero amplitude response, then AD follows almost immediately, whereas prolonged stimulation gives rise to sizable latency times.

6.3.2 MACROSCOPIC LEVEL

Unlike the unit level, AD does not immediately follow the latent stage at the macroscopic level. Instead, a switch in polarization results and the response waveform evolves into a period of alternation before the spontaneous discharge occurs. This period of alternation, as mentioned previously, is the necessary and sufficient condition for AD. It would indeed be interesting to see if it correlates with specific unit events. Since[36] macroscopic AD's can occur <u>during</u> prolonged stimulation, we must expect them to occur at the unit level if the above view is correct. In any case, latency at the macroscopic level is much more complicated than at the unit level. We shall see that in spite of this complication, the nonlinear oscillation point of view is enlightening.

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*This will be made clearer when the model is actually explained in detail.

6.4 Alternation

Since the alternation phenomenon at the macroscopic level does not seem to be reflected at the microscopic level, it could be related in some way to the overall interaction of the units. When such phenomena (for example, entrainment) are treated in the sequel, we shall see how a property of an entire system can manifest itself from the totality of all the nonlinear interactions. Viewed in this perspective, it is natural to suppose that alternation is a form of "demultiplication." The latter effect (to be described later) is a typical nonlinear resonance phenomenon. In other words, it is possible that the interaction of units could give rise to an over-all integrated behavior which is representable as a single nonlinear "phenomenological" oscillator and that, as such, it could exhibit demultiplication. It is noteworthy that there is a stage (as mentioned before) just preceeding this effect which begins with a very sudden switch of polarity and increasing delay of response. This switch, which does not seem to reflect unit polarity changes, might actually signal the start of the existence of the "mass oscillator" which is not yet spontaneous. If so, one would expect that, at this point, many of the units would have already started AD activity. This could be tested experimentally. It is crucial to these ideas that the over-all unit AD activity precedes the local AD.

6.5 Build-up of Afterdischarges

6.5.1 MICROSCOPIC LEVEL

The build-up of the amplitude at this level starts from zero amplitude to a maximum amplitude approximately equal to that of the normal resting activity. During this build-up, the frequency decreases from a high value to zero where the discharge ends (see Fig. 23). These characteristics will be explained later when the model is given. In any case, the duration of the AD far exceeds the stimulation time, and hence it cannot be simply explained as a re-polarization process as Gerin has attempted. As we shall see, a much more natural explanation in terms of limit cycles is possible involving "oscillation hysteresis."

6.5.2 MACROSCOPIC LEVEL

At the macroscopic level the initial build-up probably correlates in part to synchronization of unit activity. The explanation of the time evolution of macroscopic AD's - involving as they do gross changes in amplitude, frequency, and waveform - will be discussed later when Van der Pol oscillations are more fully treated. The continued spontaneity of macroscopic discharges can be explained by the fact that the abnormally large amplitude of such oscillation can cause the value of $\int_{t-T}^{t} \rho(t)\,dt$ in the NLDC to maintain itself at the stable equilibrium value, or in other words, the continued spontaneity corresponds to an inertial limit cycle. The cause of the final cessation will be deferred until later.

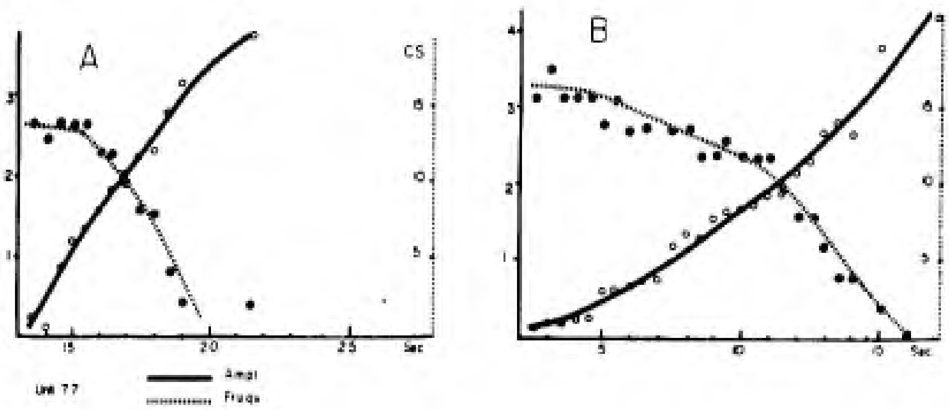

Figure 23. Evolution of Afterdischarges. A, B: evolution of spike size (black line) and frequency (dotted line) during two different afterdischarges for the same unit. Frequency (c/sec) on the right, amplitude (arbitrary units) on the left ordinate. Time in sec (from the end of the stimulation).

