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# EXPERIMENTAL EPILEPSY

BY

A. KREINDLER

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A. KREINDLER

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# PREFACE

Experimental epilepsy has been of interest to numerous neurophysiologists and neurologists. To neurologists the study of experimental epilepsy has proved to be useful for it could achieve a model of the epileptic seizure likely to provide a better understanding of some patho-physiological mechanisms of the human epileptic fit. In the neurophysiologist's hand experimental epilepsy has become an important tool for studying particular properties of the cerebral neuronal network.

In the present work the stress has been laid on neurophysiological data, but they have been grouped and discussed in a manner that we endeavoured to render as helpful as possible for the neurologist's patho-physiological interpretation of certain clinical events.

I wish to acknowledge my indebtedness to many colleagues with whom I have worked, particularly to Dr. V. Voiculescu, Dr. E. Crighel, Dr. M. Steriade, and Dr. I. Voinescu. The editorial assistance of Mrs. D. Doneaud is gratefully acknowledged.

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# CHAPTER I

# AFTER-DISCHARGES AND EPILEPTOGENIC FOCI

After-discharge is a local process representing the self-sustained repetitive discharge of a group of neurons. According to several authors a reverberant mechanism, *i.e.* the particular reactivity of some closed neuronal chains within certain neuronal circuits, forms the basis of this repetitive discharge. Isolation of a portion of the cortex does not prevent after-discharge, sometimes even favours it (Burns, 1954).

Three kinds of after-discharge can be distinguished: (1) repetitive after-discharges of certain isolated self-sustained units; (2) local after-discharges in short neuronal circuits; and (3) periodical after-discharges involving the reverberating circuits of certain long neuronal chains, connecting structures distal to one another.

The after-discharge may constitute the after-effect of a physiological sensory stimulus or the primary phenomenon that lies at the roots of long-duration discharges of epileptic type; it must be transformed by certain agents into a long-duration self-sustained discharge, the epileptic seizure proper.

## *A. Sensory after-discharges*

After-discharges may be observed when afferent impulses reach the central nervous system. In this instance, after-discharge is the phenomenon in which the efferent impulses of a group of cells outlast the afferent volley. Barron and Matthews (1938) asserted that this was due to the fact that an afferent volley, on arriving, gives rise to a long excitatory process in the region of the synapses; they believed that the negative potential in the dorsal roots is the sign of this excitatory process that takes place in the afferent spinal fibre endings. Lorente de Nó (1939), however, explains this after-discharge by the fact that these cells are forced to fire repetitively by the neighbouring cells which bombard one another with impulses after the arrival of the afferent volley. The reverberant circuit would be one of the organizing modalities of such interconnected neurons, which prolongs the effect of an afferent volley.

A potential evoked by an afferent stimulus can thus be manifested, after a long latent period of up to 100 msec, by a series of rhythmic potentials called *sensory after-discharge* (Adrian, 1941). This response may spread from the area in which the evoked potential attained the greatest amplitude, or may remain localized. The sensory after-discharge is found not only in the sensory cortex but also in the thalamic projection nucleus, representing a form of repetitive discharge in the thalamo-cortical circuits (Chang, 1950b). According to Bremer and Bonnet (1950), this repetition is

not produced by reverberant impulses in these circuits. In the non-anaesthetized animal, its amplitude may be increased by convulsant substances; it than forms the basis for self-sustained epileptic discharges induced by sensory stimulation (the so-called 'reflex epilepsy', or better described as 'epilepsy induced by sensory stimulation').

Chang (1950a) showed that the primary response of the sensory cortex to an afferent burst is followed by a train of surface-positive waves separated by regular intervals of 50–150 msec. These repetitive discharges evoked by afferent impulses differ from spontaneous waves: on the one hand, they are always surface-positive, whereas spontaneous activity does not necessarily show this characteristic, and on the other, they are not influenced by stimulation or lesion of the thalamic intralaminar nuclei (massa intermedia) as the spontaneous waves are. Hence, we have rhythmic after-discharges involving long neuronal circuits, *i.e.* a reverberant cortico-thalamic activity. Indeed, periodical after-discharge by sensory afferents depends upon the integrity of the pathway between the cortex and the corresponding thalamic nucleus.

An after-discharge is not always due to reverberation in the longer or shorter neuronal circuits. Thus, in non-anaesthetized animals or in those anaesthetized with chloralose, an after-discharge may appear following decortication, after one click, in the medial geniculate body (Galambos *et al.*, 1952).

On the other hand, stimulation of a symmetrical point on the opposite cortex, a transcallosum transmission, does not give rise to an after-discharge in the respective cortical sensory afferents, whatever the intensity of the callosum response. This would show that the appearance of a repetitive discharge in the respective sensory cortical area, mediated by a thalamic volley, depends upon the existence of a reverberant circuit and not upon the local after-discharge of an unorganized neuronal aggregate endowed with autorhythmic properties.

Chang (1959) remarks that one of the main difficulties in interpreting the periodic after-discharges according to the hypothesis of cortico-thalamic reverberations is perhaps the long interval (50 to 150 msec) between the consecutive waves, this being longer than necessary for the impulses to travel along the neuronal circuit between the thalamus and the cortex. A possible explanation is that the reverberant surface-positive waves represent, like the positive component of the primary response, synchronous discharges of the cortical neurons triggered by the recurrent thalamic volleys but not by the afferent impulses themselves. The interval between the reverberant waves probably depends on the state of excitability of the cortical neurons at the time of action, rather than on the conduction time and the number of synapses in the circuit. The activity of the cortico-thalamic reverberating circuit cannot therefore be taken as a mere circulation of impulses along a closed chain of neurons.

Bremer and Bonnet (1950), analysing the prolonged rhythmic reaction of the sensorial cortical areas, distinguish two types of non-convulsive after-discharges that succeed the primary response to a specific thalamo-cortical burst: a rapid and a slow after-discharge. Both types can be explained by the fundamental tendency towards autorhythmic activity of the central neurons.

The rapid after-discharge represents a transitory acceleration and unifying of the spontaneous activity of the receptor area, a change that immediately follows the pri-

mary response. The waves may be of higher or lower amplitude than the spontaneous waves. Their frequency, which at the beginning may attain to 60 c/s, progressively diminishes. In a sensory region, as for instance the somato-sensitive area (Adrian, 1941) or the acoustic area (Bremer, 1943), the after-discharge occurs after the rapid oscillations of the direct response to continuous pressure, or continuous tone, without any change in the frequency of the waves. The fact that the after-discharge can be recorded on the pial surface shows that these oscillations are similar in nature to standing potentials rather than to cellifuge spikes. These rapid after-discharges are enhanced by intraarterial acetylcholine injections or anticholinesterase substances, are selectively depressed by anaesthesia with barbiturates, and are more resistant to ether anaesthesia (Bremer and Bonnet, 1950). Anoxia does not depress, and may even enhance, the primary response, but markedly decreases the after-discharge.

The slow after-discharge (Adrian, 1941; Bremer and Bonnet, 1950; Chang 1950a,b, 1951) characterizes functional depression of the brain by barbiturate narcosis or by hypoxia. The waves are exclusively or predominantly surface positive; they follow the primary response after a latency of about 100 msec, and their amplitude progressively decreases like a burst of damped out oscillations. A period of facilitation, made evident by a test stimulus, coincides in the acoustic area with each wave of the sequence.

Rapid after-discharges probably originate in the thalamic nuclei, and represent a particular tendency towards autorhythmic activity, demonstrable by direct recording. The fact that the rapid after-discharge can also be produced in an isolated portion of the cortex demonstrates the contribution of cortical autogenetic activity to this phenomenon.

The slow after-discharge has been attributed to a cortico-thalamic reverberant circuit mechanism, as it is restricted to the activated sensory area and can be produced by an electric shock applied to this area (Chang, 1950a,b). The experiments of Adrian (1941), and Bremer and Bonnet (1950) do not appear to confirm this opinion, as the slow after-discharge can also be recorded from the subjacent white matter after de-

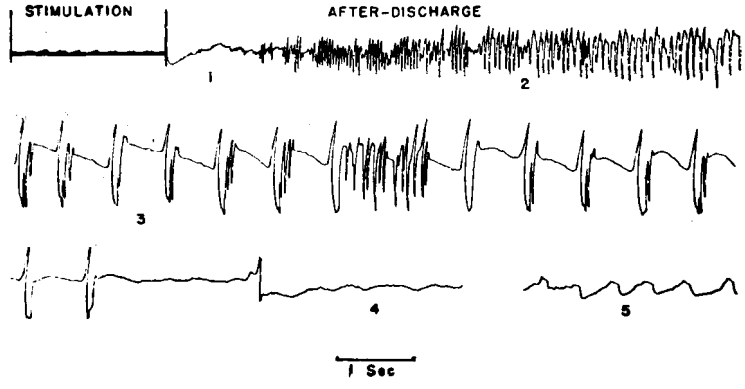



Fig. 1. Electrocorticogram showing different stages of electrical after-discharge. In stage 1 there is asynchronous firing followed by rhythmic synchronous discharge in stage 2. The clonic phase is shown in stage 3 with exhaustion or 'extinction' in stage 4. Slow waves occur during recovery in stage 5. (From Penfield and Jasper, 1954, p. 201.)

struction of the cortex, and from the thalamic relay nuclei after destruction of the reception area (Galambos *et al.*, 1952).

### *B. Electrically-induced after-discharges*

Electrical epileptic after-discharges follow focal electrical stimulation of a few seconds duration. Jasper (1955) describes five successive stages in an after-discharge of this kind: asynchronous activity, rhythmic synchronous discharge, interrupted clonic discharge, exhaustion and return to a normal rhythm. Asynchronous activity precedes the seizure proper and is manifested by a tracing that resembles the cortical activation tracing (arousal reaction). The epileptic discharge proper shows an initial 10–20 c/s high-voltage activity. During the exhaustion stage there is complete electrical silence. Electrical stimulation of several formations in the central nervous system may give rise, when sufficiently intense, to electrical after-discharges of longer or shorter duration. When the stimulus is intense, there may appear a long-duration self-sustained after-discharge that forms the basis of a focal epileptic seizure, and may even become generalized by irradiation (Fig. 1).

*(1) Neocortical after-discharges*

With reference to the genesis of electrical after-discharges, Bremer (1958) showed that in the 'cerveau isolé' non-anaesthetized cat there exists a progessive organization of the preconvulsive manifestations of the cerebral cortex to faradic stimulation. The initial stages of the surface-negative then surface-positive responses are followed by a transition stage in which the deep (positive) responses take on a convulsive character and may already be considered an epileptic after-discharge, that follows the rhythm of the stimuli (Fig. 2). Alternation phenomena reflect progressive lengthening of the subnormal post-reaction period following each response. This lengthening is explained by the repetitive character and high frequency of neuraxon discharges, which already show the functional alterations characteristic, according to Adrian and Moruzzi (1939), and Moruzzi (1950), of the convulsive state (Fig. 3). Interruption of repetitive stimulation in the stages that precede this alternation phenomenon is no longer followed by a convulsive after-discharge. On the contrary, when electrical stimulation is interrupted in this phase of evolution of the cortical potentials a seizure always ensues. Faradic epileptic after discharges, at first irregular and of relatively low voltage, become progressively organized. As the waves grow more regular in shape and frequency, their amplitude increases considerably and their focus shows a tendency to tangential displacement in the cortex. Their frequency is almost always close to that of the responses in the alternation preconvulsive stage.

After electrical stimulation Jung (1957) found different reactions to low- and high-frequency stimuli. Single stimuli or low-frequency stimulation below a repetition rate of 8 c/s produce constant inhibitory pauses with secondary activation but no epileptiform discharges. With higher frequency stimulations from 10 to 100 c/s the neurons (recordings from single neurons with microelectrodes) become able to discharge during the inhibitory pause and are apt to precipitate in every normal brain an

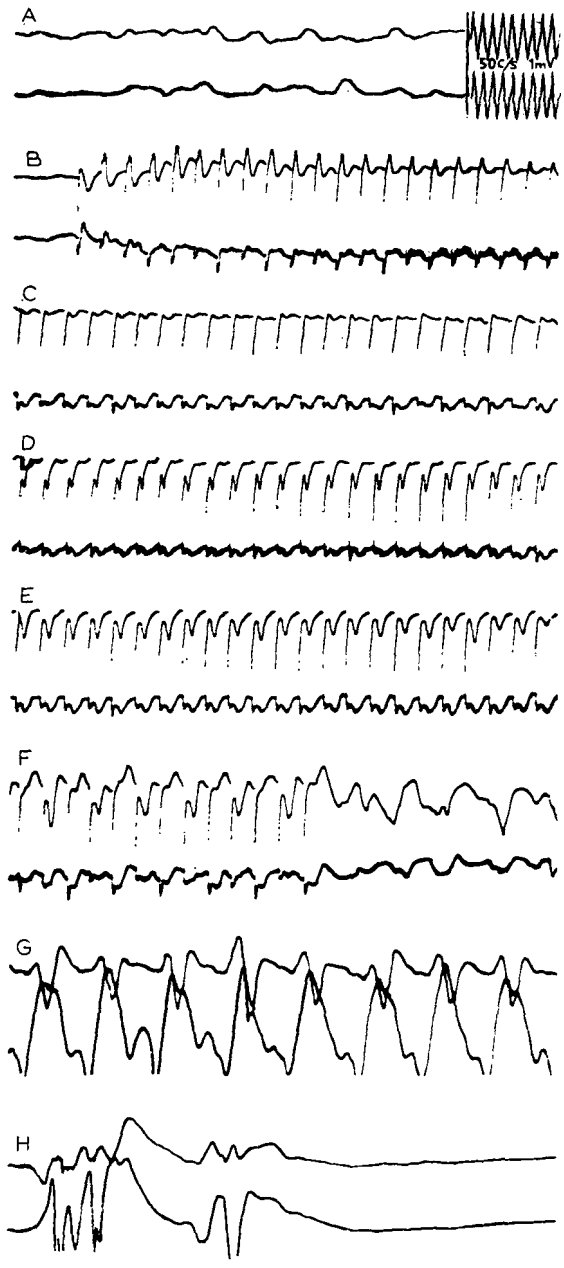



Fig. 2. Development of the electrically-induced cortical seizure. 'Encéphale isolé' cat. Stimulation of a point situated 5 mm from the point of monopolar recording in the suprasylvian gyrus. The upper trace is that of the point nearer the stimulating electrode. A = spontaneous activity before stimulation; B = beginning of the stimulation; C = cortical inertia; D = beginning of the surface-positive responses; E = two-phase responses; F = end of the stimulation which lasted 9 sec; G = full development of the seizure which lasted 30 sec; H = 35 sec later, end of the seizure and electrical silence. (From Bonnet and Bremer, 1956.)

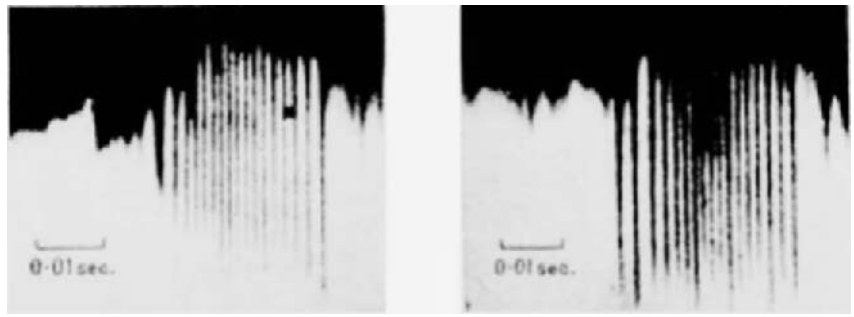


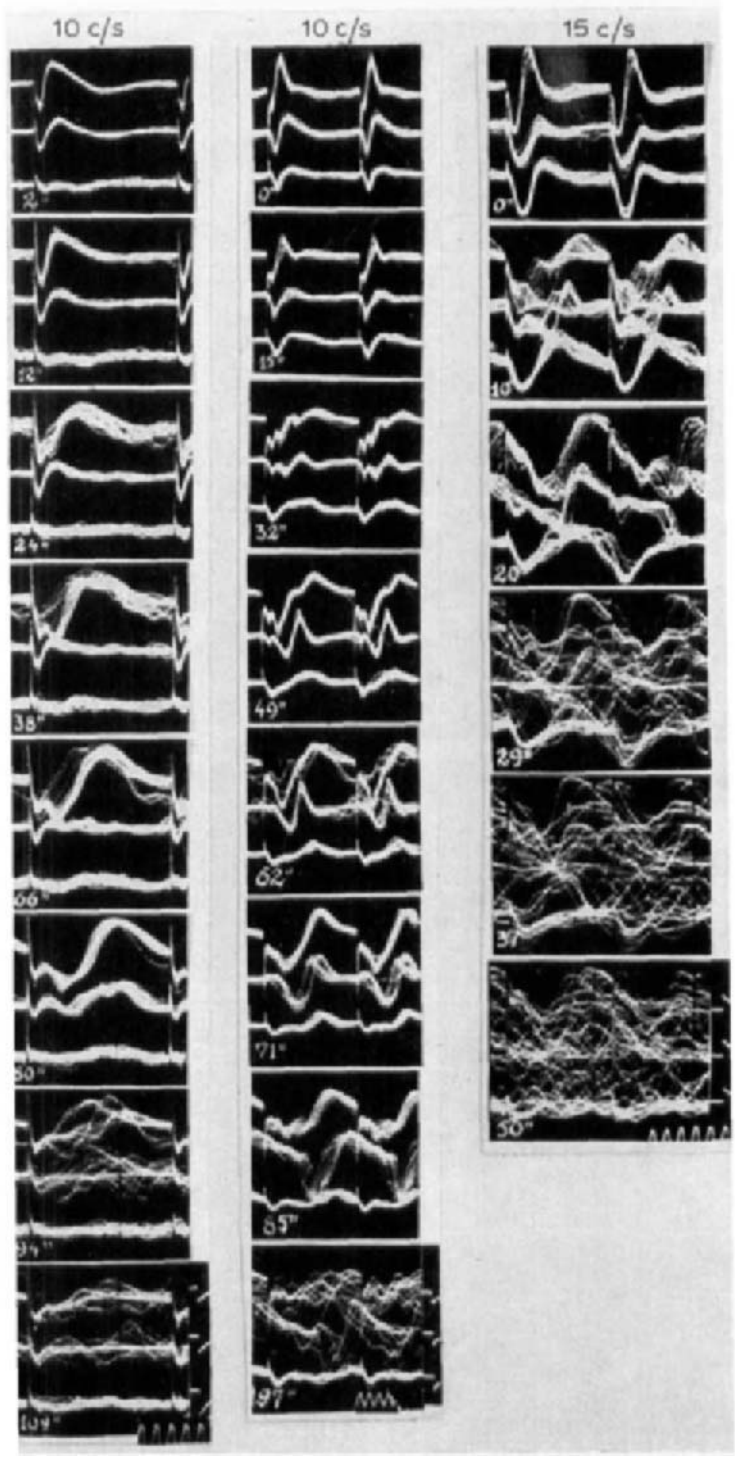

Fig. 3. Discharges of high-frequency impulses in a single unit of the pyramidal tract after application of strychnine to the motor cortical zone. There are two high-frequency discharges. Each burst is composed of impulses at 890/sec. Each corticifugal burst is accompanied by a typical strychnine spike in the corresponding motor cortical zone and a clonic jerk in the contralateral muscles. (From Adrian and Moruzzi, 1939/1940.)

epileptiform discharge. Before the convulsive stage the microrhythms show a prolongation of the primary wave, and the single neurons show repetitive discharges without prolonged pauses. The single electrical stimulus produces a short-lived summative facilitation and a more prolonged inhibition. The inhibitory mechanism fatigues with rapidly repeated stimuli, and is paralyzed by strychnine.

Kreindler, Crighel *et al.* (1962) conducted investigations into the way in which an epileptic after-discharge is organized following electric stimulation of the neocortex in the curarized cat. The cortex was stimulated at the suprasylvian gyrus level, and the responses to the direct cortical stimulus were led off at a distance of 2 mm and 4–5 mm from the stimulated point; the transcallosum-evoked potential was also recorded. The 5–50 c/s rhythmic stimulus of 0.15 msec duration was supraliminal. A long rhythmic stimulation (60–120 sec), even at the low frequency of 5–10 c/s led to disappearance of the negative phase of the direct cortical response; a second wave, at first positive monophasic, then positive–negative biphasic, appeared. This late wave was recorded in two electrodes, namely in that place closed to the stimulated point and the more distal one, and even in the transcallosum lead. Sometimes the amplitude of the negative phase increased, and the late wave was transformed into a wave of epileptic type (Fig. 4).

When the stimulus is sufficiently intense and the rhythmic frequency high enough, there appears, especially after topical application of cardiazol, a disorganization of the tracings, even during the stimulations, *i.e.* an intrastimulatory discharge. This is

Fig. 4. After-discharges induced by direct low-rate cortical stimulation. Three different experiments on three different animals. Repetitive supraliminal stimulation induces a positive–negative potential, beginning sometimes even during the positive phase of the direct cortical response having at first a latency of 30–50 msec and then a progressively longer one: in the first and second case the after-discharge appears after 94 and 97 sec of stimulation respectively, in the third case after 28 sec of stimulation. In the second case the convulsiveness is more evident at the distant point of stimulation. In each record the time of registration during stimulation is marked. Upper trace, 2 mm from the stimulated point. Middle trace, 5 mm. Bottom trace, contralaterally. Calibration, 100 $\mu$V, 10 msec. (From Crighel, 1963.)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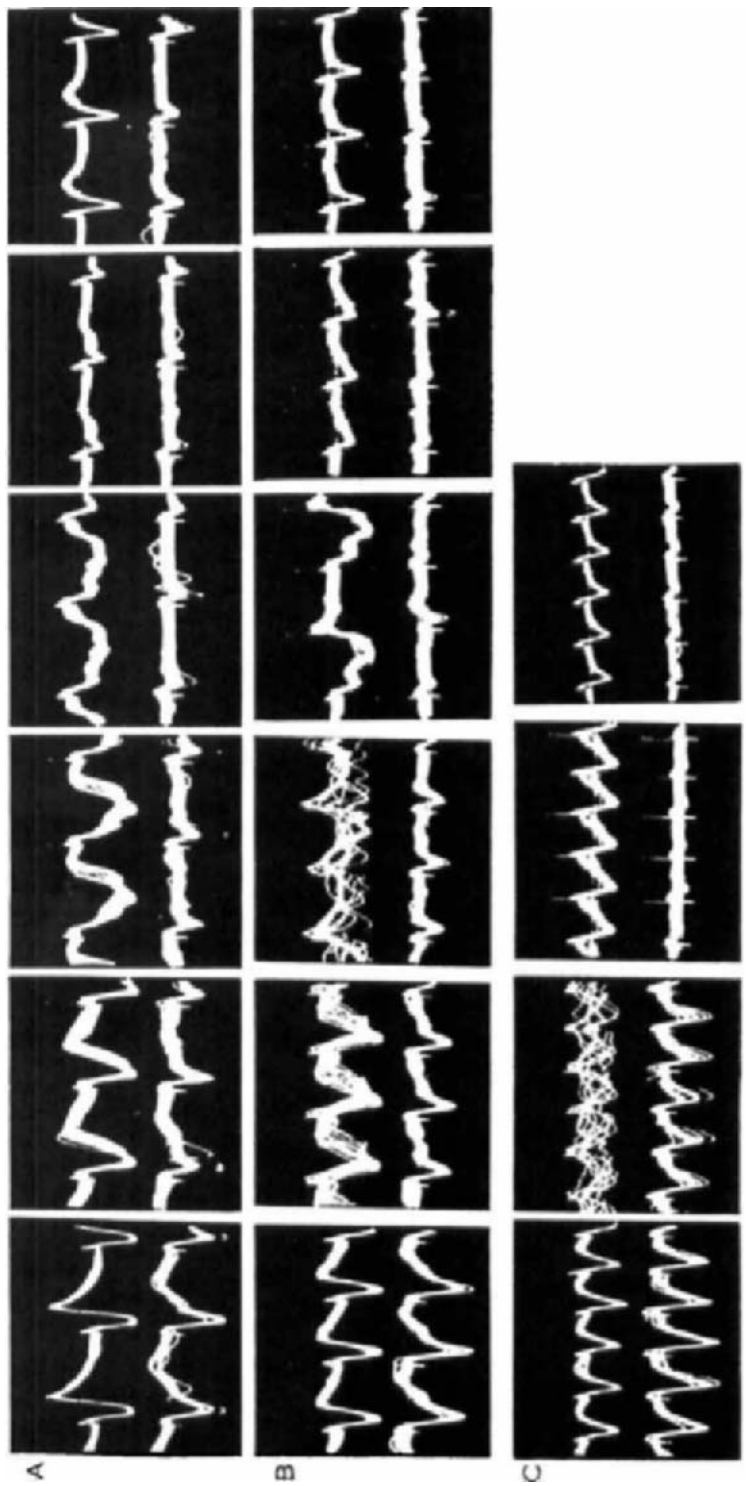


Fig. 5. Direct cortical stimulation by repetitive supraliminal stimuli induced a disorganization of the traces thus simulating an intrastimulatory discharge, disappearing if stimulation is continued. This disorganization appears only at a certain frequency of stimulation. A — stimulation at 15 c/s; B — at 20 c/s; C — at 30 c/s; D — at 50 c/s. Calibration, 500 $\mu$V, 50 msec. Upper trace, 2 mm. Bottom trace, 5 mm from the stimulating point. (From Kreindler, Crighel *et al.*, 1962.)

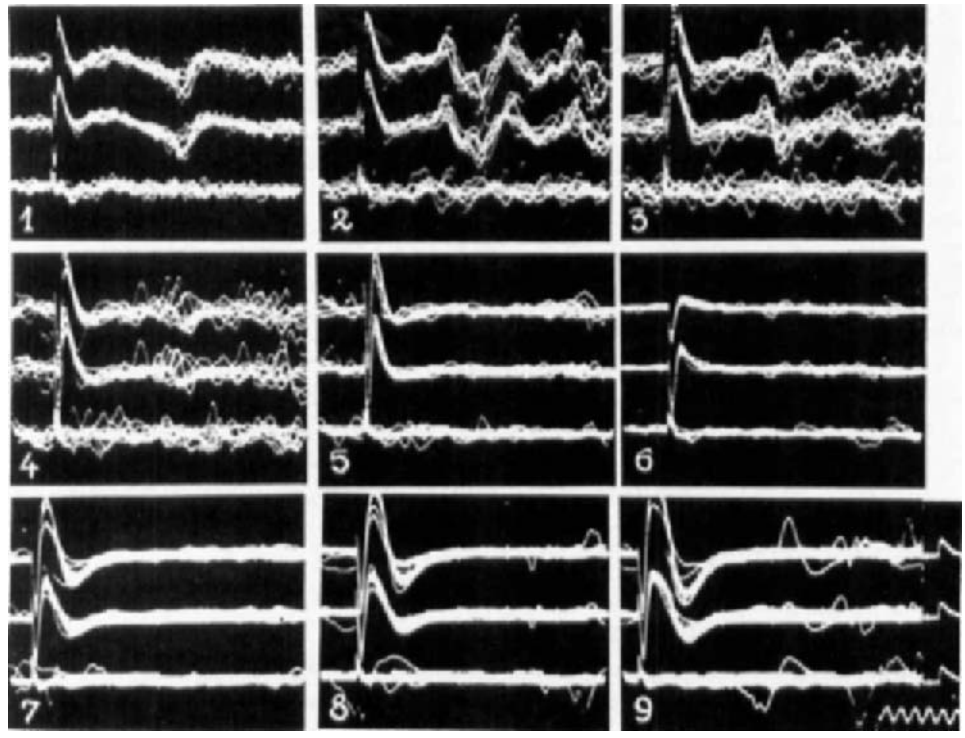


Fig. 6. Action of barbiturates and topically applied mescaline on the positive phase of the after-discharge induced by direct supraliminal cortical stimulation. 1 = control; 2 = 3 min later; 4 = 8 min later; 5 and 6 = 16 and 18 min later; 7, 8 and 9 = 17, 20 and 22 min after topical application of mescaline and 38, 41 and 43 min after pentothal injection. Upper trace, 2 mm. Middle trace 5–7 mm from the stimulating point. Bottom trace, contralaterally. (From Crighel, Stoica *et al.*, 1963.)

not an 'after-discharge' appearing during stimulation, since interruption of rhythmic stimulation is not followed by an after-discharge. When stimulation is continued, it produces reorganization of the tracings, and the direct cortical response reappears (Fig. 5).

An after-discharge is obtained when the stimuli are very intense with respect to local cortical excitability. The after-discharge appears if the secondary wave and especially the negative wave have sufficient amplitude, when disorganization occurs and is seen on the tracings or when the late wave is polyphasic.

Frequent intense rhythmic stimulation changes the functional state of the cortex, especially the local inhibitory mechanism. These changes are manifested by a disorganization, shown on the tracings, and by an after-discharge. The fact that this disorganization is preceded by a late, large wave, and especially the negative phase of this wave, points to dendritic depolarization and to intervention of the superficial structures that are progressively recruited and put into a state of disorganized hyperactivity.

Crighel, Kreindler *et al.* (1963) studied the delayed positive potential and the after-discharge induced by a supraliminal cortical stimulus. This after-discharge with a

latency of 150–200 msec is enhanced during the first period of barbiturate-induced sleep, and is depressed during deep sleep (Fig. 6). A concomitant topical application of mescaline amplifies the direct cortical response inducing epileptic spikes, but the after-discharge does not reappear. Cutting the cortex between the stimulating and the recording electrodes does not alter the after-discharge; only the sectioning of the underlying white matter leads to the disappearance of the after-discharge. Topical application of 0.1 *M* aspartic acid solution, although enhancing the appearance of the epileptic focus induced by direct cortical stimulation, depresses the after-discharge (Crighel and Manolescu, 1964), showing that there are some differences between these after-discharges and the epileptic discharge.

Analysis of the after-discharge phenomenon with the help of microelectrodes implanted at the level of the cortical neuron in the suprasylvian gyrus showed that repetitive stimulation which results in an after-discharge is accompanied by characteristic progressive changes in the spikes, activated by each electrical impulse. The units show a tendency to repetitive discharge and the amplitude of the successive spikes decreases, sometimes to the point of disappearance. During an electroencephalographic after-discharge, the spikes are generally absent at the beginning and then progressively appear, at first at high frequencies and low voltage, then at lower frequencies and higher amplitude, which gradually attains pre-stimulation values, at which moment the after-discharge comes to an end (Gerin, 1960). Changes in the spike discharges might be the expression of different depolarization levels, this phenomenon being characterized especially by excess polarization and by the long duration of the repolarization process.

Branch and Martin (1958) investigated the effects of repetitive stimulation of the thalamic nucleus ventralis lateralis and of the motor cortex on the activity of single cells in the motor cortex. Stimulation of the motor cortex at 10/sec resulted in a silent period lasting 6.3 sec after the end of the stimulation. Increasing the frequency of cortical stimulation to 15/sec instead of merely prolonging the silent period, produced an after-discharge in the Betz cells lasting approximately 6.5 sec. This was followed by a 9 sec silent period between the cell discharges. A further increase of the stimulus frequency to 20/sec resulted in a more prolonged after-discharge (9 sec) followed by a 15 sec silent period. This after-discharge could be produced either by increasing the stimulus frequency or by increasing the stimulating voltage.

Thus some cells firing in regular high-frequency bursts had at the beginning of each burst a frequency of about 1000/sec declining to about 300/sec at the end of the burst, with several gaps in discharge as frequency declined. This type of discharge was first reported by Adrian and Moruzzi (1939) after intraarterial injection or topical application to the cortex of convulsant drugs. Similar observations have been reported by Ward, Thomas *et al.* (1956a) who recorded from epileptogenic foci. Martin and Branch (1958a) are of the opinion that this may be the normal discharge pattern of a small number of cells in the cortex, perhaps arising from the absence of inhibitory connections.

Burns (1951) studied the after-discharge phenomenon on an isolated portion of the cortex. Repetitive discharges appear after a single shock applied to the isolated

cerebral cortex. Such discharges may persist for a long time, sometimes even for hours. They are evidently not the result of repetitive discharges of the directly stimulated neurons, but the responses of certain neurons stimulated by synaptic routes through neuronal circuits. Such after-discharges usually grow progressively more intense, then suddenly stop simultaneously at the moment of the acme, but may reappear after a brief interval. Chang (1959) believes that the sudden cessation or temporary arrest of after-discharges at the moment of the acme is due to the post-excitatory depression of certain neurons in the circuit which no longer respond to the impulses reaching them, so that the circuit is interrupted. Self-re-excitatory circuits exist in any part of the central nervous system where internuncial neurons exist. The main source of local after-discharges is represented especially by the neurons with a short axon and many collaterals.

Crighel and Manolescu (1964) showed that topical application of a 0.1 *M* aspartic acid solution modified the neocortical excitability. The excitability to a single cortical shock is depressed whereas that to repetitive stimuli is enhanced. Hence, the aspartic acid depresses the structures of the superficial layers which have an inhibitory function. This inhibition of an inhibitory mechanism results in a chaotic firing of the deep structures and thus in the organization of an epileptic focus.

The large pyramidal neurons whose axons have been stimulated may be re-stimulated synaptically by means of their own collaterals, which achieve a kind of feedback mechanism. Prolonged epileptiform after-discharges that follow internal stimulation of the cerebral cortex, as well as the seizures in pathological cases, may be induced, at least to a certain extent, by a feedback mechanism via the collaterals in the nearby neuronal chains.

The cerebral cortex exhibits regional variability in the threshold of after-discharges induced by direct stimulation. The most highly epileptogenic cortical area is the motor area and the middle part of the suprasylvian gyrus. The regions around the coronary gyrus and lateral gyrus are less epileptogenic, and the frontal and occipital lobes have an exceptionally high threshold (Green and Naquet, 1957).

It has been shown that there is in the monkey a definite pattern of distribution of the excitability of the cortex to convulsions induced by direct cortical stimulation (French *et al.*, 1956). The precentral 'motor' areas have the lowest threshold, and the occipital cortex the highest for seizure induction, with the frontal lobe, anterior temporal pole and parietal cortex occupying an intermediate position in the gradient of excitability. Eidelberg *et al.* (1959) studied the local cortical potentials evoked in different areas of the monkey brain. These potentials appeared as predominantly surface-negative waves: consistent patterns in the appearance and amplitude of the responses were exhibited by each area studied. Maximal voltages characterized the 'motor area', while minimal deflections were found in the prefrontal and occipital cortex, and intermediate values were present in other areas. Correlation was found between the excitability of cortical loci to single-shock stimuli as manifested by local cortical responses and to high-frequency stimulation as indicated by seizure after-discharges. When enhanced epileptogenesis was induced in a locus of the motor region by chronically circumsecting an area of cortex in a mirror site on the opposite

hemisphere, increased response to single shocks was observed in the remote cortical locus. This epileptogenic effect was not due to tonic influences from the circumsected area, since its excision or procainization or callosal section did not alter the augmented response.

It is a common clinical observation that epileptogenic lesions may elicit focal discharges at the onset, but as time passes the epileptic process tends to become more generalized. The experiments reported by Eidelberg *et al.* (1959) suggest that such spread of seizure activity is the result of enhanced excitability induced in cell masses remote from the discharging focus but connected with it by intimate association pathways.

*(2) Allocortical after-discharges*

After-discharge to electrical stimulation of the amygdala, according to Andy and Mukawa (1960) displays the following features: a dominant 4–6 c/s rhythm, duration shorter than 20 sec and amplitude of 300–1500 $\mu$V. After-discharge from the lateral amygdala was on the average 10.1 sec, from the basal amygdala 14.1 sec and from the anterior amygdala 9.2 sec. After-discharge from the mediocortical group showed a tendency to persist longer than that from the other nuclear groups.

Kreindler and Steriade (1963b) studied in detail the characteristics of after-discharges from different amygdaloid nuclei. The best frequency for inducing an after-discharge for liminal intensities is 50–100/sec, the amplitude and duration of the after-discharge diminishing with increase in frequency. The critical frequency differs from one amygdaloid nucleus to another, exceeding the epileptogenic threshold. The critical frequency is 30–35/sec in the central lateral amygdaloid nucleus (A.c.l.) and can be as low as 20/sec in the basal parvocellular amygdaloid nucleus (A.b.p.).

Stimulation of the A.b.p. may induce both intrastimulatory discharges and after-discharges; diminution of the frequency to 20/sec reduces intrastimulatory discharge, but does not reduce the after-discharge. On the other hand, the A.b.p. has a lower epileptogenic threshold than the A.c.l.

The dorsal and ventral aspects of the baso-lateral amygdaloid complex have different properties as to their capacity for organization of epileptic waves. Rapid repetitive stimulation of the A.c.l. produces an arousal response in the neocortical formations. During this desynchronization no discharges of epileptic type occur, only an after-discharge when stimulation has ceased. Seldom, when the stimulation lasts more than 5 sec, does an intrastimulatory discharge appear, preceding the after-discharge. In contrast to this behaviour of the A.c.l., stimulation of the A.b.p. with the same parameters produces an intrastimulatory discharge 1 sec after its onset, having the same amplitude as the post-stimulatory discharge, but a higher frequency (Fig. 7).

A similar differentiation exists between the anterior and the lateral amygdaloid nuclei. Stimulation of the dorsal segments of these nuclei produces desynchronization effects and after-discharges, but no intrastimulatory discharges, whereas stimulation of their ventral segments induces both intrastimulatory discharges and after-discharges.

The waves of the intrastimulatory discharges have a highly regular morphology in the hippocampus and a less regular one in the A.c.l. following stimulation of the A.b.p. After interruption of the stimulation, the frequency of these waves gradually decreases to 3–4/sec.

The desynchronizing role for paroxysmal activity generated by electrical stimulation of the A.c.l. and of the dorsal levels of the anterior and lateral amygdaloid nuclei results from repetitive stimulation not being able to induce paroxysmal potentials. Thus, with a 5-sec stimulus the after-discharge follows immediately upon stopping the stimulation; but if the duration of the latter is prolonged beyond 5 sec the after-discharge only appears at the end of the entire stimulation period and not after the first 5 sec. In this event, when the duration of the stimulation is prolonged, the seizure no longer remains focal, restricted to the amygdaloid-hippocampal circuits, but increases in duration and spreads towards neocortical areas. A stimulus longer than 5 sec does not suppress intrastimulatory discharges, but only causes them to appear at the 7th–8th sec of stimulation.

In some experiments with a low epileptogenic threshold in which the spikes induced by stimulation of the A.c.l. were small and spaced, it was demonstrated that stimulation of the A.c.l. at increasing intensities suppresses these spikes. Their appearance during stimulation and disappearance under the action of stimuli of increasing intensities was made evident on the posterior suprasylvian gyrus and lateral gyrus (Fig. 8). Disappearance of these spike discharges does not imply exhaustion of the respective neuronal populations: on the one hand the after-discharge following a 4 mA stimulation is greater than that obtained by low intensity stimulations; and on the other, return to weaker stimuli (0.2 mA) shows that it is again possible to obtain intrastimulatory discharges.

Stimulation of the A.c.l. at high intensities exerts an effect not only on intrastimulatory discharges at neocortical level, but also on the after-discharges produced by stimulation at this level. Thus, with low intensities (0.75 mA) intrastimulatory spikes appear in the lateral gyrus and suprasylvian gyrus, and an after-discharge in the coronary gyrus. With higher intensities the intrastimulatory spikes disappear and the after-discharge appears much later on the coronary gyrus, 5–6 sec after stopping the stimulation, while at the same time the epileptic seizure becomes prolonged and generalized (Fig. 9).

The more accentuated epileptogenic property of the A.b.p. as compared with that of the A.c.l., and the capacity of the ventral zones of the amygdaloid complex to organize an epileptic paroxysm from the very first second of electrical stimulation, may be attributed to the action of these formations on spontaneous cerebral rhythms. Thus, Kreindler and Steriade (1964) pointed out the synchronizing influence of the A.b.p. and of the ventral zones of the amygdaloid complex on the EEG, which is in agreement with the well-known facilitating effect of hypersynchronous states (for instance sleep) on the epileptic paroxysm. The facilitating effect of rapid repetitive stimulation (synchronization) of the A.b.p. on organization of intrastimulatory discharges can be inferred from the differences between intrastimulatory discharges and the after-discharge. The frequency of intrastimulatory discharges is always signifi-

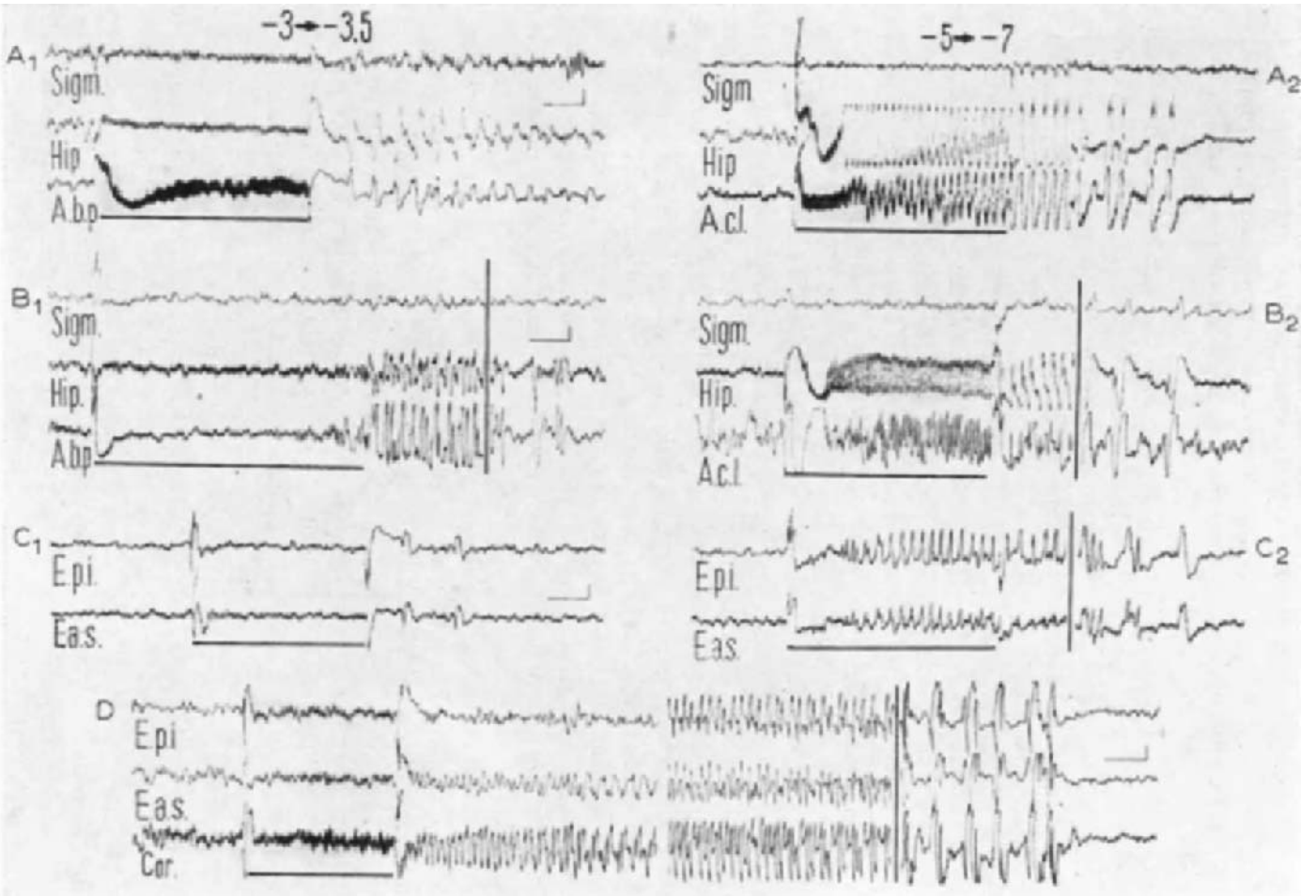


Fig. 7. For legend see p. 15.

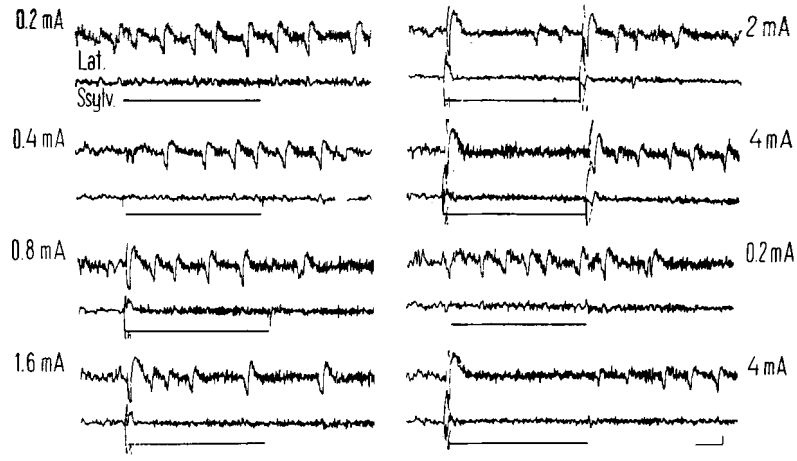


Fig. 8. Occlusive effects on intrastimulatory discharges (by stimulation of A.c.l.) shown by the increase in stimulation intensity. Stimulations reproduced according to their sequence during the experiment; the order is from top to bottom, first left then right. Note the progressive decrease in amplitude and frequency up to complete disappearance of spikes during stimulation, concomitantly with gradual increase in stimulation intensity. Lat. = g. lateralis (marginalis); Ssylv. = g. suprasylvius. (From Kreindler and Steriade, 1963b.)

cantly higher than that of the after-discharge, which suggests by its monomorphous aspect a 'tonic seizure', whereas the after-discharge takes on the 'clonic' aspect of an intermittent pulse. It is likely that a critical level of stimulation is necessary for an intrastimulatory discharge to appear. This is true only for low frequencies of 20–30/sec. When liminal intensities are attained at high frequencies (50–200 c/s) in order to obtain an intrastimulatory discharge, then the after-discharge can only be produced when supraliminal stimuli are used.

*(3) Thalamic after-discharges*

Local electrical stimulation of certain specific thalamic nuclei produces discharges in numerous cortical, sensory–motor, temporoparietal and occipital areas that begin by a simple evoked potential and then pass into a self-sustained after-discharge.

Rhythmic electrical stimulation, at 3 c/s, of the intralaminar thalamic nuclei close to the massa intermedia, induces in the cat a bilateral synchronous rhythm of the spike-

Fig. 7. Organization of intra- and poststimulatory discharges elicited by high-rate (50–200/sec) stimulation of various amygdaloid levels. A, B, C and D = 4 different experiments. A, B and C = stimulation with the same parameters of dorsal (left of figure) and ventral (right of figure) amygdaloid nuclei. In $A_1$–$A_2$ stimulation at 50/sec; in $B_1$–$B_2$ and $C_1$–$C_2$ stimulation at 200/sec; in D, 100/sec. Note that epileptic discharges induced by stimulating the dorsal amygdaloid levels (D –3 to –3.5; $A_1$, $B_1$, $C_1$ and D) only appear after cessation of stimulation, and by stimulating the ventral levels with the same parameters (D –5 to –7; $A_2$, $B_2$ and $C_2$) discharges are obtained from the first seconds of stimulation. Sigm. = g. sigmoideus; Cor. = g. coronaris; E.a.s. = g. ectosylvius antero-superior; E.p.i. = g. ectosylvius postero-inferior; Hip. = hippocampus; A.c.l. = nucleus amygdalae centralis lateralis; A.b.p. = nucleus amygdalae basalis parvo-cellularis. Vertical bars indicate 5 sec intervals. (From Kreindler and Steriade, 1963b.)

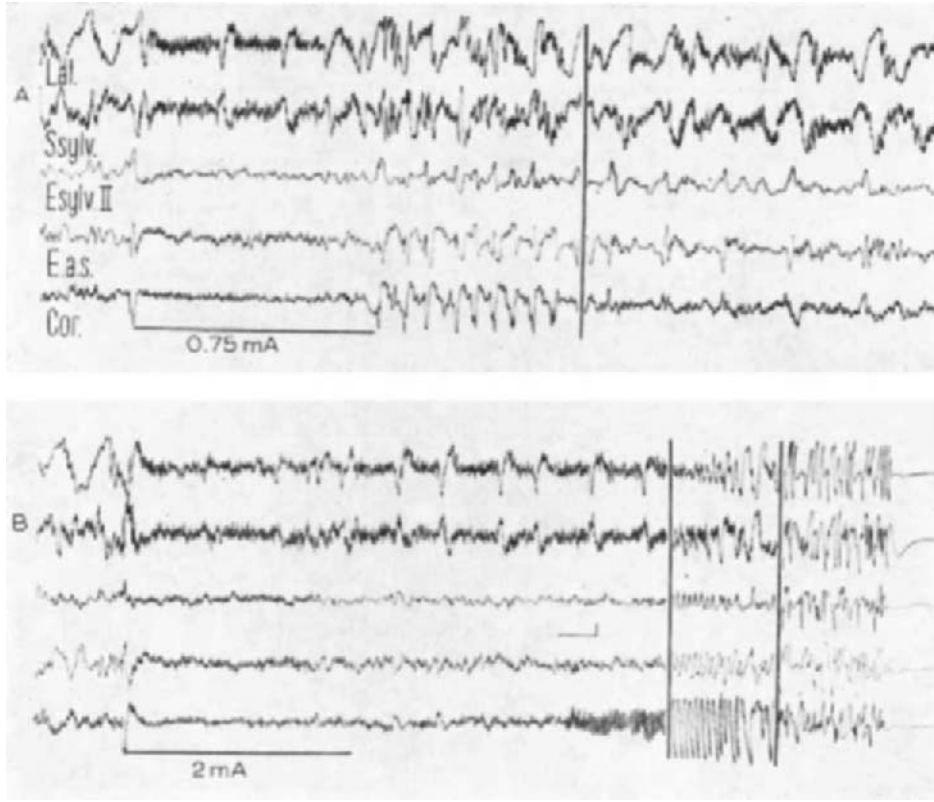


Fig. 9. Occlusive after-effect of A.c.l. stimulation. A and B, the same experiment. The increase in stimulation intensity (from 0.75 mA in A to 2 mA in B) results not only in suppression of intra-stimulatory spikes but also in an occlusive after-effect noticeable especially in gyrus coronaris. (From Kreindler and Steriade, 1963b.)

wave type, as observed in petit-mal seizures in man (Jasper and Droogleever Fortuyn, 1947).

Implantation of chronic electrodes in the median portion of the thalamus in the cat or monkey made it possible at the same time to follow the behaviour of the animals and the electroencephalographic aspect during stimulation. Low frequency stimulation (2–3 c/s) produces clonic spasms of the face and eyelids analogous to those observed in petit-mal seizures in man. Stimulation at frequencies of 10–20 c/s is followed by cessation of all movements, staring, and the absence of any response to stimuli that persists like an after-discharge for 30 sec after stimulation is over. Application of higher frequencies and intensities induces a generalized seizure with 8–15 c/s rhythmic bilateral discharges.

*(4) Brain stem seizures*

The problem as to whether or not a convulsion can be generated by the stimulation of some structures in the brain stem has for a long time puzzled many workers. The existence of such a seizure has alternately been claimed by some and denied by others,

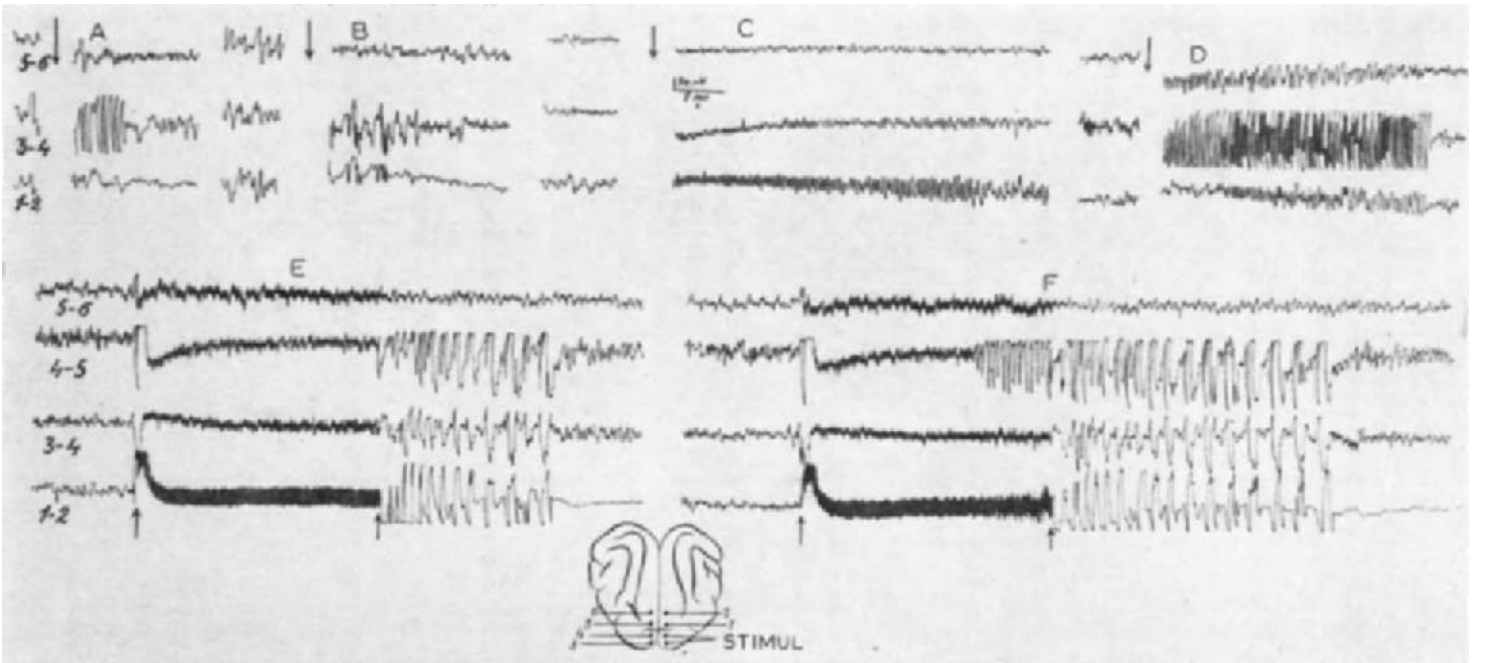


Fig. 10. Self-sustained convulsive attack in cat by stimulation of mesencephalic lateral reticular substance; e.m.g. = electromyogram; Retic. = reticular substance; sigm. = sigmoid gyrus; marg. = marginal gyrus; R. = right; L. = left. Tracings 1–2 = electromyogram of extensor and flexor muscles of right forelimb. Tracing 3 = activity of stimulating point in the mesencephalon. Tracings 4–7 = cortical activity. A = recordings prior to stimulation; B = recordings subsequent to stimulation. (From Kreindler, Zuckermann *et al.*, 1958.)

but investigations in this field were carried out many decades ago and have not been resumed.

Experiments performed by Kreindler, Zuckermann *et al.* (1958c) showed that in both rats and cats a convulsive fit of a typical pattern was regularly induced when special points in the brain stem were stimulated. The electromyogram illustrates an enormous muscular activation of a tonic type in both the extensor muscles and the flexor muscles, but prevailing in the latter. The electrocorticogram recorded during the seizure discloses not a single one of the characteristic alterations of the cortical convulsive attack. The most characteristic phenomenon (90% of all cases) is a desynchronization which more often than not shows the typical 'arousal reaction' pattern. Sometimes, in addition to an increase in frequency of the potentials, there is also an increase in amplitude. The duration of desynchronization is much longer than that of the convulsive attack and even longer than that of hypertonia revealed electromyographically. Sometimes, after cessation of the motor manifestations, rare slow waves appear, superimposed on the desynchronized activity seen in the electrocorticogram (Fig. 10).

The bioelectrical activity of the active point in the brain stem to which the releasing stimulus was applied as well as the activity in other brain stem points (reticular substance, descending tracts) does not disclose hypersynchronous activity of the convulsive type. An 'activation' of bioelectrical activity usually occurs with increased frequency and amplitude; at other times the activity is flattened. Only rarely (more often in the rat than the cat) do slow waves of small amplitude appear.

From the above observations the following conclusions may be drawn.

(a) The seizure induced by stimulation of the brain stem is a genuine subcortical seizure, *i.e.* it is a seizure which comes about relatively independently of the cortical neurons. From what is known to date, this type of seizure and the cerebellar variety described by Clark and Ward (1949) represent the only true forms of subcortical epilepsy. Seizures obtained by diencephalic excitation are really cortical seizures. This bulbopontine seizure definitely differs from the cortical seizure in that it has a very marked tonic component. The clonic component of bulbopontine seizures differs from the clonic movements of cortical attacks by its greater amplitude and greater irregularity as compared with that of the cortical seizures; moreover following these irregular clonic movements very fine and more frequent clonic movements than the cortical ones are apt to appear.

(b) In the reticular substance of the brain stem there are neuronal structures which permit the development of a convulsive self-sustained attack. Seemingly the action of a powerful stimulation gives rise to neuronal reverberation and potentiation which preserve and intensify the excitation for a certain length of time. Owing to the fact that decerebration neither prevents the onset of the seizure nor alters its appearance, it is evident that neural circuits rostral to the mesencephalon are not significantly involved in neuromuscular manifestations (Fig. 11).

(c) The electrical activity of the nervous structures involved in the brain stem seizure does not manifest itself as paroxysmal hypersynchronism as in cortical seizures, but rather resembles what has been described as desynchronization. This particular

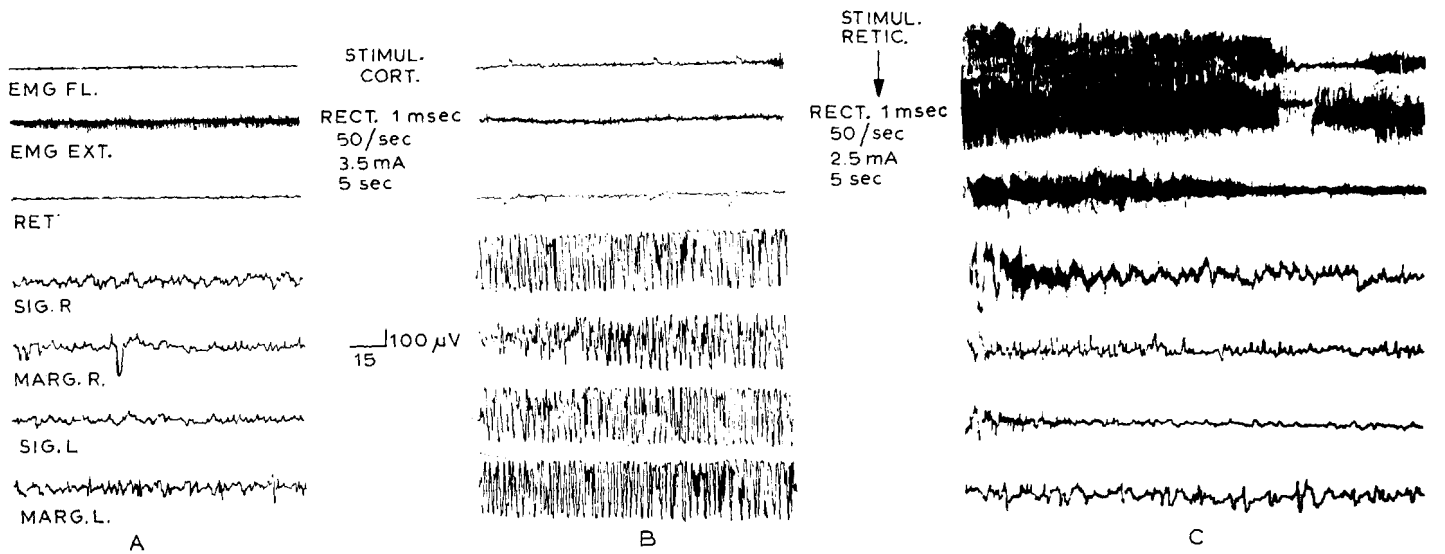


Fig. 11. Convulsive seizure induced by stimulation of reticular formation in cat decerebrated by precollicular section. Abbreviations as in Fig. 10. A = recordings prior to stimulation; B = recordings following cortical stimulation; C = recordings following reticular stimulation. (From Kreindler, Zuckermann *et al.*, 1958.)

aspect may depend on certain peculiarities of the reticular chains, which also determine the special clinical pattern of the seizure, *i.e.* the concomitant and sudden involvement of the entire musculature, the great violence of the tonic component, and the relatively short duration of the seizure.

(d) In regard to the main problem with which we are concerned, *i.e.* the functional properties of the convulsive circuits, the foregoing data are particularly pertinent in two aspects: first, they permit the delimitation to some extent of circuits involved, respectively, in cortical and brain stem seizures; second, the quite distinctive electro-clinical features of the brain stem seizure allow us to assume that the functional characteristics of reticular circuits have peculiarities which make them differ very much from cortical circuits.

Bergmann *et al.* (1963) confirmed, in the rabbit, the investigations of Kreindler, Zuckermann *et al.* (1958c) on the possibility of inducing a convulsive seizure by stimulation of the brain stem. They were able to circumscribe, in the mesencephalic reticular fomation, a low threshold convulsive area, visibly distinct from the neighbouring nystagmogenic area. Stimulation of this zone induces tonic–clonic convulsions accompanied by abolition of the pupillary and corneal reflexes. This seizure of the brain stem is accompanied by cortical desynchronization, while synchronization may appear in the hippocampus and sometimes in the reticular formation. Low doses of chlorpromazine reduce the convulsant threshold, probably by blocking communication between the caudate nucleus and this low convulsant threshold zone in the brain stem.

The tonic extensor phenomena in strychnine convulsions have been shown to be due to discharges located in the brain stem in the medullary mesencephalic divisions. Strychnine tetanus does not invade structures above the midbrain. In the convulsive phenomena the cortical activity is shown by desynchronization rather than by epileptic discharge. The episthotonic phenomenon following strychnine injection, therefore, must be considered to be due to discharges in the brain stem below the level of the diencephalon.

The anoxic syncope is never associated with an epileptic discharge. There is a flattening of the cortical electrical activity during the anoxic spasm or tonic spasm, a desynchronization and not a hypersynchronism. In the bulbar RF, activity appears to be normal.

Metrazol, on the other hand, causes a very high voltage discharge in the thalamus, and particularly in the cortex, without affecting the bulbar RF. Gastaut (1958b) suggests that the gross telencephalic discharges induced by metrazol might be likened to a massive sleep state of the telencephalon, liberating the tonic discharge of the bulbar RF causing the tonic manifestations of the seizure. The discharges of telencephalic origin, when they do reach the bulbar RF, inhibit the rapid discharge and cuase an arrest of the tonic phase of the seizure, interrupting it and causing clonic manifestations. The role of the cortex in the dissociation of the tonic attack was also emphasized by Kreindler (1955) who showed the cortex to be concerned in the arrest of the epileptic attack.

*(5) Intrastimulatory and poststimulatory discharges*

*(a) Neocortical stimulation.* Intrastimulatory discharges and poststimulatory discharges are two different effects. In general, no discharge is observed during stimulation, probably because stimulation sets in motion both suppressor and facilitatory circuits. In general, the suppressor circuits predominate and are more effective, suppressing the effects of stimulation.

Kreindler, Crighel *et al.* (1963) and Crighel, Kreindler *et al.* (1963) showed that during the neocortical stimulation with low rate supraliminal repetitive stimuli, there is a disorganization of the electrical activity simulating an intrastimulatory discharge, suggesting a suppression of an inhibitory mechanism of the epileptic activity. Immediately after stimulation, a rebound of the facilitatory circuits and exhaustion of the suppressor circuits occur, and an after-discharge appears. When an intrastimulatory discharge is produced, then the facilitatory circuits are more effective or the suppressor ones more readily exhausted (Fig. 12).

During repetitive cortical stimulation (Bonnet and Bremer, 1956) there is a first phase of suppression of the responses, followed by a phase of surface positive responses to each stimulus, and then a phase in which each stimulus produces a diphasic response, following which comes the true after-discharge. Other new units are progressively involved during repetitive stimulation. Bonnet and Bremer (1956) further remark that the after-discharge may sometimes arise in the course of repetitive stimulation.

Repetitive stimulation sets in action a 'deep' response (Adrian, 1936), that is, it leads to activation of the cellular bodies and basal dendrites of the pyramidal cells, directly or mediated by the short axon cells of the 3rd and 4th layers. Responsive depolarization now occurs at this level. At this moment, the superficial protoplasmic units, the apical dendrites, no longer respond, as the phase of suppression of the responses to repetitive stimuli intervenes. It is likely that at this moment the apical dendrites are comprised in a suppressor circuit formed by afferent axo dendrites and the short-axon internuncial neuronal network of the superficial layers of the cortex. This may perhaps prove that the superficial dendritic system, the axo dendritic system and the internuncial neurons of the superficial layers differ in their functional characteristics from the deep axo-somatic system with its internuncial neurons.

Another finding in favour of the hypothesis that suppression of the intrastimulatory discharge is due to stimulation of other circuits, is that presented by Burns (1954): he was able to show that, during repetitive stimulation of an isolated portion of the cortex, prolonged depolarization of the deep layers of the cortex does not occur, but appears immediately after interruption of the repetitive electrical stimulation, as if it had been masked during stimulation by a potential of opposite sign.

During repetitive stimulation of the motor zone in the rat, motor discharges of convulsive type can be observed, *i.e.* convulsions of the four legs that cease with cessation of the cortical stimulus and are not followed by an after-discharge, a self-sustained motor discharge that persists after interruption of the stimulus (convulsions of the limbs that persist after the stimulus is interrupted) (Kreindler and Zuckermann, 1956).

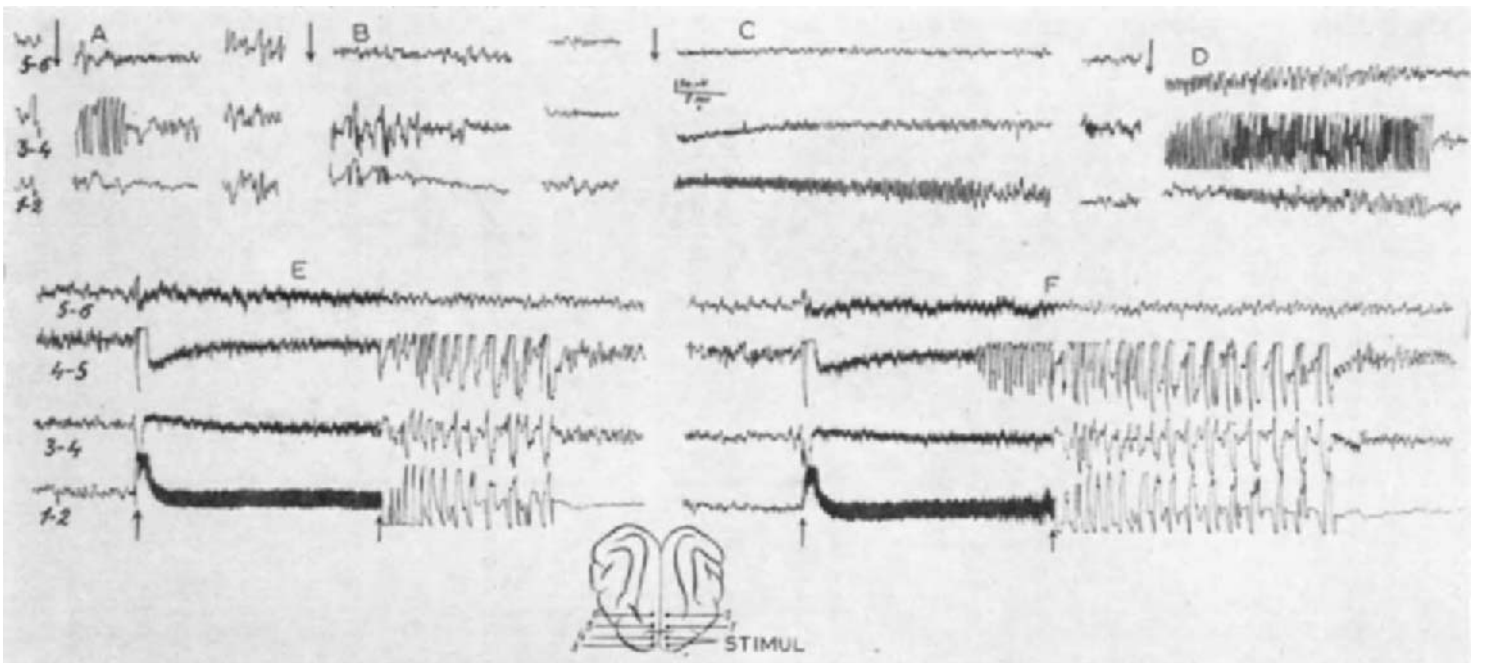


Fig. 12. Different patterns of after-discharges induced in the unanaesthetized cat by focal stimulation of gyrus sigmoideus. A, B, C and D = four different experiments. Note the spread of the after-discharge to the point contralateral to the stimulated zone. E = poststimulatory after-discharge with a liminal intensity; F = intrastimulatory after-discharges with a supraliminal stimulation. (From Kreindler and Steriade, 1960b.)

This intrastimulatory motor discharge only appears with certain stimulation parameters, especially when the duration of the stimulation is long. Intrastimulatory discharge is followed by a postparoxysmal period of inhibition much longer than that following a self-sustained convulsive seizure of equal poststimulatory duration. Intrastimulatory motor discharges may last 5–15 sec and the seizure ceases if stimulation is prolonged beyond this interval.

*(b) Allocortical stimulation.* Transition from intrastimulatory discharges to after-discharges is, we believe, an important aspect in the organization of epileptic activity. Kreindler and Steriade (1963b) followed up this phenomenon with respect to stimulation of the amygdalo–hippocampus complex. The appearance of a discharge only after the stimulation is interrupted seems to be due, in cases of stimulation of the amygdala and especially of the A.c.l., to a suppressor action exerted by the stimulus on the organization of epileptic activity. The existence of a post-inhibitory rebound or of an inhibitory after-effect, reflected by delay in the appearance of the after-discharge, likewise lends support to the assumption that epileptic potentials do not appear owing to a suppressor effect exerted by repetitive stimulation of the amygdala. On the other hand, the investigations of Kreindler and Steriade (1963b) show that epileptic discharges induced by stimulation of the dorsal amygdaloid zone (D-2.5 to 3.5) produce generalized seizures which become organized only after interruption of the stimulation; stimulation of the amygdaloid zones (D-5 to D-7) produces seizures that begin with an intrastimulatory discharge, which then passes into an after-discharge and the generalized fit. This should be related to the hypothesis of Kreindler and Steriade (1963b), according to whom there are two systems in the amygdaloid complex: a dorsal system, made up of the A.c.l. and dorsal areas of the nucleus amygdalae lateralis and nucleus amygdalae anterior whose stimulation at high frequencies produces a desynchronization response of the cortical rhythms; and a ventral system (the A.b.p. and ventral parts of the nucleus amygdalae lateralis and nucleus amygdalae anterior), whose stimulation produces synchronization of cortical electrical activity. Stimulation of the dorsal portion of the amygdaloid complex does not produce intrastimulatory discharges because it puts into action a structure with desynchronizing properties, thus contributing to auto-arrest of the epileptogenic effects. In order to be sure of this assumption electrical activity should be recorded at the point at which the stimulus is applied (Fig. 13).

Two modalities of allocortical epileptogenesis were demonstrated by the oscilloscopic analysis during low rate (5–15 sec) stimulation of the amygdaloid complex (Steriade, 1964). The development of evoked responses into self-sustained activity is as follows:

*(1)* The first modality consists in a gradual development of rhythmically evoked amygdalo-hippocampal responses. The prominent features of this first type of self-sustained discharge *(post-stimulatory discharges)* consist in the following: (a) the presence, throughout stimulation, of increasingly altered evoked responses to every shock; no self-sustained activity interferes to disorganize these responses even when they develop, in their evolution to after-discharge, a morphology which nearly reproduces epileptic patterns; and (b) a striking resemblance, or sometimes identity,

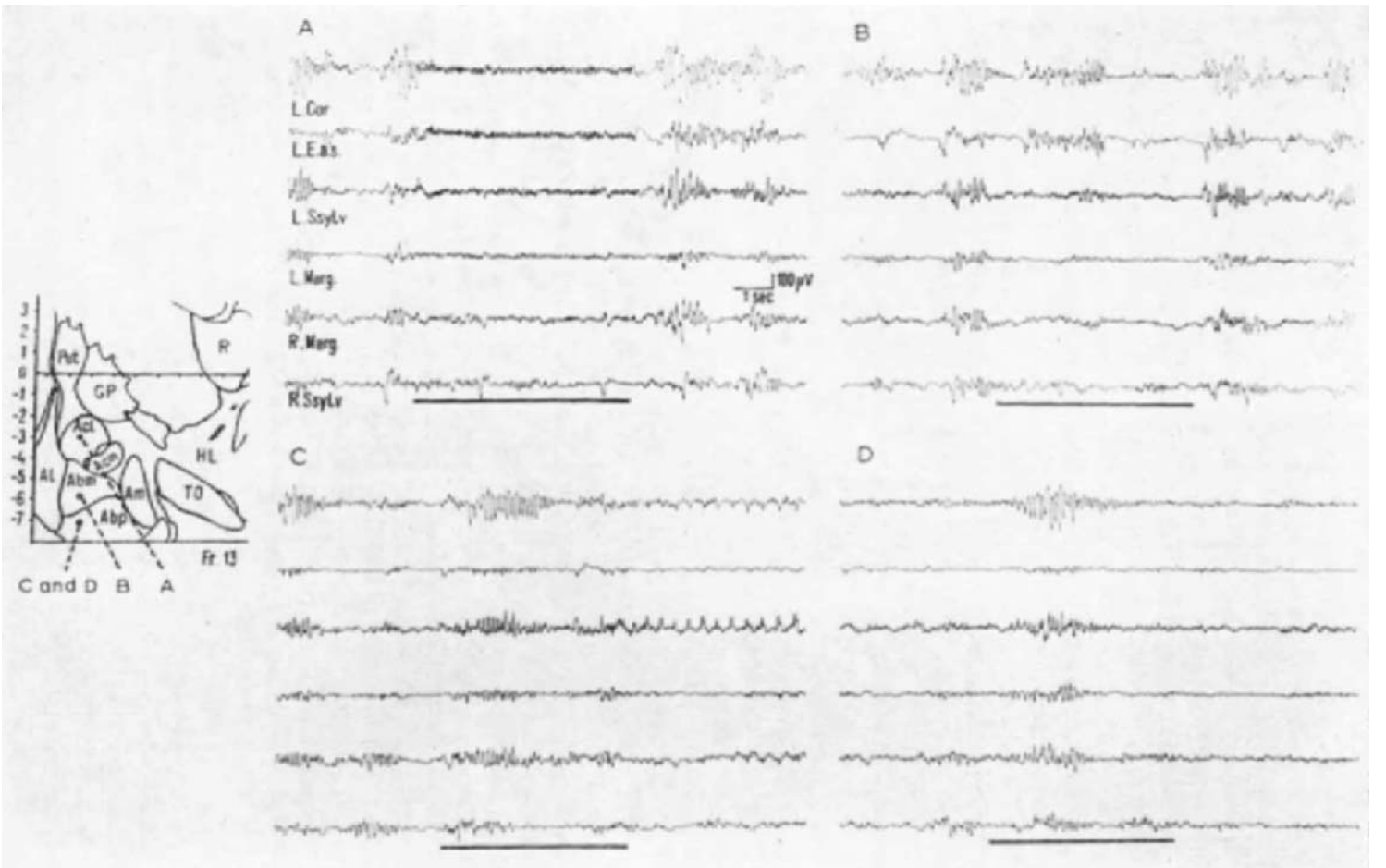


Fig. 13 For legend see p. 25.

between the after-discharge morphology and that of the responses evoked during the final stage of repetitive stimulation (Fig. 14).

The above characteristics might appear on both A.b.p. and A.c.l. stimulation. However, in most experiments the epileptogenic capacity of A.b.p. proved to be greater than that of A.c.l. The transition from evoked responses to the qualitatively different self-sustained rhythmical discharges is marked only by cessation of electrical stimulation; the absence of the stimulus represents the only characteristic distinguishing evoked potentials from 'spontaneous' after-discharge, and the form of both is similar or nearly identical. To cause self-sustained after-discharge, repetitive stimulation should be above a critical level at which responses with a certain morphology and latency can be evoked. The neuronal circuits used by the self-sustained after-discharge are the same as those mediating evoked responses. In this mode of epileptogenesis the transition from the physiological (evoked response) to the pathological (after-discharge, however small its amplitude, is the embryo of the epileptic seizure) takes place gradually without any evident discontinuity under our experimental conditions. In fact, all factors conditioning the appearance of epileptic events were present during the evoked response period. In the framework of a given anatomical structure possessing closed reverberating chains, repetitive stimulation facilitates synaptic permeability (comparable with local metabolic defects in clinical epilepsy), which results in increasing recruitment of internuncial neurons and, implicitly, in gradual increase in response latency and changes in wave form. On cessation of rhythmic stimulation the activated neuronal circuits continue to pulsate autonomously, as in 'memory' events, displaying the same wave morphology as in evoked responses. This modality of epileptogenesis may be due to the incremental organization of the evoked responses and to the transmission of epileptic waves by paths mediating evoked responses. Such a pattern may constitute one mode of genesis of reflex epilepsy. King *et al.* (1953) found a decrease in the amplitude of evoked response preceding the appearance of epileptic after-discharge. If in these experiments such a decrease of evoked responses was the effect of occlusion due to the presence of high rate epileptic activity, in our experiments the continuous incessant increase of evoked responses is further evidence of the absence of a self-sustained activity during stimulation.

*(2)* The second modality (in animals with a higher epileptic susceptibility) is the gradual disorganization and deterioration of hippocampal responses evoked by A.b.p. stimulation, due to interference by autonomous hippocampal activity during rhythmic stimulation. Characteristic of this mode of epileptogenesis are the following features depicted in Steriade's (1964) experiments: (a) decline of evoked responses, owing to the appearance of self-sustained activity which first interfered with, and then disorganized, the evoked responses, which ultimately disappeared; (b) in the epileptic discharge which followed cessation of stimulation, a monomorphous, extremely reg-

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Fig. 13. EEG patters of arousal and sleep induced by high-rate stimulation of dorsal and ventral amygdaloid areas. Cat, 'cerveau isolé'. A = stimulation of A.c.l.; B = of A.b.m.; C and D = of A.b.p. Note the arousal pattern in A (dorsal area), the lack of desynchronizing effect in B and the sleep-like spindles induced by stimulating C and D (ventral area). (From Kreindler and Steriade, 1964.)

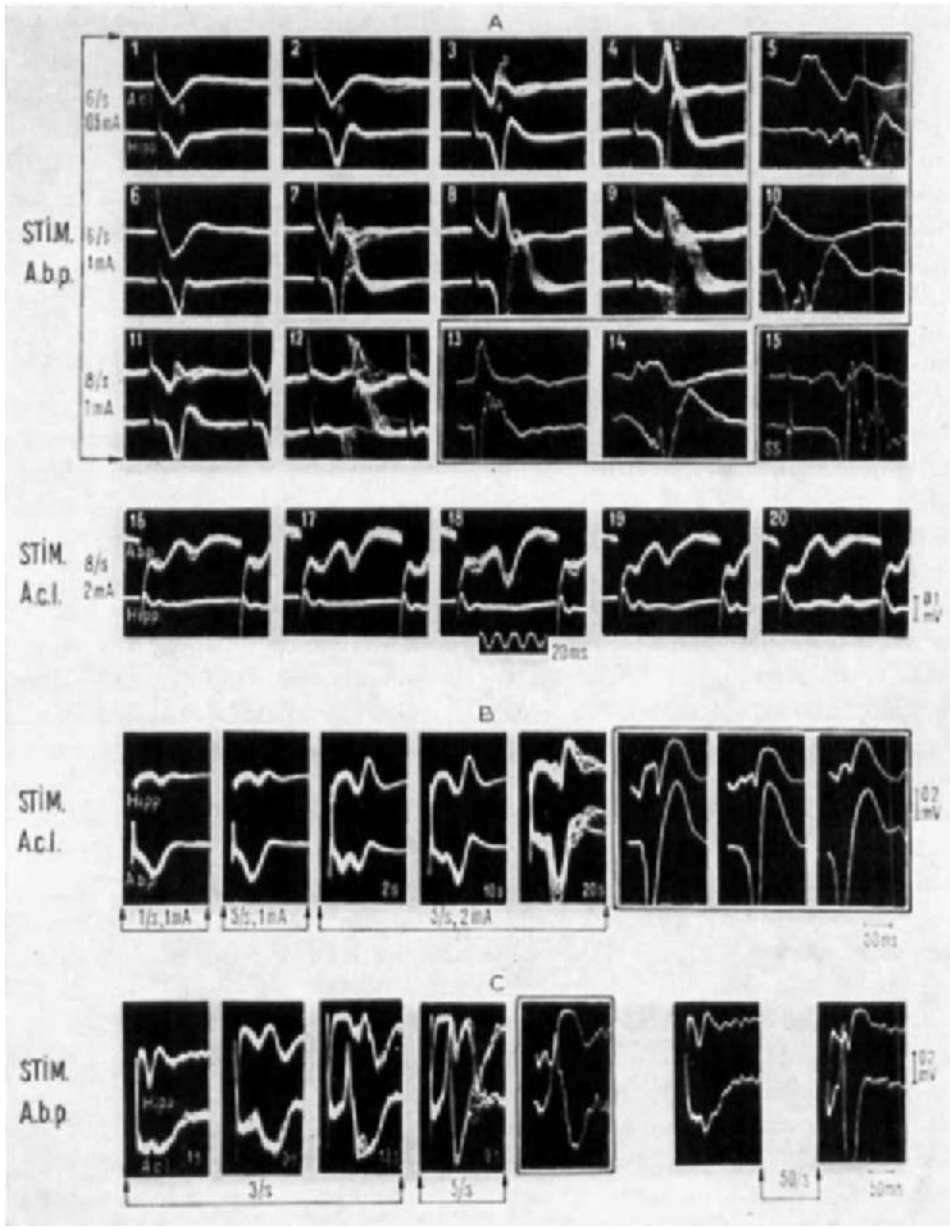



Fig. 14. Development of evoked response into self-sustained activity by gradual incremental alterations. A, B and C = three different experiments. In A different A.b.p. stimulation periods are represented by 1–4, 6–9 and 11–12. Each superimposition of responses is separated from subsequent ones by about 6-sec intervals. 5, 10 and 13–14 (within frame) represent spontaneous potentials from self-sustained after-discharges following 4, 9 and 12 respectively. In 15, potentiation and striking increase in latency in responses to single shock following cessation of after-discharge. In B, 6–8 (within frame) represent self-sustained waves immediately after stimulation from 3 to 5; 16–20 show the lower epileptogenic susceptibility of the A.c.l. nucleus. In C, one potential of the after-discharge following stimulation in 4 is depicted in 5 (within frame). At bottom right, evoked response facilitation after a 50/sec tetanization. Note the striking resemblance between the self-sustained wave morphology and that of the responses from the final stage of rhythmic stimulation. (From Steriade, 1964.)

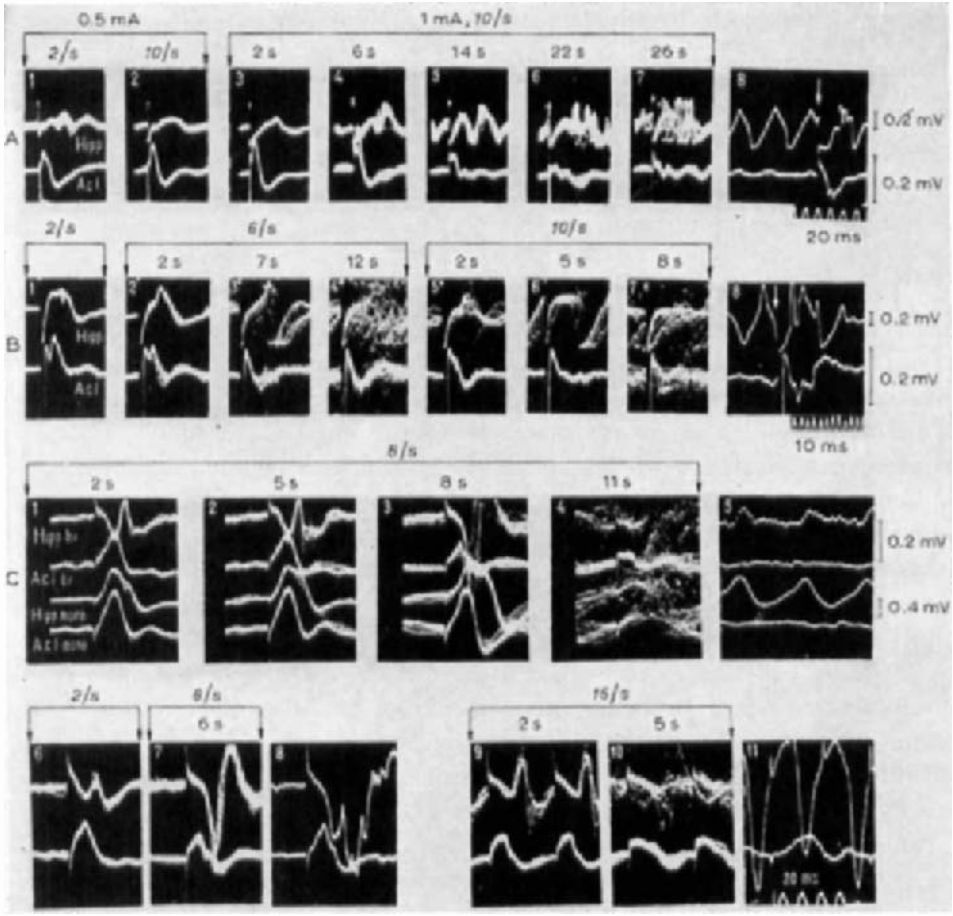



Fig. 15. Intrastimulatory disorganization and monomorphous after-discharge. A, B and C, three different experiments. A.b.p. stimulation. In A, during the rhythmic stimulation period from 3 to 7, the evoked activity is disorganized in 6 and 7. In 8, two waves of the monomorphous hippocampal self-sustained after-discharge (up to arrow). In B, during both rhythmic stimulation periods from 2 to 4 and from 5 to 7, disorganization of evoked responses by self-sustained activity in 4 and 7. In C, during stimulation from 1 to 4, abolition of evoked responses by epileptic disorganization in 4. In 5, a monomorphous after-discharge in the monopolar hippocampal lead. The same disorganization in 10, followed by hippocampal after-discharge in 11. In 8, seizure-like facilitation of evoked response following 6/sec rhythmic stimulation for 8 sec. (From Steriade, 1964.)

ular, rhythm (15 to 20/sec) prevailed (Fig. 15). This pattern seems to be peculiar to the hippocampus (see also Liberson and Akert, 1955; Kreindler, Voiculescu *et al.*, 1956a). The epileptic waves and the preceding evoked responses have different forms. The moment of cessation of rhythmic shocks represents the abrupt change from a complex neuronal circuit activity to a monomorphous activity mediated by other circuits. During electrical stimulation the evoked and self sustained activities, mediated by different paths, interfere; it is this which makes the intrastimulatory electrical activity display such intricate and disorganized patterns. Thus, in this mode of epileptogenesis, after-discharge waves escape from circuits normally mediating evoked responses and pass over other circuits distinct from the former and appropriate to a self-sustained epileptic activity.

# CHAPTER II

# THE EXPERIMENTAL EPILEPTOGENIC FOCUS

Electroencephalographic studies on man, in many cases of focal epilepsy or epilepsy with a focal onset, have produced evidence, via the scalp leads, of a focus of continuous electric activity, localized at certain points on the surface of the hemispheres.

The concept of a cerebral zone responsible for the onset of an epileptic seizure, and for clinical and electroencephalographic symptoms, is founded upon the observations of Jasper (1949), Walker, Marshall *et al.* (1947) and Penfield and Jasper (1947). In some cases, such foci have a subcortical location (Meyers *et al.*, 1950) and are not manifested electrically on the surface of the brain (Bickford *et al.*, 1953; Green *et al.*, 1951; Hayne *et al.*, 1949; Spiegel and Wycis, 1950; Delgado and Hamlin, 1958).

During neurosurgical interventions, electroencephalographic investigations have confirmed the existence on the surface of the brain, and sometimes even at the level of certain subcortical structures, of such foci of pathological electrical activity, generating large, high voltage waves, generally discharged in the form of spikes. The epileptogenic focus, however, is not represented by the lesion; the focus is to be found next to the lesion and often at a certain distance from it.

There certainly exists in the brain of an epileptic such foci of pathological electrical activity to which an epileptogenic role has been attributed. This epileptogenic focus has a continuous inter-ictal activity, which is now and then transformed, under the influence of factors that have not yet been determined, into an ictal activity, more intense than the former. Ictal activity of the epileptogenic focus forms the first stage in the development of the seizure, the second stage being represented by spread of this activity to other formations, and sometimes generalization of the seizure, when almost all the cortical and subcortical formations exhibit pathological electrical discharges.

It is common knowledge from scalp records in man that ictal and inter-ictal activity from different areas may be independent. Some discharges appear markedly localized, although similar or dissimilar activity may develop in remote areas when the amplitude increases. Bickford *et al.* (1953) found that independent spike foci in the depths tended to become synchronous when the amplitude exceeded a certain threshold. In man, abnormal activity may induce in many areas further abnormal activity, either dependent or independent, and the more that simultaneous recording is done from different areas, the more this ramification is made manifest (Fischer-Williams and Cooper, 1963). The difficulties and confusion relating to the concept of a focus in epilepsy in man were recognized by Jasper (1951) who wrote: 'The only true criterion of a focus is probably a study of the results of its removal'.

Jasper (1962a) speaks of a hierarchy of the foci. Classical cases of focal or partial epilepsy due to small, strictly delimited local lesions of the cortical tissue are extremely rare. A focus represents only a group of neurons with the lowest epileptic discharge threshold in the midst of a mass of cerebral tissue with epileptogenic properties. A hierarchy of the foci exists in the sense that the aura is determined by the focus with the lowest epileptogenic threshold within the larger epileptogenic mass. When the focus with the lowest epileptogenic threshold is removed, then another focus, that is responsible for continuation of the seizures, develops.

### *A. Epileptogenic focus induced by drugs or by freezing*

Experimental research has been designed to study the way in which such a focus of pathological electrical activity develops in the brain, the factors that may influence its activity, and its characteristics in terms of its different locations on the cortex and in the subcortical formations.

The experimental pattern most frequently used for creating an epileptogenic focus is topical application on the cerebral cortex of certain substances that have proved to have epileptogenic properties: strychnine, penicillin, mescaline, acetylcholine and others.

*(1) Application of strychnine* on the cortex increases its excitability. The potential evoked at the level of the sensory cortex is greater over the strychnine-treated area, because the number of cells discharging synchronously to an afferent impulse stimulation is much greater. If strychnine is maintained on the cortex for a longer period of time, then spontaneous discharges, called *strychnine spikes*, appear.

At first, the strychnine spike is monophasic and sometimes readily biphasic, lasting 5–10 msec. It is surface-negative, then the positive component increases and excitation spreads through orthodromic neuronal pathways to the neurons with which the strychnine-treated zone is connected (physiological neuronography). According to some workers, the cortical strychnine spikes do not pass through the synapses. But the fact the cortical strychnine spike may be accompanied by motor discharges in the form of peripheral myoclonia shows that the possibility of a transsynaptic transmission also exists.

Adrian and Moruzzi (1939/40) showed that strychnine spikes in the motor cortex are accompanied by high frequency discharges in the pyramidal tract, which demonstrates that strychnine also produces an increase in the frequency of the discharges at the level of the neuron.

Strychnine discharges have the following important characteristics of local epileptic discharges: (a) diminution of synaptic resistance to impulses from the central nervous system; (b) increase in the number of cells that fire in unison (hypersynchrony); (c) repeated spontaneous discharges; (d) high amplitude, and in most cases maximal, discharge of the respective neuron, which does not result in post-ictal exhaustion because after each spike a period of recovery exists. When the discharge becomes increasingly frequent until a tetanic discharge occurs, taking on the aspect of a seizure or of a paroxysmal after-discharge induced by electrical stimulation, then a period of exhaustion sets in until reappearance of the sporadic spike.

An increase in the state of central excitation of a group of neurons connected to the primary discharge focus (strychnine or other drug) may arise due either to temporal summation (increase in the frequency of discharges along the connection pathways), or to spatial summation (increase in the number of pathways that bombard the same neuron or neuronal group).

The strychnine spike may attain one or more millivolts. It is the consequence of hypersynchronism mostly of ephaptic origin. Rayport and Jasper (1958) investigated by intracortical recording with microelectrodes in fully strychninized unanaesthetized cats the spontaneous cortical strychnine spikes in the somato-sensory cortex. Evidence of unit activity apparently subserving the spontaneous strychnine spike was obtained at cortical depths of 0.3 to 1.8 mm. The effect of strychnine on the mechanism of the cortical specific afferent evoked potential was examined by single unit analysis. Strychnine did not appear to alter the threshold of the specific afferent evoked potential. Repetitive firing of evoked sensory units was observed to depend on the successful evocation of a strychnine spike by the thalamo-cortical volley. The strychnine spike is thus initiated by the discharge of infra-granular pyramids and it is conducted upwards in the cortex by multi-synaptic transmission through a network of cortical neurons with short and ascending axons. Recording with macroelectrodes showed that the spike is formed of a triphasic wave (positive–negative–positive) probably corresponding to certain slow potentials and to electrotonic propagation with decremental conduction in the dendritic plexuses. However, recording with microelectrodes shows an additional burst of extremely rapid spikes (400–1000 c/s) that begin with the first positive phase and end with the second negative phase.

Ralston (1958) showed that the after-discharge that follows a strychnine spike is rapid, rhythmic, of relatively low voltage, and comes after the slow terminal wave of a spike complex actually representing an embryo seizure. The more widely spread paroxysmal activity arises from this after-discharge rather than from fusion of the spike complexes between the seizures. Therefore, the seizure does not arise from a progressive increase in the frequency of the spikes between the seizures, but from interpolation of a new form of electrical activity — the after-discharge.

Ralston (1958) remarks that if we exclude the detailed experimental analysis of strychnine tetanus in the spinal cord (Bremer, 1941; Ajmone Marsan and Marossero, 1953) we find only scattered descriptions and analysis of the beginning of the rhythmical self-sustained paroxysmal discharge which characterizes an electrographic seizure. Each author who has attempted to investigate this problem discusses at length the mechanism of production of the spike, but only briefly examines the mechanism at the basis of the seizure. Moruzzi (1950) states that the elementary convulsive waves present a marked tendency to synchronize themselves, partially through electrical mechanisms, and that the frequency of the discharge of each neuron for each convulsive wave is limited by the absolute refractory period of the neuron, whereas the duration of the interval between successive discharges depends upon the phase of exhaustion of the neurons.

Under certain experimental conditions, cortical recruitment responses to stimulation

of the thalamus or of other cortical areas may attain an almost paroxysmal form of the wave, but are never transformed into an evident paroxysmal after-discharge. Application of a concentrated strychnine solution reduces the amplitude of the recruitment responses when the latter are activated indirectly (Fig. 16). Clare and Bishop (1957) found that the lowest effective concentrations of strychnine topically applied on the cat cortex cause increase of amplitude of recruiting sequences, following either thalamic or direct cortical stimulation at 6/sec. Higher concentrations, but usually below 0.1%, cause a further increase after direct cortical stimulation, but

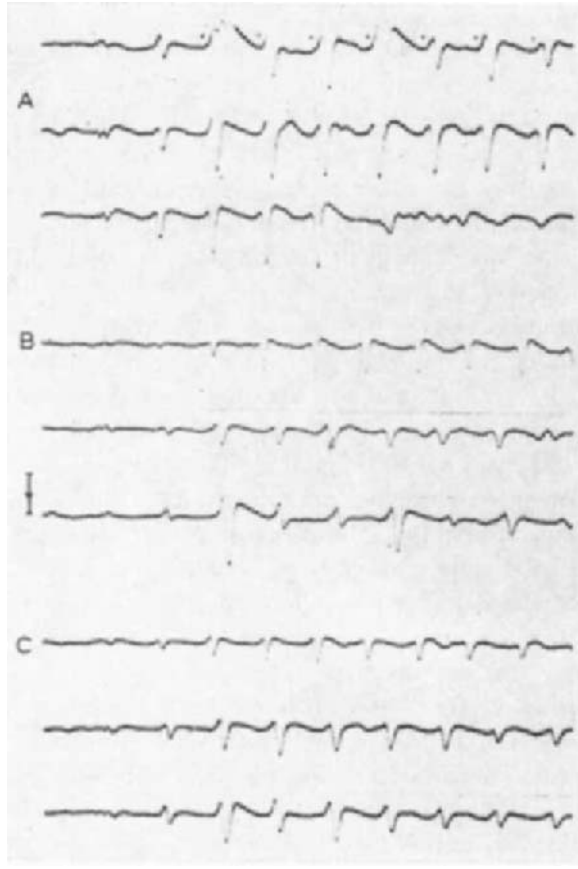



Fig. 16. Thalamic stimulation at 6/sec. A = leads from surface to white matter. B and C = records of activity in upper and middle thirds respectively from lead within cortex. Upper lines of each second, normal. Second lines, 15 min after topical application of 0.05% strychnine. Note two waves in first responses, the earlier of which decreases rapidly in successive responses and later increases. No pronounced strychnine effect is shown in A; depression of amplitude and widening of waves in upper cortical layers is apparent in B, while in C an increase in amplitude is shown in the second line. Lower lines in B and C show occasional enhanced waves; in B, upper cortical fraction, there is a tendency to depression of negative phases of certain responses, uncovering larger positive phases. Enhanced responses of lower line of B presumably indicate propagation upward into otherwise blocked superficial regions by the more powerful activity. Calibrations, 1 mV. (From Clare and Bishop, 1957.)

a decrease after thalamic stimulation. Still higher concentrations near or above those causing occasional spontaneous spikes may cause reversal of polarity of the record from surface-negative to positive. Above the threshold effect, and perhaps including this, the increase in amplitude of response under strychnine is assignable to an increase in the number of units fired in each recruiting wave. These extra-elements may be fired nearly synchronously with those responding immediately to the stimulus or after a variable delay. The observation of delayed firing suggests that the extra-elements involved are activated, not directly by the stimulus volley applied to the cortex, or by the afferent volley in nerve fibers stimulated in the thalamus, but indirectly following the immediate response in the cortex.

The same authors are of the opinion that the alteration of activity induced in apical dendrites by strychnine results from a depression in activity in nerve terminals afferent to dendrites, plus an increase in excitability of the dendrites postsynaptically. A sufficiently high concentration causes them to fire without an applied stimulus. A still higher concentration reverses this hyperexcitability to depression and block. When blocked at the cortical surface by strychnine so that the reversal of polarity is produced in the record, these blocked terminals can still be invaded by a sufficiently intense response or by a spontaneous strychnine spike, as indicated by the appearance of a pronounced surface-negative phase.

Purpura and Grundfest (1956b) have shown that after application of higher concentrations of strychnine, recruiting responses are decreased in amplitude if indirectly activated. Yet when typical strychnine spikes are fixed either spontaneously or in response to stimulations of various kinds, the amplitude of the spikes is usually far above that of any responses normally following the same stimuli. Presumably under strychnine more elements are fired in an explosive spike than are normally fired by any localized stimulus volley. This connotes that the excitability of dendrites must be raised even when synaptic passage is depressed by strychnine in the recruiting series. Strychnine hyperexcitability is therefore inferred to be postsynaptic.

They conclude that various drugs including strychnine act rather selectively at synapses, which they consider electrically inexcitable, like the muscle endplate. No other area of dendritic surface is believed to be electrically excitable; thus true conduction along dendrites in the axonal sense is excluded. The propagation of activity along dendrites is then only apparent conduction and consists actually of successive activation of successive synaptic loci.

Strychnine solutions applied locally to the cortex, in concentrations lower than those which produce strychnine spikes, increase the amplitude of recruitment sequences to direct cortical or thalamic stimulation. Higher concentrations, but below 8.1%, however give rise to a still greater increase in the recruitment responses to direct cortical stimulation, but a diminution in the responses to thalamic stimulation. Higher concentrations, close to the threshold at which a strychnine spike is produced, reverse the polarity from surface-negative to positive. This reversal appears to be due to the blocking effect of strychnine on the terminal portions of the apical dendrites at the surface of the cortex, where the concentration of strychnine is higher.

The facilitation of topically evoked strychnine spikes following high frequency

bulbar stimulation suggests additive inhibitory effects on dendrite activity of brain stem stimulation and topical strychnine (Purpura and Grundfest, 1957b). The inhibition of cortical dendritic stimulation evoked by surface stimulation by high frequency stimulation of the bulbar reticular system is further augmented by topical application of strychnine in concentrations sufficient to induce intermittent cortical spiking. Examination of orthodromic pyramidal responses evoked by motor cortex stimulation during the intermittent strychnine paroxysm shows a marked facilitation especially of the relayed (indirect) descending activity whereas the interseizure 'silent period' is associated with abolition of this latter activity without significant alteration in the direct responses.

*(2) Application to the cortex of an aqueous penicillin solution* (20,000 U/ml) produces a focal seizure in the rabbit. Ablation of the cortex at the level of the application arrests the seizure, and application of the same solution to the white matter does not induce a seizure. Barbiturate anaesthesia does not modify the dose required for bringing about a seizure, but prevents tonic attacks, which may be attributed to the preponderant action of barbiturates on the reticular formation (Ectors, 1956).

Local application of penicillin to the cortex of the cat produces spike discharges which gradually build up into large high voltage discharges, each discharge being followed by an after-discharge of shorter or longer duration not accompanied at first by a peripheral motor manifestation, which may however appear when the penicillin dose is bigger and application longer.

Ralston (1958) emphasizes the finding that the penicillin spike is followed after a certain interval by a rhythmic after-discharge of 20–40/sec. Once this rhythmic after-discharge has developed it usually appears at regular intervals and may increase in frequency and duration, taking on the aspect of a small, local larval seizure. After a number of repetitions the spike–after-discharge progressively changes, the duration steadily increasing, until it takes on the aspect of an electroencephalographic seizure clearly outlined even clinically. This rapid rhythmic after-discharge would therefore be the precursor of the electrical activity of a generalized seizure.

The phenomenon of spike–after-discharge does not appear to be a property of penicillin itself, but can be seen after local application of other antibiotics, of curare (Chang, 1953), of eserine–acetylcholine in isolated cortex (Kristiansen and Courtois, 1949), and after implantation of alumina cream into monkey cortex (Chusid *et al.*, 1953). In human epilepsy, Jasper (1949) illustrates a case in which the activity is highly suggestive of a spike–after-discharge pattern, being prominent in the electrode designated as the primary site of spiking, whereas the same pattern is hardly noticeable at another lead to which the spike is said to have been conducted.

In order to obtain electrical and motor effects similar to those produced by local penicillin applications, a 3–500-fold dose, applied intracisternally in the same animal, is necessary (Busche, 1957). In view of the epileptogenic action of penicillin, it should be applied locally with the greatest caution in the neurosurgery of septic processes and in intralumbar administration for meningeal infections. Intracortical penicillin injection in the visual area of the cat induces intermittent focal discharges of slow

spikes, followed by multiple rapid spikes which show a tendency to spread to other regions of the cortex and to be accompanied by convulsive activity (Kooi and Beck, 1956). With slow photic stimuli ($\frac{1}{2}$-3 c/s), a penicillin spike to each stimulus is obtained; with higher frequencies of 4–7 c/s the proportion is 1 : 2; and at a frequency of 7–10 c/s 1 : 3. At frequencies of about 30 c/s a penicillin spike is induced only at the beginning of stimulation. Frequencies of 10–20 c/s, repeatedly applied, produce in the end an attack of self-sustained discharges, *i.e.* they persist after stimulation has ceased. Application of penicillin to the motor cortex of a cat in the first week of life does not give rise to spike discharges (Volanschi, 1960). The fact that a rhythmical after-discharge always seems to follow the spike complex, or in other words, that a spike is capable of setting up such a self-sustained rhythm, reminds one of the so-called 'sensory after-discharge' (Bremer and Bonnet, 1950). The main difference between the activity described by Bremer and Bonnet, which can be considered physiological, and that under discussion, obviously of pathological nature, might possibly be a quantitative one, in the sense that the latter has a marked tendency for longer duration and eventually for spread, whereas the sensory activity has a limited time course and remains localized.

Ralston (1958) produced a penicillin focus in the median centre of the thalamus in the cat, that is awake and freely moving about, and observed only a typical local after-discharge without propagation to the cortical leads, whereas a focus created in the right ventral lateral nucleus of the thalamus produced an after-discharge that spread only to the ipsolateral cortex; this had a peak in the ectosylvian and suprasylvian gyri, in spite of the fact that the penicillin spikes were transmitted symmetrically and bilaterally to the cortex from this unilateral focus. Hence, it appears that propagation of the spikes and of the after-discharge are two different phenomena, organizing the neuronal discharges in different ways. Moreover the focus in the median centre does not propagate, which would be in accord with certain peculiarities in the organization of cerebral epileptic aclivity, as also pointed out by Kreindler, Voiculescu *et al.* (1956b).