6.6 Discrepancies in the Constant Energy Requirement

On the macroscopic scale we have seen that outside of the 10-100 cps range, the energy required for AD is no longer constant but can be greatly increased. Assuming this is true for both levels, a question arises as to how it can be explained by the idea of inertial nonlinearity. To explain the low frequency discrepancy, we need only assume that the height of a pulse which could be absorbed within the maximum effective PW cannot be greater than a certain amount. Such a constraint is natural in view of the analogous restraints on T and τ. Mathematically, this could be done either by making the damping very great at high velocity or by making the spring constant increase very rapidly at large displacement (that is, modify the NLDC or "k" appropriately). At the high end, another such energy "leakage" could be incorporated and clearly the model could be adjusted to take such things into account. Of course, such modification could be reflected in the waveforms and response properties to other types of stimulae. Hence, such modification could, in principle, be "checked" experimentally.

Perhaps a more interesting question is why such departures exist. Grey Walter[37] points out that the low frequency limitation serves the important purpose of limiting the ability of normal activity from causing epileptic AD's. Could it be that the "window" at the high frequency end also serves a purpose? Perhaps lower voltage with high frequency signals play an important role in the normal function of brain rhythms. Such a possibility will be discussed when asynchronous quenching is treated later.

7. PHENOMENOLOGICAL EXPLANATION OF AFTERDISCHARGE SPREAD

The mechanism of initiation of epileptic discharges in normal cells by repetitive (tetanic) stimulae perhaps also accounts for initiation of such discharges by "spike foci." The latter, also known as epileptic foci, could play the role of electrical stimulator; and when surrounding cells are sufficiently stimulated, they could go into self-sustained epileptic oscillations. As we have seen, sychronization apparently can cause relatively large voltages at the macroscopic scale; and it is easy to see, following Penfield[38], how the spread could occur by means of a "chain reaction." Hyperactive domains could repetitively stimulate neighboring domain oscillators until their inertial nonlinearities are "heated up" to where they attain their hyperactive state.*

The usual direction of spread has been observed to be along synaptic pathways. Two modes of spread are possible: (a) spread to neighboring cells, and (b) spread via projection to distant structures. At this time, the factors which determine the mode of spread seem to be unknown; however, a possible factor might involve the resonant properties of the structures involved. This last possibility will be further discussed when the phenomenon of "petit mal" is treated.

8. POSSIBLE PHYSICAL PROCESSES CORRESPONDING TO NLDC PROPERTIES

In his attempt to explain unit epileptic activity, Gerin tried to analyze his findings in terms of membrane polarization. Independently, Tower[39] has experimentally investigated the differences in membrane properties of normal cells and cells taken from epileptic foci. He finds that the epileptic cells display a very strong inability to exchange ions across their membranes in an appropriate manner. As we shall see, our approach - when used to examine the phenomenon of "exhaustion" - implies that the epileptic character of focal cells depends upon a large alteration of the NLDC. The implication is that the NLDC is directly related to membrane polarization properties.

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*It is important to notice that the high voltage of macroscopic AD can be regarded in two ways: one can consider it to be (a) simply the result of a NLDC which gives rise to a high-voltage, "hard" inertial limit cycle, or (b) the result of entrainment of microscopic oscillations summing up to a high voltage. The difference in point of view is merely the difference of phenomenological level. In either case, the high voltage is the cause of the chain reaction.

It is important to note that a relationship between NLDC and membrane activity is implied in the works of both Gerin and Tower. Of course, as Tower himself points out, the observed property of cells in epileptic foci may be a result of their epileptic activity rather than the cause. However, it is rather difficult at this time to imagine a means to relate the NLDC to physical neural processes other than the activity of their membranes. We shall therefore hypothesize that at the unit level, there is a direct correspondence between them and that at the macroscopic level, this correspondence continues to exist in a form modified by the role of nonlinear mutual interaction. Such a hypothesis could be proved false if one could show that the malfunction of epileptic cell membrane is in reality not the cause of their activity but only the result of it.