Immediately after topical application of penicillin to the cerebral cortex, an increase in the frequency or diminution in the amplitude of the waves occurs at the level of the focus, a phenomenon that has also been observed after topical application of strychnine (Hippius *et al.*, 1957; Kreindler, Voiculescu *et al.*, 1960) or mescaline (Crighel and Stoica, 1961; Mison-Crighel *et al.*, 1964). The wave spindles that periodically appear on all the leads disappear at the level of the focus (Kornmüller, 1937; Janzen *et al.*, 1951; Kreindler, Voiculescu *et al.*, 1960). About 2 to 4 min elapse between the application of penicillin and the appearance of the first epileptic discharges. These first discharges are of low voltage and become simple mono- or diphasic spikes. Later, both their amplitude and their complexity increase, and varied spike-wave complexes are formed. The discharges, rare at first, become increasingly frequent, then group together in twos and threes until they merge into a continuous response.

Subcortical foci can also be produced by penicillin injections. Thus, procain–penicillin G injected subcortically into the monkey produces spontaneous convulsions

and pathological electroencephalographic alterations in most of the experimental animals (Faeth *et al.*, 1956). From the clinical viewpoint, the seizures consisted in adversive, focal motor fits and psychomotor episodes; penicillin injections at the level of the basal ganglia induced similar phenomena.

Penicillin injection in the thalamus of the cat to which pentothal was administered intravenously diminished the frequency of barbiturate spindles from 8–12 c/s to $3\frac{1}{2}$–5 c/s, irrespective of the site of the focus at the level of the dorsal thalamus. In other experiments, the injection produced synchronization of the spindles (Ralston and Ajmone Marsan, 1956).

Penicillin introduced in small amounts into the thalamus gives rise to synchronous bursts of slow, paroxysmal high voltage waves, their distribution depending upon the location of the focus. These responses appear to be mediated by the non-specific thalamic system. After prolonged action or after a large penicillin dose a focus of discharges is produced at the level of the thalamic electrode (Ralston and Ajmone Marsan, 1956).

Application of penicillin to the human cortex during neurosurgical interventions produces, as in the cat and monkey, penicillin spikes followed by an after-discharge (Ralston and Papatheodoru, 1960).

Local cortical application of a convulsant drug is accompanied by 'activation' of units scattered throughout the whole cortical extent in that area (Enomoto and Ajmone Marsan, 1959). A few firing units are present in the superficial layers and are definitely predominant in the deeper layers. The large majority of units characterized by an early firing apparently preceding the discharge itself, are concentrated within the same deep layers (Fig. 17).

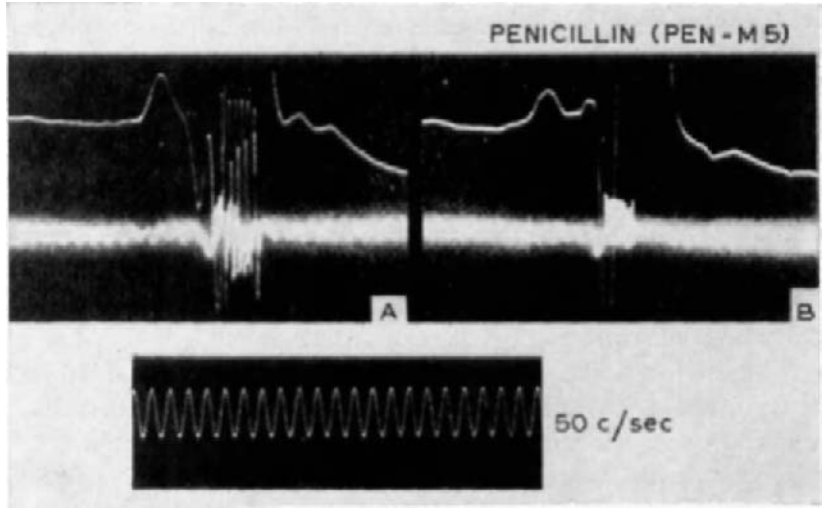



Fig. 17. A given pattern of synchronization of three different types of units accompanies a complex multiphasic EEG discharge (A) while a few seconds later, the same discharge being, however, less complex in its morphology, only one unit is seen to fire (B). A = at least three different units are active in coincidence with a complex multiphasic EEG discharge. B = few seconds after A. The activity of only one unit is seen. Note simpler shape of corresponding EEG discharge. (From Enomoto and Ajmone Marsan, 1959.)

*(3) Application of a 5–10% ACh solution to the cerebral* cortex of animals under general anaesthesia elicits an epileptiform electrical activity (Brenner and Merritt, 1942; Forster, 1945). Topical application of 1% ACh solution, which does not induce epileptic discharges, produces such discharges when preceded by topical application of 1% eserine (Chatfield and Dempsey, 1942). Topical application of ACh also elicits epileptic discharges in the acute isolated cerebral cortex, previously treated with eserine (Kristiansen and Courtois, 1949). Echlin and McDonald (1954) showed that isolated or partially isolated parts of the cerebral cortex become oversensitive to topical applications of ACh, to electrical stimulation and to i.v. metrazol injections. Intracarotid injection of 0.2 μg ACh to the eserine-treated monkey produces discharges of the spike-wave type in the chronically isolated cortex. Local application of 0.1% ACh solution to the isolated cortex previously treated with eserine again induces local rhythmic electrical activity, closely resembling epileptic discharges. Bursts of spike discharges appear, as in epileptogenic lesions in man, and not isolated spikes.

Some workers (Hyde *et al.*, 1949; Hampson *et al.*, 1950) assert that di-isopropyl-fluorophosphate, a powerful anticholinesterase, induces convulsions, but it is hardly likely that the mechanism of epileptic discharge could be due to esterase deficiency. Tower and Elliott (1952a,b) found disturbances in the binding mechanism of ACh at the level of cerebral epileptogenic lesions, which would result in too great an amount of free ACh.

*(4)* The *mescaline* focus created by *topical application of mescaline* to the cerebral cortex exhibits certain distinctive features (Crighel and Stoica, 1961). The mescaline focus stays localized for a long time and spreads first of all to the symmetrical contralateral cortical structures and then to the subcortical, especially thalamic, structures. Propagation to the mesencephalic reticular formation is the last to take place. Excision of the primary focus leads to disappearance of the convulsive potentials spreading to other structures, in the acute experiment. Evidence was found of potentiation and suppression phenomena between two or several mescaline foci.

*(5) Alumina cream* was used by Kopeloff *et al.* (1942) for producing an epileptogenic lesion. The cream is composed of ammonium hydroxide and ammonium alum. Application to the motor cortex produces, after 4–9 weeks, focal epileptic seizures that may persist for months, even after removal of the alumina cream. The focal seizure often becomes generalized. The electrocorticographic aspect of the focal seizure resembles that of focal epileptogenic seizures in man.

The strychnine focus differs from the alumina cream focus in that the appearance of the action potential of the latter is not different to that encountered in the normal cortex, whereas with strychnine it is altered, that is, the action potential of the perikaryon shows a progressive increase in the positive phase which often coincides with the appearance of high frequency bursts from the neuron that is firing (Thomas *et al.*, 1955).

*(6) Local freezing* of the cerebral cortex produces local discharges that may become generalized (Speranski, 1943) and leads to a status epilepticus and death of the animal. Dogs and cats more readily develop such convulsive accidents than monkeys. Thermo-

coagulation does not lead to such phenomena. Freezing of the cerebral tissue probably gives rise to tissue disaggregation products containing metabolites with an epileptogenic capacity.

*(7)* Spraying on the pial surface of *ethyl chloride* (Morrell and Florenz, 1958) produces local spike discharges that begin 1–3 h after application of the drug. Three months later, the zone is still sensitive to the effect of an excitatory stimulus such as intermittent photic stimulation, although the rest tracing does not show any epileptiform discharge. Sometimes the appearance of mirror focus can be observed even after removal of the primary lesion. Dilantine does not temper the discharges of the primary focus, neither does it prevent spread towards the diencephalic regions, but it does prevent transcortical irradiation. Tridione inhibits both the primary foci and all irradiations except the transcortical one (Morrell, Torres *et al.*, 1960).

### *B. The 'epileptic' neuron*

There is general agreement today upon the following scheme of function of the cortical neuron: the axon consists of a membrane responding according to the all-or-none principle; it is electrically excitable and plays the part of message transmitter. The perikaryon membrane also responds according to the all-or-none principle, and is electrically excitable. The dendrite, however, is gradually responsive for the most part, electrically inexcitable, and its membrane responds to chemical transmitter substances released by the button-like formations covering the greater part of the dendrite surface. Therefore, the dendrite membrane generates 'standing postsynaptic potentials' as a result of the chemical excitation by the synaptic input. This synaptic electrogenesis may affect, through an electrotonic influence, the electrically excitable membrane of the perikaryon (Purpura, 1959).

Except for the mechanism of electrotonic propagation, the postsynaptic potentials generated by the dendrite are thus 'standing potentials' that do not spread.

In contrast to the well-known absolute refractory period of perikaryon and axon potentials (Bishop, 1956; Grundfest, 1957), the response of the dendritic membrane to synaptic activation is characterized by the absence of an absolute refractory period. There is still a lack of certainty as to whether the gradual response of the dendrite (hence, a response proportional to the stimulus parameters and not having the all-or-none character) spreads decrementally along the dendritic tree of a neuron.

The electrical activity of single units during epileptic after-discharges in the cerebral cortex was first observed by Adrian and Moruzzi (1939). The activity of single units induced by convulsive drugs was investigated by Jung (1951), Li and Jasper (1953), Baumgartner and Jung (1955), and by chronic epileptogenic foci by Schmidt *et al.* (1959) and Morrell (1961). Epileptic activity from hippocampal neurons was reported by Green (1958). All these investigations were carried out by means of extracellular microelectrodes.

The epileptic neuron has the following functional characteristics that distinguish it from a normal neuron: abnormally great potentials in the soma and dendrites; such a high frequency of the potential spreading along the axon that it considerably

exceeds the 150/sec frequency of normal neurons, attaining even 1000/sec (Moruzzi, 1950, 1953). On the other hand, there is a disequilibrium in the epileptic neuron that facilitates the excitation process with which two distinct mechanisms are connected; the amplifying of excitatory postsynaptic potentials and the decline of postsynaptic inhibitory potentials. The first mechanism is put into action by metrazol and the second by strychnine, a curarisant of inhibitory synapses (Eccles, 1957, 1959).

The cortical units do not respond uniformly to repetitive stimulation of the cerebral cortex or to the after-discharge that follows it. Rayport (1960), taking microelectrode records from somatosensorial area 1 in the cat, found from this point of view four types of unit: units that respond with a short latency; units that fire together with spindles from the electrocorticogram; units that respond to isolated shocks applied to the surface of the cortex; and units whose activity is not correlated with any of the above-listed activities.

Recording by means of electrodes located in three different layers (dendritic and cortical somatic layers and the white subcortical matter) revealed discharges strictly confined to dendritic layers (Morrell and Torres, 1958). The inter-paroxysmal after-discharge seems to be restricted to superficial cortical layers. The involvement of dendritic branches by such discharges may partially deafferentate the cell or modify its threshold so as to render it less sensitive to the axo-dendritic impulses without producing any potential propagated from the corresponding soma.

Beritashvili *et al.* (1958) found that it was much easier to induce after-discharges in the superificial levels of the cortex than in the deeper layers when acetylcholine was applied topically after eserine. They concluded that the upper cortical layers could be the seat of the discharges, the dendritic network of the cortex thereby playing a role in the generation of epilepsy.

Ajmone Marsan (1961) distinguishes two aspects in the activity of what he calls an 'epileptic neuronal aggregate': the inter-ictal and the ictal aspects. In analysing the process responsible for the paroxysmal cyclical firing (inter-ictal) and for the organized, repetitive, self-sustained (ictal) activity in epileptic neuronal aggregates als well as for the transition from one to the other, it is felt that more than simply quantitative differences characterize these two types of activities: it is suggested that while the former can theoretically take place in the isolated neuron, the latter can only occur in epileptic neuronal aggregates. In comparing the behaviour of an aggregate of normal neurons in resting conditions with that of an epileptic neural pool, one can observe that generally, in the normal situation a lesser number of units are active and these fire sporadic, isolated or repetitive low frequency spikes. In an epileptic population there is a very close relation between slow outbursts and unit activity: the majority of unit elements in the area fire at least one, and often numerous repetitive spikes at a very high frequency. Elements whose activity is apparently unaffected by the epileptogenic process are exceptional.

The disappearance of the axo-dendritic potential during the development of an epileptic seizure might be a 'busv-line' effect due to the fact that dendrites are concerned in the generation of convulsive potentials; this is in agreement with Adrian's conclusion that the negative wave of the direct cortical response represents a depo-

larization and not a hyperpolarization of particular structures oriented medially towards the cerebral cortex surface (Abdullah and Magoun, 1957).

An argument lending support to the hypothesis that abnormal dendritic depolarization and the occurrence of epileptic after-discharge are closely related, arises from the observation by Eidelberg *et al.* (1959) of cortical local (direct) responses of high amplitude at the loci at which the cerebral cortex had been rendered epileptogenic.

Abdullah and Magoun (1957) noticed that epileptic seizures induced either by metrazol or by high-frequency stimulation of the cerebral cortex interfere with potentials evoked by local cortical stimulation that are due, according to Chang (1951, 1952) to a dendritic activity of the cerebral cortex. Brazier (1955) established a close relationship between dendritic depolarization and epileptic discharge, holding that epileptic spikes might be generated by apical dendrites of the cerebral cortex.

Orthodromic evoking of a pyramidal response by stimulating the motor cortex during an intermittent strychnine paroxysm, results in a marked facilitation especially of the descending activity but there is no significant change in the direct response. Such silence periods are not associated with neuronal exhaustion, as the dendritic responsiveness returns during the intercritical silence period, and D-tubocurarine, in doses usually not sufficient to inhibit any cortical synaptic activity, has a facilitating action on strychnine seizures. These facts suggest that at least two factors are necessary for the triggering of a strychnine- and metrazol-induced paroxysm: (a) dendritic synapse inactivation; (b) partial block of particular cortical inhibitory mechanisms that is still overcome intermittently. Electrical silence periods are thus originated (Purpura and Grundfest, 1957b).

High-frequency stimulation of the reticular formation inhibits the cortical dendritic activity evoked by surface stimuli. This inhibition persists a few seconds following cessation of stimulation, and is still more enhanced by topical application of strychnine in a concentration sufficient to produce the intermittent spike-discharge (Purpura and Grundfest, 1957b). The triggering of steady and intermittent paroxysms by intravenous injection of strychnine or metrazol is also accompanied by inhibition of dendritic responses evoked by surface stimulation or by antidromic activation of bulbary pyramids.

The role of different portions of a cell in the epileptic process is a problem pertinent to the origin and development of impulses in the normal neuron. Ajmone Marsan (1961) remarks that besides the hypothesis of Bremer (1949) emphasizing autorhythmicity or slow membrane potential oscillations as an intrinsic property of the neurons of the central nervous system, two alternative explanations of spontaneous activity are available, one which considers synaptic potentials as the major substrate (Eccles, 1951), the other relating the various aspects of EEG to 'dendritic activity' (Bishop, 1958). But we must bear in mind that in the case of EEG as well as of other phenomena recorded with gross electrodes, any so called 'graded behaviour' could well be apparent and simply express the composite, more or less synchronized, activity of many elements (including soma-dendritic decremential potentials, all-or-none spikes from axons or axon hillocks and the still unknown activity of short

axon cells) and not necessarily only that of some specific cell portions, such as dendrites, even assuming as established the exclusively graded nature of their activity.

More direct evidence, such as that obtained from verified intracellular penetrations in dendrites is lacking, although Li (1959) has demonstrated that regular, rhythmic waves with a period of 15–30 msec — the same as that of the direct cortical response — were recorded from intracellular placements from which all-or-none activity was not obtained. Von Euler *et al.* (1958) obtained data from Ammon's horn, where the stratification of cellular structures is much more convenient for analysis than in the neocortex, which suggest that quite large, non-propagating, potential changes with a similar time course are probably generated at the level of the dendritic shafts of the hippocampal pyramidal cells as well as large convulsive spike discharges.

Eidelberg and French (1961) verified the occurrence of extremely large graded responses, which parallel the direct cortical and transcallosal response. The responses picked up at the superficial basilar and deep apical dendritic layers of the dorsal hippocampus of the rabbit were larger than responses obtained from the surface of the neocortex, with the same electrodes. These findings seem to lend further support to the concept of a relationship between dendritic excitability and susceptibility to convulsive discharge.

Intracellular recordings were studied by Li (1959) on cortical neurons under local treatment with strychnine, and by Kandel and Spencer (1961) on hippocampal pyramidal cells during seizures induced by electrical stimulations. These authors found that tetanization of either intact or 'deafferented' fornex triggers the seizure-prone hippocampal cortex into convulsive activity. Seizure so induced has been recorded with a surface monitor and studied in single hippocampal neurons led intracellularly. The response of the pyramidal cell to seizure in the 'deafferented' fornix preparation was predominantly inhibitory: when spikes occurred they were of normal amplitude and configuration. The response in the intact fornix preparation was predominantly excitatory and was associated with a profound membrane polarization and abnormal spike generation.

Gloor *et al.* (1961) investigated the mechanism of epileptic discharges in the hippocampus, studying the hippocampus seizures produced by repetitive stimulation of the entorhinal cortex or of the fimbria in cats. Repetitive stimulation of the entorhinal cortex leads to a progressive shift in d.c. of the same polarity as the main transient response, which also is dipolar, negative in the apical dendritic layer and positive in the cell layer. After a while the shift reverses its direction and, after crossing the baseline, leads to a d.c. shift of opposite polarity with a negative potential developing in the cell layer and stratum oriens, and a positive potential in the apical dendritic layer. At this moment the hippocampus is capable of self-sustained seizure discharge during which the d.c. shifts are even accentuated. The d.c. shifts seem to be largely due to summation of residual depolarization of postsynaptic structures. During self-sustained seizure discharge rapid transients, typical or conducted activity, occur in the cell layers, whereas the apical dendrites follow more or less passively the activity of the cell layer. During the decay of seizure activity, in the clonic phase, characteristic and repeated resettings of the d.c. level may occur. These are of the

order of several millivolts. They are negative in the cell layer and positive in the dendritic layer.

Schmidt *et al.* (1959) postulated that the autonomous activity which characterizes the epileptic neuron is due to a relatively prolonged dendritic depolarization with a resultant difference in potential between the cell body and its dendrites. In these circumstances, the membrane potential of the soma recovers rapidly, acting as a source, with resulting current flow from the soma to the depolarized dendritic tree which acts as a continuing sink. If this current flow continues to reach the threshold, a high-frequency discharge will occur. The dendritic depolarization in the epileptic cell might be the result of neochemical deformation of the dendritic tree by the astrocytic gliosis present in epileptics. During the tonic phase of rapid cell firing, the frequency of discharge is about 100/sec although frequencies up to 800/sec can be recorded. As the dendrites or graded response membranes are progressively involved, increasingly synchronized slow wave activity replaces the phase of rapid neuronal discharge. As the height of the clonic phase is reached it appears that maximal invasion of the dendrites has taken place (Fig. 18).

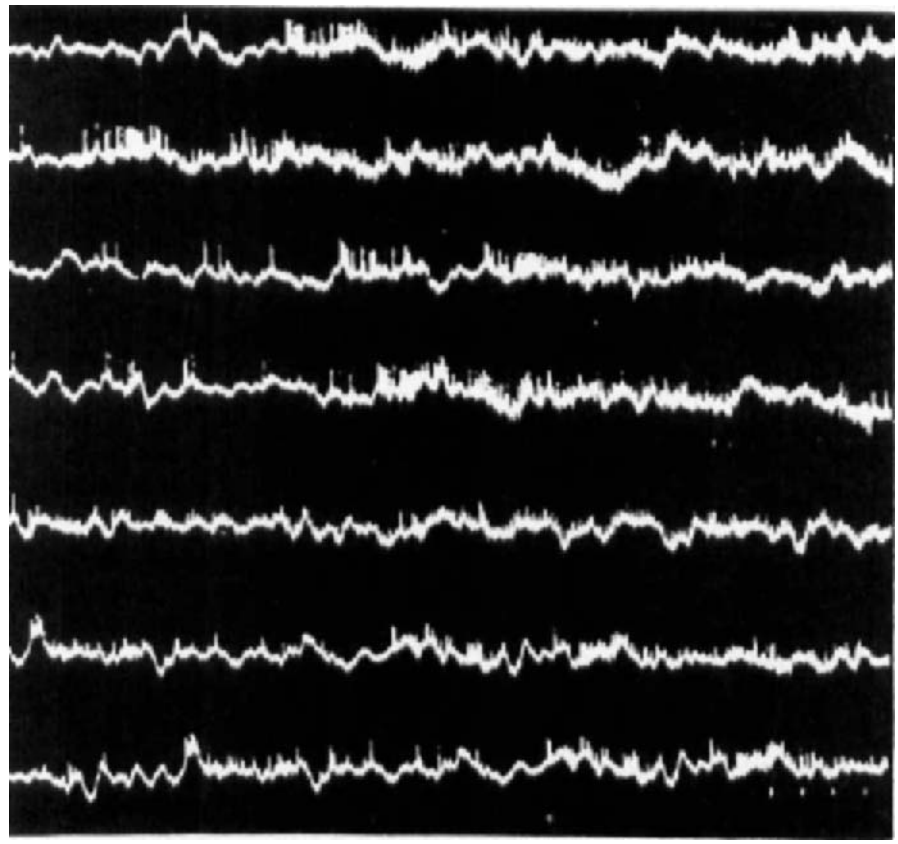


Fig. 18. Spontaneous unit activity in epileptic cortex. Note long 'tonic' trains of high-frequency unit discharge with occasional responses and higher frequency bursts. Time mark, 50 msec. (From Schmidt *et al.*, 1959.)

Sawa *et al.* (1963) studied the intracellular potentials during the whole process of epileptic seizures induced electrically in the cerebral cortex and the hippocampus by single shock and repetitive electrical stimulation. Most cortical and hippocampal neurons showed a depolarizing wave followed by a hyperpolarizing wave in response to a single pulse at the surface. Prolonged repetitive stimulation at high intensity and high frequency resulted in a progressive decrease of the hyperpolarizing wave, progressive prolongation of the depolarizing wave and temporal summation of the depolarizing waves. Finally the neuron was maintained in a state of sustained depolarization. After cessation of stimulation, the sustained depolarization continued, and large and long-lasting depolarization waves occurred periodically with concurrent waves in the corticogram. During the last stage of a seizure, the falling phase of the depolarizing wave became increasingly more marked and finally the depolarization was reduced to the level of hyperpolarization. A long-lasting hyperpolarization was then observed and concurrently the corticogram was silent.

Progressive decrease of the hyperpolarizing wave must be caused by the decreasing effect of inhibitory synaptic transmission, possibly due to a progressive diminution in the transmitter substance. The experiments of Sawa *et al.* (1963) suggest that excitatory synaptic transmission remains active after inhibitory transmission has been blocked.

### *C. The genesis of an epileptogenic focus*

The main problem in epilepsy is to know under what conditions an epileptogenic focus originates in the intact individual, *i.e.* what are the conditions that determine and favour *the genesis of an epileptogenic focus.*

Moruzzi (1950) found that a normal neuron may enter into a convulsive state by simple subjection to a bombardment with high frequency nervous activity. Abnormal input of nervous impulses therefore predisposes a normal neuron to pass from its normal activity into an epileptic state. Any neuron may therefore become epileptic as a result of bombardment by nervous activity. Hence, the essence of the genesis of an epileptogenic focus may not necessarily be an intrinsic pathological morpho-functional alteration of the neuron, but could be a dynamic factor from without.

*Synchronization* of the discharges plays an important role in the genesis of a focus, and one that implicitly functions in the seizure. Different mechanisms may be recognized in rhythmic synchronization. Adrian and Moruzzi (1939/1940) and Thomas *et al.* (1955) showed that the cell fires during a strychnine hypersynchrony at very high frequencies of 500–600 c/s and even higher. Synchronization does not depend only on recruitment of an increasingly large number of neurons (Bonnet and Bremer, 1956), but also on the frequency of neuronal discharges (Gellhorn, 1953; Moruzzi, 1950). Li *et al.* (1956) followed the synchronization of unit discharges in the cortex by recruiting waves. Spontaneous rhythmic waves of the cortex occasionally transform random spontaneous unit firing into intermittent grouped discharges on the negative crest of the spontaneous waves of a 'spindle burst'. Recording with intracellular microelectrodes shows that this process of 'regulating' of unit discharge is much

clearer, especially when a unit is in spontaneous repetitive discharge. During a recruiting response set up by repetitive thalamic stimulation, the rate of firing would be increased during the recruiting waves and decreased or abolished in the intervals between.

A synchronization mechanism appears to be that of the axon collaterals which would interfere in spread of the discharges (Chang, 1955a). But it is known that synchronization of the dendritic activity may sometimes take place without an axon discharge (spikes without a motor peripheral effect). However, since the epileptic spike — the electroencephalographic and electrocorticographic signature of the focus — represents a summation of the depolarization activity of the dendrites, synchronization must take place at this level (Brazier, 1955).

Another synchronization mechanism would be that of the effect of the electric field. Bremer (1941) showed that synchronization of ictal discharges may appear following complete transection of the strychnine-treated spinal cord. Enomoto and Ajmone Marsan (1959) have correlated the activity of one or of several units from a given microelectrode placement and of a large number of units from different placements through the cortical layers with the paroxysmal EEG discharge. The most characteristic pattern of unit behaviour, in coincidence with the EEG paroxysmal event, was a burst of high frequency spikes; other units may fire only one or two spikes, and occasionally units are found which are apparently unaffected during the EEG discharges. Hypersynchrony of firing of a large number of unitary elements, though not strictly absolute, is a characteristic feature of epileptic activation. Enomoto and Ajmone Marsan observed massive hypersynchrony throughout the entire thickness of the cortex in cortical seizures produced by local application of convulsant substances, and consider that it takes place by ephaptic pathways.

Gastaut and Fischer-Williams (1959) likewise attribute to temporo-spatial summation over the neighbouring neurons a role in the creation of a state of synchrony. These neurons must however be in a state of hyperexcitation (either due to constitutional factors or to acquired disturbances); hence, this summation is a latent process.

One of the general characters of epileptic activation of a single unit is the increase in the frequency of the discharges, generally in the form of bursts of variable duration, and a tendency to synchronization of the activity of a large number of units (Baumgartner, 1954; Baumgartner and Jung, 1955; Jung, 1957; Moruzzi, 1955; Thomas *et al.*, 1955; Ward, Thomas *et al.*, 1956b).

Von Baumgarten and Schaefer (1957) followed, with the aid of extracellular microelectrodes, the action potentials of certain nerve cells in the cerebral cortex and, in another series of experiments, in the reticular formation of the caudal part of the brain stem. They were able to demonstrate that a lax coupling, *i.e.* not always constant but statistically significant, of two or several unit discharges exists, as well as a rigid coupling, *i.e.* constant synchronization of two or more unit discharges. When the number of discharges increases, with the aid of pharmacological substances, then the lax coupling constantly passes into a rigid coupling. In general, the unit that fires more frequently exercises a 'magnetic' effect on those that fire more seldom. The

synchronized unit may, in compliance with its own tendency to discharge, fire immediately before or after the synchronizing unit.

During the 30 msec before or after discharge of a rhythmic unit, the tendency to discharge increases in a surrounding area that comprises a number of neighbouring cells. This rhythmic variation of the local conditions that favour nerve cell discharges acts independently of non-synaptic time relationships and can be considered the late effects of a preceding discharge.

These extracellular synchronization phenomena lend support to the hypothesis of Gerard and Libet (1941) and Bremer (1941), according to which epileptic activity would also be due to ephaptic, non synaptic propagation.

Paroxysmal hypersynchrony that characterizes the convulsive seizure probably arises from the competition of two mechanisms, of which one consists in progressive recruitment of an increasing number of neurons that are related functionally. The other mechanism consists in convulsive activity of the neurons, characterized by high frequency discharges permitting hypersynchronization between the neurons that are not functionally related and in which synaptic delay can not therefore occur.

The glia may likewise be assumed to interfere in the synchronization mechanism. The neurons form only 14% of the units of the striated cortex in the monkey and 18% in man (Nürnberger and Gordon, 1957). The glia may respond to electric stimulation (Tasaki and Chang, 1958) by a gradational response that lasts up to 4 sec.

Li (1959) believes that the glia plays a part in the synchronization mechanism. In the epileptic cortex, where the dendrites exhibit unusual responsiveness to electric fields, and, on the other hand, also respond to mechanical deformities (Ward, 1961), both the electrical response of the glia and the mechanical contraction of the glia should be taken into account in interpretation of the synchronization mechanism.

In the formation of an epileptogenic focus, it may be assumed that functional diminution of the intracortical inhibitory neurons intervenes (Li and Chou, 1960), which would be in agreement with Phillips's findings (1956) obtained by intracellular microelectrode recordings, showing that bursts of high frequency short discharges are followed by a hyperpolarized wave, a fact attributed to an inhibitory feedback effect.

Another likely mechanism is that of isolation. When a single weak stimulus is given to the surface of a neurologically isolated area of the cerebral cortex, with its blood supply intact, two types of response are produced. The first is a short lasting surface-negative response, which is transmitted with decrement for a distance of about 10 mm from the stimulating electrode (Adrian, 1936; Burns, 1951; Chang, 1950a,b). With stronger stimuli, this surface-negative response is followed by a second response, which spreads over the slab in all directions from the stimulated point and lasts between 0.5 and 7.0 sec, and during which active cortex becomes surface-positive (Burns, 1951). This has been called the burst response of isolated cortex. The wave front of the burst response is believed to spread across the cortex by way of synapses, while the prolonged repetitive response of each invaded neuron is thought to be maintained by a process of self-re-excitation within the network of nerve cells and their interconnecting synapses. Burns (1949–1951) was not able to record spontaneous

electrical changes from the acutely isolated cerebral cortex in the cat. However, now and then abnormal bursts of electric waves appeared, which he attributed to penetration within the isolated segment of the cortex, through the few nervous fibres that were still intact, of nervous impulses which induced discharges in the isolated cells. He found that similar bursts could be elicited by direct cortical electrical stimulation. Periodic bursts were found to occur from the partially isolated cortex in the acute and chronic state after undercutting or lobotomy (Henry and Scoville, 1952). That spontaneous changes in electrical potential may occur from isolated masses of nerve cells was demonstrated in acute experiments on the isolated brain stem of the goldfish (Adrian and Buytendijk, 1931) and the olfactory bulbs of the frog (Libet and Gerard, 1939).

Ingvar (1955b) showed that bursts from the acutely isolated cerebral cortex can be influenced by electrical stimulation of the reticular formation in the brain stem. If part of the cortex is isolated neuronally, a response burst can readily be elicited by direct stimulation, a burst that spreads far into this isolated portion (Burns *et al.*, 1957). Kristiansen and Courtois (1949) showed that in an isolated portion of the cortex, with intact pial blood circulation, high voltage rapid bursts appear at a relatively short interval after the surgical isolation intervention.

Electric stimulation of a chronically prepared isolated part of the cerebral cortex produces a prolonged epileptiform after-discharge (Echlin *et al.*, 1952; Echlin and McDonald, 1954; Grafstein and Sastry, 1957), and the resting activity of this partially and chronically isolated cortex is similar to the epileptogenic activity of the cortex.

Isolated parts of the cerebral cortex may show spontaneous convulsive activity of long duration, up to 30 min, in the form of bursts or spindles, when isolation of the cortex is not total (Watanabe and Miwa, 1957). This can likewise be observed in man during neurosurgical interventions, in the form of bursts of hypersynchronous paroxysms. The appearance of spindles may sometimes be noted in hemispherectomized dogs, from which the thalamus has been removed.

A focus of epileptic discharges may develop in a portion of the cortex, partially and chronically isolated, in man and in the monkey (Echlin *et al.*, 1959). Local application of ACh to a 2–3 $cm^2$ portion of the cerebral cortex in the monkey, with maintenance of the pial blood circulation, produces rhythmic spike-wave discharges. Isolation of part of the cortex in this way may also create a focus of discharges without the intervention of any other substance. The topical application of 0.2 to 0.5% acetylcholine over a wide area of the chronically 'isolated' frontal or parietal cerebral cortex precipitated discharges of rhythmic wave and spike epileptiform electrical activity selectively from the 'isolated' area. The local use of 1%, followed by 0.2 to 1%, acetylcholine resulted in spread of the epileptiform rhythmic potentials from the partially isolated zone to the motor cortex with clonic seizures and, less often, generalized electrical and clinical convulsions. In contrast to these findings 0.2 to 0.5% acetylcholine never caused epileptiform electrical discharges when applied topically to the unanaesthetized frontal or anterior parietal cortex of normal monkeys or to the hemisphere homologous to one containing a chronically 'isolated' block of gray matter. Thus the 'isolation factor' rather than injury or ischemia is the important

factor in the causation of the supersensitivity of chronically neuronally 'isolated' cerebral cortex (Fig. 19). Consequently, it may perhaps be assumed that partial chronic isolation of a group of cortical neurons in pathological cases, as for instance cortical cicatrices, cerebral tumours etc., should represent an important factor in the development of epilepsy, as the isolated neuronal group by its increased sensitivity has a higher epileptogenic potential.

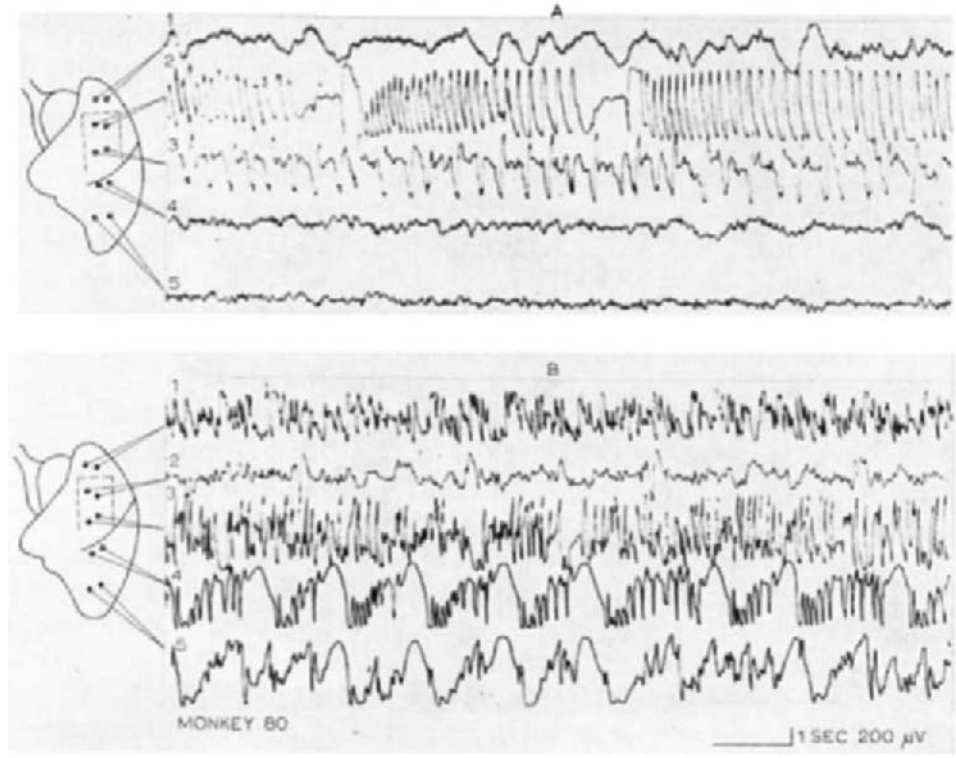



Fig. 19. Electrocorticogram from a monkey with an area of cerebral cortex partially isolated by subpial section along three sides and undercutting months previously. A = ECoG 4 min after the wide application of ACh 0.5% to the cortex from frontal pole to occiput for 2 min. Note that the abnormal electrical firing is confined to the partially isolated block. B = ECoG showing the effect of a similar application of ACh 0.5% preceded by the application of 1% eserine. Note that the abnormal discharge has now escaped from the partially isolated cortex and has involved the entire surface of the hemisphere. Clonic movements occur from the opposite extremities. (From Echlin, 1959.)

Partial isolation by subpial circumsection without undercutting of a segment of the motor cortex modifies excitability and propagation of the convulsive capacity both of the area isolated and of the exact homotopical area in the contralateral hemisphere, although the latter region is not directly affected by the intervention. This homotopical area exhibits spontaneous spike discharges and an increased capacity for producing convulsions after intervention on the opposite motor cortex (Livingstone *et al.*, 1959).

In cats immobilized by coagulation of the mesencephalic reticular formation (without other cortical lesions that would represent an epileptogenic focus), rapid 'spon-

taneous' discharges, up to 1000/sec, can be observed in some of Betz's cells. Thus, Martin and Branch (1958a,b), using extracellular microelectrodes applied to Betz's cell, found, in the normal non-epileptic cat cortex, isolated units that had a spontaneous activity characteristic of the epileptic neuron, that is discharges in bursts at regular intervals with high frequencies of 300–1000/sec, showing a tendency to decrease steadily. These were not lesional discharges, because they lasted over an hour, and the frequency could be changed by antidromal pyramidal stimulation or by cortical stimulation. Moreover, it appears characteristic of certain preparations with extensive lesions of the brain stem to find the activity of the perikaryon appearing in bursts (Martin and Branch, 1958a,b).

Investigations conducted with microelectrodes have brought to light certain facts concerning *the changes that take place in the dynamics of neurons within the epileptogenic focus.*

It was found that around the epileptogenic focus, created in the monkey with alumina cream, in the inter-ictal periods the units fire spontaneously in greater number than in the more distant cortical tissue, that is normally and not governed by the irritative action of the focus. The amplitude of the discharges of the spontaneously active cells in the epileptogenic focus is lower than in the neighbouring cortex. Whereas in the sensory-motor cortex an afferent peripheral stimulus elicits activity of the cell fairly easily, in the epileptic preparations of this zone it is difficult to obtain this activity by afferent stimulation.

Inter-ictal activity of the epileptic unit is usually manifested by recurrent bursts of discharges. The rate at which these bursts are repeated is remarkably constant for each unit, and varies from 3 to 6/sec from cell to cell. At other times, cellular inter-ictal activity is reflected by long 'tonic' discharges of 100–400/sec, sometimes interrupted by still more rapid discharges of 800/sec.

According to Schmidt *et al.* (1959), autonomic activity that characterizes the epileptic neuron is due to a relatively persistent dendritic depolarization, which results in a difference in the potentials of the cellular body and its dendrites. In these circumstances the membrane potential of the perikaryon is quickly re-established, giving rise to a current from the latter to the depolarized dendritic tree. If this current attains the threshold then a high frequency discharge occurs. Dendritic depolarization in the epileptic could result from continuous mechanical stimulation of the dendrites by the glial cicatrix.

The behaviour of a cell in the neighbourhood of an epileptogenic focus, created in the monkey by alumina cream, varies during propagation and development of an epileptic seizure from cell to cell. In some cells all activity ceases during the paroxysm: the cell no longer fires. In others, activity begins and becomes more intense before the spontaneous cortical seizure begins (recorded electrocorticographically). As the seizure develops and more and more repetitive waves appear, some cells fire at high frequencies of up to 1000/sec.

The capacity of the cortical neurons to generate seizures is directly related to disturbances in the functions of the cell structures that mediate the direct cortical response. White *et al.* (1960), studying the direct cortical response with the aid of

electrodes implanted in epileptic monkeys (rendered epileptic by alumina cream), found an initial depression in the amplitude of the direct cortical response immediately after the operation, followed several weeks later by an increase in the dendritic response concomitant with the onset of epileptic activity on the EEG. Hence development of the epileptogenic focus runs parallel to an increase in excitability of the membranes with a gradational response, *i.e.* of the dendrites.

In general it is admitted that the epileptic spike, as recorded on the scalp or on the pial surface, represents summation of the activity of the membranes with a gradational response (dendrites). Because of its high amplitude it is considered that relatively large areas of the dendritic membranes must be depolarized in order to generate such a potential.

It is likely that the classical epileptic spike that appears on the encephalogram is induced by fluctuations of the membrane potentials with a duration longer than that of the cellular body of the neuron (of the perikaryon). These membrane potentials probably have the properties of gradational responses. In the cortex, such responses to local stimulation have been attributed to the dendrites (Bishop, 1954; Bishop and Clare, 1953); the EEG abnormal waves in epilepsy have been attributed to summation of abnormal dendritic potentials (Brazier, 1955).

It is difficult to establish a correlation between the electroencephalographic phenomena and those occurring at cellular level. Sometimes the epileptic unit fires repetitively in the course of a slow wave. During a seizure it is evident that massive dendritic potentials arise, sufficiently synchronized to induce summation. But the mechanism of this synchrony has not yet been sufficiently well defined. Schmidt *et al.* (1959) believe that this synchronization is not induced by the all-or-none discharges of the perikaryon, because the latter cannot fire even during the most active phase of the seizure. It may be assumed that the preterminal axons of the intercalated cortical neurons are activated by massive fluctuations of the dendritic potential. A dendro-dendritic conduction may perhaps also intervene. Autonomic activity, which characterizes the epileptic neuron, is probably due to persistent dendritic depolarization, which gives rise to a difference in the potentials of the perikaryon and the dendrite.

Records taken at the level of the epileptic cortex, on the pial surface with a surface macroelectrode and at the same level in the depth with an intracortical microelectrode, showed that, although the 'epileptic' cell sometimes spontaneously fires high frequency bursts, there is no relation between this activity of the soma (of the perikaryon) and dendritic activity recorded by the pial electrode. Although the paroxysmal epileptic discharge is manifested from the viewpoint of cellular behaviour by a burst of high frequency spikes, there exist within the focus cells that fire only once or twice, and whose activity does not appear to be connected with the epileptic paroxysms (Enomoto and Ajmone Marsan, 1959). There is therefore no close correlation between dendritic activity and that of the cellular body in epilepsy. Nevertheless, under the action of certain convulsant substances a correlation may exist between dendritic activity and the spikes of the neuronal units (Enomoto and Ajmone Marsan, 1959). According to Ward (1961) this shows that a difference exists between ictal activity induced by convulsant substances and 'spontaneous' epileptic activity.

An epileptic discharge in the form of spikes may or may not be accompanied by bursts of perikaryon discharges recorded with microelectrodes; but even when the spike is accompanied by such bursts no correlation exists between the slow potential phase of the spike and these neuronal discharges (Ward, 1960), a fact which also appears to have a clinical corollary as the epileptic spikes observed in the motor cortex are not as a rule accompanied by muscular jerks. The onset of seizure discharges is accompanied by massive dendritic depolarization (Von Euler *et al.*, 1958).

In their experiments, Ward (1961) showed that the epileptic neuron in the vicinity of an epileptogenic focus, induced by alumina cream injection in the monkey cortex, fires recurrent high frequency discharges ranging between 200 and 800/sec continually and rhythmically also between the seizures. Recording with microelectrodes around an epileptic focus, in man, during a neurosurgical intervention, showed that in this case too the epileptic neuron continually discharges at high frequencies.

The periphery of an epileptogenic focus has a different behaviour to that of its centre (Konigsmark *et al.*, 1958). At the periphery of an epileptogenic focus, produced by electric stimulation of the cerebral cortex in the monkey, in the centre of which there are continuous bursts of spikes at a frequency of 25–40/sec, lasting 25 msec, slow surface-negative waves are observed instead of biphasic waves with abortive spikes overlying these slow waves. At the periphery of the discharging island of cortical cells it was possible to see waves of similar frequency to those in the seizure centre but which were less well developed, surface-negative instead of biphasic, and frequently devoid of superimposed spikes. Moreover, these waves did not completely erase intrinsic activity of the area, and upon termination of the nearby seizure discharge, the waves disappeared from the tracing without leaving it in a state of isoelectric exhaustion. This undulating activity appeared, therefore, to represent the initial abnormality displayed by a group of cells becoming invaded by a locally propagating seizure, and represents pre-epileptic changes in dendritic activity, if we bear in mind that slow changes in the cortical potential represent, according to Clare and Bishop (1955) and Purpura and Grundfest (1956a), electrotonic changes in the polarization of dendrites.

The epileptogenic focus has a lower threshold for the after-discharges induced by electric stimulation, which would be due to an increase in the superficial cortical response (Eidelberg *et al.*, 1959). Epileptogenic lesions localized in a hemisphere are always accompanied by a state of diffuse hyperexcitability of the neurons, reflected by diminution of the convulsant threshold of the neurons. Therefore, it is not only the focus that is hypersensitive, but also the formations to which it is connected (Johnson and Walker, 1952). This hypersensibility is reflected by diminution in the threshold to electrical and chemical stimulation, and seems to be the result of functional disturbance of the normal neurons due to the influence of the epileptogenic focus.

### *D. Peculiarities of epileptogenic foci in different cerebral structures*

The epileptogenic focus has different characteristics according to the structure of the formation in which it arises.

Penicillin injection into the *non-specific thalamic system* produces spindle-like discharges of high amplitude slow waves at a frequency of 3.5–5 c/s. They appear synchronously in the ipsilateral hemisphere when the focus is located in the intralaminar nuclei, and appear in both hemispheres when the focus is on the medianline (Ralston and Ajmone Marsan, 1956). These discharges are transmitted by the non-specific thalamo-cortical projection system. When the penicillin focus is fairly widespread, spikes also appear, first in the thalamus and then projected on to the cortex, where they may appear grouped together with the hypersynchronous wave discharges, sometimes forming a spike-wave complex. It is therefore possible that the 'petit mal' seizure has its origin in a focus in the non-specific thalamic system close to the median line, notwithstanding that the spike and wave have their origin in different systems.

The focus in 'grand mal' seizures appears to be located in the thalamus, and to involve the non-specific reticular formations being projected upon the cortex by the mechanism of the generalized recruitment response relayed along diffuse cortical projection pathways. Gastaut and Fischer-Williams (1959) compare hypersynchronous discharges in generalized epilepsy with a kind of paroxysmal 'sleep' localized in the thalamo-cortical system and inducing functional exclusion of this system. This can be understood if we bear in mind that the recruitment response system is responsible both for the generalized epileptic discharge and for the periodical discharges during barbiturate sleep. Functional elimination of the thalamo-cortical system is directly responsible for loss of consciousness, and indirectly for the convulsions by liberation of the subjacent reticular structures.

However, we cannot speak of a centrencephalic focus, for centrencephalic epileptic seizures cannot be attributed to a single focus, as it can for a focus in the cerebral cortex. The centrencephalic seizure is due to neuronal system disturbances. Several experimental investigations have shown that the brain stem at the level of the mesencephalon, the thalamus and the cerebral cortex all play a part in generating centrencephalic discharges (Jasper, 1962b).

The cardiazol epileptic discharge resembles that produced by local electrical stimulation of medial thalamus. According to Ajmone Marsan and Marossero (1950), cardizol does not appear to exercise its convulsant action on the structures situated caudally at the level of the diencephalon. In the presence of an experimental epileptogenic focus produced in the animal by alumina cream, cardiazol in subconvulsive doses activates this focus, leading to spread of the epileptic excitation from this focus and to a generalized seizure.

Not all the formation are equally sensitive to local application of convulsant substances. Injection of a 2–3% strychnine solution at the level of the thalamic nuclei, on one or both sides, did not produce during neurosurgical interventions any convulsive activity in a number of patients; the same result was obtained with strychnine injections in the white matter (Kendryck and Gibbs, 1958).

Local application of strychnine, penicellin or cardiazol on the suprasylvian gyrus in the non-anaesthetized cat produces discharges that can be recorded with microelectrodes implanted in the different neurons of the respective cortical layers (Enomoto

and Ajmone Marsan, 1959). On comparing neuronal discharges with the paroxysmal discharges recorded on the surface EEG, it was found that the neurons showed grouped discharges of high frequency spike potentials, whereas neighbouring neurons fired only one or two spike potentials or none at all. When paroxysms appeared on the EEG, it was found that many of the neurons with frequent spontaneous discharges ceased to fire during the electroencephalographic paroxysm.

A penicillin focus on the gyrus cinguli in the cat, induces equal, synchronous activity on the convexities of both hemispheres, in the form of 8–12 c/s spindles (Ralston, 1961). This focus may be transformed into a seizure of several seconds, that may remain localized or become generalized on both hemispheres. Synchronia neither disappears in the cingulus after section of the corpus callosum, nor after destruction of the neighbouring lateral gyrus, and nor even after incision of the white matter that separates the gyrus cinguli from the suprasylvian gyrus. Synchronia disappears, however, after destroying the massa intermedia and the adjacent median thalamic nuclei, which shows that it is probably transmitted by the median thalamic reticular formation.

The electric discharges, produced by stimulation of the gyrus cinguli in the non-anaesthetized freely moving cat, are of low frequency and 5–10 sec duration, in contrast to those produced in the hippocampus whose duration is much longer. The seizure in the gyrus cinguli spreads to the hippocampic system only when supraliminal stimuli are used. When the discharge spreads to other cortical and subcortical structures, the cat which had gone to sleep on stimulation of the gyrus cinguli wakes up (Andy *et al.*, 1957a) (Fig. 20).

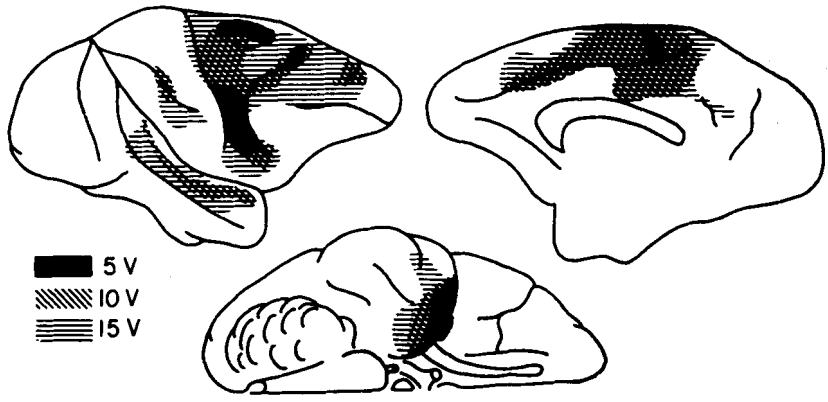



Fig. 20. Diagrams of the monkey brain to show the difference in threshold voltages in electrically-induced seizures in various cortical areas. (From French *et al.*, 1956.)

A penicillin focus in the region of the massa intermedia of the thalamus produces bilateral synchronia in the form of spindles similar to that produced by application of penicillin to a single gyrus cinguli (Ralston, 1961).

Convulsive discharges induced by local mescaline application also appear at the

level of the cortex isolated in its nervous connections, but with maintained pial circulation. These discharges are similar in form and amplitude, but appear much later than in the normal cortex.

Injection of alumina cream into the anterior part of the temporal lobe in the cat produces electroencephalographic alterations followed by convulsive seizures. Some animals have motor automatism seizures at the level of the head, more seldom of the limbs. In monkeys, the seizures closely resemble, from the clinical point of view, temporal epilepsy in man. Sometimes focal jerks are also observed on the face (Youmans, 1956).

Stimulation of the median supracallosal cortex in the non-anaesthetized cat during 5–10 sec induces 16–20/sec rhythmic discharges in gyrus suprasplenialis, 26–28/sec discharges in the posterior limbic area, and 16–18/sec discharges in the anterior limbic area. After numerous stimulations eliciting considerable epileptogenic activity, seizure discharges from the anterior limbic area show a decrease in the amount of faster 16–18/sec seizure activity, an increase in the amount of the slower subharmonic 8–9/sec seizure activity, and an increase in the threshold seizure discharge. Full-blown electrographic seizures of the limbic area feature high amplitude 2–3/sec spike and wave-like complexes, not usually seen on the lateral surface, but spreading to the hippocampus. Photic driving of relatively high amplitude is seen on the posterior mesial surface, especially at the frequency of 5/sec. Photic driving can also be seen on the most anterior portion of the mesial surface. Convulsions originating in the limbic region have high amplitude 2–3/sec spike-wave complexes and show a tendency to propagate to the hippocampus; they are accompanied by particular changes in behaviour and in the autonomic system (Hughens, 1959b).

Subcortical injection of certain convulsant substances may induce an epileptic seizure. Injection of sodium fluoroacetate into the thalamus elicits an epileptic discharge in this formation before reaching the cortex (Ward, 1947b).

*Chronic epileptogenic lesions* produced in the subcortical zone by alumina cream injections may induce severe generalized convulsive seizures, either by secondary activation of the cerebral cortex or by downward projection of the epileptogenic impulses along motor pathways. Electrocoagulation of both Ammon's horns in the cat produces, two weeks after the operation, motor and sensitive fits that can be triggered either by intermittent photic stimulation or by sensitive stimulation (Green and Naquet, 1957). These motor seizures have an adversive character, and are accompanied by movements of the mouth, sniffing, clonic movements of the face, paroxysmal hyperaesthesia, continual scratching, fear, etc. Alumina cream injections in the amygdaloid nucleus in the dog may induce seizures similar to those in psychomotor epilepsy in man (Aida, 1956).

The hippocampal focus experimentally produced by alumina cream injections behaves differently in a state of arousal and during sleep. At the moment of arousal, the hippocampus in the normal cat shows a rapid 20 c/s short activity, followed by slow synchronization. In the epileptic cat (the epilepsy having been induced by alumina cream), spontaneous activity of Ammon's horn consists in bilateral phasic and continuous discharges and slow asynchronous spikes which are smaller on the healthy

side. During sleep, the spikes are more frequent, and epileptic activity of the hippocampus can be either decreased or enhanced, in the form of rapid wave discharges (Passouant *et al.*, 1958).

An amygdaloid epileptogenic focus produced by alumina cream injections induces, between the seizures, sporadic discharges of slow waves, spikes or spike-wave complexes at the periphery of the amygdala, in the hippocampus or the septal region. These sporadic discharges spread to one or several of the following formations: uncus, insula, temporal pole, temporal lobe, and posterior orbital region (Gastaut, Vigouroux *et al.*, 1952). These discharges may be homolateral or contralateral to the lesion, but they are never bilateral and synchronous.

An apparent cortical focus may have its origin in a subcortical focus and be only the projection of such a focus. Sometimes the subcortical focus may produce in the cortex a self-sustained secondary focus whose discharge duration is longer than that of the primary, subcortical focus. At other times a subcortical focus may induce bilateral and symmetrical cortical discharges, as for instance a focus in the septum giving secondary discharges in both temporal lobes.

Leads with depth electrodes in man have confirmed certain experimental data. Evidence was obtained of primary and secondary foci in man, and of the fact that a lesion in the median structures of the temporal lobe (amygdalo-unco-hippocampal region) makes the homologous area become epileptogenic (Fischer-Williams and Cooper, 1963). In 6 patients with temporal lobe epilepsy who had tempral lobe EEG abnormalities before operation, Brazier *et al.* (1954) found spike discharges in the amygdaloid region, but they noted no predictable relationship between spikes in the depth and spikes at the cortex. In some cases, a rhythmic or non-rhythmic thalamic activity, in the form of bursts of 14–18/sec waves, was recorded (Fischer-Williams and Cooper, 1963).

Electroencephalographic foci in man are not always the expression of anatomic lesions. The focus may sometimes be 'functional', or maintained by lesions in the subcortical centres. In the latter, the cortex forms part of a subcortico–cortico–subcortical circuit: interruption at the level of the cortex by extirpation of the cortical focus may influence the course of the disease favourably.

Artificial strychnine foci in the frontal and temporal cortex during neurosurgical interventions in man points to a close functional relationship between the median temporal and the median orbito-frontal regions.

### *E. Pharmacological drugs, asphyxia and epileptogenic foci*

As regards the action of certain *pharmacodynamic substances* it was found that the cortical epileptogenic focus is as a rule little influenced by known anticonvulsant substances. Thus the epileptogenic focus produced by minimal cortical stimulation is not influenced by intracarotid phenobarbital injection in 10 mg amounts/kg body weight (Whieldon and Van Harreveld, 1951). Gangloff and Monnier (1957) studied the local action of some clinical familiar anticonvulsant drugs on the brain of the unanaesthetized rabbit on seizures elicited by electrical stimulation of the cortex, the dienceph-

alon and rhinencephalon. They analysed the threshold, the duration and the pattern of the electrically induced after-discharge. This action may raise the threshold, shorten the duration and modify the electrographic pattern of the after-discharge in a definite way: reduction of the spikes in voltage and quantity, with enhancement of slow wave components and reinforcement of the refractory periods between the spikes. Dilantin (30 mg/kg) given into the carotid artery produced some slowing in the frequency of spike discharge, and given orally in doses of 100–150 mg/kg increased the threshold only of those seizures which were elicited by diencephalic stimulation. Focal electric seizures produced in the lateral gyrus of the non-anaesthetized cat are depressed by dilantin and phenobarbital, in doses that are usually sufficient to abolish status epilepticus in man (6–11 mg/kg body weight), whereas tridione has no significant effect (Vastola and Rosen, 1960).

Chlorpromazine injection (12 mg/kg body weight) has no evident effect on the cortical penicillin focus in the cat, on the primary focus, nor on propagated activity (Kreindler, Voiculescu *et al.*, 1960). On the contrary, chlorpromazine in a 2.5% solution topically applied to the cortex at the site at which mescaline was previously applied first reduces the negative phase amplified by mescaline, then the positive phase of the click-evoked potential in the anterior superior ectosylvian gyrus. Chlorpromazine injected into the carotid or into the general circulation blocks mescaline discharges for several minutes.

Stoica and Marcovici (1960) showed that the cortical cicatrix modifies cardiazol reactivity in the cat. The lesions were produced in the sigmoid gyrus, and in the anterior and posterior suprasylvian gyrus. Duration of the cardiazol seizure varied with the interval that had elapsed after cicatrization. The authors conclude that there is in the first phase, at the level of the damaged hemisphere, a post-traumatic inhibitory process, and in the late phase a deinhibition phenomenon.

*Asphyxia* influences discharges from the penicillin focus, as well as their spread to other formations (Kreindler, Voiculescu *et al.*, 1960) in the curarized cat after artificial respiration has been stopped. As a rule, epileptic activity disappears at the same moment in all the formations; however, discharges sometimes persist in certain subcortical formations after cessation of cortical activity, as for instance at the level of the periaqueductal grey matter or of certain thalamic nuclei (Fig. 21). When artificial respiration is taken up again after 2 min, the paroxysmal discharges reappear after an average interval of 95 sec. In general, renewed epileptic activity is preceded by the appearance of wave spindles, and is first re-established at the level of the primary focus. Sometimes, however, it first reappears in other formations, for instance in the sigmoid gyrus in the case of a primary focus on the lateral or suprasylvian gyrus, or in the parafascicular nucleus, the mid-line or lateral ventral nuclei in the case of a primary focus on the sigmoid gyrus (Voiculescu, Broşteanu *et al.*, 1960); Voiculescu and Broşteanu, 1960).

There is an evident distinction, from the viewpoint of cerebral electrical activity, between a seizure in a normal animal and an asphyxiated one. Whereas in the former the electric seizure ends suddenly with waves of very large amplitude on all leads, though with somewhat decreased amplitudes in the last paroxysmal waves and also

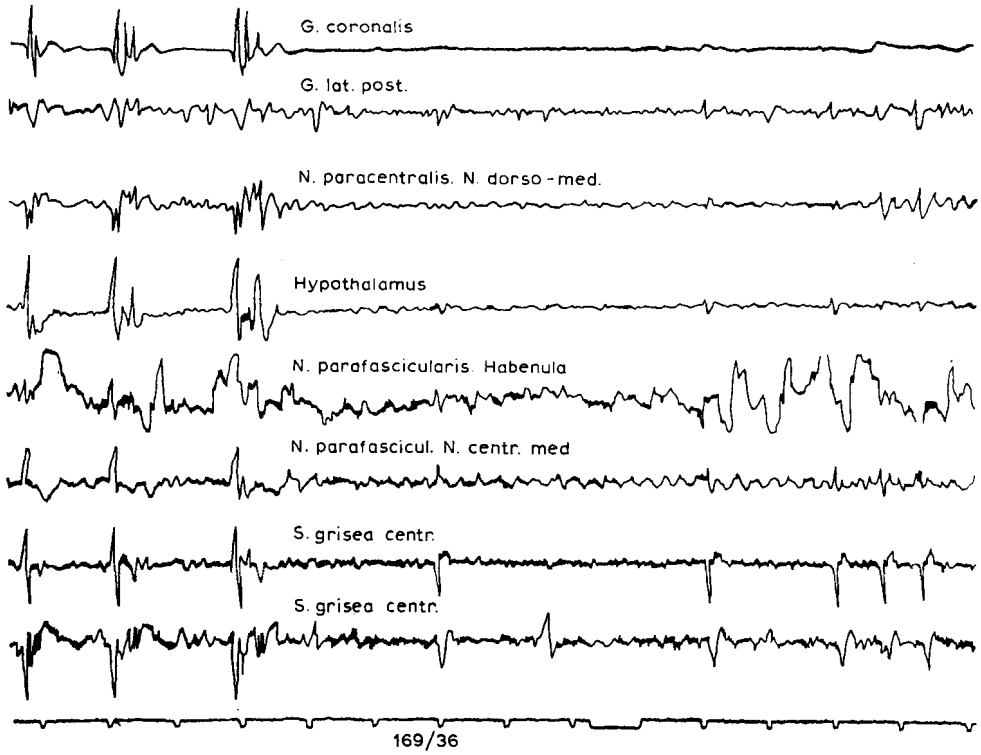



Fig. 21. Influence of asphyxia on convulsive activity induced by penicillin in the sigmoidian gyrus of the cat. Suppression of the cortical and thalamic discharges. They persist at the level of the periaqueductal grey matter. (From Kreindler, Voiculescu *et al.*, 1960.)

with slower frequency simultaneously occurring over the cortex and the subcortical structures; in the asphyxiated animal the waves show a very reduced amplitude and are almost completely absent over the cortex. From the electric point of view, therefore, the end of the attack differs completely in the normal animal from that in the asphyxiated animal.

The paroxysmal discharges induced by the application of penicillin over the cerebral cortex likewise undergo alterations under the action of asphyxia in the curarized cat. Three or four min after the arrest of artificial respiration the discharges become rarer and rarer, their voltage falls and the complex discharges consisting of several oscillations become simpler and simpler. Electrical activity comes to a complete standstill about 90 sec after respiration has ceased. Sometimes discharges may be seen to occur in some deep structure although the paroxysmal activity of the cortical focus has ceased (Fig. 22).

Asphyxia usually suppresses the cortical focus without appreciably influencing the discharges propagated to certain subcortical formations. The effect of asphyxia is preferentially exercised at the level of the dendritic potentials of the cortical penicillin focus, while axonal discharges led off at the level of the subcortical formations still persist. The epileptic waves recorded on the electrocorticograph demonstrate sum-

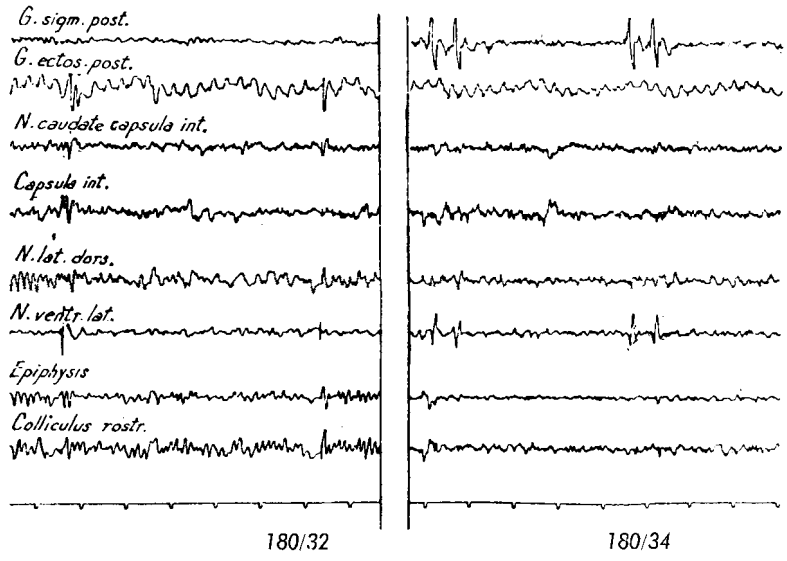



Fig. 22. Penicillin focus in the posterior sigmoid gyrus. Following 3 min of asphyxia artificial ventilation is resumed. Left half of the figure: 1 min after resumption of respiration the paroxysmal discharges are missing at the penicillin focus level but present in posterior ectosylvian gyrus and various subcortical structures. Right half of the figure: 2 min after resumption of respiration the penicillin focus discharges re-appear (From Voiculescu and Brosteanu, 1960).

mation of the abnormal dendritic potentials (Schmidt *et al.*, 1959). Chang (1955b), analysing the electric response of the pyramidal cells to antidromal stimulation, showed that a dendritic, a somatic and an axonal component exist and that the dendritic component is more sensitive to anoxia. Hence, in the case of a penicillin focus, asphyxia would suppress only the dendritic potentials in a first phase, leaving intact the axonal potentials which can be led off in certain subcortical formations for some time.

### *F. Epileptogenic focus and evoked activity*

Smith and Purpura (1960) investigated the interaction of a surface evoked potential and focal paroxysmal discharges produced by epileptogenic lesion due to local freezing of the cortex over a very small area. When superficial cortical responses were evoked from previously traumatized cortical sites giving rise to low-frequency (less than 1/sec) spontaneous paroxysmal discharges, consistent changes in evoked responses were observed during various phases of the focal spikes. The superficial cortical response increased in amplitude and duration before and sometimes after the spontaneous discharges. Responses evoked during the 600–800 msec period occupied by diphasic negative–positive spontaneous discharges underwent more complex alterations. During the initial rising phase and negative peak of the focal spike, the superficial cortical response was reduced, whereas during the late positive components the evoked responses were augmented. This kind of interaction between surface evoked

responses and focal discharges was encountered in different cortical regions (*e.g.* posterior sygmoid gyrus, suprasylvian gyrus).

Specific thalamo-cortical evoked responses are altered by discharges arising in posterior sygmoid gyrus in a manner similar to transcallosally evoked responses in anterior suprasylvian gyrus lesions. Repetitive stimulation of primary or inter-hemispherical afferent pathways produces facilitatory or inhibitory effects on focal discharges which are, in part, dependent on stimulus frequencies (Smith and Purpura, 1960).

In the cortical neurons of the sensory cortex, discharges of the all-or-none type can be fairly easily evoked and recorded with microelectrodes. This evoked activity is generated by axo-dendritic and also probably by axo-somatic inputs. On the contrary, in the epileptic cortex (alumina cream) such an activity cannot be evoked in the vicinity of the cicatrix in the postcentral cortex (Schmidt *et al.*, 1959), which contrasts with the activity evoked in the strychnine-treated cortex. The nature of the focus appears therefore to determine certain reactivity peculiarities.

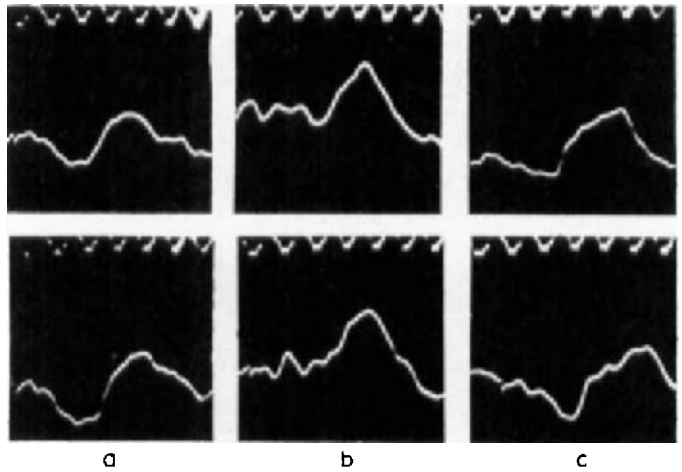



Fig. 23. Influence of pentilenetetrazol in topical cortical application to the primary somesthetic evoked potentials in the cat. a = before the application; b (upper trace) = 3 min, (lower trace) 5 min after the application; c = after washing off the pentilenetetrazol by physiological serum (From Kreindler, Steriade *et al.*, 1961.)

An epileptic focus induced in the cat under various experimental conditions (flaxedil-treated non-anaesthetized 'encéphale isolé' or deep barbiturate sleep) by topical application of mescaline to the sensory-motor, acoustic and optical areas, changes the responses evoked in these zones by specific peripheral stimulation. The evoked response is characterized by high amplification of the negative phase. This potentiation of the evoked response appears before the spontaneous discharges. Similar results are obtained when epileptogenic foci are produced by topical application of pentamethylenetetrazol and penicillin (Crighel, 1959; Kreindler, Crighel *et al.*, 1961; Crighel, Stoica *et al.*, 1962) (Fig. 23).

Intermittent photic stimulation potentiates mescaline discharges in the acoustic area,

rendering them rhythmic. Acoustic or optic stimulation does not influence the discharges organized in the ectosylvian area and prevents the potentiation and rhythmic phenomena produced by intermittent photic stimulation.

Topical application of mescaline changes evoked potentials of the primary and secondary type. Crighel, Stoica *et al.* (1962) found that in the cat in deep barbiturate sleep (for the study of secondary potentials recorded from the anterior marginal gyrus following stimulation of the sciatic nerve), or in the curarized cat or the 'encéphale isolé' (for click-induced primary potentials recorded on the anterior superior ectosylvian gyrus), the application of mescaline to the recording zone induces inversion of the polarity of the evoked potentials: the positive phase which is more accentuated at the beginning gradually fades and the late phase, having less amplitude before the application of mescaline, grows in amplitude in the case of secondary evoked potentials. Potentiation of the negative phase of the evoked response is also noted in the case of primary potentials from the anterior superior ectosylvian gyrus after mescaline application in the curarized cat. Two min after mescaline application the amplitude of the positive phase diminishes and that of the negative phase increases. Moreover, a negative, low amplitude phase precedes the positive phase. Ten min after mescaline application, the negative phase that follows upon the positive phase has a high amplitude, is of short duration and takes on the aspect of a spike (Fig. 24). Application of reserpine to the site where mescaline was applied and the potentials were recorded produces a change in the click-induced primary evoked potential from the anterior superior ectosylvian gyrus, that is, the initial negative

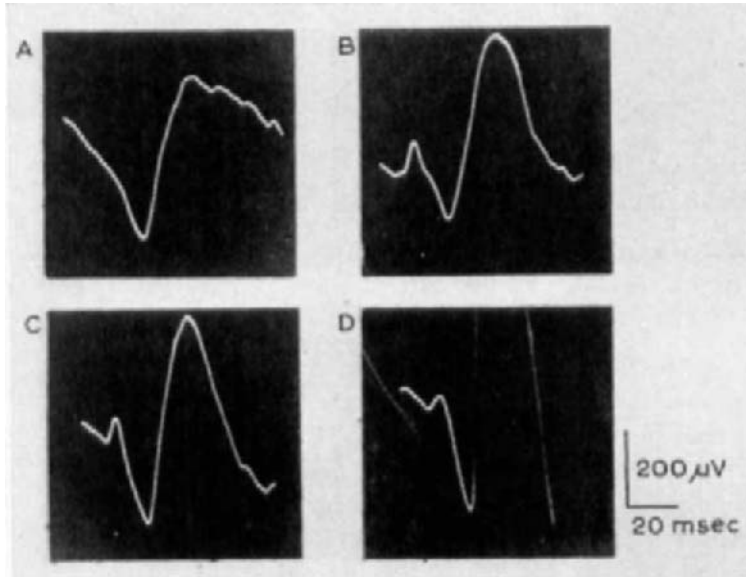



Fig. 24. Primary evoked potential by click in E.a.s.(a). Two minutes after application of mescaline on E.a.s. there is a diminution of the positive phase and an amplifying of the negative one, and there appears an initial negative phase of low amplitude (b). c = 3 min after application of mescaline and (d) 10 min after this application when the negative phase is much amplified. The mescaline was applied near the recording electrode. (From Crighel, Stoica *et al.*, 1962.)

phase, which is sometimes hardly delineated after mescaline application, increases in amplitude and the positive phase becomes deeper.

Therefore mescaline, topically applied to the cerebral cortex and inducing discharges of the epileptic type, changes the primary and secondary responses to acoustic, visual and somesthetic stimuli, acting upon the positive and especially upon the negative phase, which it strongly amplifies: its action is thus similar to that of strychnine topically applied to the cortex and, to a certain extent, to that of penicillin or pentamethylenetetrazol (Kreindler, Voinescu *et al.*, 1961b). Hence, amplification of the negative phase of the evoked potential to sensory stimuli appears to be the common characteristic of substances which, topically applied to the cortex, induce epileptic discharges. This amplification of the negative phase indicates that the action of epileptogenic substances in topical application is first exerted upon the superficial structures that interfere in the organization of the negative phase of the primary or secondary cortically evoked responses. This action affects the apical dendrites of the pyramidal neurons and internuncial neurons of the superficial layers.

The organization of an epileptic discharge, however, also demands the intervention of the deep layers. The response evoked to a sensory stimulus is changed according to the topical action of mescaline not only by a huge amplification of the negative phase, but also by the appearance of positive waves, *i.e.* a late positive and sometimes an initial positive phase. This points to the intervention of certain deep cortical structures. A second, late negative phase then appears and is transformed into an epileptic potential only when the stimulus is very strong.

The changes induced by a cortical epileptogenic focus (penicillin, mescaline etc.) in a sensory-evoked potential can be used as an experimental pattern for studying the role of afferent impulses in inducing an epileptic seizure. The experiments of Smith and Purpura (1960), as well as our own, show that afferent impulses influence the activity of an epileptogenic focus. During the various phases of focal discharge differences are observed in the organization of the synaptic systems that intervene in the production of the surface-negative, dendritic postsynaptic potential, the cortical focus being produced by local freezing (Smith and Purpura, 1960). The surface-negative components of the responses evoked by transcallosal stimulation or stimulation of the lateral thalamus show similar interaction phenomena with individual focal discharges. Postsynaptic potentials evoked by direct cortical stimulation are at first increased, then abolished during and increased after the focal spikes. In contradistinction, the recruitment responses produced by medial thalamic stimulation are not affected by spontaneous, recurrent discharges. The ability of evoked responses to fire focal spikes shows variations in the interaction. Such firing, which depends upon the frequency of spontaneous discharges, is marked in the periods before and immediately following a relatively sustained paroxysmal activity. Firing is more readily induced by repetitive transcallosal or lateral thalamic stimulation, while medial thalamic stimulation is inefficient. Direct cortical stimulation produces focal spikes mediated by intermediary s'ages characterized by complex alterations of the evoked postsynaptic potential. These results appear to indicate that intermittent paroxysmal discharges produced by local freezing occur partly through the synaptic systems that

interfere in the direct cortical, transcallosal and specific conduction responses, but not through those responsible for thalamo-cortical recruitment. This suggests that the superficial postsynaptic potentials of certain varied evoked responses are generated at different dendritic levels by a route of differently organized interneuronal systems.

Four factors interfere in this process: (i) the phenomenon of organization of the epileptogenic focus within the superficial dendritic network with its internuncial neurons; (ii) the deep network with pyramidal and internuncial neurons; (iii) and (iv) the afferent impulses under their two aspects, competition and convergence.

Kreindler, Steriade *et al.* (1961) conducted investigations in the non-anaesthetized cat on the relationship between after-discharges of the epileptic type induced at the level of the posterior sigmoid gyrus or coronary gyrus and the somesthetic response evoked by a shock applied to the contralateral sciatic nerve; and further investigation compared the after-discharge induced at the level of the marginal gyrus and the potentials evoked by single or repetitive photic stimulation.

The response evoked by a single stimulus applied to the sciatic nerve cannot be made evident during 8–10 sec after focal electric stimulation of the specific sensory area, even when the stimulus is subliminal for producing an after-discharge. Only after 10–12 sec does the evoked potential reappear, now however reduced in amplitude at the level of all the areas recorded.

Intermittent photic stimulation induces in the visual area, rhythmic potentials that can be made evident during an after-discharge induced by focal stimulation of the marginal gyrus both on the symmetric contralateral point, and sometimes also at the

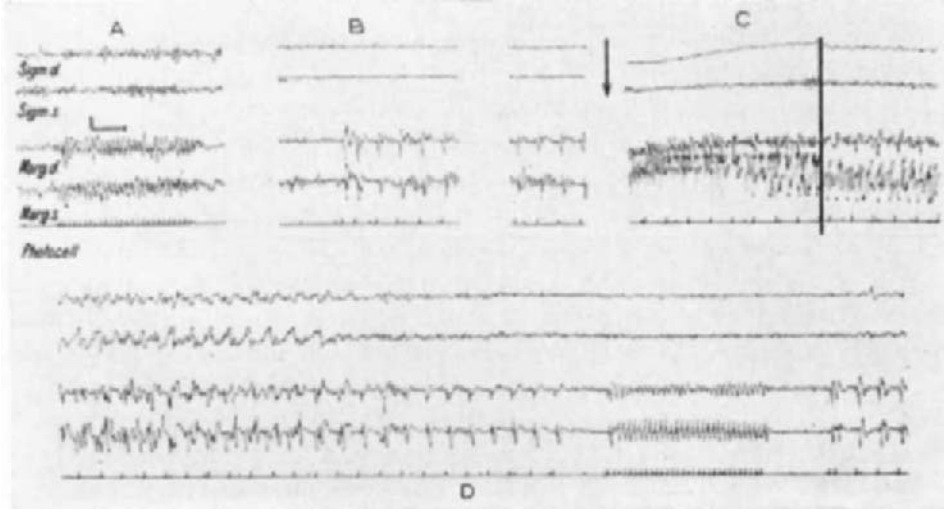



Fig. 25. A and B = responses evoked in the g. marginalis by rhythmic photic stimulation with different frequencies. C = stimulation of the left g. marginalis with a liminal electrical stimulus induced an after-discharge on the same side and a reduced one on the contralateral side. During these discharges the photic stimulation induced responses even on the left, among the great waves of the after-discharges. D = in a later period of the after-discharge the evoked responses are evident and become generalized. During the postparoxysmal silence, the responses in the g. marginalis have a simple, schematic pattern. (From Kreindler, Steriade *et al.*, 1961).

level of the stimulated point, provided that amplitude of the after-discharge wave does not cover or interfere with these visual responses. The response evoked by a single photic stimulus behaves in the same way. At the end of a paroxysm with focal onset, even if it becomes generalized, photic responses appear more clearly than in the controls, and the potentials evoked by repetitive photic stimulation at 7–10 c/s are far more sketchy and larger (Fig. 25).

Epileptogenic stimulation of an associative thalamic nucleus (posterior lateral nucleus) does not prevent the appearance of photically evoked potentials in the visual area. Even during ample electrical discharges from the secondary focus created by stimulation of the marginal gyrus, visually evoked potentials are superimposed upon the paroxysm, but can be differentiated from the waves of the latter. They only disappear from the leads on which the waves take on a complex morphology and have a very rapid frequency, but reappear as soon as the epileptic paroxysm is over.

Therefore while in the somesthetic area the specific sensory response disappears for several seconds following an after-discharge, in the visual area this response persists even during the after-discharge. This may be due to a different spatial distribution of the neuronal chains at these two cortical levels. In the case of a somesthetic after-discharge it may be assumed that the neuronal circuits involved in the focal paroxysm are the same as those also used by the somesthetically evoked potential. Disappearance of the potential following an after-discharge in the somesthetic area would be due to functional exhaustion of some of the neuronal chains that took part in the after-discharge. The photically evoked potential, however, uses neuronal chains different from those that participate in the after-discharge from the marginal gyrus, so that it can appear even during a focal paroxysm. Smith and Purpura (1960) noticed differences in the behaviour of certain evoked potentials of various origin — thalamocortical or superficial cortical response — depending on the spikes generated by a focal epileptogenic lesion. In their experiments, however, the potential evoked by a shock applied to the posterior lateral ventral nucleus reappeared after a shorter period than the potential evoked by stimulation of the sciatic nerve in the experiments of Kreindler, Steriade *et al.* (1961). This might be accounted for by the fact that the volley applied to the posterior lateral ventral nucleus is more homogeneous and can more readily overcome the barrier opposed by neuronal exhaustion of the sensory-motor area.

The convulsive attack causes significant photic driving alterations not only in the visual pathways and projections but in many other structures as well. In the literature there is no agreement regarding the structures which react to repetitive photic stimuli, probably because the experimental conditions were not identical (Hunter and Ingvar, 1955). Upon investigating the behaviour of different cerebral structures to repetitive photic stimuli before and after the electroconvulsive attack in the cat, Broşteanu and Voinescu (1958) found that the attack may alter the capacity of a given structure to follow the photic stimulation rhythm. Mostly it is only a question of small variations. However, some structures, such as the anterior colliculi, the posterior gyrus splenialis and the lateral ventral nucleus and medial ventral nucleus of the thalamus display a very marked photic driving after the attack as compared with that preceding it. On

the other hand, the changes in this reactivity of the various structures after the convulsive attack vary very much from one moment to another after the end of the seizure, there being variations in both directions. These observations supply another argument in favour of the view that reactivity becomes normal at variable intervals after the attack and that during this restoration there are periods of oscillations above or below the normal average.

White *et al.* (1960) studied *changes in the direct cortical response* from the motor and visual areas after a metrazol induced seizure and found that, in the motor area, the amplitude of the response sharply increases in the precritical period, disappears in the postcritical electrical silence period, then rapidly returns; whereas in the visual

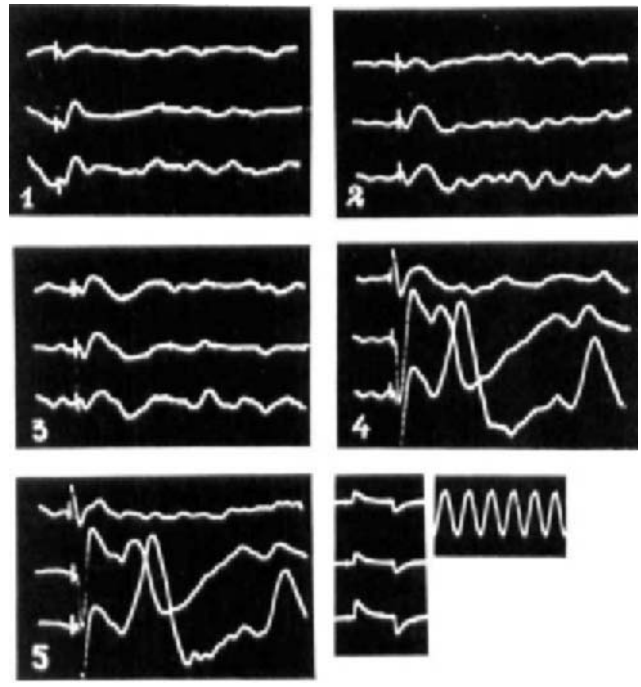



Fig. 26. Stimulation of the anterior suprasylvius. Records (1) in the contralateral and (2) in the homolateral g. suprasylvius at 6 mm anterior to the stimulating electrodes (3) at 8 mm from stimulating electrodes. 1 = control; 2 = 5 min after application of mescaline between the stimulating and recording electrodes; 3 = after 16 min; 4 = after 30 min a supraliminal stimulus induced, after the direct cortical response, a mescaline convulsive potential; 5 = 30 min later a supraliminal stimulus, but not so strong as the foregoing, produced a mescaline convulsive potential having greater latency. Calibration, 100 $\mu$V, 20 msec. (From Kreindler, Crighel *et al.*, 1962.)

and frontal region precritical amplification does not exist, the response being continually depressed. There exists therefore a difference in the behaviour of these two areas, not only to the sensory-evoked response but also to the direct critical response, *i.e.* in dendritic excitability.

Mescaline was applied topically to the suprasylvian gyrus between the electrodes for direct cortical stimulation and for recording results; after 3 to 5 min, this application

produced slight amplification of the negative response and lengthening of its duration (Kreindler, Crighel *et al.*, 1962). Concomitantly, a late potential produced by the threshold stimulus was observed and then, after 10 to 15 min, a second negative phase that progressively increased in amplitude. After application of mescaline, a supraliminal stimulus induces, after the direct cortical response, a convulsive, biphasic, negative–positive potential of the mescaline type and of variable latency, proportional to the intensity of the triggering stimulus; the latency is curtailed with increase in the intensity of the stimulus. Sometimes an epileptic potential develops instead of the late negative component that appears after topical application of mescaline (Fig. 26). Mescaline application close to the stimulating electrodes leads to amplification of the initial negative phase and deepening of the subsequent positive phase; and mescaline application close to the recording electrodes strongly amplifies the secondary negative phase, which takes on the aspect of a convulsive potential (Fig. 27).

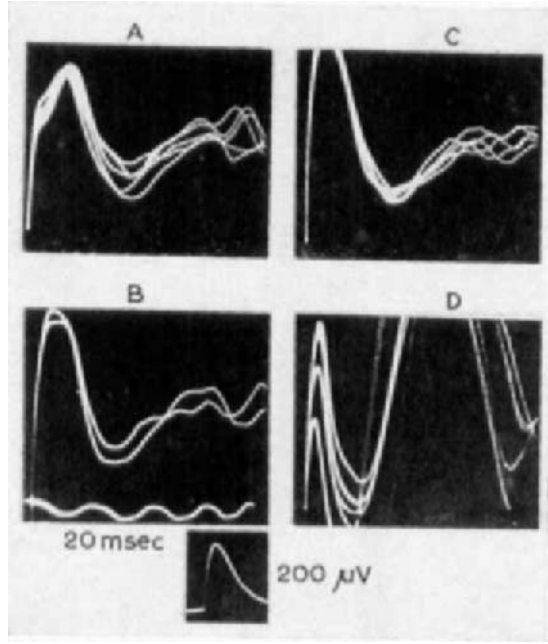



Fig. 27. Stimulation of the median g. suprasylvius. Recording in the homolateral g. suprasylvius at 5 mm from the stimulating point. A = control; B = 90 sec after topical application of mescaline near the stimulating electrode; C = after 6 min there is a great amplification of the surface-negative potential; D = 20 min after application of mescaline near the recording electrode there is an amplifying of the positive–negative and late phases. (From Kreindler, Crighel *et al.*, 1962.)

Reserpine topically applied on the suprasylvian gyrus does not change the aspect of the direct cortical response. When it is applied following mescaline, after the changes induced by the latter, deepening of the positive phase between the direct cortical response and the convulsive potential is observed, and of the initial positive phase, when it exists. This effect of reserpine on the initial and late positive phases is inconstant.

These investigations show that the intracortical circuits are the first to interfere in the organization of the discharges of an experimental epileptogenic focus induced by topical cortical application of certain substances. Both the late spread of the discharges and the existence of discharges in the isolated cortex support this hypothesis. The subcortical structures and other cortical regions have the role of regulating the discharges from the neuronal circuits at the level of the mescalinized cortex. On the other hand, the experimental epileptogenic focus modifies the reactivity of the cerebral cortex over a large area.

# CHAPTER III

# TRIGGERING OF THE EPILEPTIC SEIZURE

The factors that induce a seizure in the epileptic patient are but little understood, even when the EEG shows typical, interparoxysmal alterations. We do not know for certain which are the factors that intermittently induce the convulsive activity of the epileptogenic focus to spread at a given moment to a large number of cortical or subcortical formations and, possibly, even to lead to generalization of electrical activity throughout the whole brain.

Experimentally, repetitive electrical stimulation of the cerebral cortex or of different subcortical formations can be used in animals and even in man in the course of a neurosurgical intervention to trigger propagated convulsive activity. In the same way, a convulsive seizure can be induced by administration of convulsant substances. It is evident, however, that these means of triggering a seizure cannot show how it is induced in man, but may supply indications about the epileptogenic properties of different neuronal formations, that is their greater or lesser capacity to organize epileptic activity. In this connection, certain experimental results obtained by electrical stimulation can be used in order to determine the formations that have greater chances of inducing the seizure.

Triggering of an epileptic seizure must lead to an epileptic discharge, and not to a simple local after-discharge or even a propagated after-discharge. Therefore there is a threshold for inducing a propagated after-discharge in the stimulated structure, a threshold for inducing an after-discharge propagated from the stimulated structure to other structures with which it is connected morphofunctionally, and a threshold for epileptic seizures.

An epileptic discharge may be defined as the abnormal paroxysmal discharge of a larger group of neurons in the central nervous system, manifested bioelectrically by hypersynchrony; it is self-sustained, it can sometimes be induced by certain provoking factors, and it has a clinical correlate. Epileptic discharge can be experimentally triggered by electrical stimuli, by certain so-called convulsant substances, or by producing lesions.

According to Green and Naquet (1957), epileptic activity can arise in very small parts of the grey matter: therefore it is not necessary to postulate the existence of reverberant circuits in order to explain epileptic discharges. An epileptic discharge can spread along neuronal pathways and through the electric field, that is, ephaptically.

Today we have some understanding of the *neuronal mechanism* that forms the basis of the triggering of an epileptic seizure. Explosive self-recruitment appears to be a

decisive factor in triggering the activity of an epileptogenic focus and in the development of an epileptic seizure. This self-recruitment is due, according to Fessard (1958), to several causes: lowered neuronal excitability threshold, structural arrangement that favours synaptic or ephaptic interactions, alteration of the recovery cycles, etc.

The seizure occurs when these interactions become unusually marked and especially when they thus create the conditions for explosive autorecruitment. This may come from different causes, according to Fessard (1958): lowering of the excitability threshold of neurons, failure of inhibitory mechanisms, structural arrangements favourable to synaptic or ephaptic interactions, alterations of the recovery cycles so that those of a whole population of neurons come to have more similar periodicities, etc. The fact that the synchrony, whatever its cause, results in wider synchronization is the basic principle of the paroxysmal character of seizures.

Goldring and O'Leary (1950) showed that epileptic seizures of the cerebral cortex can be induced by direct surface-positive polarization of the cortex and, indirectly, by repetitive stimulation of the thalamic relay nuclei, as for instance the lateral geniculate body for the optical cortex. In both direct polarization and indirect repetitive stimulation, positive shift of the slow potential occurs in parallel with triggering of the epileptic discharge, a shift that continues during the discharge and is replaced by an opposite negative shift at the end of the seizure and the beginning of the postcritical electric silence. The authors believe that the positive shift is due to summation of the positive after-effects of spike genesis. But the postictal negative shift is far more difficult to account for by summation of a negative after-effect, as the shift endures beyond the end of the seizure.

Enomoto and Ajmone Marsan (1959) maintain that the functional substrate of epileptic disturbances in the cerebral cortex consists in a sharp and iterative depolarization of a large number of units producing high frequency bursts of variable duration. The activity of the units in the immediate vicinity of, or at a certain distance from, the convulsive agent (strychnine, penicillin, etc.) is closely connected to development of the electroencephalographic epileptic discharge. The number of units activated at a given moment, their discharge pattern and temporo-spatial interrelations are likewise closely linked to the form, amplitude and polarity of the slow electroencephalographic phenomenon.

Crighel and Neştianu (1957a,b) studied the way in which convulsive activity is induced in a cortical region by photic driving. They showed in preliminary investigations that the increased state of excitability of the cortex is characterized by an increase in the latency period of the cortical responses to each intermittent stimulus, whereas states of inhibition are manifested by diminution of latency. A generalized convulsive seizure induced by cardiazol or caffeine in the normal non-anaesthetized cat or in 'cerveau isolé' preparations showed that changes occur in the reactivity of the cortex to intermittent photic stimulation in the precritical period of 1 to 3 min between the beginning of the injection and the seizure.

Sometimes biphasic spikes suddenly or progressively appear, at an amplitude of 600–800 $\mu$V. In these cases, preconvulsive activity is manifested by a slight increase in latency at the beginning of the injection; the cortex then loses its photic driving

capacity and tachyrhythmia or electric depression appears. Sometimes, and this is more frequently observed in cardiazol seizures, a progressive increase in the amplitude of cortical responses to intermittent stimulation occurs, as well as oscillations in the mean latency values. Immediately before the seizure, the response waves to repetitive photic stimulation have a considerable amplitude, up to 1 mV, with a latency that increases up to 162%. The seizure is then characterized by high voltage waves of 800–1000 $\mu$V, at a frequency of 3–10 c/s, which no longer respond to the rhythm of the photic stimulation.

Convulsive activity that can be triggered by electric stimulation varies with *the degree of maturity of the cerebral cortex*. Newborn kittens may have characteristic discharges of the spike–wave type even in the first week of life. Both focal and diffuse discharges can be observed. In older animals high frenquecy spike discharges are noted. Hence, spike–wave discharges to local stimulation are more readily produced in the immature brain (Grossman, 1954).

Electric shock produces in the newborn kitten a tonic seizure with cortical and subcortical spindles of 5–13 c/s. In the second week of life, the electric convulsive seizure is accompanied by discharges of biphasic waves and low amplitude slow waves. The seizure is tonic and is followed by irregular clonic spasms, corresponding to asynchronous convulsive wave discharges between the cortex and subcortex (Volanschi, 1960).

In immature cats the direct cortical stimulation elicits a response with a long latency. The supraliminal stimulus is soon reached, and the response shows that the entire neuronal complex is involved, which is characterized by a great fatiguability to repetitive stimuli. The absence of an intercalary-dendritic system in the cortex of immature cats may account for the impossibility of organizing an epileptic focus (Crighel and Sotirescu, 1964).

The efficiency of the epileptogenic foci also depends upon the site at which it develops, the degree of hyperexcitability of the region, and the magnitude of the epileptogenic threshold.

The *convulsive thresholds of the different cerebral regions*, in decreasing order, are the following: hippocampus, motor cortex, cingulus, the pole of the temporal lobe, uncus and amygdala, then the cortical, parietal, frontal and occipital regions.

Certain of the cerebral formations show a special sensitivity to electric and mechanical stimulation. Electric or mechanical stimulation of the hippocampus may lead to local or propagated seizures at a much lower stimulation threshold than for the isocortex, corpus striatum or thalamus (Liberson and Akert, 1955).

Electrical stimulation of the globus pallidus, subthalamus tegmentum and some parts of the bulbar reticular formation may lead to tonic-postural movements of the members and body that continue for some time after stimulation ceases. Stimulation of the subthalamus may induce bilateral myoclonic movements. These movements can also be produced after bilateral ablation of the sensory-motor cortex and frontal lobes.

Stimulation of several subcortical formations produces adversive movements which do not demand the intervention of cortical circuits; therefore, the presence of an

adversive seizure in the clonic or the adversive onset of an epileptic fit in man do not necessarily imply its cortical origin.

### *A. Triggering of focal seizures by repetitive stimulation*

Triggering of a focal seizure by repetitive stimuli depends upon the caracteristics of the stimulus, *i.e.* the duration and frequency of the stimuli, tension of the current, and total duration of stimulation. Kreindler and Zuckermann (1957) studied the effects of these different characteristics on the rat motor cortex, varying one of the parameters and keeping the others constant.

The direct motor response to repetitive stimuli, that is, the response elicited only during cortical stimulation and which ceases with it, varies as follows:

(a) to stimuli of relatively long duration (0.5–25 msec) of sufficient intensity for each stimulus to induce a motor response, and at a frequency of 2–8/sec, the motor response is characterized by clonic movements of the rat's paws, synchronous to the cortical stimuli, the muscular tonus being hardly influenced at all in the interval between two jerks;

(b) to stimuli of the same duration and tension, but at a frequency of more than 10/sec, the muscular tonus increases in the interval between two jerks, and at a frequency of 16–20/sec a powerful tonic plateau develops, upon which large clonic spasms are grafted, not synchronous to the rhythm of stimulation;

(c) to very short stimuli (0.025–0.05 msec), the motor effects only occur at high tensions and are never synchronous to the stimulation rhythm at frequencies below 10/sec. The response consists in irregular movements with a low tonic component, that appear only after a certain number of cortical stimuli and are interrupted by relatively long breaks.

Kreindler and Zuckermann (1957) carried out investigations on the role of the different frequency, duration and intensity characteristics of the repetitive stimulus in triggering nonconvulsive and convulsive motor phenomena. They reached the following conclusions.

(1) Both the direct motor response — that arises during cortical stimulation and does not persist after it has stopped — and the self-sustained seizure with features of an after-discharge are not only the products of stimulation of the efferent neurons, but also of stimulation of certain closed neuronal circuits.

(2) The neuronal circuits that trigger the convulsive seizure have functional peculiarities different from those that generate the direct motor response. The convulsive seizure is generated by the putting into action of certain neuronal chains longer and with more internuncial neurons than the chains that generate the direct motor response, because summation in the convulsive chains takes place even at intervals of 500 msec between two stimuli, whereas summation in the direct motor response chains only takes place when these intervals are shorter than 100 msec. On the other hand, repetitive stimuli of very short duration (0.020–0.25 msec) do not stimulate directly, at a critical level, the efferent neurons but can induce a convulsive seizure.

(3) Low frequency repetitive stimuli, below 10/sec, which do not produce summation

in the shorter chains of the direct motor response, may induce summation in the long convulsive chains if they are of a certain intensity, and may even lead to a convulsive seizure.

Lengthening of the convulsant focal repetitive stimulus applied to the *motor cortex* in the rat exerts a suppressor action on triggering of the convulsive seizure, a phenomenon which is neither exhaustion nor extinction (Kreindler and Zuckermann, 1956, 1957). Stimuli at a frequency of 8–10/sec, lasting 0.25–5 msec and at a corresponding threshold of intensity to induce a generalized convulsive seizure, elicit, during repetitive stimulation, rhythmically synchronous responses. After stimulation ceases the convulsive self-sustained seizure appears with the character of an after-discharge. The duration of this seizure is maximal when the duration of repetitive stimulation is 3–5 sec, and gradually decreases with increase in the duration of stimulation, so that at a repetitive stimulation of 20 sec duration the seizure only lasts 1–2 sec, and sometimes does not even occur. Therefore, lengthening of the neuronal stimulation time at the level of the epileptogenic focus prevents or curtails the duration of the convulsive seizure. It is hard to believe that the seizure does not appear because of exhaustion (or inhibition) of the local, directly stimulated units, since the response synchronous to the rhythm of stimulation persists without being modified, even when stimulation is protracted to 60–120 sec. Prolonged repetitive stimulation therefore produces certain changes in some of the neuronal chains and others in other chains; long-duration repetitive stimulation prevents organization of the epileptic seizure by the convulsant chains, while the direct motor response chains suffer less from this prolonged repetitive stimulation. By using various parameters of stimulation, Steriade (1964) was able to induce certain changes in morphology of the amygdalo-hippocampally evoked response which precede and announce the appearance of the epileptic self-sustained activity. These changes cause the evoked responses to become more complex, and their morphology is comparable to that of certain amygdaloid or hippocampal after-discharges. By using appropriate stimulation parameters, 'rupture' of the simple biphasic potential and a 'serrated' very complex potential of epileptic type are obtained, but only at frequencies above 2/sec and supraliminal intensities. Below these values, no matter how long the stimulation, the initial morphology of the evoked potential is maintained from beginning to end. When both increased shock intensity and frequency were used, changes in morphology gradually developed 7 to 10 sec after the beginning of rhythmic stimulation: evoked responses became gradually bifid, trifid and multifid, concomitantly increasing their latency and assuming an epileptic pattern. An epileptic after-discharge might appear, after cessation of protracted stimulation, whose morphology was practically identical with that of evoked responses in the late phase of repetitive stimulation (Fig. 28).

### *B. Triggering of generalized seizures*

Generalized epileptic seizures may be produced both in man and animals by injection of convulsant products, especially cardiazol.

*Cardiazol* produces in the animal an electrocorticographic tracing that closely

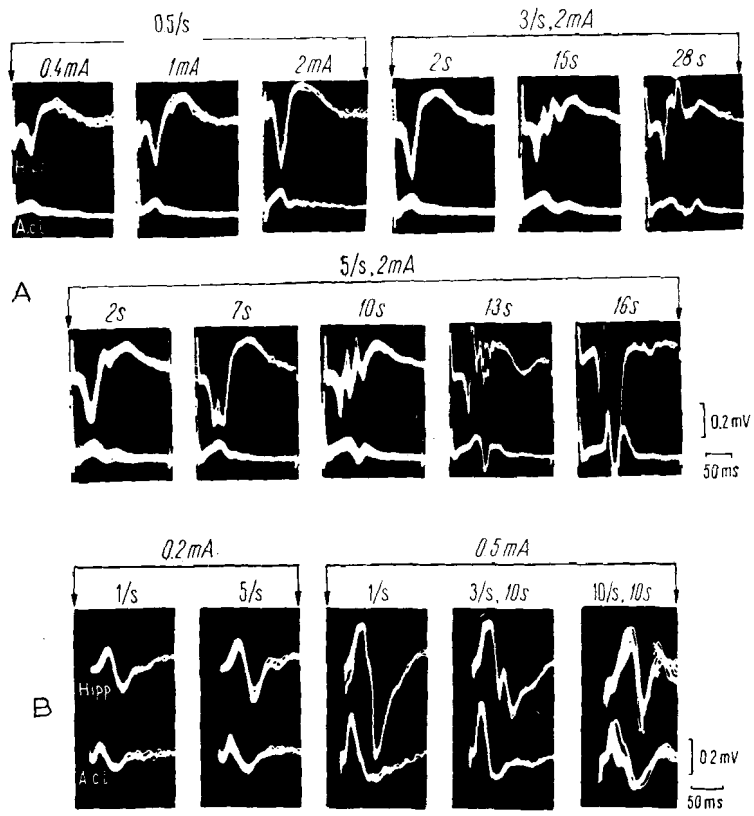



Fig. 28. Complication of evoked response pattern during rhythmic stimulation. A and B = two different experiments. A.b.p. nucleus is stimulated in both experiments. No change occurs in response morphology during stimulation below a certain rate (A = 0.5 sec) or at threshold intensity (B = 0.2 mA), in spite of the increase in amplitude of evoked potentials. With supraliminal shocks (A = 2 mA; B = 0.5 mA) and rates above 3/sec, evoked responses increase in complexity becoming gradually multifid increasing their latency and assuming an epileptic configuration. (From Steriade, 1964.)

resembles that of grand mal seizures in man, *i.e.*, high voltage rapid rhythmic discharges, followed by a clonic stage, electric silence and return to normal. The discharges are synchronous and symmetrical, embracing wide areas in both hemispheres, which points to the existence of a central pacemaker with widespread connections in both hemispheres. The discharge produced by cardiazol resembles that obtained by local electrical stimulation of the median thalamus. According to Ajmone Marsan and Marossero (1950), cardiazol does not seem to exercise its convulsant action on the structures situated caudally to the level of the diencephalon.

In the presence of an experimental epileptogenic focus produced in the animal by alumina cream, cardiazol in subconvulsant doses activates the focus and leads to spread of the epileptic excitation from this focus, and hence to generalization of the seizure.

Suboccipital atebrine injections do not induce epileptic seizures, but the same dose

administered intravenously produces epileptic seizures that end in death of the animal (Uzunov *et al.*, 1957). Intravenous chlorpromazine injection prior to pyramidon, cardiazol or atebrine administration prevents the onset of epileptic manifestations.

Each convulsant substance introduced into the general circulation has another point of attack and induces epileptic seizure by creating epileptic foci in different regions. Gastaut and Hunter (1950b) and Starzl *et al.* (1953), by injecting pentylenetetrazol, recorded discharges from the whole of the cerebellum and cerebral cortex and all the subcortical structures from the caudate nucleus to the mesencephalon. Gastaut and Hunter (1950a) observed that bisynchronous discharges appear first in the diencephalon whereas Starzl *et al.* (1953) found that a convulsant dose of pentylenetetrazol produced first a cortical discharge which was secondarily driven to the subcortical structures by projection fibres. Gastaut supposes that generalized discharges originate in the diencephalic structures, whence they irradiate to the whole brain, a hypothesis that is confirmed by direct stimulation of the median diencephalon. Pentazol produces an intensive hypersynchronous discharge in the telencephalon and diencephalon, and at the same time produces a smaller discharge in the mesencephalon and the metencephalon; but it produces no discharge in the bulbar reticular formation where no change in electric activity is observed (Gastaut, Toga *et al.*, 1958).

Sensitivity to convulsants varies in the animal scale. For example pentazol injection produces in the tortoise *(Bufo vulgaris)* a tonic–clonic seizure, accompanied at first by 4–5 c/s waves that pass into a 3 c/s rhythm and then to a 1 c/s rhythm towards the end of the seizure, which finishes with a flat 4–5 sec tracing (Morocutti and Vizioli, 1957).

The phylogenetically youngest regions of the central nervous sytem play an important role in the onset of seizures produced by pyramidon and cardiazol (Uzunov *et al.*, 1957).

Administration of lysergic acid diethylamide (LSD) or of mescaline, both hallucinogenic substances, produces characteristic alterations of the bioelectrical activity of the brain. LSD and mescaline, administered intravenously to the rabbit, diminish the threshold of the cortical arousal reaction to reticular stimulation; in large doses, without reticular stimulation, they produce a persistent arousal response; LSD in still larger doses leads to the appearance of slow waves and sleep, while the threshold of the cortical arousal reaction to reticular stimulation increases. Mescaline produces similar phenomena, except that the convulsant doses do not produce inversion of the responses as does LSD (Rinaldi and Himwich, 1955).