Assuming the above hypothesis, the parameters would then correspond in some way to polarization, and the NLDC's functional dependence upon it would be related to membrane properties and especially to the metabolism of the cell which in turn "operates the ion transport pump."

9. CONCLUSION

In the preceding pages, we have discussed the nature and the role of phenomenological theories and certain aspects of nonlinear oscillation theory. After considering bioelectric data obtained from externally induced AD's, we considered this data from the point of view of a mathematical model involving nonlinear oscillations.

A general equation of the form

$$g(x,\dot{x},\overline{\rho})\,\ddot{x} + f\,(x,\ \dot{x}\,,\ \overline{\rho})\,\dot{x} + g\,(x,\dot{x},\overline{\rho})\,x = 0\ , \tag{40}$$

where

$$\overline{\rho} \equiv \int_{t-T}^{t} x^2\,dt\ ,$$

was proposed as one which could "explain" many of the phenomena associated with the initiation of AD's. The following table summarizes the connection between the model and the EEG observations up to this point.

TABLE I.

EEG Phenomena	Model
1. Normal spontaneity	1. Limit cycle activity
2. Excitation (constant energy requirement)	2. Hard limit cycle with inertial nonlinearity
3. Evolution of initiation of unit AD's	3. Relaxation oscillator model (to be discussed in next paper)
4. Cortical inertia and latency	4. Inertial nonlinearities limiting the amplitude of oscillation
5. Alternation	5. Entrainment and demultiplication (to be further discussed in later paper)
6. Long duration of AD	6. Self-sustained limit cycle oscillation
7. Spread	7. Tetanic stimulation of normal cells by foci, subsequent AD's with entrainment giving rise to tetanic stimulation in neighboring cells, and so on in chain fashion

1. In this report, an inertial nonlinearity was introduced into all three terms of the oscillation equation. The coefficients of the "mass" and "spring constant" terms (g in Eq. 40) were inserted to account for "cortical inertial" and "latency" in macroscopic EEG afterdischarge initiation. Further examination, however, has shown that it is not necessary to include these two "g" terms since an appropriate value of b_1 in the damping coefficient (Eq. 10) is sufficient to account for these effects. This is because an increase of x_o^2 (or ρ) causes the b_1 term to make the damping become positive for all values of x. Sufficient positive damping would account for "cortical inertia". Continued stimulation would eventually make the b_3 term become dominant and the "paroxysmal mode" of oscillation would then become effective.

The "latent" period would be "eliminated" by overstimulation (as observed by Penfield) while a stimulation which succeeded only making the NLDC slightly negative would result in a period of "latency" during which the oscillation would "build up" very slowly at first and then with increasing rapidity. The elimination of the g terms of course, implies that $T \equiv T''$.

2. Although the square of the voltage (PA) corresponds to a power, it is the <u>integral</u> of this power or the energy which determines the effectiveness of a stimulus for provoking AD's. Hence the term "energy requirement" is not a misnomer as might appear at first.

Acknowledgments

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33. MINORSKY, op. cit., p. 406-407. The interested reader would find this to be a good exercise.

34. MINORSKY, op. cit., p. 589. Incidentally, the sign on the right hand sides of his equations (3.6), (3.8), and (3.9) in his discussion should be minus instead of plus and the resulting inequalities reversed.

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AF Cambridge Research Laboratories, Bedford, Mass.
NONLINEAR OSCILLATION AND NEUROELECTRIC PHENOMENA, by E. M. Dewan, June 1963. 40 pp. incl. illus.
AFCRL-63-149 (I) Unclassified report

First of a series of papers treating normal and epileptic electroencephalographic phenomena from a new point of view. Phenomena such as (1) spontaneity of normal discharges, (2) epileptic involvement of normal neurons, (3) epileptic hypersynchrony, (4) "exhaustion," and (5) normal and epileptic excitation and suppression effects are compared to phenomena of nonlinear oscillations such as (a) "soft" limit cycle behavior, (b) "hard" limit cycle behavior, (c) nonlinear entrainment effects, (d) oscillation hysteresis and Van der Pol oscillations, and (e) asynchronous excitation and quenching effects, respectively. The present paper treats (1), (2), and (a), (b), leaving the remainder to future communications. The eventual goal is a mathematical phenomenological scheme which shows relationships between seemingly diverse neuroelectric activity and to suggest new experiments which will increase our understanding of the brain mechanisms responsible for both normal and abnormal activity.

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