Largactyl prevents the appearance of epileptic seizures induced by cardiazol, pyramidon or atebrine, but does not influence those produced by picrotoxin. It curtails the duration of the cardiazol seizure and that of the atebrine seizure (Uzunov *et al.*, 1957). Hence, largactyl has a wide range, also inhibiting the superior regions of the central nervous system.

*Electroshock* is a violent stimulation of the entire brain and probably triggers the convulsive seizures by mechanisms other than those of focal electric stimulations. It has been experimentally proved that a large number of electroshocks (an electroshock daily for many months) may lead at a given moment to the onset of spontaneous

epileptic seizures, sometimes even to spontaneous status epilepticus (Barucci *et al.*, 1954).

Deep electrodes record, in the course of generalized convulsive seizure produced by hexafluorodiethylether (indoklon) inhalations, intravenous metrazol injections or electroshock, induce alterations characteristic of the prodromal, tonic and clonic phases of the seizure, as well as certain individual and regional variations characteristic for the same cerebral area and for the same individual from one fit to another, irrespective of the nature and mode of administration of the convulsive agent. Post-paroxysmal alterations are likewise relatively constant in whatever way the seizure is produced (Chatrian and Petersen, 1960). This shows that the general convulsive agent acts upon the human brain by a common triggering mechanism.

Vanasupa *et al.* (1959) studied the action of certain convulsant drugs (caffeine, picrotoxin, metrazol, strychnine, thiocarbohydrazide and methionine sulphoxamine) on electroencephalographic and slow potential alterations in the brain and cerebellum of the rabbit. Slow potential alterations begin shortly after intravenous injection of the convulsive drug and continue throughout its action. It is difficult to understand the significance of these slow potential alterations, especially as they appear before the convulsive discharges. No correlation exists between the appearance of these slow potential alterations and the appearance and disappearance of the convulsive discharge (Fig. 29).

Investigations on cerebellar electric activity changes during the development of epileptic seizures induced by convulsive agents (metrazol, strychnine, picrotoxin, caffeine) were carried out by Markham *et al.* (1951), Marossero and Garrone (1952), Swank and Brendler (1951) while the cerebral and cerebellar alterations were investigated by Goodwin *et al.* (1940) and Purpura and Grundfest (1957a). Generally speaking the convulsive drugs differed from one another by the various thresholds at which they gave rise to convulsive discharges in the brain and in the cerebellum, there being different latencies between the injection and the appearance of these alterations.

These alterations exhibit certain peculiarities for each convulsive drug. Methionine sulphoxamine has a more distinctive effect and is stronger in the period of

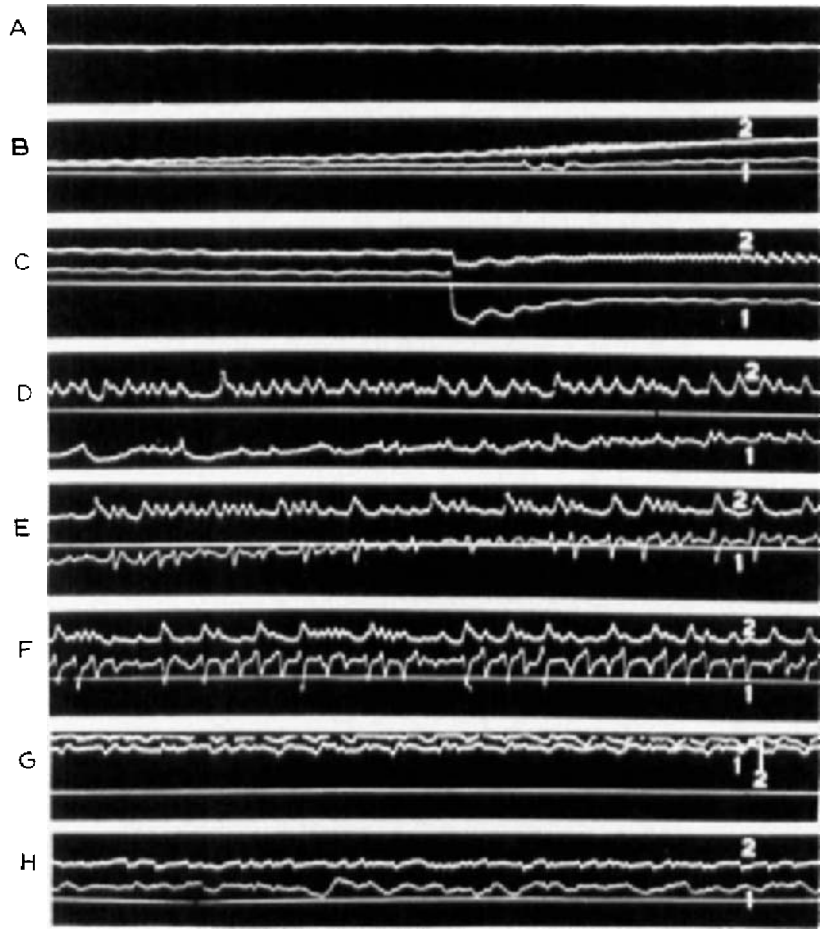



Fig. 29. Changes accompanying picrotoxin-induced seizure discharges. 1 = cerebral; 2 = cerebellar. A = resting slow potential (SP) prior to injection; B–H = continuous strips following 6 mg picrotoxin. Two to 5 min after injection both cerebral and cerebellar SP commenced to shift negatively. Then a suddenly developing negative cerebral shift ushering in a sequence of slow waves is seen only in traces C and D. (From Vanasupa *et al.*, 1959.)

Methionine sulphoximine induced epilepsy was discovered during investigations upon the pathogeny of the so-called 'canine hysteria'. Mellanby (1946) showed for the first time that the strange clinical picture sometimes encountered in the dog, manifested by sudden fits of anxiety with dilatation of the pupils, cocking of the ears, fearful searching, running fits, barking, behaviour strongly suggesting hallucinations, sometimes ending in a convulsive seizure, is due to the biscuits with which the animal is fed, made of nitrogen-trichloride-treated flour. Subsequent researches on this flour showed that the toxic agent is not nitrogen trichloride itself, but a part of the gluten fraction of wheat flour that had been treated with the chemical, namely methionine sulphoximide (Bentley and Whitehead, 1950; Reiner *et al.*, 1950).

Proler and Kellaway (1962) carried out a detailed clinical study on epilepsy induced in the cat by methionine sulphoximine. The following features were most

consistently observed: sniffing movements, involving the upper lip, nose and lower eyelid, and accompanied by profuse salivation and impairment of consciousness; episodic behavioural changes consisting of head turning, sniffing, and crouching movements strongly suggesting apprehension, orientation and fear; running fits, at the onset of which the animal may appear fearful or hysterical; generalized tonico-clonic convulsions. These episodes are intermittent in nature, but may be so frequent as to appear as one continuous attack. The behavioural episodes may be prolonged or even triggered by auditory stimuli, such as a loud hand clap. Tactile stimuli, such as holding the animal, are generally more effective than photic stimulation. The better the state of nutrition, the higher the dosage of methionine sulfoximine required to produce the behavioural and convulsive changes. Younger cats show more ataxia and more fear and apprehension than do older animals.

Electroencephalographic studies on dogs with extradural electrodes revealed inter-ictal waves in all regions: their voltage was high and their frequency only 2–3/sec. Convulsions were associated with spiking activity (Erickson *et al.*, 1947; Newell *et al.*, 1947). Gastaut, Toga *et al.* (1958) noted diffuse bilaterally synchronous bursts of slow waves of $\delta$- and $\theta$- frequency as background rhythms. Inter-ictally, focal sporadic paroxysmal spikes or spike and wave complexes were observed mainly in the temporal and insular regions. Seizures were accompanied by rhythmical spike discharges unilaterally in the temporo-insular region, which spread to the other temporal lobe and then became generalized. Lodin (1958) made electroencephalographic studies in dogs and arrived at the conclusion that methionine sulphoximine inhibits central cortical function, thereby releasing subcortical centrencephalic structures which give rise to the bilaterally synchronous cortical epileptiform activity.

Neuropathological studies showed patchy necrosis of the cerebral cortex in intoxicated dogs, complete loss of architecture of both the pyramidal layer and fascia dentata of the hippocampus and severe changes in the basket-cells and Purkinje cells of the cerebellum with less marked changes in the dentate and roof nuclei (Lewey, 1950), generalized neuronal degeneration and proliferation of glial elements, with sclerosis and pallor of cytoplasm, shrinkage of dendrites and nuclear swelling (Gastaut, Toga *et al.*, 1958).

With regard to the biochemical mechanisms involved in the convulsive and behavioural changes produced by methionine sulphoximine, Mellanby (1948) suggested that the toxic effect of agenized flour might be due to alteration of a single amino acid. It is probable that sulphoximine is converted to other compounds which are toxic to the central nervous system (Roth *et al.*, 1953), or that it exerts its primary effect on an extraneural target organ, possibly endocrine, with the nervous system changes being secondary.

Proler and Kellaway (1962) insist upon the significance of the methionine sulphoximine preparation as a tool in the investigation of the pathophysiology of epilepsy, methionine sulphoximine being presently the only agent capable of producing a semi-chronic epileptic syndrome in animals which have not been subjected to focal irritative lesions. On the other hand, the methionine sulphoximine syndrome resembles human epilepsy behaviourally more closely than do the changes associated with the

convulsant, the generalized tonic–clonic convulsions alternating with behavioral changes closely resembling certain forms of human psychomotor seizures.

Tower (1958a) carried out studies on dogs, using the 75% agenized flour diet. There were different forms of clinical manifestations such as simple quiet, staring episodes in which the dog was out of contact, episodes of whining, fixed staring, mastication, salivation and barking, episodes of furious barking and running around in circles for 2 to 10 min and generalized convulsions with clonic, rhythmical movements, running, mastication, incontinence. Histopathological studies by Tower showed no significant abnormalities, whereas Silver (1949) reported variable dropping out of Purkinje cells of the cerebellum.

Large doses of methionine will prevent or control the seizures (Reiner *et al.*, 1950), and in mice the seizures can be controlled by a single injection of L-glutamine or L-asparagine with complete recovery of the animals (Tower, 1958b).

### *C. Triggering by sensory stimulation*

Of interest for clinical applications are the experimental studies showing the possibility of triggering an epileptic seizure by sensitive or sensory stimuli.

Experimental investigations have demonstrated that exteroceptive stimuli may induce the convulsive seizure under certain conditions (Amantea, 1921; Clementi, 1929; Servít, 1957). 'Musicogenic' epilepsy described by Critchley (1937) and photic epilepsy in man studied by Gastaut (1950) have contributed clinical data in this sense.

Clementi (1929) applied strychnine to the optical cortex and produced clonic spasms of the eyelids, and sometimes even generalized convulsions by visual stimulation; and Amantea (1921) applied strychnine to the somatomotor area in an amount that does not produce strychnine clonic spasms; however, stimulation of the corresponding cutaneous reflexogenic zone during strychnine treatment induces a Jacksonian fit or even a generalized seizure.

Terzian and Terzuolo (1952) showed that optical stimulation induces an afterdischarge in the strychnine-treated visual cortex of the rabbit, which spreads to the contralateral visual area and the masticatory area. Masticatory transmission is due to rapid irradiation of the convulsive discharge.

The experiments of Amantea and Clementi have shown that a convulsive cortical focus is selectively activated by specific influxes. Moruzzi (1950) defines this form of epilepsy as pure cortical epilepsy linked to the spread of a local cortical activity following bombardment of specific afferent influxes in animals with a certain predisposition. Arduini and Lairy-Bounes (1952) and Lairy-Bounes *et al.* (1952) showed, however, that facilitation of a strychnine cortical focus can be obtained with any stimulation and is not linked to the specific effect of the latter but to the overall activating action, stimulation of the reticular formation producing the same effect as sensitivo-sensory stimuli. Keeping these results in mind, Moruzzi (1952) assumes that there exists a double mechanism inducing epileptic activity along the specific and along the non-specific pathways of the ascending activator system.

'Reflex' facilitation of localized or diffuse convulsive activity appears to be due to

a breakdown of the equilibrium between the non-specific systems. One or a series of afferent impulses may produce immediate facilitation, determined by activation, deactivation or startle reactions, or by rhythmic stimuli (Lairy, 1956).

Repetitive stimulation of certain sensory influxes may trigger an epileptic seizure. King *et al.* (1953) repetitively stimulated the lateral geniculate body in the rabbit, and induced an epileptic paroxysm in the visual cortex. This was immediately preceded by diminution up to disappearance of the responses to stimuli, and followed after cessation of the stimulation by an after-discharge with, at first, low voltage frequent potentials, that gradually slowed down and increased in amplitude. At the beginning of the paroxysm, the initial phase of the convulsive waves is surface-positive, and in full seizure it is negative. The authors emphasize the analogy of the electrocorticographic aspects of this kind of epilepsy and that produced by local strychnine applications.

Protracting the rhythmical acoustic stimulation (1/sec clicks) evokes, after a certain time interval in the absence of any stimulus, 'spontaneous' potentials reproducing the appearance and frequency of responses to sensory stimuli (Steriade *et al.*, 1962). When such remanence (memory) events are developed on a background of cerebral excitability increased by activating stimulations of the RF, there occur spontaneous responses of an epileptic type and even epileptic seizures localized in the auditory cortical areas and the medial geniculate body (Steriade and Demetrescu, 1964, unpublished data).

Morrell (1959) showed that, in cats with an epileptogenic lesion in the visual cortex, repetitive photic stimulation may trigger a rhythmic discharge, strictly limited to the normal zone. From the superficial visual cortex a discharge of occasional spikes is recorded and, at the same time, at a few millimeters depth a discharge of rapid spikes.

Dell *et al.* (1951) found that in the metrazol sensitized cat a 2–3 c/s acoustic stimulus produces a seizure that almost always begins in the auditory cortex.

Bremer *et al.* (1954) induced a convulsive discharge in a strychnine-treated cortical area by intracortical associative influxes. One point of the strychnine-treated secondary auditory area responds to a click, or to an electric shock applied to the primary auditory area, by a high convulsive potential.

Intermittent photic stimulation enhanced the epileptic focus induced by topical application of mescaline to the ectosylvian gyrus. Each stimulus releases an epileptic spike. The acoustic rhythmic stimulation did not influence the epileptic discharge, thereby showing that the afferences articulating on the dendrite are probably more able to enhance the epileptic activity (Crighel and Stoica, 1962) (Fig. 30).

Another example in which the seizure is induced by a sensory stimulus is the 'audiogenic epilepsy' of the rat, studied by Servít (1959). The seizure begins by tonic turning of the head and tail to one side, bending of the body (adversive phase), after which the animal starts to run very quickly (procursive phase) and convulsions may follow (convulsive phase). Under the influence of an acoustic stimulation a motor dominant with an electroencephalographic correlation arises. The dominant can be influenced by artificial irritative foci produced by local application of strychnine.

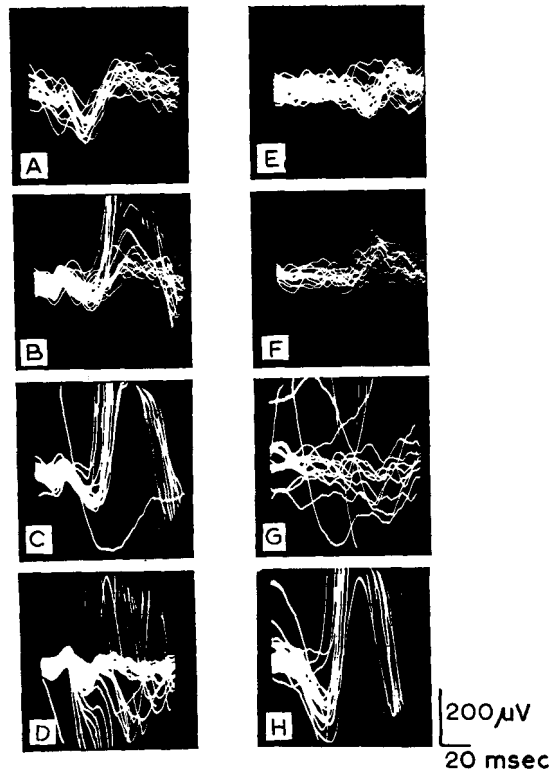



Fig. 30. A = responses in E.a.s. to click before application of mescaline to the cortex (cat); B = responses in E.a.s. to click at high frequency after application of mescaline. C = same at click at low frequency; D = 30 min after application there are no more responses; E = responses to flash in g. marginalis posterior before application of mescaline in E.a.s.; F = after application of mescaline to E.a.s.; G = responses in E.a.s. to flash after mescaline application to E.a.s. the eyes being covered; H = the same but with the eyes opened. Only the flash induced mescaline spikes in E.a.s. while the click failed to induce such spikes in E.a.s. (From Crighel and Stoica, 1962.)

Krushinski (1959) studied the experimental conditions that induce audiogenic epileptic seizures, and distinguished three main pathological states in the central nervous system of animals subject to these seizures: (1) decrease in the excitability of the nervous system characterized by total absence of responses to the epileptogenic stimuli used; (2) a pronounced state of stationary excitation of the superior segments with different relationships between the intensity of the stimulus used and the response of the nervous system, pointing to the presence of a stabilized transliminal inhibition; and (3) an increased state of excitation of the brain, the stimulus determining convulsive seizures.

In the audiogenic epileptic seizure, triggering probably occurs at the level of the medulla oblongata, where a powerful excitation focus would be produced and would increase with activation of the sound. From here it spreads over large areas in the brain (Semiohina, 1959).

During an audiogenic epileptic seizure in the rat, large hypersynchronous waves

appear in the hippocampus and piriform gyrus, separated by short intervals when the motor excitation is immediately followed by the clonic phase. However, when the clonic phase follows a tonic phase, only slow high amplitude waves, without grouping, are observed in the same regions. Synchronization during motor excitation is similar to that observed in the hippocampus in the course of the arousal reaction (Guselnikova, 1959).

In the phase of motor excitation in audiogenic epilepsy, frequent high amplitude waves appear in the motor analyser, and synchronization of the biocurrents in the auditory analyser, striate body and median geniculate ganglion. Clonic spasms are accompanied by slow waves in the motor region and tonic convulsions, by bursts of high amplitude rapid waves, followed by a synchronized rhythm that disappears at the end of the seizure (Semiohina, 1959).

Injection of a subconvulsant dose of cardiazol sensitizes the cerebral cortex to photic stimuli, so that intermittent photic stimulation may induce, under these conditions, an epileptic seizure or bilateral myoclonic jerks of the musculature of both body and limbs (Gastaut and Hunter, 1950b). The clinical picture, known under the name of myoclonic petit mal seizure can thus be experimentally reproduced. The optimal frequency of intermittent photic stimulation for inducing myoclonus is 15/sec. In this case, in the animal sensitized with a subliminal dose of cardiazol and subjected to the action of intermittent photic stimuli, the EEG shows high voltage spikes in the optical cortex to each stimulus, followed after a latency of 20–30 msec by spikes in the frontal region. The frontal spikes may be followed by slow waves, thus forming a spike–wave complex.

Triggering of the epileptic seizure by association of cardiazol and photic stimulation may have two different mechanisms (Crighel, Broşteanu *et al.*, 1957). Sometimes the seizure takes on the aspect of high amplitude 3–100/sec waves, which reflects hypersynchrony of the neurons in certain neuronal complexes and hypersynchrony of several complexes: at other times it takes on the aspect of rapid 80–100 c/s spikes, which would reflect only synchronization of the neurons in a cellular complex without concomitant synchronization of the complexes between one another.

Cutaneous stimulation can likewise be used to induce the epileptic seizure. In some dogs with a particular convulsant predisposition, rhythmic stimulation of the skin associated with strychnine applied to the corresponding sensitive cortical zone produces typical after-discharges, characterized by one or more potentials on the descending branch of the strychnine spike (Ferrari and Galasso, 1957).

*Sino-carotid afferent impulses* may perhaps also be invoked as playing a role in the triggering of a convulsive seizure. Kreindler (1946) showed for the first time that mechanical stimulation of the baroreceptors of the carotid sinus by endosinusal distension produces in the dog, under evipan anaesthesia, evident hypersynchrony of the waves recorded on the scalp. The EEG tracing showed large 200–300 $\mu$V waves at a frequency of 5–6/sec that attained 1.5–3/sec with lengthening of endosinusal compression. Sinusal compression had an after-effect, that is hypersynchrony persisted 20–30 sec after the compression had ceased.

Schulte *et al.* (1959) found that stimulation of the carotic glomus exercises a power-

ful effect on the medullar motor neurons; and Bonvallet and Hugelin (1961) observed that acute progressive hypoxia induces in the curarized cat facilitation of the excitability of the motor neurons of reticular origin. Evolution of the phenomenon showed that it depends upon three factors: an early process of chemoreflex reticular excitation, a direct excitation process of the reticular cells, and a liberation process from under corticofuge inhibitory influences. The origin of anoxic convulsions would be sudden predominance of the activity of the facilitatory system of the reticular formation (Noëll and Dombrowski, cited after Bonvallet and Hugelin, 1961; Ward, 1947b). It should be mentioned that in these experiments hypoxia acts not only directly upon the nervous system but also indirectly, mediated by the sino-carotid and cardio-aortic chemoreceptors stimulated by the lack of oxygen. Therefore, stimulation of the carotid sinus may induce slow, hypersynchronous waves.

Bonvallet *et al.* (1954) showed that distension of the carotid sinus reduces cortical electric activity. Nakao *et al.* (1956) found that adrenaline and nor-adrenaline injections produce in the cat barbiturate spindles on the EEG in the hypertensive phase, as well as an increase in the number of slow waves and decrease of the rapid waves. Sino-aortic denervation abolishes this effect. Hypotensive drugs, as for instance acetylcholine, produce cortical excitation characterized by increase in the amplitude of the rapid potentials, and decrease in amplitude of the slow potentials, an effect that also disappears after sino-aortic denervation. The baroreceptor reflexes therefore appear to exercise a homeostatic action on the activity of the cerebral cortex.

Mazzella *et al.* (1956) studied the effect of stimulation of the sino-carotid presso-receptors on the EEG in the recently-woken, curarized dog or in the animal under slight barbiturate anaesthesia. Mechanical distension of the carotid sinus, isolated or *in situ*, produces uneven spacing of the EEG and a predominantly unilateral effect when a single sinus is stimulated. The electroencephalographic alterations were independent of arterial pressure; intravenous injection of hexamethionine (ganglionic block) does not modify the sinusal effect on the EEG. The waves are bilateral and appear before the terminal alterations; they are therefore not the consequence of cerebral circulatory disturbances. This shows that strong stimulation of certain interoceptors may lead to hypersynchronic discharges of the epileptic type.

But it is not only *a non-conditioned but also a conditioned stimulus* that may induce a convulsive activity. Dolin (1939) induced in the dog a convulsive seizure to a conditioned stimulus, associating the interoceptive stimulus with intragastric administration of a convulsant substance, camphor oil. Ungher *et al.* (1952) were able to induce in the dog convulsive seizures to indifferent exteroceptive (optic, olfactory and acoustic) or interoceptive (intragastric pressure) stimuli by associating them with intragastric administration of camphor oil. During 8–10 days running they associated camphor oil with one of those indifferent stimuli or to the laboratory environment of the animal, following which the animal began to show some of the vegetative manifestations that precede the seizure (polypnea, salivation, micturition, and dilatation of the pupils). After 10 to 15 associations clonic spasms began to appear in the cephalic segment and hind quarters, sometimes accompanied by generalized clonic fits. An electroconvulsive seizure can be conditioned to the laboratory environment

and to the sound produced by the click of the electroshock apparatus. After 19 convulsive seizures, the dog exhibits clonic spasms, loss of urine and salivation immediately on application of the electrodes on the head, without letting the electric current pass. These conditioned convulsive seizures cease to occur (they undergo extinction) if the conditioned stimulation (the indifferent acoustic, olfactory, etc. stimuli) is continually repeated without being followed by the non-conditioned stimulation (camphor seizure or electroconvulsive seizure).

Kiyono and Matsumoto (1963) tried to establish reflex-conditioned convulsions in the rat, the non-conditioned stimulus being a convulsant injection (paracresol or a catechol solution), the conditioned stimulus being the sound of a bell. Clonic convulsions were induced only by the acoustic stimulus in the rats receiving a daily paracresol injection for a long time, without it being associated to the conditioned stimulus. It was therefore, actually, a 'reflex', and not a conditioned, convulsion.

Chivu and Steriade (1952) conditioned in the dog a focal seizure of the Jacksonian type produced by direct stimulation of the motor cortex, with the aid of permanently implanted electrodes also in contact with the dura mater. The electric focal seizure presented the following aspect: tonic deviation of the head, bilateral clonic spasms of the musculi orbicularis oculi and orbicularis ori, and of the left anterior paw. By means of a device controlled by the experimenter and connected to the current generator, a sound could be made to precede or coincide with the epileptogenic electric stimulation.

The first sign of a conditioned focal response, tonic deviation of the head to the left on application of the acoustic stimulation, appeared after the first five associations of the latter with focal electric stimulation in the course of the first séance. When an attempt is made to increase the number of associations in the course of a séance, the animal becomes agitated at the sound of the acoustic stimulus, no longer responds to this conditioned stimulant and gives signs of fatigue. If, after elaboration of the conditioned focal convulsive response a renewed attempt is made to increase the number of associations between the conditioned (acoustic) stimulus and the non-conditioned electric stimulus, it is found that the conditioned response to more than 5–6 associations appeared only after the 5th or 6th application of the conditioned stimulus, only to disappear with the following conditioned stimuli, the response to the focal electric stimulus (non-conditioned) sometimes even being suppressed. Moreover, the interval between the associations in the course of the same séance must be fairly long — at least 8 min. If the associations are repeated at shorter intervals the animal becomes hypotonic and sleepy, and the conditioned focal seizure no longer appears.

The conditioned focal seizure is obtained gradually, starting with tonic deviation of the head, followed in the subsequent serial séances by the first conditioned clonic spasms on the left half of the face. Only after 110 associations does the acoustic stimulus induce a focal seizure which is almost identical to that induced by focal electric stimulation of the motor cortex, made up of all its components as mentioned above. From this moment, the conditioned focal seizure is well established and can be produced regularly. It was possible to film it, as the stimuli concerned could not inhibit its development by an external inhibition mechanism.

These experiments therefore show that association of an acoustic conditioned and a non-conditioned stimulus (electric epileptogenic stimulation of the motor cortex) may produce a conditioned epileptic focal seizure. Loucks (1934) was not able to condition a simple motor response (lifting of the paw) induced by direct stimulation of the motor cortex to an indifferent stimulus, not even after 600 associations. This failure is probably due to the short 2–3 min intervals which Loucks left between the associations, which gave rise to a supraliminal inhibition at the level of the nervous structures generating the seizure.

Generalized hypersynchronous discharges induced in the cat by a chronic epileptogenic lesion can be conditioned (Morrell and Naquet, 1956) in the non-anaesthetized animal with permanently implanted electrodes. The conditioned stimulus was a weak sound, and the non-conditioned one a repetitive photic stimulus. The non-conditioned stimulus produces in the animal with an epileptogenic focus in the gyrus marginalis an asymmetric photic driving in the epileptogenic focus, followed by

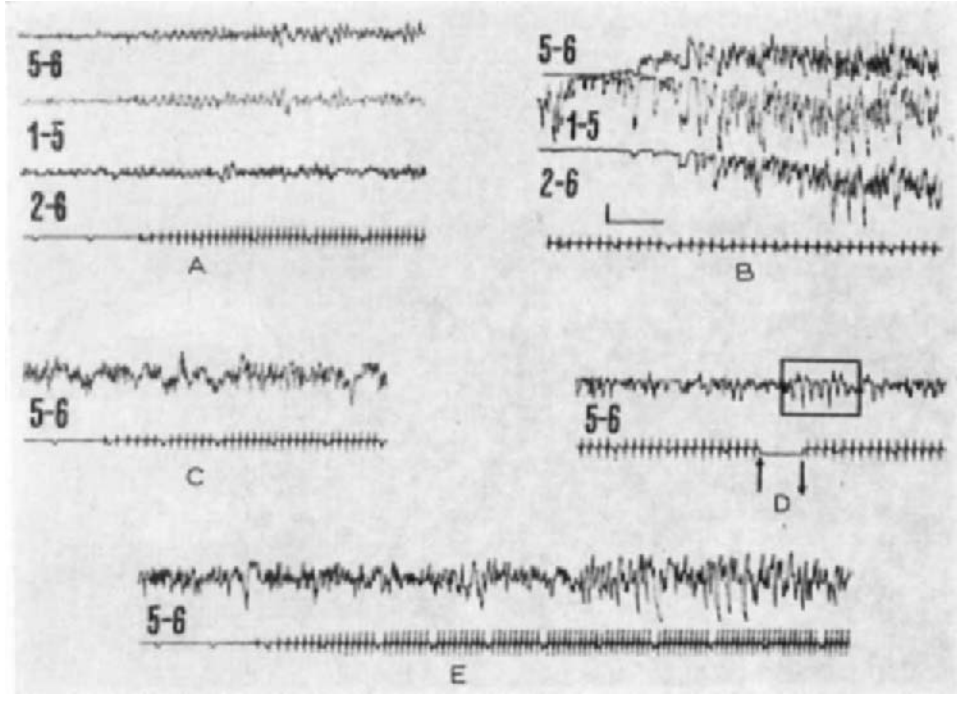



Fig. 31. Conditioning of epileptic discharges in the dog. A = control. Action of the intermittent photic stimulation (I.Ph.St.). B = electroconvulsive seizure (unconditioning stimulus). The I.Ph.St. precedes by 5–6 sec the electroconvulsive seizure. C = after 10 associations between the electroconvulsive stimulation (unconditioning stimulus) and the I.Ph.St. (conditioning stimulus), no alteration of the electrical activity by I.Ph.St. D = I.Ph.St. does not alter the electrical activity but the application of the stimulating electrodes on the head of the dog which is part of the conditioning stimulus (between the arrows) produced hypersynchronous waves during I.Ph.St. E = after 27 associations I.Ph.St. induced an epileptic discharge with a latency of 6 sec. 1 and 2 = frontal; 3 = fronto-parietal right; 4 = fronto-parietal left; 5 = occipital right; 6 = occipital left. (From Ungher and Steriade, 1960.)

generalized and sometimes self-sustained hypersynchrony. This response could be conditioned to sound, could be differentiated and could be extinguished.

The generalized or myoclonic hypersynchronous response, obtained by combined cardiazol injections and repetitive photic stimulation, can likewise be conditioned both in the normal animal and in the animal with an epileptogenic focus (Naquet and Morrell, 1956). Gastaut, Regis *et al.* (1956) were able to condition spike wave complexes produced in epileptics photosensitive to repetitive photic stimulation.

In the dog, Ungher and Steriade (1960) demonstrated the conditioning of the cerebral electric activity produced by an electric convulsive seizure, by intermittent photic stimulation at a 6–9 c/s frequency. Repetitive photic stimulation produces in the normal dog only inconstant, low amplitude driving. The electric shock brought on a generalized seizure with rapid, ample waves. After 27 associations of repetitive photic stimulation and electric shock, photic stimulation alone produced hypersynchronous discharges with an epileptic morphology similar to that produced by the electric shock. This discharge does not appear immediately after application of the photic stimulation, but after a latency of 2–6 sec in terms of the interval that separates application of the conditioned stimulus (photic stimulation) from application of the non-conditioned stimulus (electric shock). The conditioned critical discharges first appeared on the gyrus marginalis, then on the anterior leads from the gyrus suprasylvius, and eventally became generalized (Fig. 31). The conditioned electric seizure can be made to disappear (the phenomenon of extinction) when the conditioned stimulus (photic stimulation) was applied alone several times running, without being followed by the electric shock, and could be made to reappear when photic stimulation was again associated with the electric shock (Fig. 32). Bilateral occipital lobectomy led to disappearance of the activity evoked by intermittent photic stimulation, both that governed by photic driving and the pathological convulsive wave activity, although associated photic stimulation and the electric shock were continued for several months after the surgical intervention. Reticulo-occipital neuronal complexes appear to interfere in the elaboration of this temporary pathological connexion of conditioned pathological electric activity. Indeed, the non-conditioned stimulus acts especially upon the deep mesencephalic structures, owing to the diffuse and synchronous character of the epileptic discharges. On the other hand, the non-conditioned stimulus, photic stimulation, shows in the dog preference for the specific visual pathways, since it no longer elicits an evoked response in other cortical zones after bilateral occipital lobectomy with retrograde degeneration of the lateral geniculate bodies.

It might be objected that in the foregoing experiments repetitive stimulation may act as a non-conditioned stimulus, since it is known that this type of stimulation can in itself induce critical activity ('photic epilepsy'). A number of arguments can be made against this interpretation. Firstly, in the animals that were subjected before beginning the experiments to a large number of electric shocks, repetitive photic stimulation applied at random — and not constantly and systematically associated with electric shock — did not induce a pathological activity. Epileptic paroxysms to photic stimuli only appeared after systematic association of the stimuli to electric shock, the animals having a normal basic bioelectrical activity in the inter-critical period.

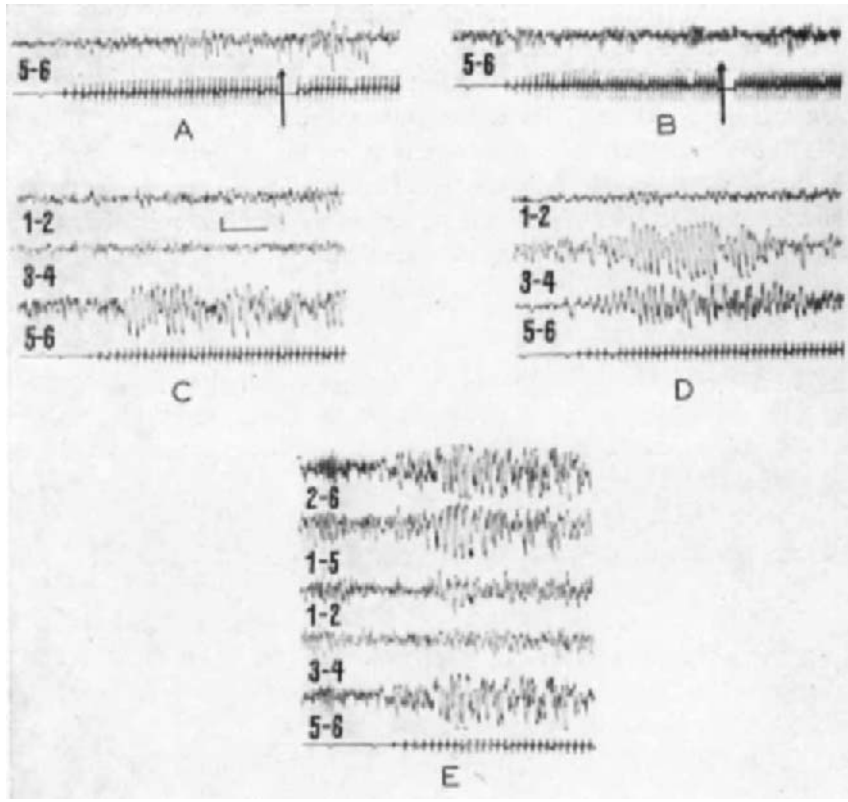



Fig. 32. Extinction and new conditioning with another latency of the hypersynchronous discharges. A = application of the stimulating electrodes on the head of the dog induced a burst of hypersynchronous waves (38th application of the conditioning stimulus); B = extinction of this conditioned reaction after the 47th application of the conditioning stimulus alone; C = new establishing of the conditioned reaction (electroconvulsive seizure preceded by I.Ph.St.) at first (at the 7th association of two stimuli) only in the occipital lead; D and E = spread of the hypersynchronous discharges to frontal leads at the 14th association. (From Ungher and Steriade, 1960.)

On the other hand, hypersynchronous discharges do not appear simultaneously to the action of the photic stimulus, but only after a latency always equal to that with which the non-conditioned stimulation follows the beginning of the action of the repetitive photic stimulation (electric shock), latency constantly equal to 2–6 sec. The fact that the conditioned response could be subjected to extinction likewise pleads in favour of a conditioning process.

Human pathology also offers examples in which an epileptic seizure can be triggered by an extero-, proprio- or intero-ceptive stimulus. Kreindler *et al.* (1958) observed a case in which the proprioceptive stimulus (percussion of the patellar tendon) was able to induce a focal sensitivo-motor seizure, starting with paraesthesia of the leg, then involving lhe entire left side of the body, after which a partial motor seizure developed on the same side. The EEG showed the presence of a slow wave focus

on the right parieto-temporal leads; and a group of high voltage waves was induced on the same leads in the right hemisphere by percussion of the patellar tendon.

In man, complicated psychical processes may induce a seizure in an epileptic patient. In this group we may list musicogenic epilepsy and reading epilepsy. Bickford (1954) observed such cases and considers that the epileptic seizure is due to an optical stimulus, the eyeballs following the written lines by jerky, lateral movements. But the case of Bingel (1957), in which the seizure was induced only when the patient also tried to understand the meaning of the text and not when he read 'mechanically, automatically' without bearing in mind what he was reading, shows that it is not

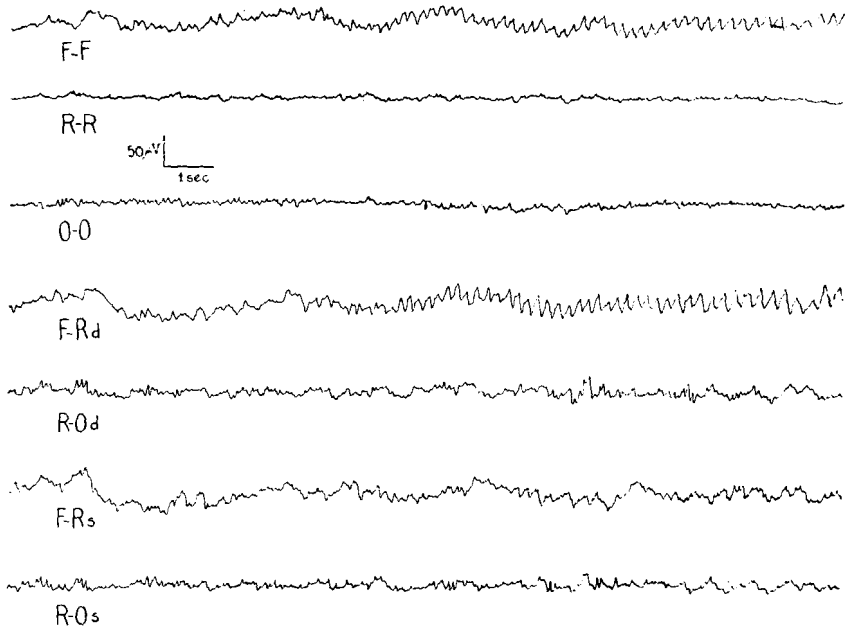



Fig. 33. Bursts of $\theta$-waves in the right fronto-rolandic lead contralateral to the paraesthetic seizures. (From Kreindler, Steriade *et al.*, 1958.)

a simple peripheral mechanism. Kreindler *et al.* (1958) studied a patient with head injury, and paraesthetic focal seizures triggered by putting his feet into water. After a few years, the paraesthetic seizures began to appear spontaneously, and putting his feet into water no longer induced the seizure every time, but they were triggered by gently rubbing the skin of the left arm or leg. On the right frontal rolandic lead there was a focus of $\theta$-wave spindles alternating with rapid 11–14 c/s wave spindles (Fig. 33). Transition from the slow to the rapid waves could not be correlated with any particular sensation of the patient. The contact of the feet with water did not bring about any electroencephalographic alterations worthy of note, nor did the tactile stimuli, but the latter together with mental effort on the part of the patient who concentrated on the paroxysmal paraesthesia that was to follow produced on the central and right parietal leads slow waves of increasingly high amplitude, without the

patient complaining of any special sensation (Fig. 34). Therefore, association of a psychic process (mental representation of paraesthesia) and an unconditioned stimulation (tactile) induces focal paroxysmal electric activity. Goldie and Green (1959) described a similar way of calling forth epileptical electric activity. On the other hand, Efron (1957) showed that, in certain circumstances, an epileptic seizure of the uncinate type can be inhibited reflexly.

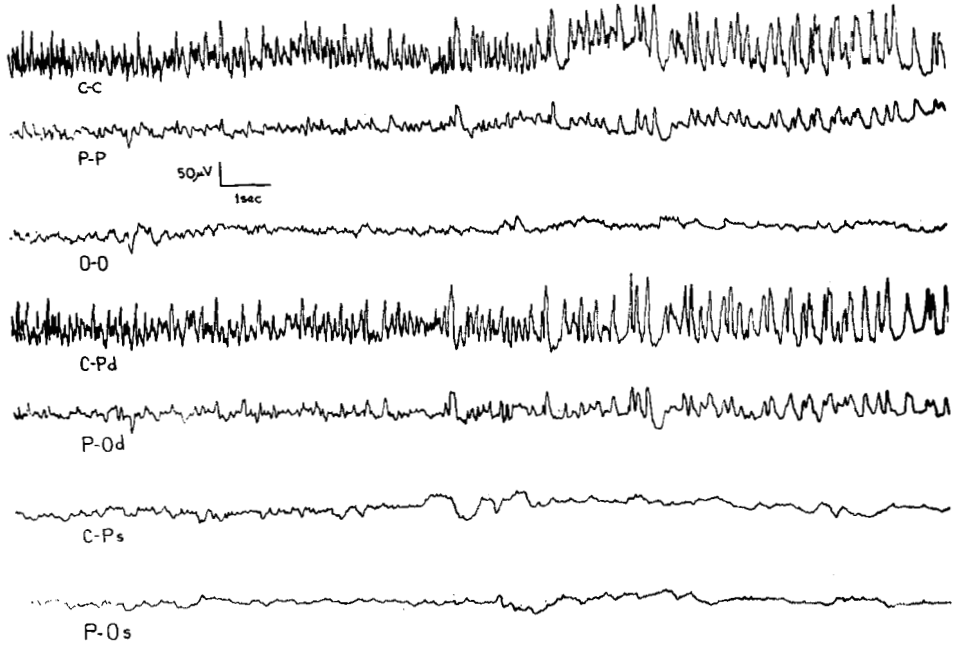



Fig. 34. Same patient as in Fig. 33 during an attempt to trigger a seizure by combining a light tactile stimulation of the left hand with the mental effort required for thinking continually of paraesthesias to come. About 2 min after the beginning of these manoeuvres increasingly large slow waves appear in the central and parietal right leads, but clinically there is no special complaint within this interval. This focal alteration of the electrical rhythms thus prepared the paraesthetic paroxysm at the left upper limb corresponding to a high amplitude (100 to 140 $\mu$V) slow (3 to 4 c/s) activity with focal discharges of typical spike-wave complexes. (From Kreindler, Steriade *et al.*, 1958.)

Therefore, an epileptic seizure can be induced by simple exteroceptive (optical, acoustic, olfactory, tactile), proprioceptive (as in our case by percussion of the patellar tendon) or interoceptive stimuli. It can be triggered by conditioned stimuli, as shown by the foregoing experiments. This greatly broadens the spectrum of the afferent influxes able to induce a seizure, a spectrum of still broader dimensions if we take into consideration the fact that certain psychical processes may also, in exceptional cases, trigger the seizures, as mentioned above.

Triggering of the seizure by non-conditioned, conditioned or psychical stimuli is characteristic of rare clinical cases and only certain experimental conditions. In current practice they are seldom met, as in most of the clinical cases of epilepsy the seizure appears 'spontaneously' and no triggering factor can be made evident. The

reason why this triggering agent cannot be determined is its extreme complexity. In most cases the paroxysm is not induced by an isolated stimulus, but by an 'afferent constellation' that is difficult to define in each separate case. Such a constellation may perhaps be composed of both non-conditioned and conditioned stimuli, of stimuli forming part of what Pavlov called the second signalling system, and of certain elementary psychical processes. An elementary psychical process may very well form an 'afferent' influx at the moment at which it encompasses within its neuronal circuits the cells of an epileptogenic focus, becoming at that very moment an 'afferent' impulse for the focus. The epileptogenic focus must therefore be considered as a trigger-zone whose pathological activity is induced by a certain 'afferent constellation', always the same in the same epileptic case.

In the triggering process there are two different phenomena that must be followed up: first, what is triggered, and second, what triggers.

Essentially, a phenomenon of synchronization with, let us say a 'chronic' process of hypersynchronia — the epileptogenic focus — is triggered. The triggering factor must transform the hypersynchronic discharge of the focus into a propagated self-sustained after-discharge, and then into a self-sustained epileptic discharge, as defined above.

What triggers this chain of processes? In the foregoing paragraphs we insisted upon the role of the afferent influx. But it is also likely that other factors intervene, as for instance sporadical, intermittent alterations of the general or local cerebral metabolism, or intermittent changes in cerebral circulation in certain segments of the cerebral circulatory tree.

# CHAPTER IV

# DEVELOPMENT OF THE EPILEPTIC SEIZURE

When the seizure is triggered by factors that favour spread of epileptic activity from the epileptogenic focus level, then the seizure develops according to the way in which this propagation takes place, that is, to the electrobiological and neurochemical processes that occur in the different formations of the central nervous system and even of the peripheral, vegetative and spinal nerves during the epileptic seizure. The boundary between the triggering process and the onset of the seizure is not sharply delineated, because at the basis of both processes are the phenomena of propagation of epileptic activity. Triggering consists in the beginning of the propagation, and development of the seizure in propagation to increasingly numerous formations and participation of a great number of formations in the convulsive process.

In the preceding chapters we insisted especially on convulsant drugs applied locally (penicillin, strychnine, mescaline, etc.) and upon the role of epileptogenic focus played by certain cerebral lesions. These indeed represent a biological pattern of epilepsy, much more closely resembling that encountered in human clinics than the biological pattern produced by focal faradic stimulation or by electric shock. Epileptogenic lesions and the local action of convulsant drugs show us the way in which a seizure arises, and indicate the behaviour of a cerebral epileptogenic focus, as known to exist also in the epileptic patient. The physiopathology of such an epileptogenic focus can therefore be followed up with the aid of this experimental pattern.

However, faradic epilepsy and particularly the electro-convulsive seizure can help us also to understand the way in which an epileptic seizure develops once it is triggered; this can also be asserted for the convulsive drugs introduced into the general circulation. These methods can help us follow up the mechanism of development of the seizure and, to a lesser extent, the triggering mechanism.

In the development of an epileptic seizure several phases can be schematically distinguished: spread of epileptic activity from the epileptogenic focus to different intracerebral formations; generalization of the seizure, the peak of the paroxysm in which many cortical and subcortical formations are involved; and finally the phase of electric silence that coincides with the end of the seizure.

## *A. Propagation of epileptic activity*

The spread of epileptic activity in the brain has certain characteristics which we shall try to bring out in the following paragraphs.

The epileptic seizure — the paroxysm — once triggered, is essentially characterized by spread of the pathological excitation from the epileptogenic focus to other cerebral formations. The phenomenon of propagation forms the basis of the mechanism of development of an epileptic seizure. The paroxysm is preceded by marked alteration of cortical reactivity. Study of preparoxysmal reactivity has shown that a great number of neurons are put into a state of activity. Hypersynchrony, that characterizes the convulsive activity of a complex neuronal structure, appears to be caused by hyperactivity of each neuron, permitting synchronization of electrical activity. The convulsive activity of a neuronal complex, marked by increase in the number of neurons in a state of activity, is characterized chiefly by the quality of the activity of each neuron discharging at high frequencies. This synchronization of the electrical activity of various neurons could occur without the existence of synaptic linkages between them.

For Green and Naquet (1957), local propagation represents extrasynaptic irradiation from cell to cell, following dendritic depolarization. Sporadic discharges and after-discharges spread differently; the after-discharges spread much farther, and actually they alone represent propagation of an epileptic seizure. A step in the organization of an epileptic seizure is the *propagated after-discharge.*

The propagation of epileptic activity is sometimes ephaptic (French *et al.*, 1956), but it is also interdendritic, *i.e.*, an ephaptic interdendritic propagation. An axosomatic spread certainly also exists since transcallosal propagation cannot be explained by an ephaptic route. Spread by interdendritic ephaptic transmission is also sustained by dendritic depolarization manifested on the EEG by slow negative deflection associated with increase in the firing activity of the cell, which discharges in bursts (Li and Jasper, 1953).

In certain experimental circumstances the after-discharge has special propagation characteristics. Torres *et al.* (1958) isolated in the cat under barbiturate anaesthesia a portion of the cerebral cortex, and recorded simultaneously electrical activity of the isolated cortex, of the intact surrounding cortex and of the white matter underlying the slab. Electrical after-discharge was induced by stimulation with a square wave at 50 c/s for 3 to 5 sec with varying voltages from 3–10 V. When the stimulus was applied to the isolated cortex, the after-discharge remained within the boundaries of the surgical cut. When the after-discharge was initiated in the normal cortex, there was spread to the isolated cortex, across the cut. Local application of strychnine to the isolated cortex produced typical strychnine spikes in it, and they remained limited to it. When induced in the normal cortex, the strychnine spikes spread to the isolated cortex. The record from the depth electrodes was not affected by strychnine spikes or by after-discharges to electrical stimulation occurring in the surface. The same results were obtained by applying the same stimuli after injection of a paraffin-oil mixture around the isolated cortex and also after removal of a narrow strip of cortex between this and the normal cortex. It is therefore possible that the transmission takes place across a solution of continuity between areas of cortex.

Konigsmark *et al.* (1958) concomitantly recorded from 64 different points of the cortex, the propagation of an after-discharge obtained by stimulation of the precentral

gyrus in the curarized monkey. They observed that the propagation developed along a zone of cortical contiguity. The size of the cortex invaded by the epileptic discharge depends upon the strength of the stimulus, the duration of the induced discharge and the relative excitability of the cortex (Fig. 35). At the beginning, the discharge is manifested on the EEG by a train of high voltage spikes, and then the seizure is characterized by bursts of spikes or waves, both aspects being closely interrelated.

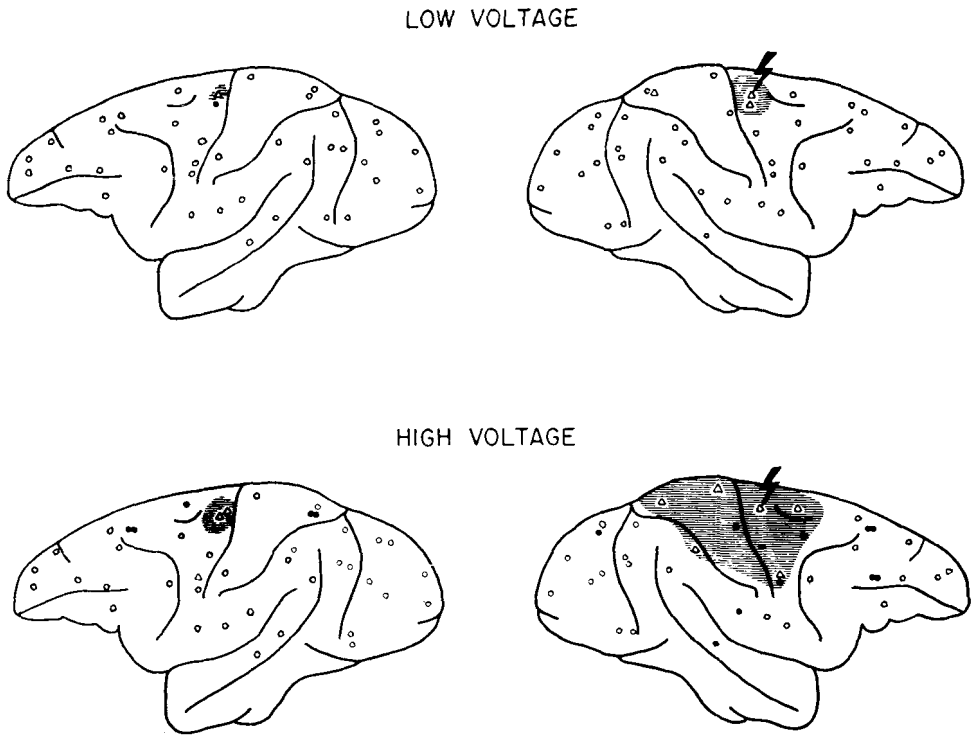



*Fig. 35. Local seizure spread. Hatched area on diagrams of hemispheres indicates bilateral extent of seizures induced by excitation of point on right motor cortex (jagged arrow) with low intensity (4 V) and high intensity (10 V) stimulation. Open circles indicate recording points (composite of 2 animals) to which discharges did not extend. Open triangles indicate well-developed slow wave activity, and filled circles designate poorly developed waves. (From Konigsmark et al., 1958.)*

Local spread of the after-discharge seems to be preceded by the progressive appearance of surface-negative waves in the cortex surrounding the focus of paroxysmal activity. The discharge is disseminated by transcallosal conduction to an area homotopic to the stimulated locus. Remote conduction to other surface regions was lacking. This suggests that propagation of critical activity is closely linked to the induced alterations of the dendritic potentials, as the transcallosal contacts between the two hemispheres are axo-dendritic (Chang, 1952).

Propagation of epileptic activity is achieved by spread of the local after-discharge to other cerebral formations. Spread of the after-discharge (or of the discharge) takes

place either in the grey matter and can be compared to an oil spot that comprises increasingly large groups of neighbouring neurons, or along certain pathways, namely longer or shorter nervous fibres with which the epileptogenic focus is connected. Secondary foci can develop at a distance from the initial focus and persist after the latter has disappeared, and even after extirpation of the cortex at the level of the initial focus. Sometimes the initial focus continues to discharge, as the discharges comprise by propagation increasingly large zones of the cortex, which begin to fire simultaneously, often synchronously, over an extensive surface, followed by simultaneous and sudden arrest of the entire portion that is discharging. Synchronous, simultaneous discharges are due to the action of a pacemaker, and the electrical silence period occurs when the pacemaker ceases to function.

The partial section of the cerebral peduncle in the monkey causes the convulsions to become less intensive in the distal segments of the contralateral limbs both in focal and in generalized seizures (Walker and Richter, 1963). Hence, very likely, cortico-spinal as well as more primitive, probably multisynaptic, pathways play a part in the mechanism of generation of a convulsion.

Hayashi (1952) was able to elicit in the dog, after medullary bilateral pyramidal section, focal tonic and clonic convulsions which became generalized. In other dogs in which the protuberance was sectioned in such a way as to leave only the pyramids intact, no kind of convulsion whatsoever could be provoked. Merlis and Misrahy (1959/1960) used a combination of metrazol and intermittent photic stimulation in order to study the effect of pyramidotomy in the course of the convulsive seizure. Unilateral section of the pyramid did not prevent the development of a generalized attack, but the limbs corresponding to the section, and particularly to the hind leg, were slower in developing convulsions which were weaker on that side. Bilateral pyramidal section in the cat does not prevent the generalized attack but distal portions of the limbs, particularly the forelegs, exhibit clonic movement in extension instead of flexion.

We may therefore distinguish certain characteristics peculiar to the convulsive cortical circuits from those of subcortical structures. The cortical circuits do not include structures that are situated more caudally than the diencephalon, which does not, however, exclude the possibility of the meso-rhombencephalic structures being influenced during an attack by the propagation of some cortical impulses. On the other hand the reticular reverberating circuits have certain peculiarities which distinguish them from those of the circuits situated more rostrally and particularly from the cortical ones.

The investigations mentioned above have therefore succeeded in giving us a picture on the mechanism underlying the generalization of epileptic activity starting from the epileptogenic focus, and have shown the main pathways followed by this propagated activity. The development of the epileptic attack is connected with the mechanisms that cause the self-sustained after-discharge to propagate. The self-sustained after-discharge at the level of primary foci is propagated over certain preferential pathways. But the transmission of the after-discharge phenomenon along certain tracts of fibres does not depend on facilitation and summation phenomena but rather on the alter-

ation of the excitability of the subcortical nuclei of the discharge effect itself. This after-discharge does not appear to be a specific mechanism acting within small neuronal masses, but is probably the effect arising from large homologous cortical areas (Walker *et al.*, 1956) (Fig. 36).

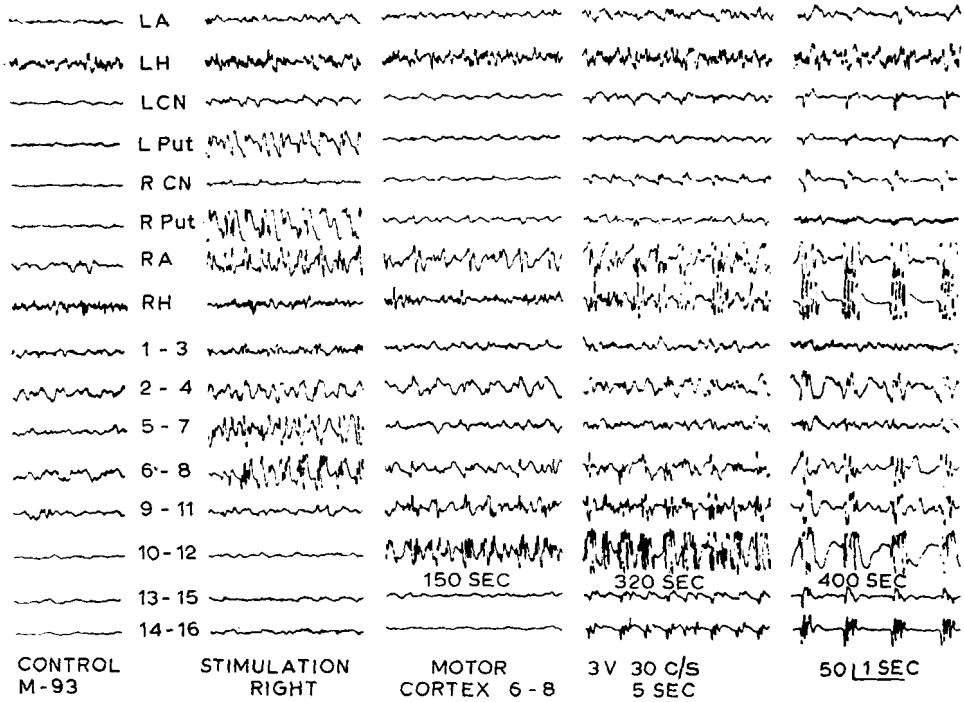



Fig. 36. Late interaction between different cortico-subcortical systems. Immediately after stimulation of the right motor cortex (monkey), convulsive discharges are present in both motor cortices (6–8, 5–7), right and left putamen and right amygdala. After 2 min 30 sec the activity in the centro-putamen-thalamic system is greatly reduced in amplitude and frequency, but discharges are building up in the right occipital cortex. At 2 min 30 sec later a consistent, low voltage convulsive activity is recorded from the right occipital cortex; synchronous discharges are present in the ipsilateral and contralateral temporal cortex (14–16, 13–15) in the ipsilateral hippocampus, amygdala and caudate. Some responses are recorded also from both the contralateral occipital and ipsilateral motor cortices. At 1 min 20 sec later a well-organized widespread synchronous epileptic activity can be recorded from all the structures on the right side and from the left caudate nucleus, occipital cortex and to a lesser degree in the temporal and motor cortices and putamen. The seizure continues 3 sec more and eventually ends abruptly in all the structures. The second portion of the tracing (150 sec) shows that the right amygdala perhaps played a prominent role in the interactions of these systems. (From Walker *et al.*, 1956.)

A chronic cortical focus may produce *secondary* functional alterations in subcortical structures in such a way that at a given moment they become the site of continuous discharges, independent of the initial cortical focus.

The genesis of a 'mirror focus' was experimentally demonstrated by Morrell *et al.* (1960). They produced a cortical epileptogenic focus with ethyl chloride, and noticed that after 24 h, in the contralateral homotopic cortex, a mirror focus develops that

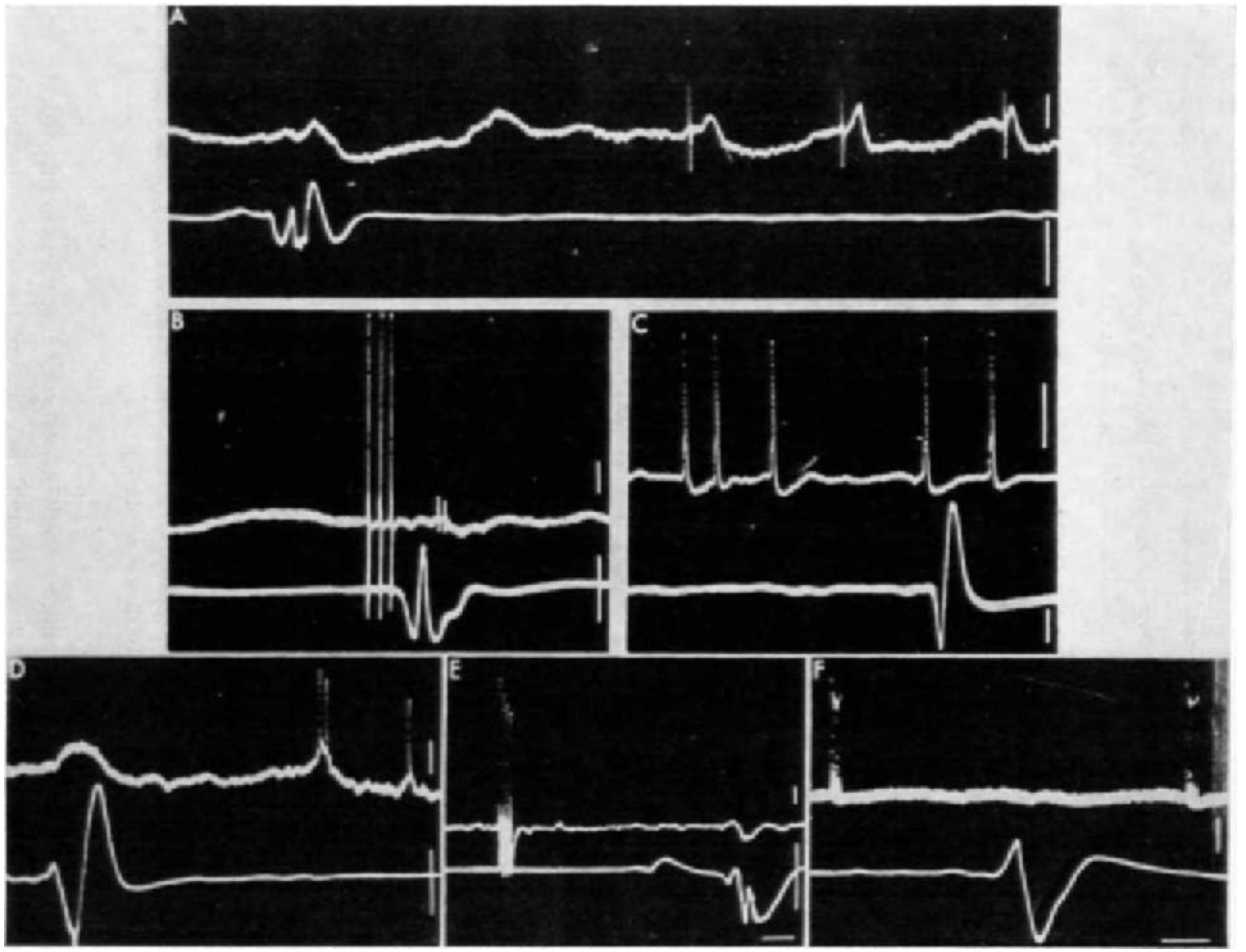



Fig. 37. The lower tracing is from gross surface electrodes (bipolar) placed on the suprasylvian gyrus close to the site of application of the convulsant drug. The upper tracing is from a microelectrode inserted in the same gyrus of the opposite side in the homologous region. Positive polarity for the latter is an upward deflection. The epileptiform discharges were induced by penicillin (A, B, D, E) and strychnine (C, F). Note the evidence of a projected discharge (small deflection in the microelectrode tracing) in A, B, D, E. Presence of spikes from two different units in B, only one type firing in coincidence with the paroxysmal discharge. (From Ajmone Marsan, 1963.)

becomes autonomic, *i.e.* it also persists after ablation of the primary focus, when this is done a week after the initial focus is created. The authors attribute to certain humoral factors a role in the formation of secondary foci, synaptic bombardment continually modifying the blood-brain barrier.

A 'mirror focus' is produced by transmission of the spikes from the initial focus to the homologous area in the opposite hemisphere. During generalization, the spikes first spread to the homolateral hemisphere and then also comprise the contralateral hemisphere. The spikes transmitted to the contralateral hemisphere are suppressed by section of the corpus callosum, but secondary, independent spikes may persist in the contralateral hemisphere after section of the corpus callosum, showing that an autonomic focus has developed in the homologous area, due to prolonged bombardment by the initial focus.

Ajmone Marsan (1963) induced in the cortex of cats, by means of local application of penicillin or strychnine, epileptogenic foci, and compared the activity of cortical units at the site of the focus with that of units located in the contralateral homologous region. There are characteristic features which seem to differentiate, at the neuronal level, a local from a projected epileptic process. In the latter a substantially smaller number of units is activated and their firing seldom consists of high frequency bursts of spikes (Fig. 37).

The epileptic focus induced by topical application of mescaline to the sigmoidian gyrus propagated contralaterally 15–20 min after application, this minor focus con-

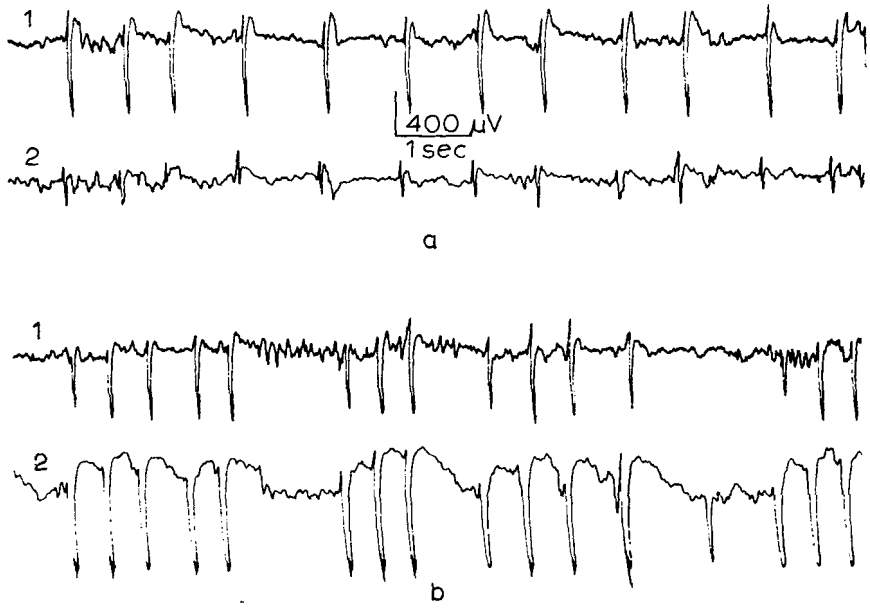



Fig. 38. Interaction between two symmetrical foci in the right and left g. sigmoideus. a = mescaline applied topically on the left g. sigmoideus posterior. (1) = the spikes propagate into the right g. sigmoideus posterior. (2). b = mescaline also on the right g. sigmoideus posterior; the spikes on the right side are driven rhythmically by the left focus. (From Crighel and Stoica, 1961.)

sisting in spikes of the same shape but of smaller amplitude (Crighel and Stoica, 1961). Application of mescaline to the contralateral sigmoidian gyrus induced here a new focus with discharges either in the same rhythm or in another rhythm with the first focus. The second focus depressed the first (Fig. 38).

Wada and Cornelius (1960) produced a chronic epileptogenic focus in the cat with alumina cream, in the sensory-motor region, and found recurrent, spontaneous discharges in the caudate nucleus, globus pallidus, putamen and nucleus ventralis postero-lateralis, that were independent of the initial cortical focus a few months after it was produced. In some animals, the clinically generalized convulsive seizure began with electrographic changes in the deep layers and not in the cortical focus. Paroxysmal activity of the deep formations was not only ipsilateral to the cortical focus, but also involved the contralateral formations.

Propagation of the discharge takes place along certain pre-established pathways or connections of functional projection as for instance along the uncinate fascicle towards the frontal and temporal lobes, along the occipito-frontal fascicle (Rosenblueth and Cannon, 1942), or from one motor zone to another in the corpus callosum (Erickson, 1940). Subcortical propagation likewise occurs, such as that from a cortical focus to the specific thalamic nuclei (Jasper *et al.*, 1952) or from the pole of the temporal lobe to the mesencephalic reticular formation, from the frontal pole to the median centre in the thalamus.

From anatomical studies it seems that a multiplicity of pathways is available for transmission of discharges from any particular portion of the temporal lobe (hippocampal gyrus, precentral leg area, globus pallidus, pulvinar, superior colliculus, dorso-medial thalamus nucleus, etc.). Stimulation of the middle temporal cortex, however, gives rise to discharges in the ipsilateral temporal cortex and hippocampus much more commonly than it does in the basal ganglia and thalamus. Poblete *et al.* (1959) suggest that in temporal lobe epilepsies the transmission of temporal spiking to the opposite site probably indicates a cortical origin of the discharge. Predominantly unilateral spiking favours an amygdala focus. Discharges originating in the hippocampus may be propagated more widely over both temporal and frontal regions because of the multiple pathways for dissemination (Fig. 39). The corpus callosum, psalterium, massa intermedia and posterior commissure do not seem to play a significant role in the interhemispheric transmission of the after-discharge induced from the temporal pole, or second temporal gyrus, the preferential way being the anterior commissure. The transmission seems to be direct and not by way of the amygdala or hippocampus.

But the anatomical connections alone cannot account for the preferential routes of propagation of the epileptic discharge. Thus, as noted by Poblete *et al.* (1959), anatomical studies show that the temporal lobe has at its disposal a great number of pathways for transmitting the discharges generated at its level. For instance, the second temporal convolution has anatomical connections with the superior temporal convolution, the anterior temporal cortex, gyrus hippocampi, precentral area, globus pallidus, pulvinar, dorso-median nucleus of the thalamus, and with many other formations. Nevertheless, stimulation of the medial temporal cortex gives rise to

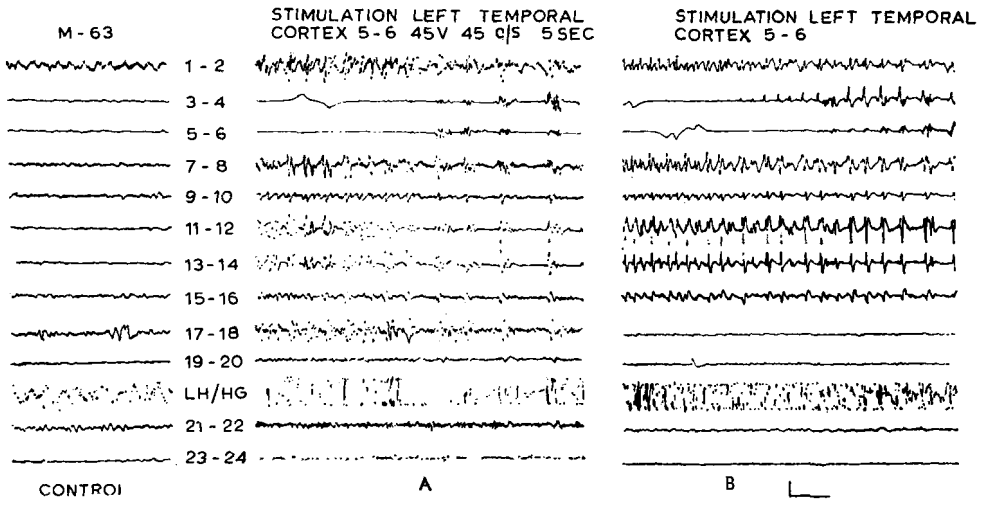



Fig. 39. A, electrograms after stimulation of second temporal gyrus in the monkey before operative procedures; B, electrograms following stimulation of second temporal gyrus after section of most midline structures by three incisions, *i.e.* partial section of anterior commissure, left septal region, rostral half of corpus callosum, dorsal half of midline structures of thalamus, damaged posterior medial structures of thalamus, posterior commissure and superior colliculus. (From Poblete *et al.*, 1959.)

after-discharges propagated far more frequently in the hippocampus than in the basal ganglia or in the thalamus. Therefore, although there are so many anatomical pathways available for propagation, only some of them are activated.

Projection may also take place from a subcortical focus to the cortex. An interaction sometimes develops between the cortical and subcortical centres. Jasper (1955) showed that an after-discharge in the median thalamic nuclei projects on the 9th and 10th areas (Brodman's area in the monkey) towards the end of the discharge; the thalamic discharge has a spike–wave aspect. The cortex then suddenly stops firing, although the thalamus continues to discharge, but these discharges are no longer in the form of spike–waves but take on the aspect of serial, rhythmic waves, pointing to a thalamo-cortico-thalamic reverberant effect. Sometimes the subcortical focus may induce in the cortex a self-sustained secondary focus in which the duration of the discharge is longer than in the primary subcortical focus. In certain cases a subcortical focus may produce bilateral, symmetrical cortical discharges, as for instance a focus in the hippocampus that gives secondary discharges in both temporal lobes.

It has been shown in experiments on animals that at a given moment, after creating an experimental focus by electrical stimulation or chemical agents, it becomes very difficult to recognize the region that initiated the discharges from other cortical or subcortical areas towards which the epileptiform activity has spread (Jasper *et al.*, 1952).

The propagation that takes place along the neuronal circuits is arrested by interruption of these circuits. Kristiansen and Courtois (1949) were able to produce after-

discharges in isolated portions of the undercut cortex with maintained pial circulation; but excitation did not spread to the neighbouring cortex adjoining the isolated segment; therefore it was not a physical irradiation but one taking place along neuronal, physiological pathways. The most likely mechanism of irradiation is successive facilitation by short synaptic pathways within the cortical neuronal network. The epileptic excitation may irradiate at velocities of 10 to 40 cm per second, or the velocity may attain only a few millimeters per second. It is therefore likely that, apart from neuronal irradiation, other mechanisms, such as electrotonic or chemical processes, exist.

Propagation of the discharges along the pathways that link the epileptogenic focus to the rest of the brain may be prevented under certain conditions. Thus, French *et al.* (1956) showed that, although the orbital and para-occipital cortex possessed rich connections with the centrencephalic system, stimulation of these regions seldom brought about a generalized seizure. The authors explain this by the observation that certain pathways transmit inhibitory effects. Therefore, in the mechanism of propagation of epileptic activity the pre-existing morphofunctional connections between the different formations of the brain appear to interfere in the first place. But propagation does not take place strictly along anatomical pathways: preferential pathways for the propagation of epileptic activity also exist.

It may be possible, as already mentioned, that extrasynaptic propagation, linked to variations in the electric field, intervene in the mechanism of generalization (Gerard and Libet, 1941; Bremer, 1941; Rosenblueth and Cannon, 1942). To this must also be added the hypothesis of Chang (1951) according to whom propagation may also take place along the surface of the cerebral cortex, from one dendrite to another, without involving the perikaryons and the axons.

Today it is generally agreed that propagation of convulsive activity does not take place only over the surface of the cortex like an oil spot, but also along cortico-subcortical circuits to which an important role in propagation has been attributed. Selikov (1959), studying propagation of strychnine-induced convulsive activity, shows that it is not a question of intracortical activity, but of activation of the reticular substance in the diencephalon and mesencephalon, with secondary activation of the cortex. However, the role of the cortex in propagation and generalization of epileptic activity cannot be denied.

In animals in which Amantea's so-called 'reflex epilepsy' can be triggered, treatment with cocaine of a narrow region of the cerebral cortex around the cortical strychnine-induced focus does not influence focal epileptic activity, but prevents the convulsive activity from generalizing (Ferrari and Galasso, 1957). This shows the importance of intracortical diffusion for generalization of an epileptic focus in the sensitivo-motor zones. Starzl *et al.* (1953), on the other hand, found that in a convulsive seizure induced by intravenous injection of a liminal metrazol dose epileptic activity of the different thalamic nuclei strictly depends upon the epileptic activity of the cortical regions connected to these nuclei. For instance, paroxysmal activity of the nucleus lateralis posterior only reflects the activity of the cortex in the lateral or median suprasylvian gyrus.

In some investigations, attempts were made to penetrate still deeper into the mechanism of propagation of epileptic activity and the development of an epileptic seizure. In their experiments on alumina-cream-induced seizures, Schmidt *et al.* (1959) led off with microelectrodes implanted in the neurons close to the scar during an epileptic seizure and found an increase in the spontaneous activity of the neuron before the onset of propagation. With the development of repetitive dendritic waves this hyperactivity becomes very intense, attaining a discharge frequency of up to 1000/sec. This initial progressive increase in the discharges of the unit gradually passes into a high frequency decremental discharge, followed by a 'clonic' phase characterized by massive, synchronous formation of 'dendritic' waves, during which discharge of the unit is seldom visible. The seizure ends with electrical silence during recovery, and the first spontaneous discharges of the unit appear only 2 min after the seizure is over. However, other cells may exhibit another aspect of the discharges, for instance they may discharge steadily throughout the duration of the seizure. Some cells, with continuous high frequency inter-ictal bursts, may cease to discharge during the seizure and resume their activity only some minutes after it is over.

Sawa *et al.* (1963) used intracellular microelectrodes during an epileptic seizure induced by electrical stimulation. Repetitive stimulation, prolonged so as to produce a seizure, has the following intracellular effects: progressive decrease of the hyperpolarization wave, progressive lengthening of the depolarization wave, and then temporal summation of the depolarization and temporal depolarization summation. Gerin (1960) and Ajmone Marsan (1961), using extracellular microelectrodes, also found these two factors, but they neglected a third factor, that of the depolarization wave alterations, recorded on the microelectrode leads. This hyperpolarization would be the equivalent, at cellular level, of the mechanism that slows down the seizure.

Most of the cortical and hippocampal neurons exhibit a depolarization wave followed by a hyperpolarization wave as response to a single surface shock. Prolonged stimulation at high intensities and frequencies produces progressively a decrease in the hyperpolarization wave, a progressive lengthening of the depolarizing wave and temporal summation of the depolarization waves. Towards the end the neuron is maintained in a state of sustained depolarization. After stimulation ceases, sustained depolarization continues and large, long duration, depolarization waves periodically appear with corresponding waves on the corticogram.

In the last stage of the seizure, phases of decline of the depolarizing wave become increasingly accentuated, until eventually depolarization is reduced to the level of hyperpolarization. A prolonged phase of hyperpolarization is seen on the corticogram concomitantly with electrical silence (Fig. 40).

In the mechanism of propagation of an epileptic discharge starting from an epileptogenic focus, the 'spreading depression' phenomenon described by Leão (1944) may be assumed to interfere. Mechanical, electrical or chemical stimulation of a local zone of the cerebral cortex may lead to gradual disappearance of its electrical activity and diminution of its excitability, which spreads very slowly over the surface of the cortex. The propagation velocity is 2–3 mm per min and spreads equally in all directions in the form of a wave. Depression of electrical activity may be preceded by

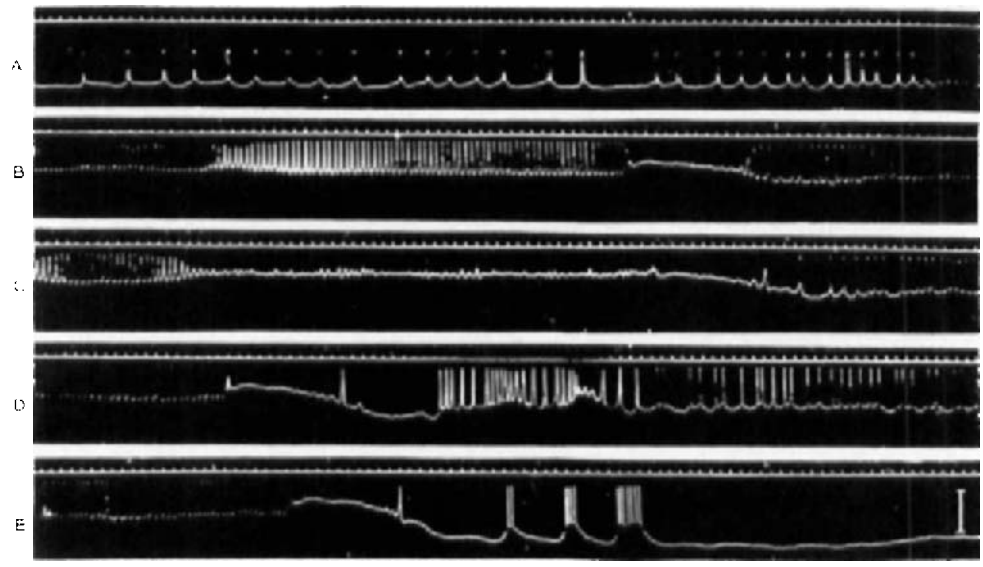



Fig. 40. Activity of a pyramidal tract neuron during a seizure. The seizure was induced by electrical stimulation under strychnine. A = prestimulus activity; B = activity at 1 sec; C = at 3–5 sec; D = at 5 sec, and E = at 11 sec after cessation of stimulation. During the course of the poststimulus seizure 10 depolarizing waves occurred periodically. After each depolarizing wave the membrane potential rose for about 200 msec with concurrent increase in the rate of firing. (From Sawa *et al.*, 1963.)

abnormal electrical activity somewhat similar to an epileptic discharge (Bureŝ and Bureŝová, 1960). It is therefore likely that a phenomenon analogous to this spreading depression should interfere in the mechanism of propagation of the epileptic discharge. Spreading depression is not a phenomenon that depends upon the interneuronal connections, because it also takes place when the zones are separated from one another by incisions, provided the pial circulation between these zones is maintained. Depression is always accompanied by a slow change of the d.c. potential of the cortex, and the electroencephalographic depression may be substituted by various forms of hyperactivity (Bureŝ and Bureŝová, 1960).

Topical application of glutamic acid in 0.01 *M* solution produces an increase of cortical excitability to repetitive stimuli, lowering the threshold for epileptic discharge (Crighel and Manolescu, 1964). A stronger concentration (0.1 *M*) produces a spreading depression with some characteristics of hyperexcitability of the deeper neurons. Hence, it might be assumed that both inhibitory and excitatory events take part in the depression accounting for the production of the epileptic discharge (Fig. 41). Marshall (1959) believes that in 'spreading depression' the properties of the syncytial potentials of the dense neuronal interconnections and of the dense neuronal contiguities combine with cellular lamination and dendritic organization, in order to produce a syncytial type of propagation reaction. However, the mechanism of the 'spreading depression' is not yet well understood, and hence we are far from being able to use it in explaining propagation of the epileptic seizure.

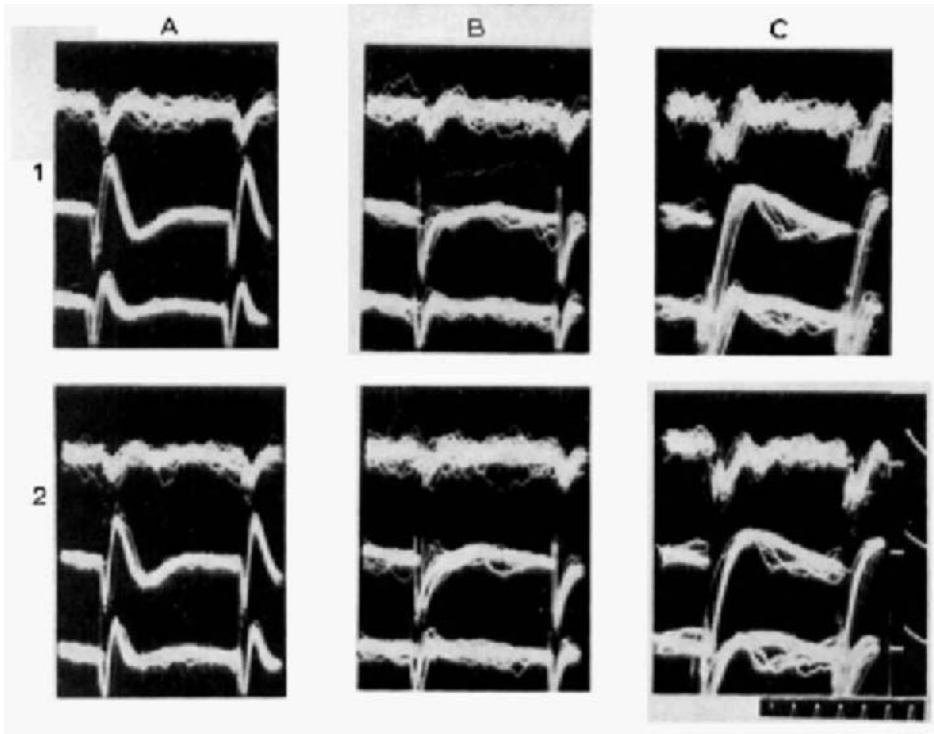



Fig. 41. Topical application on the neocortex of L-glutamic acid (0.1 *M*). Continuous stimulation during 45 sec with supraliminal stimuli, at 9 c/s rate. 1 = before stimulation; 2 = at the end of the stimulation; A = control; B = 3 min after application. Depression of the negative phase; the transcallosal response without alteration. C = 14 min later. Enhancement of the positive phase. Calibration: 10 msec, 200 $\mu$V. (From Crighel and Manolescu, 1964.)

### *B. Spread of epileptic activity from different cerebral structures*

Spread of epileptic activity from the different cerebral structures in which it arises to other intracerebral structures shows during the epileptic seizure, as mentioned above, certain characteristics of a preferential order, that is, electrical activity originating in a certain formation tends to spread to certain formations more than to others.

(1) Electrical stimulation of the *motor cortex*, in the dog, produces convulsive potentials in the homolateral thalamus, homolateral globus pallidus and bilateral mesencephalon. Convulsive potentials are also often found in the contralateral motor cortex, but in phase opposition to the potentials of the initial focus. Motor cortex stimulation in cat induces an after-discharge at the symmetrical points of the contrololateral hemisphere before the occurrence of epileptic potentials at the adjacent points of the homolateral hemisphere (Kreindler and Steriade, 1960b). Convulsive potentials are not observed in the subcortical nuclei on the opposite side (Utsumi *et al.*, 1957).

The frontal after-discharge spreads especially to the reticular formation of the brain stem and secondarily to the nucleus caudatus, amygdala and hippocampus. The

cingulus after-discharge spreads especially to the amygdala and hippocampus. The preferential pathways of irradiation in the motor cortex are the contralateral homologous motor cortex, putamen, thalamus, brain stem nuclei, amygdalo–hippocampal complex and cerebellum (Faeth *et al.*, 1954).

Strychnine applications to the precentral region in the rabbit, produce grouped discharges when the basic tracing takes on an active aspect, whereas a slow basic tracing only produces isolated spikes (Hippius *et al.*, 1957). Similarly, strychnine activity transmitted from the initial focus to a homologous, contralateral point induces spindle discharges only when the basic tracing is active. Administration of evipan favours irradiation to the homologous contralateral zones and diminishes grouping of the spikes. This shows that the functional state of the cerebral cortex at the moment in which the seizure is triggered is of importance for the development of a seizure.

After-discharge of the motor region also spreads to the reticular formation of the brain stem, to the septal region and the striatum. Strychnine spikes and potentials evoked by a single shock in Rolando's region spread to the reticular formation, manifested by facilitation or inhibition of the spontaneous discharges of certain isolated reticular units, recorded with microelectrodes (Baumgartner, 1954).

The discharges of a penicillin cortical focus and their spread takes place according to the site of the focus in the cortex. When the penicillin focus is situated in the sigmoid gyrus, the discharges spread from the initial focus to the subcortical nuclei and then to the rest of the cortex. Kreindler, Voiculescu *et al.* (1960) and Kreindler, Voinescu *et al.*, 1961a) showed differences between propagation from such a sigmoid focus and an ectosylvian gyrus focus.

Topical application of penicillin to the sigmoid gyrus of the cat results in early and marked propagation of the discharges to the ventral thalamic nuclei (Fig. 42), *i.e.* the ventral lateral nuclei and posterior ventral and anterior ventral nuclei. Early spread to the dorso-median and parafascicular nuclei and mesencephalic reticular formation is fairly frequently observed. Spread to the lateral thalamic nuclei or to the pulvinar is not often noted. Neither do the mid-line nuclei take part in propagation not does the caudate nucleus show any early epileptic activity.

Propagation to the sigmoid gyrus on the opposite side only takes place after a large number of subcortical formations, especially the thalamic nuclei, take part in the paroxysmal discharges. Spread to the posterior cerebral cortex only occurs after invasion of the thalamic nuclei.

Walker *et al.* (1956) used the method of focal electrical stimulation and topical application of penicillin in the monkey for study of the propagation of cortical foci, and found that the sensory motor cortex (pre- and postcentral gyrus) shows the following preferential spread: the central heterolateral cortex and the homolateral putamen in 90% of the cases, the lateral nuclei of the thalamus in 30% of the cases, then the subthalamic nucleus, locus niger, pontine reticular formation. No propagation is observed in the caudate nucleus, hypothalamus, hippocampus and amygdala. They emphazise that so-called cortical epileptic seizures when studied with depth electrodes in the monkey, are seen to be accompanied by marked involvement of many subcortical structures, depending upon the site of origin of the cortical discharge.

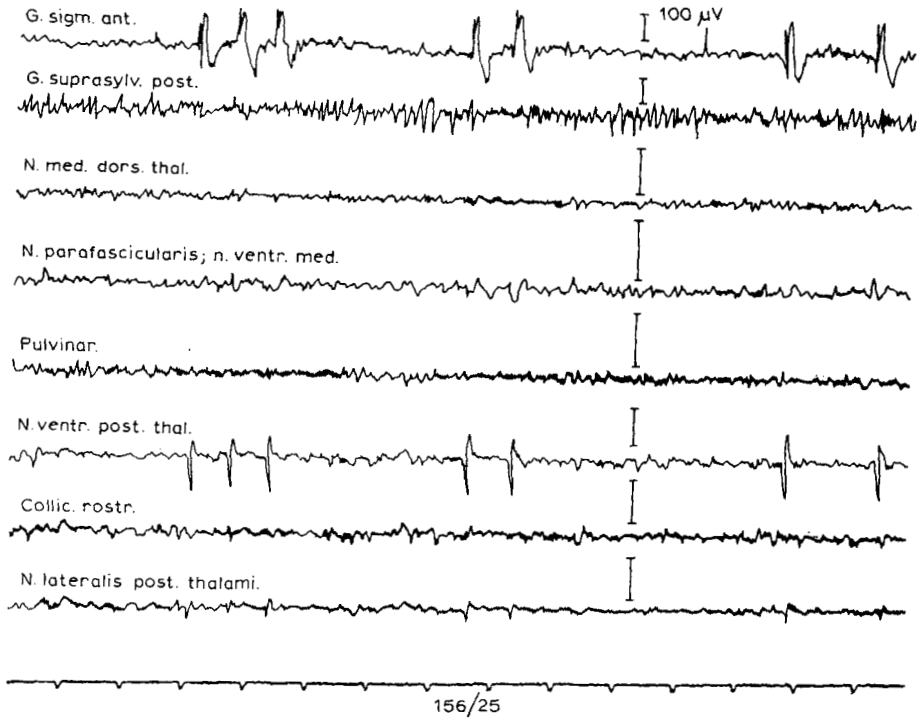



Fig. 42. A penicillin focus on the g. sigmoideus anterior (cat) induced synchronous discharges only in the nucleus ventralis posterior of the thalamus. (From Kreindler, Voiculescu *et al.*, 1960a.)

The after-discharge from the frontal granular cortex propagates to the caudate nucleus and to the contralateral frontal granular cortex and subsequently to many other subcortical structures. From the central cortex there is a propagation to the ipsilateral putamen and thalamus and to the contralateral homologous central cortex, and from the temporal cortex to the amygdaloid–hippocampus complex and its subcortical projection sites.

The epileptic focus induced by topical application of mescaline to the sygmoidian gyrus showed a propagation to the homolateral putamen and to the reticular nucleus of the thalamus, to the VPL and PL thalamic nuclei. Before generalizing there is also a propagation to the mesencephalic reticular formation (Crighel and Stoica, 1961). Hayashi (1952) and Jinnai *et al.* (1950) noted the importance of the putamen for spread of the discharges from the cortex and recommended lenticulotomy in the treatment of epilepsy.

Epileptic activity in the motor cortex, induced by topical application of penicillin or strychnine in the curarized monkey, produces discharges in the ipsilateral thalamus and putamen, seldom in the ipsilateral globus pallidus, and never in the caudate nucleus (Poggio *et al.*, 1957). In the putamen there appears to exist a trispatial organization.

The epileptic activity in the motor cortex, either induced by penicillin or strychnine is able to elicit responses in the basal nuclei. The structures particularly involved are

the ipsilateral putamen and thalamus. Some responses are also present in the ipsilateral globus pallidus, but no discharges have been recorded from the caudate. In the putamen a certain amount of trispatial organization seems to be present. The epileptic cortical bursts in the motor face area fire the mid part of the putamen, at the level where the globus pallidus is well differentiated in the medial and lateral portions. Posteriorly the putamen seems to respond to discharges in the postcentral cortex. The lateral portion of the globus pallidus close to the above mentioned region of the putamen may also show responses to the cortical discharges, but its firing is less constant and defined than that of the putamen. The thalamus is recorded in its ventrobasal portion but responses are also present more medially in the centromedian nucleus and in the inferolateral part of the medial dorsal nucleus. The contralateral responses are localized to the putamen showing the same spatial arrangement as the ipsilateral homologous structures. They seem to be secondary to the involvement of the related cortex and greatly dependent on the type of cortical activity, being much more pronounced during the course of a seizure.

(2) Starzl *et al.* (1953) showed that epileptic activity of the different thalamic nuclei depends strictly upon the activity of the cortical regions with which these nuclei are connected. Thus, paroxysmal activity of the posterior lateral nucleus reflects only the activity of the *lateral cortex or median suprasylvian gyrus.* With liminal metrazol doses, the activity of the thalamic nuclei would therefore depend first of all upon corticofugal impulses. Nevertheless, Kreindler, Voiculescu *et al.* (1960), in experiments with penicillin foci, observed intense paroxysmal discharges in the thalamic nuclei whose cortical projection zone showed no epileptic activity. With cortical epileptogenic foci, therefore, with a sigmoid site, propagation first takes place towards the respective projection thalamic nuclei (lateral and posterior ventral nuclei) and the reticular formation of the brain stem. Here, internuclear circuits develop, leading to generalization of the epileptic activity to the thalamic nuclei and then to the entire cortex.

Chronic epileptogenic foci produced in different species (cat, monkey) in the *visual cortex* have different propagation pathways (Morrel and Torres, 1958). Spontaneous variations in the frequency and amplitude of the spike discharges are associated with marked variations in the degree of propagation. Ample surface-negative, slow or sharp waves recorded on the surface of the cortex do not spread in a corticofugal direction towards the pulvinar or lateral geniculate body, but were sometimes restricted to very small parts of the cortex. When thalamic propagation appears, it is regularly associated with the appearance of a cortical diphasic negative–positive potential.

(3) Propagation of the discharges from a penicillin cortical focus on the *ectosylvian gyrus* in the cat first takes place (Kreindler, Voinescu *et al.*, 1961b) towards the ventrolateral ectosylvian gyrus, then to the sigmoid gyrus and the homolateral-lateral gyrus. At the moment when discharges appear in the sigmoid gyrus, they already exist to a great extent in the thalamic nuclei (in 15 cases the discharges appeared in the thalamic nuclei before appearing in the sigmoid gyrus, in 6 cases they appeared concomitantly in both formations, and only in 2 cases did precession exist in the sigmoid gyrus). Sometimes the discharges first appeared in the heterolateral thalamic

nuclei. Propagation often takes place towards the mesencephalic formations and then to the homolateral sigmoid gyrus.

Isolation of the penicillin-induced focus in the gyrus ectosylvius from the remaining cortex by subpial section does not suppress the propagation of the paroxysmal discharges to the encephalic mass but reduces it considerably (Fig. 43). Thus, the syn-

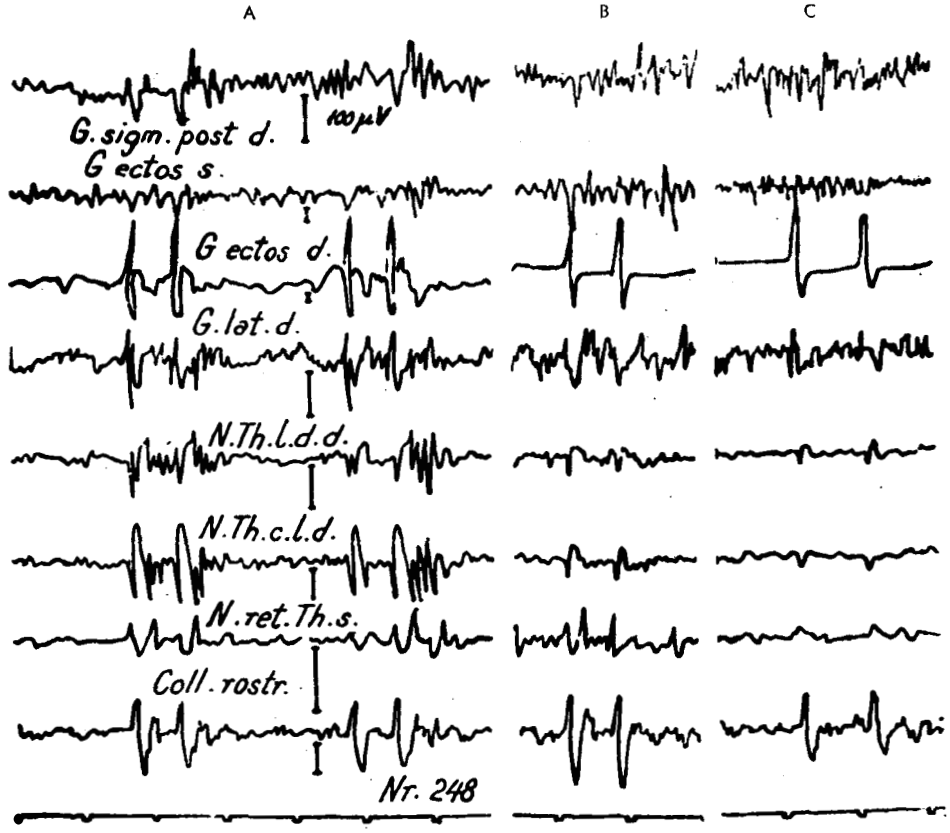



Fig. 43. Penicillin focus on the right g. ectosylvius (cat). Spread of the spikes to other cerebral structures. A = before the isolation of the focus by subpial section; B = 15 min and C, 30 min after this isolation. This isolation does not suppress the spread of spikes but it diminishes the amplitude of the propagated spikes. (From Kreindler, Voinescu *et al.*, 1961b.)

chrony between the discharges recorded in the different leads if often disturbed after the focus has been isolated, and very often paroxysmal discharges are seen to appear unrelated to those of the penicillin-induced focus. Transmission of discharges from the penicillin focus occurs less regularly, the most affected transmission being the one to the homolateral cortex and particularly the one to the homolateral sigmoid gyrus, whereas transmissions to the contralateral ectosylvian area and to the deep structures are relatively well preserved (Fig. 44). The isolation of the focus reduces by about 50% the amplitude of the propagated waves which at the same time tend to assume a rounded shape.

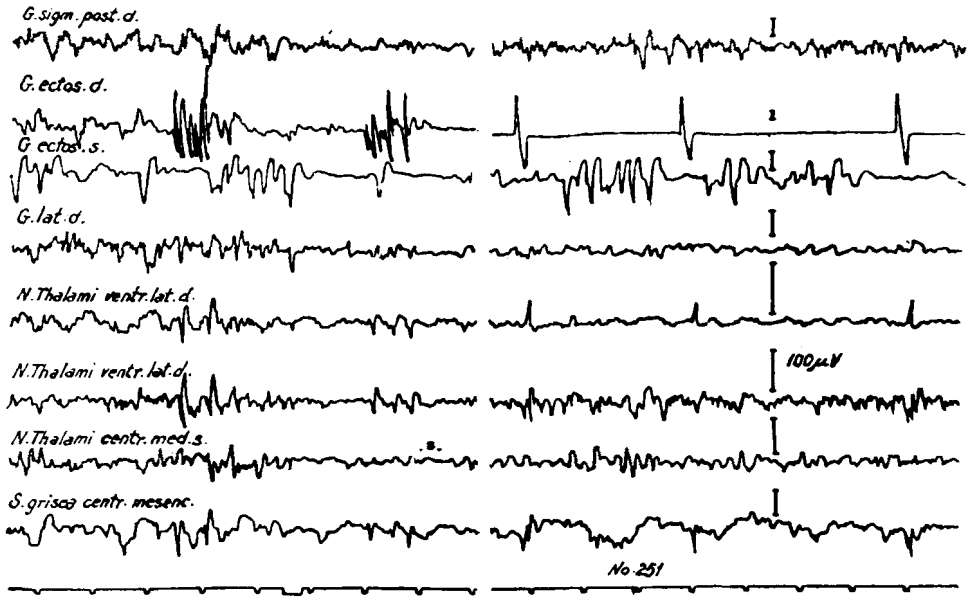



Fig. 44. Penicillin focus on the right g. ectosylvius (cat). Spread of the spikes to subcortical structures without involving the g. sigmoideus and g. lateralis. After isolation of the focus from the surrounding cortex, there is only a spread into the n. ventrolateralis thalami and mesencephalon. (From Kreindler, Voinescu *et al.*, 1961b.)

The propagation of discharges from a temporal focus was studied in the monkey by Ajmone Marsan and Stoll (1951), by Stoll *et al.* (1951), by Segundo *et al.* (1955) who laid special stress upon the propagation to the extrapyramidal nuclei, the putamen, the globus pallidum, the head of the tricaudate nucleus, the reticular formation, the hippocampus and the amygdala. However, the investigations of Kreindler, Voiculescu *et al.* (1960) and Kreindler, Voinescu *et al.* (1961a) show that, in the penicillin-induced focus of the cat, discharges in the thalamic nuclei occur early. The thalamus is therefore believed to play an important role in the propagation of epilepsy from a limited cortical focus. Intracortical propagation from the focus likewise plays a role as can be seen by changes produced when the cortical epileptogenic focus is separated from the remaining cortex by a subpial section. Stimulation of the temporal convolution in monkey, particularly the anterior portion of the temporal lobe, gives rise to after-discharge of the ipsilateral temporal cortex, the ipsilateral amygdala and hippocampus, and frequently in the frontal granular cortex and face area of the motor cortex (Walker *et al.*, 1956). With further propagation of the seizure, structures related to the hippocampus and amygdala are progressively involved, or the spread may be through the orbital frontal cortex to the caudate nucleus.

Electrical stimulation of the temporal cortex in the monkey brings about a discharge in almost the entire homolateral temporal cortex, in the nucleus amygdalae and in the hippocampus. Quite frequently, the excitation irradiates into the homolateral precentral cortex but very seldom into the parietal and occipital cortex. Involvement of the septum is unusual. The contralateral temporal cortex is frequently involved in

after-discharge which is not so with other contralateral structures. Section of the anterior commissure prevents contralateral irradiation (Poblete *et al.*, 1959). Its interruption usually suppresses this propagation. The corpus callosum, the psalterium, the massa intermedia and the posterior commissure do not appear to play an important role in connection with this interhemispheric transmission. The transmission seems to be direct and not to be effected via the amygdala or the hippocampus. Therefore the main route of contralateral irradiation of a temporal stimulation appears to be the anterior commissure. Unilateral stimulation of the nucleus amygdalae seldom gives rise to discharges in the temporal cortex or in the contralateral part. It would appear that temporal epilepsies which in man have a bilateral temporal activity, are of cortical origin, whereas those with a unilateral temporal focus are due to a focus within the nucleus amygdalae.

Temporal discharges are propagated, apart from the amygdala, the hippocampus and the septal area, also to the subthalamus, the hypothalamus and the mesencephalic reticular formation, and secondarily towards the corpus striatum and the pulvinar. Occipital discharges particularly involve the thalamus (pulvinar, corpus geniculatum lateralis and the adjoining intralamellar nuclei), and secondarily the subthalamus and the reticular formation (Green and Naquet, 1957).

Stimulation of the limbic cortex does not cause an obvious activation of cortical electric phenomena. It does not bring about emotional behavioural or somatic alterations, and hence the supracallosal area of the limbic system does not appear to be involved in the psychic and behavioural symptoms associated with hippocampal and amygdaloid after-discharges. Electric discharges from the cingulate gyrus are characterized by a relatively slow frequency, simulating the patterns obtained from the cortical area. In contrast to hippocampal seizures, cingulate gyrus seizures will spread to the hippocampal system only if suprathreshold stimuli are employed. Behaviourally, the cat has a marked tendency to sleep during a cingulate gyrus after-discharge. If the discharge spreads to other cortical and subcortical structures, the cat will wake and become activated (Andy *et al.*, 1957b).

Ectors (1956) showed that the penicillin focus of a hemisphere in the non-anaesthetized rabbit is characterized by sporadic spikes transmitted to the other hemisphere through a commissural pathway and by paroxysms of rhythmic waves. In the barbiturized animal the pattern merely consists of synchronous sporadic spikes in both hemispheres. Sometimes, however, the hemisphere to which penicillin was applied still shows, from time to time, a high frequency epileptic activity while the opposite hemisphere during the paroxysmal stage continues to display the same sporadic spikes as before. It therefore appears that the barbiturate has raised the critical discharge threshold of the neurons within the hemisphere to which no penicillin was applied, so that the stimulating load reaching it from the penicillin focus via the commissure no longer attains the discharge threshold.

The propagation of an epileptogenic focus is preferentially directed towards the homotopic areas of the contralateral hemisphere and then towards the central subcortical structures (Garner and French, 1958). It is therefore likely that phenomena of an axodendritic nature contribute to the diffusion of the epileptic seizure. The surface

epileptogenesis is a function of the richness with which an area is connected to its counterpart on the opposite hemisphere.

The subcortical propagation of the electrical discharge was studied by Poggio *et al.* (1956) who showed that certain circuits are preferentially involved in the propagation. The investigations carried out by Kreindler, Voiculescu *et al.* (1960) and Kreindler, Voinescu *et al.* (1961b) on the propagation of a penicillin focus established the importance of subcortical structures in the propagation of discharges from this focus. The sigmoid penicillin-induced focus first propagates to the subcortical nuclei, then the focus in the ectosylvian gyrus propagates to the thalamic nuclei and thence to the cerebral cortex. Isolation of the focus of the cortical structures around it does not prevent propagation towards the thalamic nuclei. In chronically prepared monkeys with epidural electrodes White *et al.* (1960) elicited direct cortical responses from the frontal, motor, parietal and occipital cortex during natural and drug-induced light sleep. The direct cortical response was increased in the motor cortex, but responses in the occipital cortex showed neither enhancement nor depression. Deeper sedation, however, caused diminution of all direct cortical responses. Activation by pentylenetetrazol produced repeated augmentation of these responses in the motor cortex in each pre-seizure period, but responses in the occipital cortex were not enhanced after the initial seizure (Fig. 45).

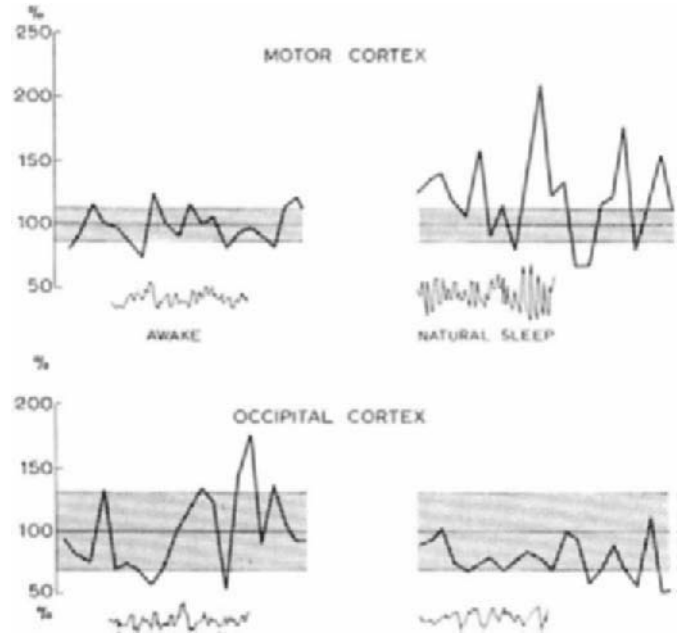



Fig. 45. Amplitude of local cortical responses in all figures plotted as per cent of control. Standard deviation of the control is shown as the stippled band beyond and below the 100% level. Control amplitudes were those obtained in the animal when awake and undisturbed. Short pieces of the EEG from the corresponding states have been inserted below each graph. There is a marked increase in variability during sleep in the motor cortex as opposed to the occipital responses. (From White *et al.*, 1960.)

The part played by the corpus callosum in the interhemispheric propagation of epileptic activity was shown by Moruzzi (1939), Rosenblueth and Cannon (1942), McCulloch (1949), Terzian and Terzuolo (1952), Erikson (1940) and Kopeloff *et al.* (1950). Kreindler (1955) showed that in the chronic section of the corpus callosum of the cat there is a difference in propagation according to whether the epileptogenic focus is situated in one hemisphere or concomitantly in both hemispheres. Homolateral convulsions set in somewhat later than heterolateral ones if the hemispheric focus is unilateral; the homolateral seizure is shorter and less violent than the heterolateral one.

(4) A characteristic generalized cortical response to visual, tactile or auditory stimulation is obtained from an animal with an epileptogenic focus induced by stereotaxic injection of penicillin into the nuclei of *the diffuse thalamic system.* This response is in many ways similar to that observed in an animal which was given subconvulsant doses of metrazol and was then subjected to the action of the same stimuli (Schmidt and Toone, 1958). In these cases, the frequency of the stimulation is of great importance. Below a certain critical level the ratio between each stimulus and response is 1 : 1. A slight increase in this frequency may reduce the responses to 2 : 1 and cause the appearance of after-discharges. At still higher frequency of stimulation convulsive discharges set in more seldom.

A thalamic penicillin focus is propagated to the cortex according to its localization, *i.e.*, a focus of the intermediate mass is propagated to both gyri proraeii, a focus in the immediate neighbourhood of the median line and laterally from it gives rise to synchrony and decrease in frequency in the anterior cortical areas; a focus limited to the lamina medullaris interna on one side gives rise to synchronization over a large area; a focus in the specific primary relay nuclei diminishes the frequency and synchronizes the spindles in the anterior two-thirds or within the whole homolateral hemisphere; a focus in the dorso-lateral thalamus reduces the spindles in the homolateral suprasylvian gyrus (Ralston and Ajmone Marsan, 1956).

The pattern of propagation of the epileptic after-discharge to different nuclei of the diffuse and associative thalamic system was shown by Kreindler and Steriade (1962) (Fig. 46). Kreindler, Voinescu *et al.* (1961b) investigated the propagation of the discharges generated by a thalamic penicillin focus; by means of a stereotaxic apparatus small quantities of penicillin were injected into the thalamus of curarized non-anaesthetized cats. Cortical and deep recordings were made. On comparing discharges obtained after intrathalamic penicillin injections with those generated by a cortical penicillin focus the following differences have been noticed.

(1) The latency period between penicillin injection and appearance of the first discharges is much longer in the case of the thalamic focus.

(2) The discharges originating from a cortical focus are first localized, and propagate only later to other cortical or deep structures; conversely discharges originating from the thalamic focus are sometimes from the very beginning diffuse in character, appearing concomitantly in several deep and cortical leads (Fig. 47). The discharges recorded from deep structures are greater than cortical ones. Discharges recorded from the frontal cortex are smaller than those recorded from the temporal or occipital

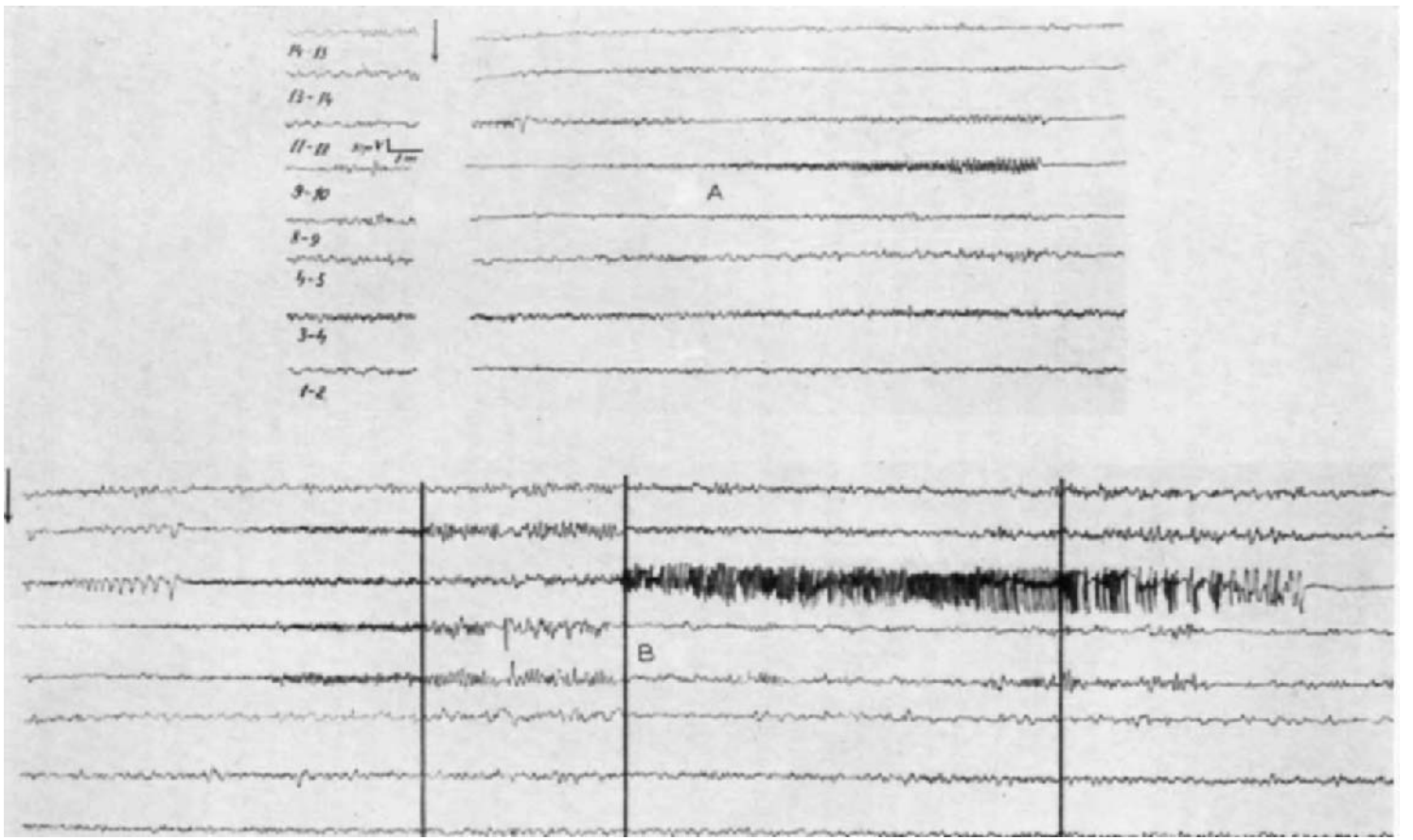



Fig. 46. The pattern of propagation of the epileptic after-discharge to different thalamic nuclei. 1–2 = g. sigmoideus posterior left; 3–4 = g. sigmoideus anterior right; 4–5 = g. sigmoideus posterior right; 8–9 and 9–10 = g. marginalis left; 11–12 = n. lateralis posterior left; 13–14 and 14–15 = midline thalamic nuclei left. A = stimulation of n. ventralis anterior left (0.4 mA), after-discharge in the n. lateralis posterior left and then in the g. marginalis left; B = stimulation with 0.6 mA, generalized after-discharges prevailing in n. lateralis posterior left. (From Kreindler and Steriade, 1962.)

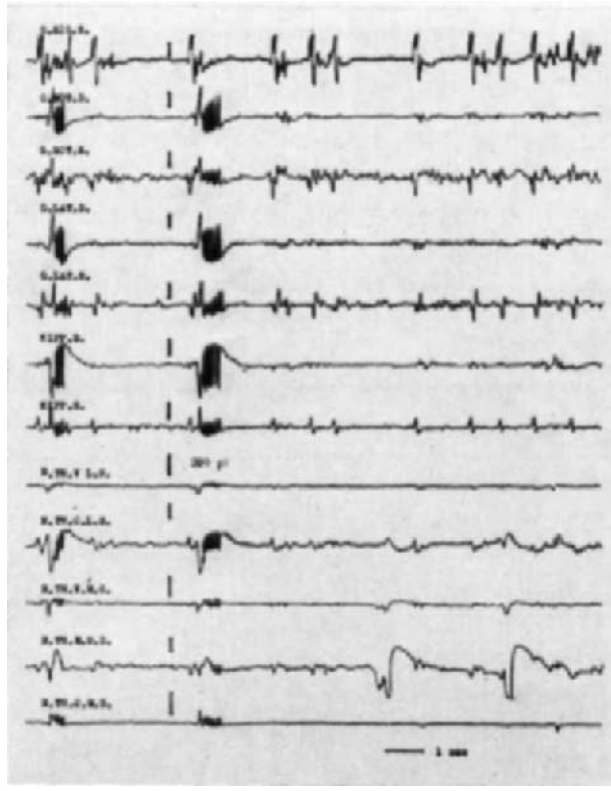


Fig. 47. Penicillin focus in the right n. thalami medio-dorsalis. Onset of seizures by generalized discharges from the beginning, the discharges appearing concomitantly in all leads. (From Voiculescu, Voinescu *et al.*, 1964.)

cortex. The discharges obviously predominate in the hemisphere corresponding to the thalamus into which the injection was made.

But as a rule, hippocampal discharges have greater amplitudes than those recorded in other structures, and the rhythm in all the deep leads is rapid and regular, characteristic of hippocampal discharges. It therefore seems likely that any seizure generated by a thalamic penicillin focus would necessarily imply the early involvement of the hippocampus (Fig. 48). If a penicillin focus is simultaneously created in the sigmoid gyrus of the hemisphere contralateral to the thalamic focus, the discharges of both foci develop independently, one focus exerting no influence upon the other (Fig. 49).

Phenobarbital or neuroplegic injections as well as asphyxia are liable to affect the discharges originating from the thalamic focus, or the hippocampal discharges respectively, rather than those arising from the cortical focus.

The most important propagation phenomena are to be found at the level of the limbic system where the appearance of isolated discharges is, however, possible, particularly at the level of the uncus and hippocampus.

(5) The convulsive phenomenon caused by electrical stimulation of the amygdalo–hippocampal complex is propagated to the ispilateral subcortical structures, whereas

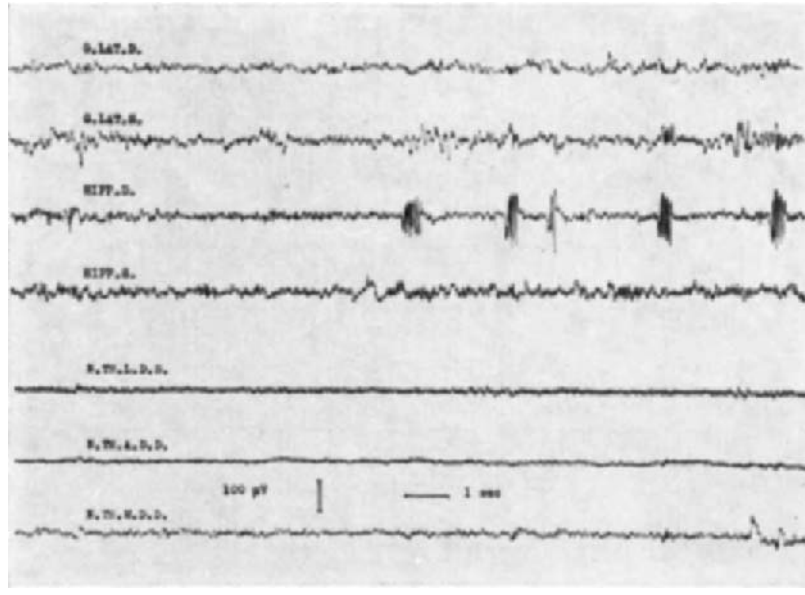


Fig. 48. Penicillin focus in the right n. thalami medio-dorsalis. Onset of seizures in the hippocampus. (From Voiculescu *et al.*, 1964.)

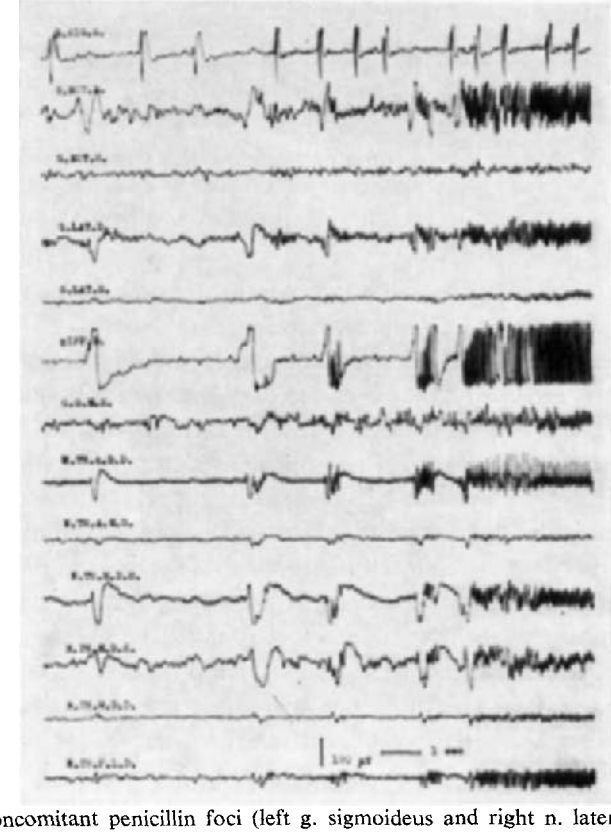


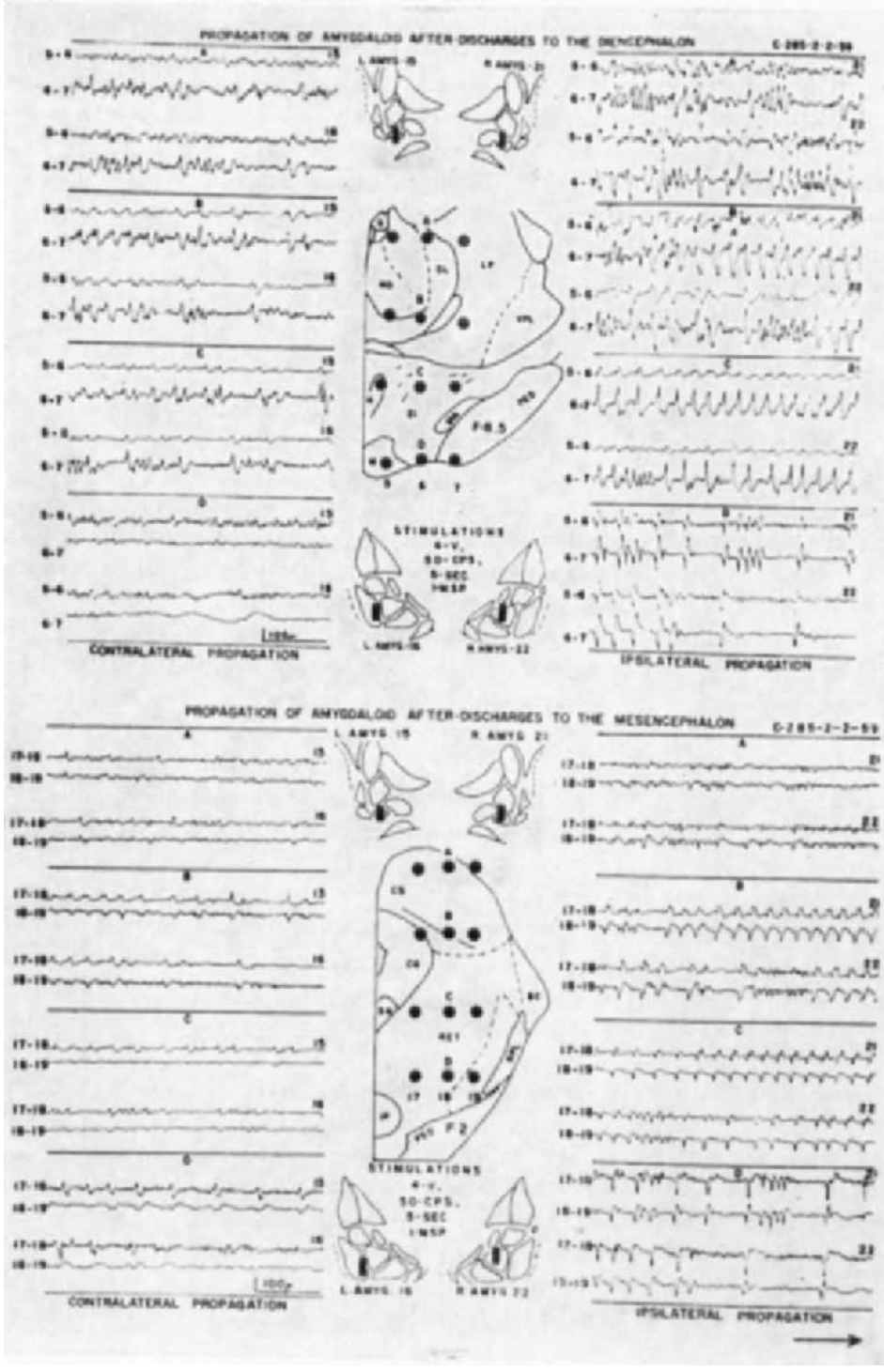
Fig. 49. Two concomitant penicillin foci (left g. sigmoideus and right n. lateral medio-dorsails). Each focus discharges on its own rhythm. (From Voiculescu *et al.*, 1964.)

propagation to the cortex is restricted to a very small area and is readily inhibited by anaesthesia, blood loss, etc. (Gloor, 1954). The subcortical structures that are most frequently activated by amygdaloid after-discharges are the ipsilateral septum, the hypothalamus and the mesencephalic tegmentum. Very often the thalamus is likewise involved. Propagation to the opposite homotopic formations is infrequent. The most usual cortical propagation involves the hippocampus, the anterior and posterior sylvian gyri and the inferior part of the posterior ectosylvian gyrus. These observations appear to confirm Penfield's hypothesis according to which epileptic automatism in man, associated with a discharge in the region of the amygdala, results from propagation of this discharge towards centrencephalic subcortical systems. Andy and Mukawa (1960) studied the propagation of the electrical after-discharges of the amygdala to the brain stem. Analysis was made according to the spatial distribution and amplitude of the after-discharges. The medio-cortical-central group of amygdaloid nuclei appear to propagate diffusely into the diencephalic and mesencephalic brain stem. The basolateral and anterior amygdaloid nuclei were less inclined to propagate to the mesencephalon: they appeared to concentrate in the diencephalon. After-discharges originating from the medial-cortical group have a tendency to be longer than those from other subdivisions. After-discharges originating from the anterior amygdaloid area are shorter in duration. Points containing propagated activity with an amplitude greater than 200 $\mu$V appeared to be most numerous in the hypothalamus (Fig. 50).

Discharges from the amygdala or Ammon's horn are conveyed to the contralateral homologous area, *i.e.* the hypothalamus, septum, antero-dorsal thalamus, corpus striatum and mesencephalic tegmentum, the pyriform cortex, the orbito-insulo-temporal cortex, and secondarily to the anterior part of the *gyrus cinguli*: the remaining isocortex is seldom involved, according to some authors more frontally, according to others, more occipitally. Segundo *et al.* (1955) have found that amygdaloid discharges in the monkey give rise to occipital electric seizures.

Amygdalian propagation to the hippocampus has been demonstrated by Gloor (1954), Arana-Iniguez *et al.* (1955), and from the hippocampus to the amygdala by Green and Shimamoto (1953). In this connection, Kreindler and Steriade (1963a) investigated some intra-amygdalian relations as well, using circumscribed stimulation with threshold stimulation parameters which provoked only very focalized and short-lasting after-discharges.

Stimulation of the parvocellular basal amygdaloid nucleus (A.b.p.) induces a rhythmic intrastimulating discharge both in the hippocampus and in the lateral central amygdaloid nucleus (A.c.l.). Stimulation of the A.c.l. causes intrastimulatory discharges in the A.b.p.; and conversely, stimulation of the A.b.p. causes intrastimulatory discharges in the A.c.l. Stimulation of the A.c.l. nucleus gives rise to after-discharges with smaller stimulation intensity than the stimulation of the A.b.p. nucleus. Stimulation of the hippocampus does not provoke intrastimulatory discharges in the A.c.l. and A.b.p. but merely an after-discharge. When greater stimulation intensities are used which give rise to generalized long-lasting discharges similar propagation phenomena may be revealed, namely stimulation of the A.b.p. nucleus provokes an intrastimulatory discharge and an after-discharge both in the hippocampus


PROPAGATION OF AMYGDALOID AFTER DISCHARGES TO THE DIENCEPHALON
L. AMYG. 15
R. AMYG. 21
STIMULATIONS
4-V.
50-CPS.
5-SEC
1/MIN
L. AMYG. 15
R. AMYG. 22
CONTRALATERAL PROPAGATION
IPSILATERAL PROPAGATION
PROPAGATION OF AMYGDALOID AFTER-DISCHARGES TO THE MESENCEPHALON
L. AMYG 15
R. AMYG 21
STIMULATIONS
4-V.
50-CPS.
5-SEC
1/MIN
L. AMYG. 15
R. AMYG 22
CONTRALATERAL PROPAGATION
IPSILATERAL PROPAGATION

and in the A.c.l., with generalization in the neocortex and final localization in the hippocampus (Fig. 51). Stimulation of the hippocampus provokes a generalized discharge preceded by 10–12 sec by a post-discharge of high amplitude selectively located in the A.b.p. nucleus.

The two-way relationships between A.c.l. and A.b.p., and between A.b.p. and the hippocampus were also demonstrated in Steriade's (1964) oscilloscopic analysis of intraamygdaloid and interamygdalo-hippocampal evoked responses.

In these experiments the two-way circuits between A.b.p. and A.c.l. nuclei or between the hippocampus and the A.b.p. are implied by the 7–20 msec latency responses obtained in 'encéphale isolé' unanaesthetized cats. Such values, shorter than those found in the above-mentioned researches, result from single shock or low frequency (under 2/sec) liminal stimulation. The differences in individual excitability might account for the variations in latency from animal to animal. In fact, the latencies of evoked responses can be considerably increased or decreased under certain experimental conditions when rhythmic stimuli, exceeding a certain rate or intensity, result in local excitability changes.

The absence of any responses between A.c.l. and the hippocampus grew into distinct responses when the rate of stimulation was higher (from 3/sec upwards) or the shock intensity was supraliminal (Fig. 52). However, these responses showed latencies much longer than those evoked between A.c.l. and A.b.p. or between the latter and the hippocampus. Their value was about 30 msec (hippocampal responses to A.c.l. stimulation) or 6–70 msec (A.c.l. responses to hippocampal stimulation). As far as the 30 msec latencies of hippocampal responses to A.c.l. stimulation are concerned, they might result from summation of the latencies of responses between A.c.l. and A.b.p. and between A.b.p. and the hippocampus.

The close relationship of A.b.p. to the hippocampus, mediated by direct oligosynaptic paths under certain conditions of rhythmic stimulation, may account for a functional kinship of these structures. First, the effects on neocortical electrical activity induced by stimulation of the hippocampus strikingly resemble those elicited by A.b.p. stimulation. The electrographic 'sleep' pattern, characterized by spindles and slow waves in neocortical leads, obtained by A.b.p. stimulation at 50–200/sec, contrasts with the desynchronizing effects, in the form of arousal reactions obtained by the same parameters of stimulation applied to A.c.l. (Kreindler and Steriade, 1963b). The same electrographic pattern, consisting of slow waves, is produced by stimulating the hippocampus or pyriform cortex. Similar electrical patterns, either associated or not with drowsiness, have been found in humans by stimulating the uncus (Liberson

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Fig. 50. Composite of simultaneously recorded after-discharges in the diencephalon and mesencephalon during amygdaloid after-discharges induced at ipsilateral points 21 and 22 and contralateral points 15 and 16. Recordings were taken at four different horizontal levels as designated. Note the marked difference in the amplitudes between ipsilateral and contralateral propagated activity, the tendency to uniformity throughout the dorsal and ventral diencephalon, the apparent lack in uniformity between the dorsal and ventral mesencephalon, the ventral possessing higher amplitude activity, and the ratio between the ipsilateral versus the contralateral progagation which is approximately the same in the diencephalon and mesencephalon. (From Andy and Mukawa, 1960.)

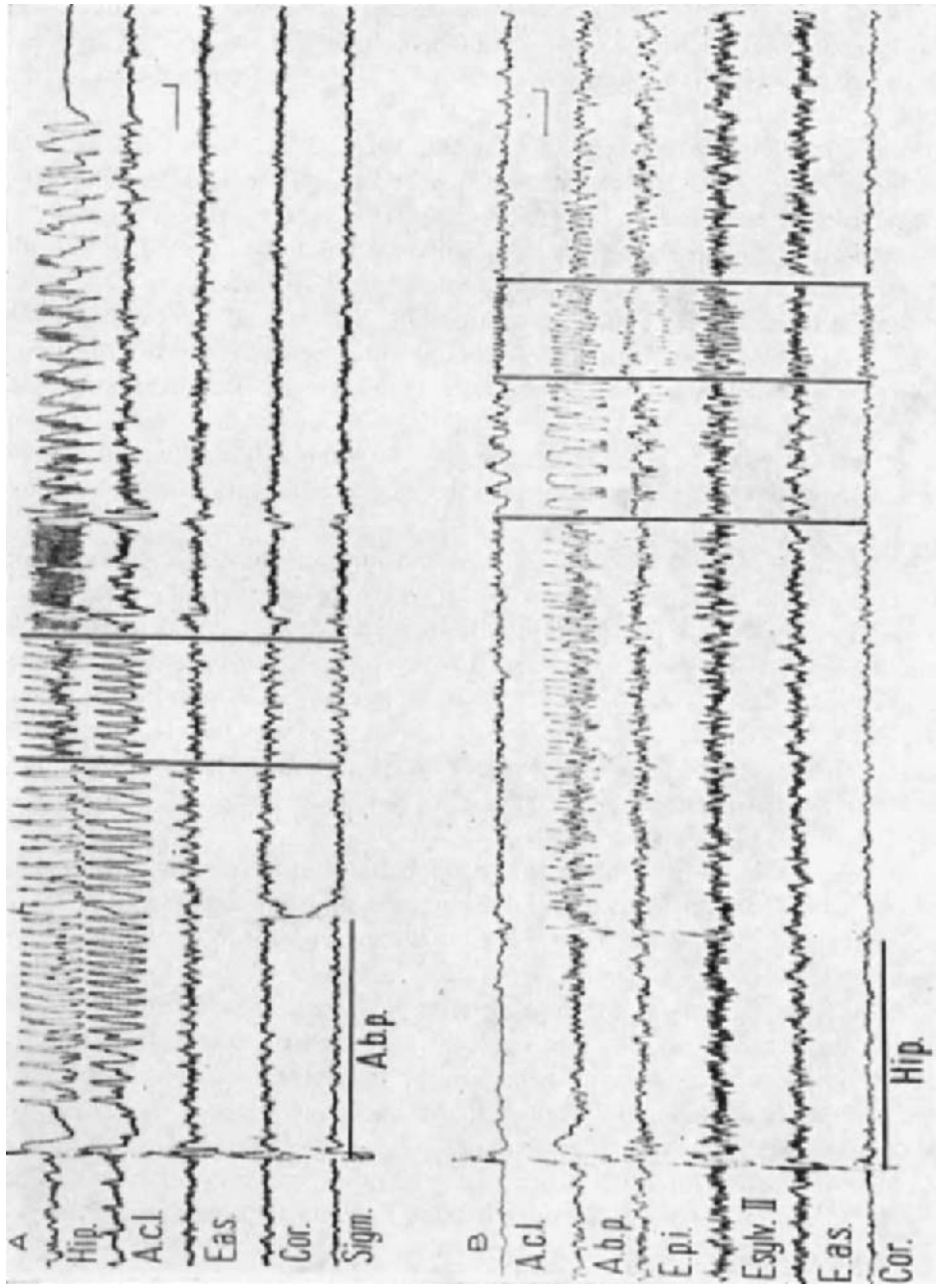


Fig. 51. Relationships between A.b.p. and hippocampus as inferred from the generalized epileptic seizures. A and B = two different experiments. In A, supraliminal stimulation of the A.b.p. nucleus elicits a seizure which generalizes but ends by selective localized hippocampal discharge. In B, supraliminal hippocampal stimulation elicits a seizure that becomes generalized after a period of 12 sec, during which discharges are selectively localized in A.b.p. nucleus. (From Kreindler and Steriade, 1963b.)

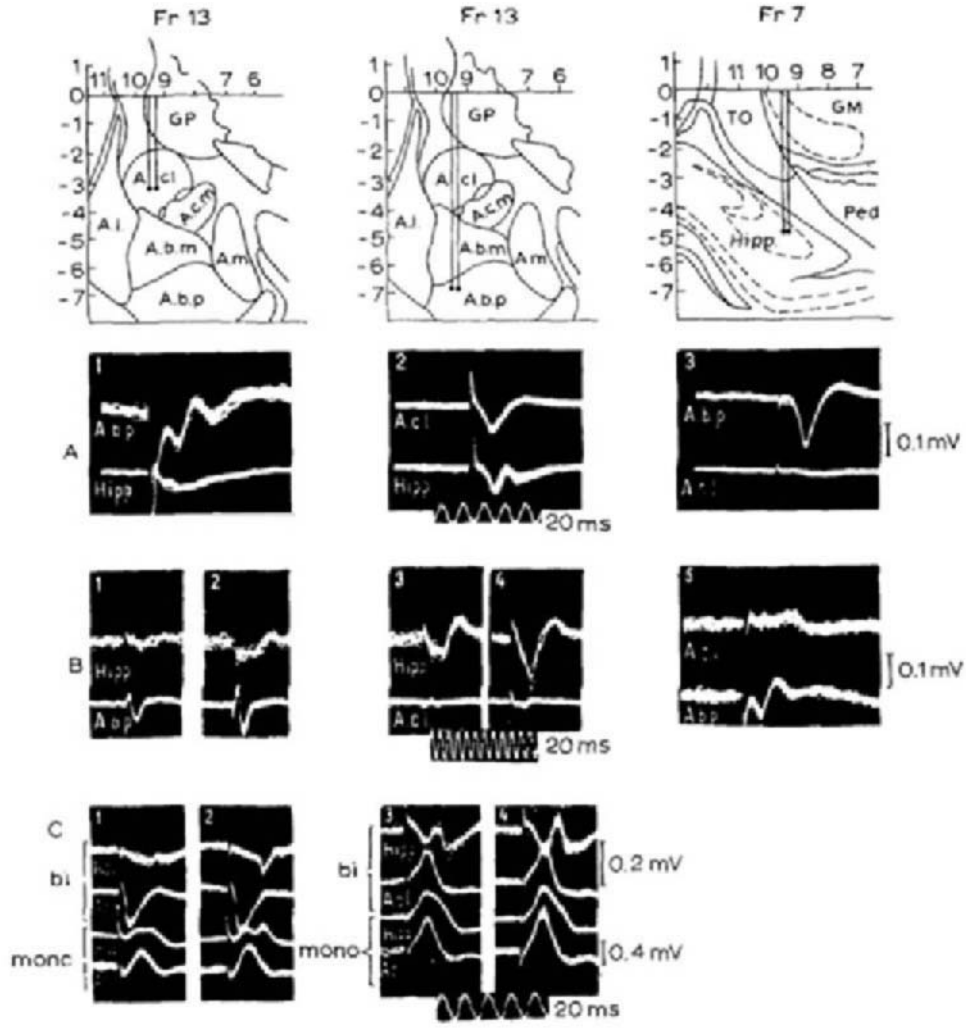


Fig. 52. Intra-amygdaloid and interamygdalo-hippocampally evoked responses. A, B and C, three different experiments. In each experiment, a stimulus is applied in turn to A.c.l. (left column), A.b.p. (middle column) and hippocampus (right column), and evoked responses are recorded from the other two structures. Bipolar leads, except in C, in which monopolar recording was also carried out (the last two traces); in the latter and in Fig. 9, $C_{1-5}$, an upward deflection indicates negativity of the active electrode. In $B_1$ and $B_3$, $C_1$ and $C_3$, stimulation with threshold intensities at rates up to 2/sec. In $B_2$ and $B_4$, $C_2$ and $C_4$, stimulation with supraliminal intensities, at 3/sec. Each trace represents the superimposition of 8 to 12 successive sweeps. Note the two-way responses. A.c.l. = A.b.p. and A.b.p. — hippocampus (A); the appearance of a clear long latency response between A.c.l. and hippocampus only at supraliminal stimulation ($C_2$). (From Steriade, 1964.)

*et al., 1951) and the fornix (García-Austt et al., 1954). Further experimental evidence* is the very marked epileptogenic capacity of A.b.p. (almost identical with that of the hippocampus, the structure having the lowest epileptogenic threshold), in contrast with the much higher epileptogenic threshold of the A.c.l. nucleus.

The neocortical propagation of amygdaloid after-discharges is particularly directed

towards areas homologous with the insular and temporal lobe (Gastaut, Vigouroux *et al.*, 1952; Gloor, 1954). Kreindler and Steriade (1963b) found that the first spikes or discharges provoked by threshold stimulation of the A.c.l. nucleus appeared in the gyrus lateralis and the posterior suprasylvian gyrus. Walker *et al.* (1954) maintain that the motor areas and the primary somaesthetic areas are not involved in amygdaloid discharges; Gastaut, Vigouroux *et al.* (1952) never succeeded in obtaining discharges in the gyrus proreus, gyrus coronaris and gyrus ectosylvius anterior. Kreindler and Steriade (1963a) observed a propagation of amygdaloid after-discharges to the gyrus coronarius or the gyrus ectosylvius anterior and posterior. Stimulation of the A.c.l. nucleus is propagated to the gyrus coronarius and the anterosuperior gyrus ectosylvius without being propagated to other neocortical areas. Stimulation of the

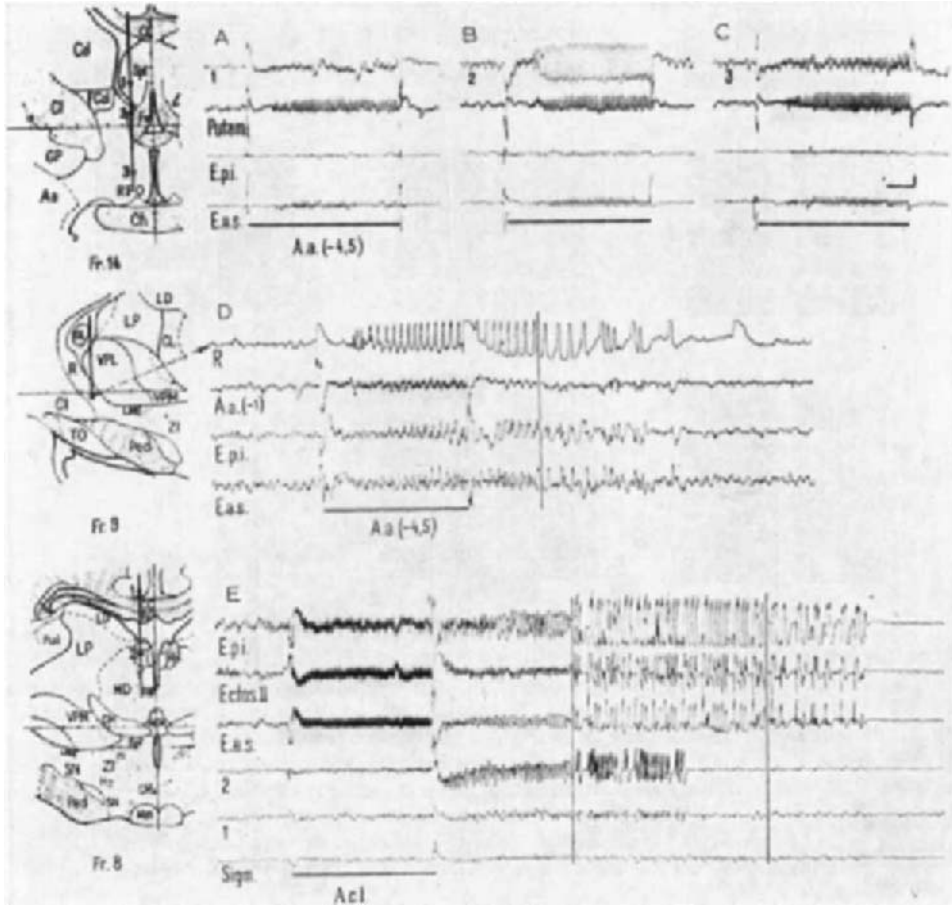


Fig. 53. Some aspects of subcortical propagation of the amygdaloid discharge. In the experiment illustrated at the top, records were taken within the septum (A,) fornix (B) and anterior hypothalamus (C), maintaining the other leads from the putamen and ectosylvian cortex. The same parameters of stimulation of A.a. nucleus were used. Note in the experiment illustrated by D the prevalence of discharges from the reticular nucleus of the thalamus over those from neocortical areas. In E, independence of habenular discharges (point 2) with respect to those from neocortical areas. (From Kreindler and Steriade, 1963b.)

A.b.p. nucleus or of the hippocampus is propagated to the posterior ectosylvian areas rather than to anterior ectosylvian ones (Fig. 53).

Propagations of amygdalian discharges to subcortical structures were described by Naquet (1953) and Gloor (1954) as involving the septum, hypothalamus and tegmentum, and by Walker *et al.* (1954) and Carreras *et al.* (1955) as involving the thalamic system diffusely and associatively. Kreindler and Steriade (1963b) were able to confirm this propagation towards the subcortical structures. Threshold stimulation of the anterior nucleus amygdalae causes an intrastimulatory discharge of great amplitude in the fornix, in contrast to the much smaller amplitude of the waves evoked by the same stimulus in the septum and the supra-optic anterior hypothalamic area (Fig. 54). The same stimulation also causes the intrastimulating discharge and the after-discharge to propagate to the nucleus reticularis thalami with a higher amplitude and an earlier onset than the paroxysmal waves in the ectosylvian area. The most important propagations of the amygdaloid and hippocampal post-discharges are to the habenula and the nucleus medialis dorsalis. Propagation to the nucleus medialis dorsalis is very early and sometimes the only one to be detected, while adjoining thalamic points and the neocortex have as yet not been touched by the propagation. Such isolated propagations to subcortical structures resulting from amygdalian stimulation are also to be found in the mesencephalic tegmentum and in the mesencephalo-diencephalic transition area around the peri-aqueductal grey matter without involvement of the neocortex, and furthermore in the specific thalamic relay nuclei among which the corpus geniculatum medialis is generally involved in the after-discharges of the amygdala.

Propagation of the amygdaloid after-discharge to several subcortical formations, or to a single one, such as the thalamus or the tegmentum without concomitant invasion of the neocortical areas (Kreindler and Steriade, 1963b), might account for the fact that many psychomotor seizures in man are accompanied only by a flattening of the EEG, and possibly by no electroencephalographic alteration (Gastaut, Naquet *et al.*, 1953b). This flattening might be considered desynchronization of certain cortical rhythms due to paroxysmal activity of the amygdaloid activating system.

Propagation of the amygdaloid after-discharge into the specific thalamic relay nuclei or to the associative nuclei might explain certain sensory phenomena in human temporal epilepsy (Goodfellow and Niemer, 1961; Kreindler and Steriade, 1963b).

According to Faeth *et al.* (1956), the preferential propagation routes of an epileptic focus, provoked either by electrical stimulation or by topical application of penicillin within the amygdalo-hippocampal complex, are the amygdala, and the contralateral hippocampus, the ipsilateral anterior temporal cortex, the hypothalamus, the thalamus, the caudate nuclei, the putamen and the agranular frontal cortex.

The role of the hippocampus in the development of the epileptic attack has been demonstrated both in experimental investigations and in man. The hippocampus has a very low threshold for determining an after-discharge (Gibbs and Gibbs, 1936; Jung, 1949), and its mechanical stimulation may trigger an after-discharge similar to the epileptic one (Liberson and Akert, 1951). In man, electrical stimulation of the uncus of the hippocampal gyrus, a structure in close relationship with the hippocampus,

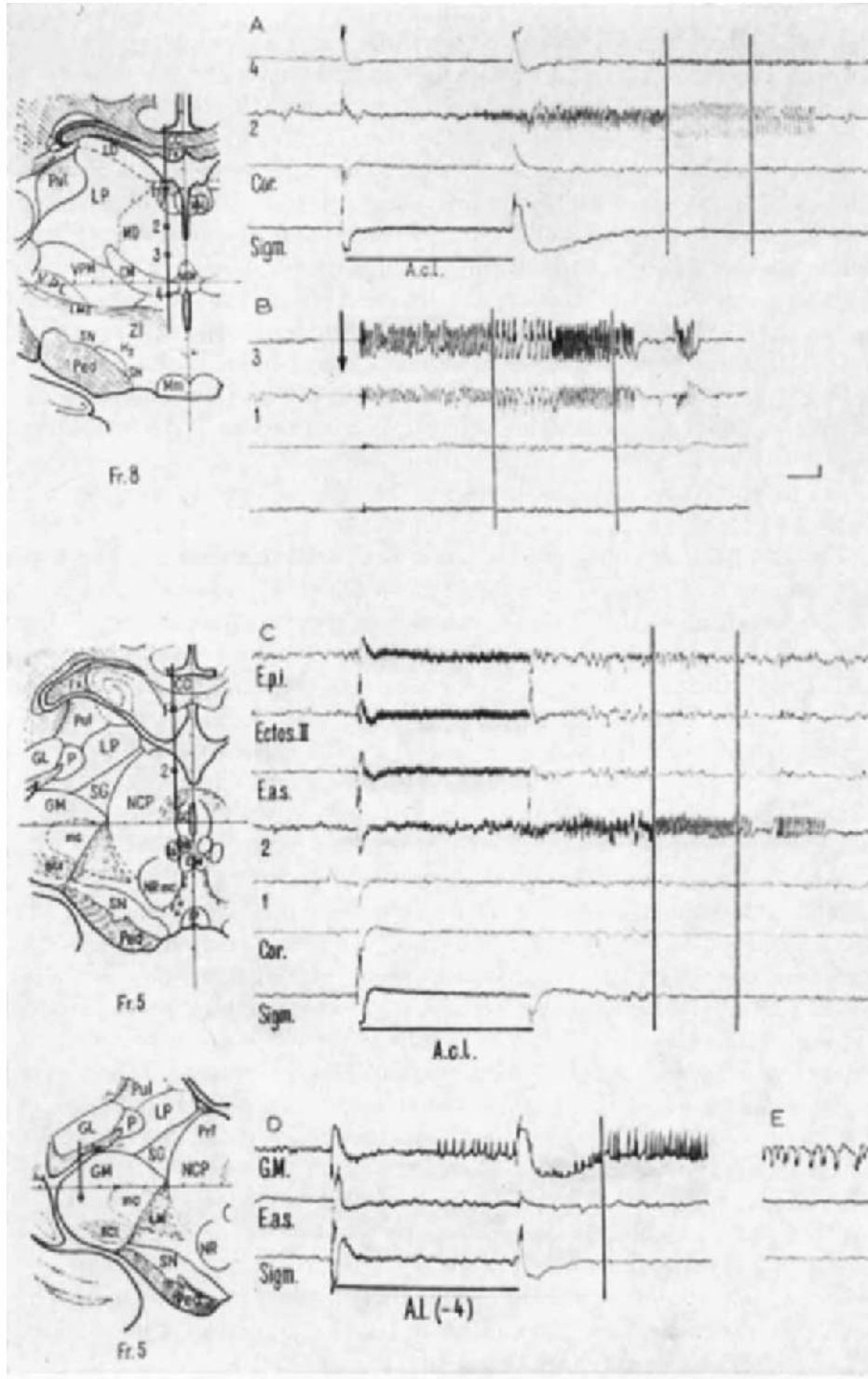


Fig. 54. For legend see p. 119.

gives rise to alterations in consciousness to apnoea and convulsions (Liberson and Akert, 1951; Scoville *et al.*, 1953); while in temporal epilepsy neurosurgical operations disclosed hippocampal epileptogenic foci the excision of which was followed by the disappearance of the attacks (Guillaume *et al.*, 1953).

Zislina *et al.* (1963) showed that on stimulation of the hippocampus with rectangular currents, having a frequency of 50–70/sec and a duration of 0.2 msec at 1–10 V, a convulsive activity appears in the electroencephalogram, the so-called 'post-action discharge' which comprises a tonic and a clonic phase. The intensity of this discharge is proportional to the intensity of the stimulation current. Immediately after the 'post-action discharge' follows a period of depression of the cortical and subcortical electrical activity. Stimulation of the hippocampus with a current that does not provoke a 'post-action discharge' results in an important increase in the number of spindles, with a progressive decrease in the frequency of the waves of these spindles as well as an enhancing of the slow activity.

Von Euler *et al.* (1958) consider that repeated stimuli applied to the hippocampus lead to a gradually increasing depolarization in the dendritic field. A single shock does not depolarize the dendrite in an all-or-none way but results only in a decrementally conducted electronic change; however, repeated shocks lead to an all-or-none depolarization in the dendritic tree. When this occurs, it is apparently possible for seizure discharges to spread not only by the ordinary axonal route, but from cell to cell, presumably via the dendrites. After stimulation of the hippocampus the thresholds of the activating reaction evoked by the mesencephalic reticular formation are 2–3 times higher. This activating reaction induced by the reticulum is characterized, upon stimulation of the hippocampus, by a clear instability, as it appears in the EEG only as long as the stimulating current acts. Cessation of the stimulation of the reticular formation in such experiments brings about a still greater intensification of electroencephalographic slow activity. Stimulation of the hippocampus with high frequency stimuli (300/sec) is expressed in the electroencephalogram by an activating reaction which, however, is not stable and is extinguished upon repeated stimulation.

The authors were led to conclude that the hippocampus as well as the non-specific system of the thalamus and of the caudate nucleus are inhibitory structures. This inhibiting function of the hippocampus and its antagonistic relationships with the reticular formation have not as yet been clearly defined. Thus, under certain conditions, the hippocampus may act synergistically with the reticular formation and may participate in determining the arousal reaction.

Green and Adey (1956) studied hippocampal seizures in hippocampi which were isolated from the rest of the brain by section, so that they were attached only through

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Fig. 54. Subcortical discharges of amygdaloid origin, without neocortical invasion. A and B, the same experiment. Invasion of the habenula (point 1) and nucleus medialis dorsalis (points 2 and 3), no neocortical invasion by A.c.l. stimulation (A) or by protrusion of the needle into hippocampus (B). Note, in the experiment illustrated by C, a discharge confined to the rostral mesencephalic tegmentum, near the border of diencephalon (point 2). In D and E (same experiment), discharges from medial geniculate body but no corresponding discharges from ectosylvian and sigmoid cortex. (From Kreindler and Steriade, 1963b.)

their blood supply. It was observed that, when the hippocampus was stimulated repetitively by applying single shocks to the fornix, a seizure discharge could be initiated in it, and that when records were taken from the surface of the hippocampus, the seizure discharge showed a curious development. Repeated single shocks evoked a gradually changing potential. The potential inverted and at the moment of maximal inversion the seizure would break through. If, however, stimulation ceased at a point just before the seizure discharge broke through, then the seizure discharge would begin at the moment the stimulation ceased.

Studies on the hippocampus have shown that the state of the neuron membrane is altered in the course of a seizure, and that inexcitable areas become excitable and synchronized with one another. This has been demonstrated by means of microelectrodes which recorded the induction and propagation of the convulsive potential, by vector analysis of the discharge and by leads from units which are discharging during the seizure; the neighbouring neurons have thus been shown to be capable of stimulating one another (Green, 1958).

Discharges from the hippocampus are characterized by regular high amplitude spikes of 10–20 c/s in the course of a spontaneous or induced generalized attack, and propagate to the temporal or occipital cortex, the thalamus or in the mesencephalon. They are to be found in the fimbria, fornix, and gyrus splenialis posterior, and disappear after bilateral ablation of the hippocampus (Voinescu, 1960).

At the beginning of the generalized convulsive attack a 10–14 c/s rhythm may be noticed in the hippocampus which is at first synchronous with the one that is also to be found in other subcortical structures. The rhythm then tends to decrease to 2–3 c/s but at the end of the seizure a faster rhythm of 16–24 c/s than the initial one appears (Kreindler, Voiculescu *et al.*, 1956b).

Hippocampal discharges irradiate over great cortical and subcortical surface areas, and even as far as the cerebellum. Irradiation preferentially involves the centrocaudal isocortex and, to a lesser extent, the rostral neocortex. The fact that stimulation of the hippocampus so readily gives rise to convulsant attacks, and that hippocampal seizures are prone to irradiate so easily has caused some authors to assign the hippocampus an important role in epilepsy, ascribing an active part in the initiation and trigger of epilepsy to this formation.

Propagation of the hippocampal electrical attack may be obtained by intense electrical stimulation (20–30 V for a period of 0.5–2 sec) of the hippocampus with deep electrodes (Kreindler, Voiculesco *et al.*, 1956a) (Fig. 55). The electric activity may be seen to pass from the hippocampus towards the cortex and subsequently to subcortical structures as well. Propagation to the cortex may either occur very rapidly or with a delay up to 25 sec. Sometimes propagation is directed to the subcortical structures without invading the cortex (Fig. 56). Thus, discharges synchronous with those of the hippocampus were recorded in the upper colliculus, the mesencephalic reticular formation and the nucleus ruber. Sometimes an identical and regular rhythm having the same frequency of 16–22 c/s is recorded in the thalamic nuclei. At other times, the hippocampal rhythm is at 10 c/s while the frequency of the simultaneous thalamic rhythm is twice as great.

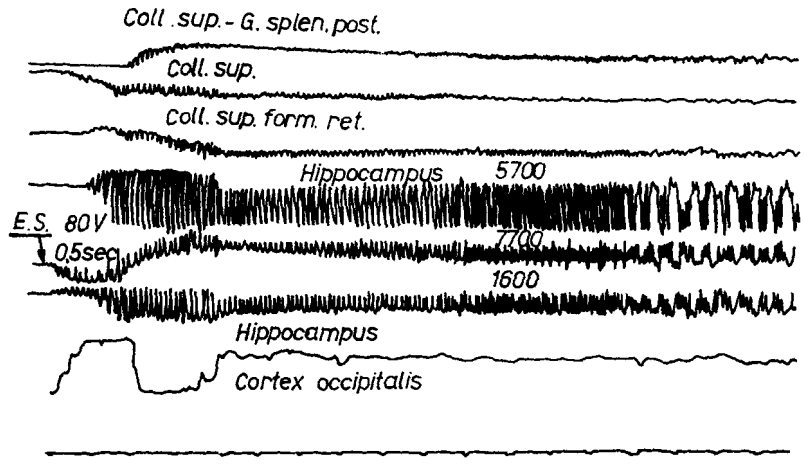


Fig. 55. Hippocampal discharges obtained by localized stimulation of the hippocampus. (From Kreindler, Voiculescu *et al.*, 1956.)

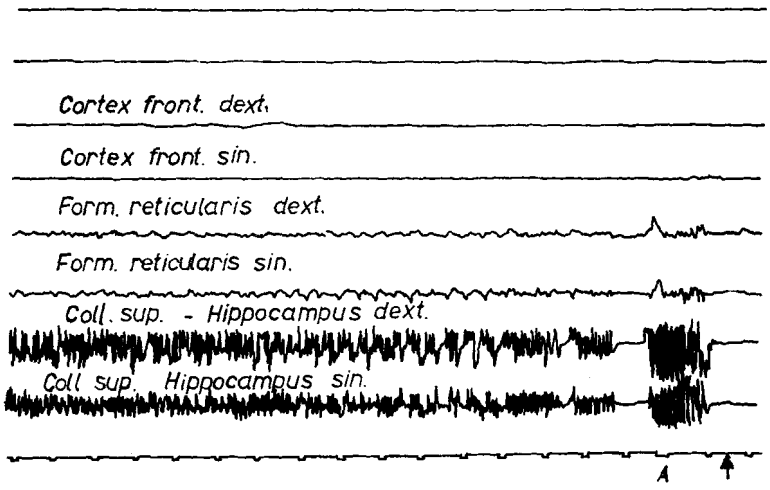


Fig. 56. Hippocampal seizure (localized stimulation) without progagation to the cortex. (From Kreindler, Voiculescu *et al.*, 1960.)

Determination of the epileptogenic focus in man meets with difficulties not only in the electroencephalographic leads but also in the electrocorticographic leads, even when the tracings are recorded simultaneously from the surface of the cortex and from the subjacent subcortical formations, by the stereotaxic method. Pagni *et al.* (1963) pointed out the impossibility of electrographically identifying a superficial or deep, extremely limited cortical focus, in typical cases of psychomotor epilepsy with a temporal EEG focus. Sometimes, the whole temporal lobe is involved in paroxysmal activity, which is not only localized on the lateral aspect of the lobe but also comprises its inferior medial aspect, Ammon's horn, the hippocampal convolution and some-

times even the amygdala. Neither can definite chronological relationships be established between superficial and deep amygdalo-hippocampal discharges, which would prove that superficial discharges are spread by axonal pathways towards the convexity of the temporal lobe, where they would form 'secondary' foci. It is worthy of note that the stereo-electroencephalographic method developed by Talairach permits better appraisal of the electrical activity of the nervous formations, since it avoids the tracings of the injury discharges in the 'acute' recordings, as the electrodes are implanted chronically and the records taken several days later.

What is the participation of the subcortical structures in an epileptic seizure in full development?

Walker *et al.* (1956), on recording with chronic electrodes an electrocorticogram in the monkey found that as the convulsive seizure provoked by cortical stimulation becomes more intensive, convulsive activities may be recorded in the cerebellum, the pontine reticular formation, the hippocampus, globus pallidus, putamen, caudatum, thalamus, amygdala, etc. Cortical discharges from the different areas tend to be propagated to the various subcortical structures. Three well-defined systems of propagation may be distinguished: (1) the granular frontal cortex with irradiation to the caudatum, to the contralateral frontal cortex, and subsequently to several subcortical structures; (2) the central cortex with irradiation to the putamen and thalamus; and (3) the temporal cortex with irradiation to the amygdaloid-hippocampal complex, and subsequently to the hypothalamus and thalamic nuclei.

Fernandez-Guardiola *et al.* (1962) have shown that after megimide and metrazol injections the cerebellar units (neurons) are the first to present an acceleration of the discharges while the electric activity of the brain is still normal. Relatively and significantly much later, the frequency of the discharges of the cortical units also begin to increase. In some cases each slow high voltage wave is accompanied by an increase in frequency of cerebellar unit discharges. During the clonic period the activity of the cerebellar units is depressed; however, they begin to discharge again after the end of an attack, when the cerebral units are completely silent. Dow *et al.* (1962) found that an electric low-voltage (2–5 V) stimulation of the cerebellum during a generalized attack cannot inhibit convulsive movements.

The subcortical structures play an important part in the propagation of epileptic activity. The attention of investigators was focused on the thalamo-cortical and cortico-thalamic circuits. Moruzzi (1941, 1945) investigated the electric activity of the extrapyramidal structures in the cat chloralozed and injected with strychnine. Ajmone Marsan and Stoll (1951) investigated the propagation of cortical discharges towards subcortical formations.

According to Gastaut and Hunter (1950b) the cardiazol attack is characterized by bisynchronous discharges which first appear in the diencephalon; while Starzl *et al.* (1953) hold that the discharges first appear in the cortex and spread from here to the subcortical structures through projection fibres. The relations between the cortical structures and the subcortical ones in experimental epilepsy were also studied by Vediaev (1961) who showed that local electrical stimulation of the motor cortex or

of the thalamic nuclei in the rabbit may result in convulsive seizures when the cortex and subcortex are simultaneously stimulated as well as when the cortex or subcortex precedes. The course and duration of the seizure depend on the initial functional condition of the structures that gave rise to the pathological process.

According to Starzl *et al.* (1953) epileptic generalization and irradiation are believed to come about essentially by intra- and inter-cortical propagation, without any obligate interference on the part of the nuclei of the thalamic system of diffuse projection. They studied epilepsy in the cat and monkey, and have shown that the destruction of these thalamic nuclei has no appreciable effect on the generalization of convulsive activity despite the fact that electrographic changes point to the functional alteration of these nuclei.

The generalization of partial epilepsy is believed to occur through the propagation of the discharges to the 'centrencephalic' structures. Most of the cortical after-discharges are transmitted to the thalamic and mesencephalic reticular formation (Jasper *et al.*, 1952) and even to the septal and amygdaloid areas, *i.e.*, subcortical structures with a diffuse projection (French *et al.*, 1956).

According to Servít (1955), generalization of the epileptic seizure is due to the fact that the attack disturbs the equilibrium between stimulation and inhibition processes. The existence of a strong excitation at the level of the epileptogenous focus causes the inhibition to be minimal here, and from this focus of disturbed excitation–inhibition balance, excitation is further irradiated over large brain masses. This author established in rats, with and without audiogenic epilepsy, reflex stereotypes, and found that in rats with audiogenic epilepsy it was impossible to obtain a fine acoustic discrimination; with discriminations for optical stimuli these were however possible. Hence, the inhibition process at the acoustic analyser level is decreased in these animals owing to the preponderance of the excitation process; therefore the excitation irradiating from this focus is likely to involve generalized extensive masses of the brain substance, thus giving rise to a generalized epileptic seizure.

The generalization of a localized epileptic activity is a slow process in man, lasting 10–20 sec or even longer, and the propagation assumes the character of an all-or-none phenomenon, and not of progressive propagation.

Delgado and Hamlin (1958) concluded from their studies with deep electrodes in epileptic patients that in some cases of petit mal the electrical characteristics of generalized seizure activity appeared to be the result of the primary effect of a focus or pacemaker plus the secondary reactivity of each of the local areas activated by the focus. The hypothesis of a pacemaker seems necessary to explain simultaneous firing to all points of the surface and depth on both sides, and the synchronization of wave and spike rhythm in all points during seizures. The probability that local patterns in generalized seizures were largely dependent upon local factors was also demonstrated by the observation that local after-discharges evoked by electrical stimulation of the brain were often similar to the local patterns of spontaneous bilateral seizures.

Direct recording showed considerable independence of electrical patterns in areas of anatomical proximity. This demonstrated that in the surface and depth records of Delgado and Hamlin (1958) there is represented local electrical activity and real

volume conductor effects; this also proved the considerable independence of bipolar recordings of electrical activity of different cerebral areas.

A generalized convulsive seizure may be obtained not only be transcerebral stimulation of the entire brain mass by bilateral application to the scalp of the electrodes inducing the electrical shock in the parieto-temporal areas, but also by their local application, for instance, to the frontal area. Thus a generalized convulsive attack may sometimes be elicited, which begins, however, by an initial clonic phase of Jacksonian type followed by a tonic phase of longer duration.

In reflex strychnine-epilepsy induced by the method of Amantea, the generalization of a convulsive activity seems also to depend on a certain intensity of spike formation. When the frequency of these spikes in the strychninized area is below 11–13 c/s, no generalization of the convulsive attack occurs in reflex epilepsy (Crepax and Fadiga, 1958). It is true that, as a rule, the irregular spike discharges during the course of a convulsive attack are related to rhythmic peripheral discharges. Yet the attack is not due to an increased frequency of the spike potentials but to the appearance of a new, peculiar electric activity, due to the appearance of the after-discharge. There are interrelations between the spike potentials with and without after-discharges and the epileptic seizure (Ralston, 1958).

The generalized electroconvulsive seizure is usually characterized by the perfect synchrony of a great number of cortical and subcortical structures. Yet there are also cases of asynchrony in the sense that the cerebral cortex and thalamus suddenly cease to behave synchronously: concomitantly to the clonic movements of the end of the seizure, discharges of grouped spikes continue to appear in the thalamus while an electrical silence has already been established over the cerebral cortex. At other times the final stage of the seizure is marked by a rapid continuous discharge of spikes having an amplitude of 200–300 $\mu$V, lasting several seconds, in the thalamic leads, while over the cortex electrical silence had already been established. This continuous discharge of rapid spikes ('comb rhythm') was not associated with clinical manifestations.

In man, the electroencephalographic alterations during the generalization of an epileptic attack could be observed by inducing electroconvulsive seizures following injection of curarizing substances (Radtke and Duensig, 1955). The injection of succinyl, a curarizing substance, is followed either in man or in animals by no change in the electroencephalographic pattern. When a short-lasting narcotic is associated with succinyl, the slow potentials accompanying the tonic phase decrease in frequency and, in the spike groups of the clonic period, these dissociate into isolated waves or spikes. The convulsive attack appears later with a longer latency period after the injection of the curarizing substance. Convulsive type discharges as well as hypersynchronous slow waves are more marked in the temporal areas. The addition of pentothal to the curarizing substance produces monomorphic waves at 3 c/s during the tonicoclonic phase and shortens the duration of convulsive discharges (Piette, 1958).

In man the electrocorticogram and electric activity of some deep structures were recorded during a spontaneous or induced epileptic seizure by means of chronic electrodes implanted for a few days (Delgado and Hamlin, 1958). The interparoxysmal recording in these epileptics showed discharges of frequent, grouped, hypersynchro-

nous spikes as well as sharp or slow waves. During the spontaneous seizures the discharge had always the same spatial distribution. The oscillographic study of these localized spikes and waves showed the electroencephalographic change as remarkably constant in type; it also showed that the propagation of the spike from depth to surface occurred with a progressive delay that was not shown by slow components. The electrographic alterations were already apparent during the aura, and a transition from the localized to the generalized discharge took place within 10 to 20 sec. Sometimes there was an epileptic activity in the deep structures that was not expressed at the brain surface. A mutual influence was found to exist between cortical and centrencephalic mechanisms during the spontaneous seizure.

However, there still remain some neuronal chains that the generalized seizure itself does not involve in its development. Thus, the direct motor response (stimulation of the motor area) could be dissociated from the phenomenon of self-sustained afterdischarge in the sense that a stimulation of the motor area was able to elicit a peripheral motor response even during the course of the generalized seizure (Kreindler and Zuckermann, 1957).

The generalized convulsive attack displays some peculiar characteristics as regards both the manner in which it is triggered and the cortical reactivity during its development. Thus, the generalized convulsive attack due to repetitive stimulation of a cortical point may be obtained also from an area situated outside the motor area. By stimulating with very short stimuli (0.025–0.25 msec) at a 20/sec frequency and with great intensity of such a 'non-motor' area in the cat, a generalized convulsive motor attack is obtained 5–6 sec after cessation of the stimulation; the attack will last for 30–35 sec. If the same point is, however, stimulated at low frequencies ranging from 4 to 8/sec but with a longer duration of the stimuli (5–25 msec) and even with a lower voltage, an intra-stimulatory motor response to each stimulation is elicited, without any ensuing generalized convulsive attack after cessation of the stimulation.

Hence, in response to stimuli of short duration at high intensity and frequency a generalized convulsive seizure may be obtained, while with long lasting and low frequency stimuli the 'non-motor' area will only yield an intrastimulatory motor response following each stimulus. Therefore, the convulsive chains that are put into action by the stimulation of 'non-motor' areas have other characteristics of excitability than the neuronal chain for the direct intrastimulatory motor response. It may be mentioned that such a dissociation cannot be obtained in the rat, as the motor projections are much more diffuse in the rat than in the cat.

During a generalized convulsive seizure induced in the rat by repetitive focal stimulation of the motor area, the cortex cannot be stimulated by a strong stimulus (discharge of a condenser of 1.5 $\mu$F at the threshold intensity necessary for obtaining a peripheral muscular contraction). The stimulation caused by discharging the condenser in the very focal point which gave rise to the seizure by repetitive stimulation does not induce any response during the first 1–4 sec after the onset of the attack (Fig. 57). The stronger the convulsive repetitive stimulus and the longer the period of its application, the more violent and longer the seizure and the more prolonged the refractory period following the simple cortical stimulus.

When a single stimulus is applied in the same animal by condenser discharge, not to the focal point that originated the convulsion but at some distance from this point, the direct motor response to the single condenser discharge is obtained immediately, or within less than a second after the onset of the convulsive attack, and may be obtained continually throughout the development of the attack (Fig. 58).

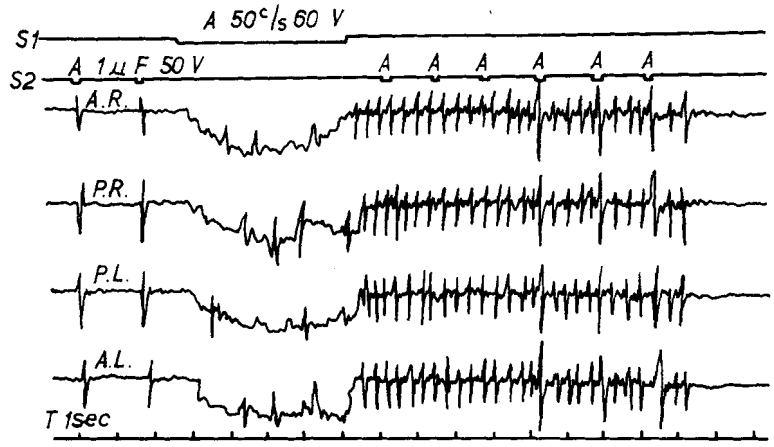


Fig. 57. Mecanogram of the four limbs of a rat during a convulsive seizure induced by electrical stimulation of the cortex. Motor responses to single shocks applied during the development of the seizure. The stimulus is applied at the point from which the seizure was induced. There is no response to single shock (condenser of 1 $\mu$F) in the first seconds of the seizure. From above: stimulation inducing the seizure, single shocks, mecanograms of the four limbs. Time in seconds. (From Kreindler and Zuckermann, 1956.)

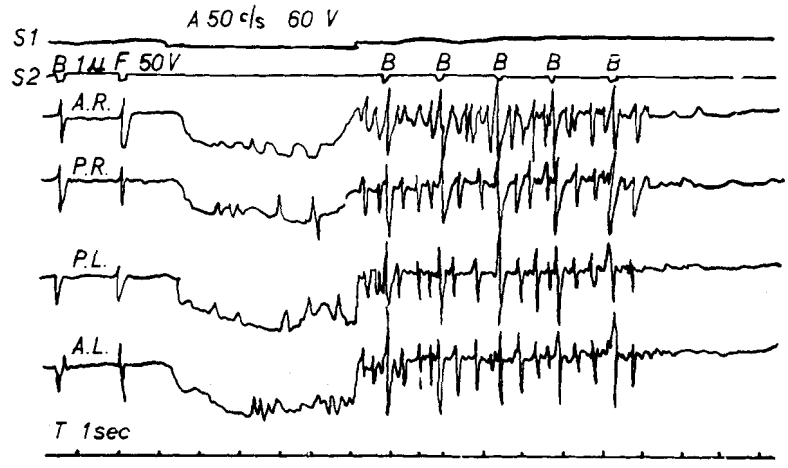


Fig. 58. Same as in Fig. 57 but the single shocks were applied to another cortical point than that from which the seizure was induced by direct repetitive cortical stimulation (50 c/s, 60 V). There is a response to a single shock just from the beginning of the convulsive seizure. (From Kreindler and Zuckermann, 1956.)

Consequently, during the first stages of development of the generalized motor convulsive seizure induced by repetitive stimulation, a state of refractoriness is observed at the stimulated point that does not appear in other cortical points up to the end of the seizure. This refractoriness is not due to the participation of the neurons of the stimulated point in the convulsive activity, for their response to the single condenser discharges reappears during the very course of the attack, the movement produced by the single cortical stimulus being superimposed upon the clonic movements.

Nor can the phenomenon be due to the blocking by convulsive impulse of the common final pathway since the stimuli applied to other cortical points elicit muscle responses from the same muscles during the very first seconds of the attack. What must be considered noteworthy in connection with these data is the observation that during a convulsive attack some neuronal chains and circuits undergo a phenomenon of occlusion or suppression while others do not, and as the seizure develops the dynamics of the different chains and circuits tend to change.

During the development of an epileptic seizure, rhythms of a peculiar type may be recorded over the various cortical and subcortical structures of which two are more characteristic, namely the rapid and the complex spike–wave rhythms.

*Rapid rhythms* in the subcortical structures characterize the development of the convulsive seizure: they are more usually met in the hippocampal leads and in the thalamic leads. In this connection we shall only refer to the rapid rhythms that occur during and towards the end of the generalized convulsive attack and not to the rapid rhythm characteristic of a focal attack. The rapid hippocampal and thalamic rhythms develop simultaneously with the much slower generalized electric activity of other cerebral structures. In general, the hippocampal, thalamic and mesencephalic rapid rhythms generated by a focal stimulation of the hippocampus are synchronous; however, while the hippocampal ones have an amplitude of 1 mV and more, the amplitude of the thalamic and mesencephalic ones does not exceed 300 $\mu$V. It must consequently be inferred that the rapid thalamic and mesencephalic rhythms are irradiated from the hippocampus.

Kreindler, Voiculescu *et al.* (1956b) studied the behaviour of electric activity of the hippocampus in the cat during electroconvulsive attacks. During the attack the ammonian tracing does not follow the general cerebral synchrony. At the beginning of the attack a 10–14 c/s rhythm may be observed in the hippocampus which is at first synchronous with the activity recorded in the other leads; however, this synchrony is of short duration, for while the other leads display a tendency to slow down, the *hippocampal rhythm* maintains its initial frequency; towards the end of the seizure the activity tends to become more rapid, *i.e.* 16–27 c/s. Hippocampal discharges assume a spike pattern, the spikes succeeding each other in an irregular manner being often followed by slower waves of about 2–10 c/s while the relationship between spike and wave is not of a constant chronological type.

Local stimulation of the hippocampus with deep electrodes and a strong current (20–50 V for 0.5–2 sec) produces a rapid 10–14 c/s activity which shortly thereafter is followed by a more rapid regular rhythm of 16–24 c/s (Fig. 59). Sometimes the

rhythm displays an alternating pattern, an oscillation of high amplitude being regularly followed by one of less amplitude. This ammonian activity resembles the 'comb rhythm' described by Kreindler, Voiculescu *et al.* (1953) in the thalamic leads. But whereas the latter shows amplitudes between 100 and 300 $\mu$V, the ammonian rhythm usually exceeds a millivolt, attaining 3 and even 5 mV.

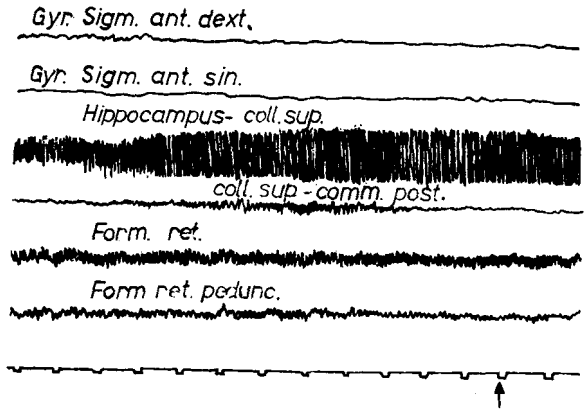


Fig. 59. Stimulation of the hippocampus in cat induced a very regular rapid rhythm (20/sec) in this structure. (From Kreindler, Voiculescu *et al.*, 1960.)

The ammonian rhythm may disappear concomitantly with the cessation of the electric activity in the other structures; it may disappear before them or may persist by being broken into fragments by the appearance and intercalation of slow waves or pauses that are synchronous with the clonic movements or may even persist for a long time, *i.e.* several seconds (Fig. 60).

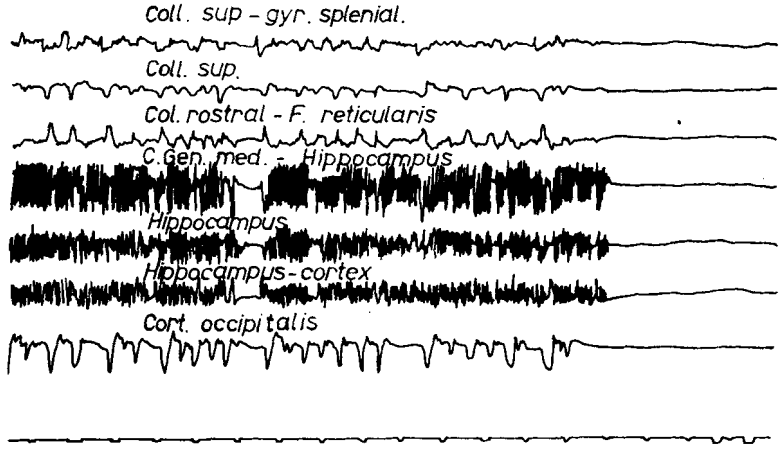


Fig. 60. At the end of an electroconvulsive seizure the rapid discharges of the hippocampus persisted during the slowing of the electrical activity of other structures. (From Kreindler, Voiculescu *et al.*, 1956a.)

In fact, the acute or chronic bilateral lesions of the hippocampus in the cat cause all these fast rhythms of the subcortical structures to disappear (Voinescu *et al.*, 1959). The mechanical destruction of the ventral hippocampus in the cat abolishes, after the electroconvulsive attack, any rapid rhythm in the subcortical leads (Fig. 61). If destruction of the hippocampus is not sufficiently extensive so that, for instance,

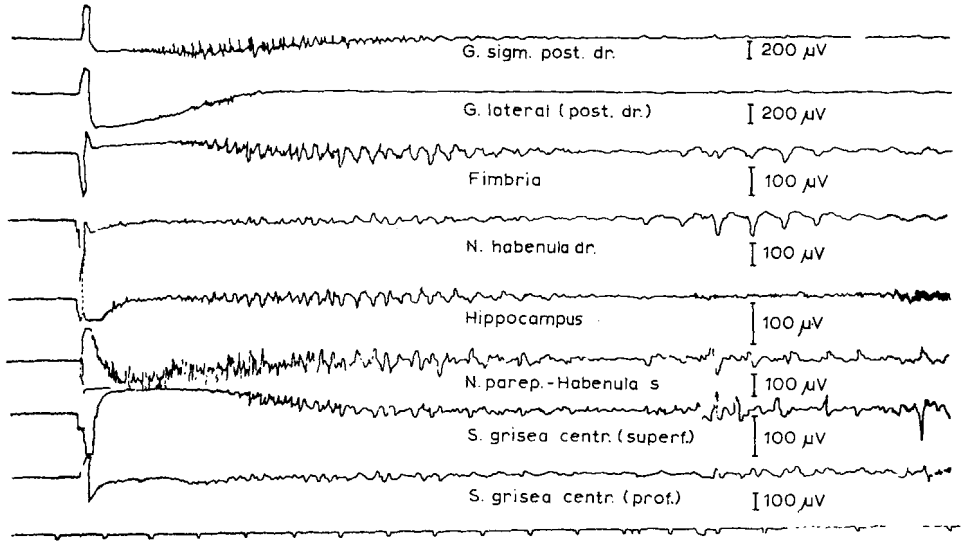


Fig. 61. After bilateral destruction of the hippocampus in the cat an electroconvulsive seizure does not produce any rapid rhythm in different subcortical structures. (From Voinescu *et al.*, 1959.)

anterior and posterior, or dorsal portions remain intact, rapid rhythms may still appear in some thalamic nuclei (nucleus ventralis posterior, nucleus lateralis ventralis, nucleus anterior). Control experiments consisting in extensive operations on the brain, such as bilateral decortication, massive lesions of the thalamus and hypothalamus, have not led to the disappearance of paroxysmal rapid rhythms. Hence, the disappearance of rapid rhythms after an extensive lesion of the hippocampus could not be ascribed to a non-specific effect of the surgical act.

Kreindler, Voiculescu *et al.* (1956) described a peculiar 'comb rhythm' with a high frequency of 13–24 c/s, an amplitude varying between 50–800 $\mu$V, and — what is most characteristic — which were very regular. This rhythm is noticed more frequently during the electroconvulsive attack and more seldom in seizure induced by metrazol or amidopyrine; they are also noticed in spontaneous attacks (Fig. 62).

*The rapid 'comb' rhythm* most frequently appears in the thalamic leads, in the grey periaqueductal matter, in the fimbria, and only rarely in the cortex, cerebellum, caudate nucleus, and hypothalamus where, even if it does appear, it does not exceed an amplitude of 150 $\mu$V. The greatest amplitudes are reached in the lateral, median and anterior nucleus of the thalamus and in the fimbria. Disappearance of the 'comb rhythm' generally occurs suddenly; at other times, this rhythm gradually becomes slower by the disappearance of every other wave. The rhythm has a dynamic character,

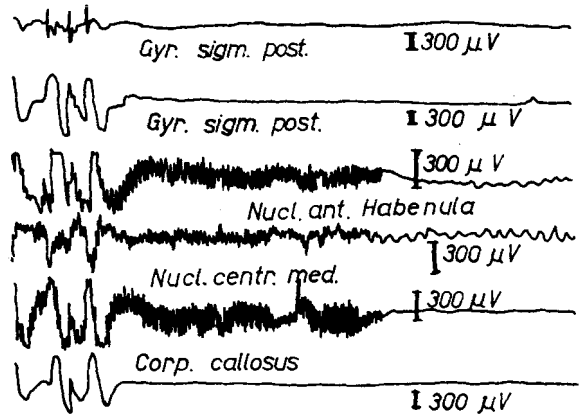


Fig. 62. Rapid rhythm in the thalamic nuclei at the end of an electroconvulsive seizure in the cat, during the electrical silence in the cortex. (From Kreindler, Voiculescu *et al.*, 1956b.)

for within the same structure it will appear, increase or decrease in amplitude or disappear.

Spreading of the 'comb rhythm' towards other structures usually starts from the thalamic nuclei. Thus, at the onset of an attack it usually has a high amplitude in the nucleus lateralis dorsalis, and nucleus medialis dorsalis (200–300 $\mu$V), being absent from the nucleus ventralis, the cerebellum, and from the frontal cortex. Towards the end of the attack or after its cessation it disappears from the above mentioned nuclei to reappear within 10–30 sec with a lower amplitude in the ventral nuclei, in the cerebellum or even in the frontal cortex. At other times it passes from the paracentral and centromedial nucleus where it appears during the seizure, to the frontal cortex where it appears some time after the cessation of the attack. Evidently what we are observing is a migration phenomenon.

*The spike–wave complex* is met during the development of an electroconvulsive attack, most commonly in the cortical leads, particularly in the sigmoid gyrus and more rarely in some thalamic nuclei (nucleus anterior medialis, nucleus centralis lateralis, nucleus posterior ventralis and more seldom in the nucleus parafascicularis, nucleus dorso-medialis, nucleus centralis medialis and centrum medianum; but never in the nucleus lateralis of the thalamus, in the hypothalamus, fimbria, corpus callosum, cerebellum, nucleus caudatum) (Kreindler *et al.*, 1956).

The spike–wave complex sometimes displays a particularly low frequency and sometimes appears after the convulsive attack has ceased, particularly in the leads where it does not exist during the attack, above all in the posterior cortical leads (gyrus lateralis). Here, perhaps, we have to deal with a migration phenomenon of the complex.

According to the investigations made by Kreindler *et al.* (1956) the spike–wave complex would appear not to be the characteristic feature of a certain anatomical substrate, particularly of the thalamus, as asserted by Spiegel and Wycis (1950) and Williams (1953). It represents a kind of reaction common to many cerebral areas during the phenomenon of paroxysmal synchronism.

The spike–wave complex is a kind of discharge that must not be mistaken for or identified with petit mal epilepsy. The spike–wave complex may be determined by the functional properties of the cortex itself. But its symmetrical synchronous genesis in both hemispheres cannot be a cortical one.

Very likely, however, the spike may have an origin other than the wave, as is asserted by Williams (1953). Thus, in some of the experiments performed by Kreindler, Voiculescu *et al.* (1956b) the frequency of the spikes exceeded that of the waves: very often, the spike and wave did not appear concomitantly; the size of the spike and the wave were not the same in all leads, as in some the spikes had a greater amplitude while in others the waves were greater. Still another important observation to plead in favour of a different origin is that by recording with deep, stratified electrodes it has been possible to ascertain that whereas the spikes always occurred in phase, the waves were found to exist in various thalamic nuclei.

Penfield and Jasper (1954) ascribed a thalamic origin to the spike–wave complex. Jasper and Droogleever-Fortuyn (1947) recorded symmetrical and synchronous spike–wave complexes after stimulation of the intermediate mass of the thalamus. Sager *et al.* (1957) recorded cardiazolic attacks in bilaterally decorticated animals and found a rapid rhythm of 8–12 c/s in Reichert's innominate substance, in the anterior hypothalamus and the mesencephalic reticular formation, followed in the same structure, by spike–wave complexes which, in turn, were followed by spike discharges. In the acute experiment the authors recorded from the isolated sigmoid gyrus in the dog from which the two posterior thirds of the cerebral cortex, thalamus and extrapyramidal nuclei had previously been removed. In these animals the cardiazolic attack induced in the isolated cortex solely a rapid rhythm and never spike–wave complexes. According to the authors the spike–wave complex has a diencephalic–mesencephalic subcortical origin whereas rapid rhythms can only be generated in different segments of the brain.

Mention must be made of the fact that Wada and Cornelius (1960) have found in the cat in which an epileptogenic focus was created in the sensorimotor cortex by alumina cream, bilateral and synchronous 3 c/s discharges without any disturbance of the midline structures.

The origin of the spike–wave complex in the upper mesencephalic segment could not be confirmed by experimental investigation (Ingvar, 1959), for neither by the local electrical stimulation of the upper mesencephalic segment nor by its local chemical stimulation could the typical 3 c/s spike–wave complex be reproduced in animals.

The experimental study of the circulation in the cerebral cortex and of the electroencephalogram during metrazol-induced epileptic discharges have shown that if cortical discharges are triggered in such a way as to come on slowly, a transition phase may be observed in which they assume the pattern of a 3 c/s spike–wave complex. This form of activity must probably be ascribed to defective cortical circulatory homeostasis, when excitability of the cortex attains abnormally high values (Ingvar, 1959).

Petsche (1963) believes the spike–wave complex to be of cortical origin. By means of the toposcopic method he recorded the electroencephalogram in patients suffering from petit mal attacks and found, apart from other things, that the speed of the waves

was 2–7 m/sec whereas that of the spikes was 4–15 m/sec. The site from which the spike and the wave arise is not where the highest amplitude is found. The generating site likewise moves at a much lower speed of some cm per sec. These sites differ for waves and for spikes and their behaviour is also different. From the spatio-temporal viewpoint they remain constant from one attack to the next and prefer the borderline areas of the frontal and parieto-occipital cortex. Petsche reaches the conclusion that the spike–wave phenomenon is due to a process of synchronization, that it originates wholly from the cortex and that the thalamus plays but a minor role in its appearance.

An important aspect for understanding the development of the epileptic seizure is the migration phenomenon of epileptic activity *i.e.* the migration of epileptic activity during the course of the attack from one structure to another. McCulloch and Dusser de Barenne (1935) noticed the passing of an after-discharge from one structure to another in animals anaesthetized with diallyl-barbituric acid. Walker and Johnson (1948) showed that in the normal monkey after-discharges stop suddenly, whereas in monkeys with epileptogenic lesions they are transmitted from one cortical area to another, continuing for several minutes. In the same way, in the epilepsy induced by certain kinds of drugs, epileptic discharges may be seen to occur in one point of the cortex, to disappear and to appear again in another quite unexpected place (McCulloch, 1949). Stimulation of the amygdala causes multiple and successive cortical foci which do not arise independently of one another in various parts of the cortex but represent the same discharge conveyed from one point of the cortex to subcortical structures connected with it, and thence to other cortical areas (Gastaut and Roger, 1955).

The discharges may have a 'wandering', *i.e.* an erratic, character. For instance, they may be transmitted from the amygdala to the septal and temporal areas, then to the posterior hypothalamus and from there to the frontal cortex, and then again return to the temporal area (Gastaut *et al.*, 1952). Walker and Johnson (1948) describe erratic discharges ('wandering discharges') *i.e.* discharges released at a distance from a structure and then evolving on their own.

The migration phenomenon of epileptic waves was demonstrated by Kreindler, Voiculescu *et al.* (1956b) by the shifting of rapid rhythms and of the spike–wave complex, as well as by the different origin of the spike and of the wave within this complex, which brings about the shifting of phase oppositions during the development of an attack. Thus, some rapid rhythms ('comb rhythm') pass from one structure to another in the course of an attack.

If recordings are made with multiple, stratified electrodes, it sometimes happens that after two recordings the waves having a common pole are in phase, *i.e.* have the same direction and hence have a common origin in another place; at other times, they are in phase opposition which means that their place of origin is at the level of the electrode common to the two recordings. Leads with multiple electrodes, stratified at the level of the thalamic nuclei during and after an electroconvulsive attack, have shown that frequently there is such a phenomenon of phase opposition but that in some instances it may vary and be inconstant from one attack to the next, the focus being found, on the occasion of one attack, in a thalamic structure, and of some other

attack, in another structure. In yet other cases, on the contrary, it may be found to be constant, occurring at repeated attacks in one and the same structure.

Sometimes, during the same attack, passages from phase opposition to phase, or conversely may be noticed, passages which are quite sudden (Fig. 63). This shows the tendency of some epileptic waves to migrate through the brain structures. The latter phenomenon is particularly significant, for it shows that during an epileptic attack the points between which differences of electric potentials are established, are not fixed, their variations corresponding to some changes in the reverberating circuits involved in the epileptic phenomena. The development mechanism of an epileptic seizure is not made up of fixed and constant processes along the same circuits, but of variable dynamic phenomena.

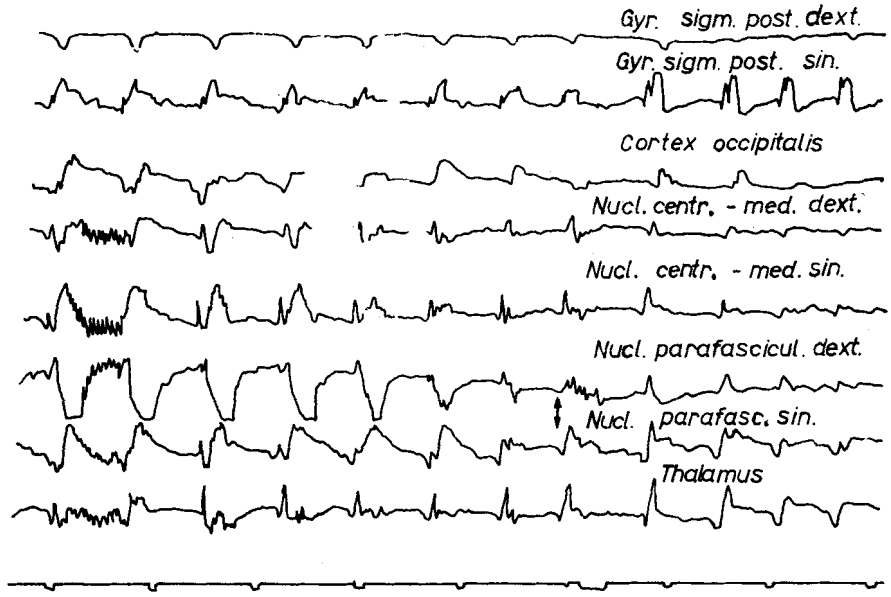


Fig. 63. Electroconvulsive seizure in the cat. Passage from phase opposition to phase (marked in the 6th lead by an arrow). (From Kreindler, Voiculescu *et al.*, 1956b).

If numerous experimental epileptic attacks are recorded the phase opposition will be found to occur rather frequently, but it varies greatly from one attack to the next even in the same animal. Sometimes, during the first attack, there is a concordance of phases between the synchronous large waves, only to be followed, in the next attack, by a phase opposition in the same group of recording electrodes. Sometimes a sudden passage from phase concordance to phase opposition may be noticed within the same attack, and more seldom, even a return to the initial pattern.

This mobility is evidence for the migration of the epileptogenic focus. Moreover, the focus generating large synchronous waves should not be mistaken for the focus triggering off focal epilepsy.

### *C. Electroclinical correlations*

An important problem in the study of the development of an experimental epileptic seizure is the correlation of the alterations of cerebral electric activity with the clinical symptomatology of the seizure. Our data in this connection are rather scanty owing to the experimental conditions of the study of electric activity, the great majority of investigations requiring a curarized animal or 'encéphale isolé'. A valuable technique in this regard is the implantation of chronic electrodes into animals, but conditions are such that the number of these electrodes has to be limited.

Cerebral electric epilepsy and convulsive epilepsy represent two different patterns. Electric epileptic activity comprises most varied and multiple cortical and subcortical structures and sometimes only a very few efferent pathways. Convulsive epilepsy is one of these efferent pathways. The study of this motor efferent pathway of convulsive epilepsy in its peripheral component can give us detailed information as to the organization and development of an epileptic seizure (Kreindler, 1955).

In the phylogenetic range there is a predisposition with characteristic features for the convulsive seizure. Tonic–clonic convulsions can be induced in animals phylogenetically as early as Cyclostomata. Whereas in Amphibia typical cerebral convulsions can already be provoked, tonic and clonic phases succeed each other in Cyclostomata and the Teleosts in a non-charactisteric pattern. From the reptiles onward, however, a typical three-phase development of the convulsive attack may be distinguished, namely an initial short clonic phase, a tonic phase and a terminal clonic phase (Servít, 1957).

Kreindler (1955) investigated the pattern of the epileptic attack through the animal scale and found that in fishes the electroconvulsive attack assumes a purely tonic pattern. In the frog, an abolition of the law of mutual innervation was found to exist during the convulsive attack. The convulsive discharges in the frog represent a reactive modality of a very great number of structures in the central nervous system, both of the higher structures and of the bulbo-protuberantial and medullary ones. After the convulsive epileptic attack the dynamics of the spinal cord undergoes important changes. In reptiles, the electroconvulsive attack is manifested by a long tonic phase followed by a short clonic phase, whereas in birds the tonic phase is short and the clonic one much longer.

Between the convulsive aptitude of the rat and of the cat there are important differences (Kreindler and Zuckermann, 1957). The threshold intensity of the stimulus required for inducing a convulsive attack is lower in the cat than in the rat. The threshold differences between the motor areas and the other cortical areas are 10–15% lower in the rat as far as the motor areas are concerned, whereas in the cat the difference is of 200–300%, as regards the convulsive phenomenon; the hypersynchronous epileptic electric activity shows differences ranging from 30% to 80% for both species of animals between the motor areas and the other cortical areas. On stimulation at threshold intensity, the duration of the generalized convulsive attack provoked by repetitive cortical focal stimulation is shorter in the rat than in the cat.

In the rat, the clinical convulsive seizure sets in concomitantly with the electric

seizure, whereas in the cat this happens only if the motor area is stimulated. Focal stimulation of a non-motor area in the cat first of all provokes an electric attack whereas the clinical one only appears after a 10–120 sec latency in relation with the area of stimulation and the nature of stimulation. In the latter instance there is a propagation phenomenon which is more delayed in the cat than in the rat, probably owing to the more complex structure of the cortex and to a greater number of internuncial neurons.

The attack induced in the rat with a threshold intensity is generalized from the start whereas in the cat the same intensity brings about a focal seizure.

The refractory period during which no convulsive attack may again be induced in the same cortical place lasts much longer in the rat (140 sec on average) than in the cat (15 sec on average) both as regards the motor activity and the hypersynchronous cortical electric activity. The amplitude of convulsive potentials in the rat does not exceed 200–350 $\mu$V whereas in the cat it reaches 1000–1200 $\mu$V.

The differences between the rat and the cat as regards their convulsive amplitude is accounted for by the greater structural complexity of the chains and neuronal circuits in the cat, and by the greater number of internuncial neurons. The greater duration of the attack is due to a longer reverberation maintained by larger circuits with a greater number of internuncial neurons. The greater amplitude of hypersynchronous waves in the cat supports this argument. In the cat there is a degree of localization of the attack characterized by a more definite focal pattern both of the motor phenomena and of the electrocorticographic pattern. The greater number of associative neurons in the cat permits the creation of convulsive chains within a certain area whereas in the rat this is only possible on extensive cortical surfaces.

Mettler and Mettler (1940) found that convulsive attacks cannot be released from the cortex if the pyramidal tracts only are preserved, but can be induced when they alone have been destroyed, hence it would appear that the extrapyramidal pathways and structures play a dominant part in the mechanism of generalized convulsions. Zanchetti and Brookhart (1955) have shown that there do not exist changes in the pyramidal responses during pentylenetetrazol-induced attacks. The convulsants seem not to involve directly pyramidal neurons or internuncial cortical neurons but particularly to involve the reticular formation.

A correlation is believed to exist between the site of the discharge focus and the clinical type of the epileptic fit (Gastaut, 1958a). Generalized tonic convulsions are believed to depend only on the caudal reticular formation, whereas the loss of consciousness would depend on the rostral reticular formation, the thalamus and the cortex. The generalized grand mal seizure depends on subcortical structures, corresponding at first to a paroxysmal discharge of the thalamic reticular system spreading to the cortex through the diffuse thalamo-cortical projection system, thus accounting for the loss of consciousness.

During a convulsive fit in patients curarized with succinylcholine an electromyogram with irregular continuous repetitive oscillations of 18–20 c/s lasting 3–5 sec may be observed in the phase during which the electroencephalographic tracing displays a

typical grand mal pattern. This myoelectric activity ceases, however, 10–20 sec before termination of the cerebral convulsive activity (Mosier *et al.*, 1957).

A chronic alumina cream induced epileptogenic focus in the monkey in the optic, auditory or somato-sensitive cortex alters the conditioned response. *i.e.* produces the conditioned blocking of the $\alpha$-rhythm to a sound or a tactile stimulus, or produces a conditioned driving phenomenon of the $\alpha$-rhythm to a sound or a tactile stimulus (Morrell *et al.*, 1956). Electrical conditioned reflectivity is altered for the stimuli whose cortical projection area lies within the epileptogenic lesion. An epileptogenic lesion in the area of the amygdala induces a more general alteration of conditioned reflectivity. Removal of the epileptogenic focus considerably re-establishes these disturbances. Conditioned reflectivity is not changed by an epileptogenic lesion in the frontal cortex. The epileptogenic focus in a sensorial or somato-sensitive cortical area hinders the normal functioning of the respective receptive system in elaborating a conditioning process in which this system interferes; it prevents the establishing of temporary connections between this sensitive area and the other parts of the brain.

A number of investigators (Chow an Obrist, 1954; Henry and Pribram, 1954; Pribram, 1951) have studied the action of chronic epileptogenic foci, induced with alumina cream in monkeys, on their ability to retain certain ideas learned before the focus had been created. If the monkey was subjected to memory tests before and after the placing of alumina cream on the frontal, inferotemporal, occipital or preoccipital areas no significant defects in visual discrimination or in the alternation of the given tasks were noticed. If, however, the teaching process started after the epileptogenic focus had been created, important defects in this process were noted. These observations show that epileptic discharges influence the process of the acquisition of knowledge, but not that of memorizing (Stamm and Pribram, 1960).

Stamm and Warren (1961) studied learning and retention in monkeys with epileptogenic implants in the posterior parietal cortex (alumina cream). Two groups of 5 monkeys were used, a retention group and a learning group. All subjects responded accurately on the easy discriminations, but on the difficult discriminations the learning group was inferior to the retention group. In the learning group those subjects which did not reveal behavioural seizure signs attained the same threshold values as the retention group, whereas those monkeys that exhibited seizure symptoms continued to respond at poorer threshold levels than did the other monkeys. Hence, memory is not impaired by the onset of epileptogenic discharges. In the acquisition of new tasks, however, the epileptoid monkeys were deficient on several quantitative indices when compared to normals.

There are some correlations in man between the paroxysmal and interparoxysmal tracings and the vegetative phenomena (Kreindler, Broşteanu *et al.*, 1957). Thus, continuous alterations of the tracing may be accompanied by an undulant plethysmogram. Yet electrogenesis disturbances of a focal type without simultaneous peripheral vegetative alteration (plethysmogram, respiration) may be encountered. The inverse can also be true, namely such alterations can exist without any electroencephalographic correlation.

The epileptic fits induced by electroshock or the application of penicillin to the

cortex are associated with an enhanced electric activity in the sympathetic nerves as well as in the spinal (median, radial, sciatic) nerves; however, it has not been possible to establish closer relationships between these alterations of the neurograms with the electroencephalic alterations accompanying the attack. In the sympathetic nerve, series of discharges lasting 0.1–2 sec may be found that are partly synchronous with the activity of the somatic nerves (Colle *et al.*, 1957). During its development the convulsive fit is accompanied by a rich viscero-vegetative symptomatology which points to a spreading of excitation to vegetative central structures. The focal attack in the curarized dog by faradic excitation is accompanied by changes in blood pressure, *i.e.* a hypertension that is synchronous with the electric convulsive activity (Morin and Corriol, 1958). Small doses of barbiturates or chlorpromazin prevent hypertension without changing the clinical and electric pattern of the fit. In fits with progressive generalization the invasion of the frontal poles is a requisite but not sufficient condition of hypertension as shown by the study of the generalized attack with focal onset in different cortical areas. Hypertension is generated by the spread of the paroxysmal activity towards diencephalic pressor centres: the spread may be prevented by small doses of barbiturates or chlorpromazine. The peripheral mechanism of hypertension consists of a vasoconstriction accessorily associated with the adrenaline release. The arterial blood pressure is always lower in the non-anaesthetized and wakeful cat in which an amygdaloid electrical epileptiform after-discharge is elicited. Here the pressure is decreased more with shorter after-discharges (20 sec or less) than with those exceeding a duration of 20 msec. High blood pressure is only noticed when the amygdaloid after-discharge is propagated to the hippocampus or the fornix. The lowest blood pressure is associated with the after-discharge in the anterior amygdala or central-medial nucleus. The pulse rate and its rhythm are not changed during the after-discharge (Andy *et al.*, 1959). Kreindler (1955), using the chronaximetric method, studied the changes in the excitability of the vegetative nerves during and after the generalized convulsive attack induced by electroshock.

Following a convulsive seizure, the threshold of excitability of the vago-sympathetic trunk for the heart decreases in the same manner as that for the gastric wall contractility. The excitability threshold for pupillary dilatation is lower in dog and cat and. higher in rabbit. After a generalized convulsive seizure, the chronaxy of the vago-sympathetic nerve for the threshold of both the depressor and the respiration inhibiting reflexes is higher. Hence, after a generalized fit, excitability of both efferent and afferent vegetative pathways decreases.

During a petit mal fit in man, respiration is disturbed and the plethysmogram is often inert with undulant asymmetry between the two branches. Sometimes, a fit is accompanied by vasodilatation but no respiratory disturbances; at other times, there occurs an acceleration of respiration but the vasodilatation only follows the seizure. These results show that propagation to the cortex is both symmetrical and synchronous, whereas the downward propagation from the centrencephalic area to the caudal brain stem reticular formation is sometimes neither symmetrical nor synchronous (Kreindler, Broşteanu *et al.*, 1957).

Vardaptean (1963) studied the bioelectrical activity of the vegetative nervous system

in the rabbit during metrazol-induced convulsions. The experiments were carried out on unanaesthetized rabbits mechanically fixed in a special device. Bioelectrical potentials were led off, using unipolar platinum or bipolar electrodes according to whether the records were taken from the central cortex and hypothalamus or from the upper cervical sympathetic ganglion respectively. Convulsions were induced by subcutaneous administration of a 10% pentamethylenetetrazol (metrazol, cardiazol) solution in a dose of 100 mg per kilogram of body weight.

The results showed that the onset of convulsions is preceded by an enhancing of the bioelectrical activity of the sympathetic nervous system, manifested by an increase in both the amplitude and frequency of potentials recorded from the upper cervical sympathetic ganglion. Against this background of enhanced bioelectrical activity of the sympathetic nervous system there occurs a progressive and successive activation of the hypothalamic area, followed by that of the central cortex leading to the appearance of convulsions when strong bioelectrical discharges are recorded from all the segments of the nervous system.

The interruption of convulsions is accompanied by the inhibition of bioelectrical activity in the sympathetic ganglia. Such inhibition is initially manifested by isolated periods of disappearance of the biopotentials soon followed by a general background of inhibition of electric oscillations. Thereafter, the bioelectrical activity of the hypothalamic area and of the cerebral cortex diminishes. It is on this background that the convulsive attack comes to an end.

The generalized convulsive fit induced by electrical shock is also accompanied by marked disturbances in the function of viscera (Kreindler, 1955). Motility of the digestive tube is impaired: there occurs either a considerable reduction or a disappearance of the gastric movements, the seizure being followed by gastric atonia. Atonia and akinesia exist to a lesser extent also in the other segments of the digestive tube. The convulsive fit is accompanied by a violent contraction of the spleen which is longer in duration than blood pressure alterations. The apnoea occurring with convulsive seizures is a phenomenon often independent of the tonic contraction of the respiratory muscles, being determined by inhibition of the respiratory centres. Both the thermal and the morphine-induced polypnea disappear in the animal after a convulsive fit. The rabbit's convulsive attack is associated with bradycardia, ventricular extrasystoles, either isolated or in bursts of atrioventricular block; all are reversible alterations, less marked in the cat. The plethysmogram shows a peripheral vasoconstriction. The renal volume decreases during the attack, reaching a minimum at the end of the seizure, after which it slowly returns to normal. The renal volume does not depend on variations in blood pressure. Urine secretion during the seizure either decreases or stops completely, but slowly returns to its initial value thereafter. The convulsive seizure also causes a delay in the elimination of phenolsulphonphthalein.

The viscera recover their functional equilibrium only late, after the cessation of the convulsive seizure, the vegetative seizure lasting longer than the motor one. The restoration to normal of the visceral functions altered by the convulsive attack is neither sudden nor slowly progressive, but oscillatory and characterized by an alter-

nation of normal periods and ever shorter periods of recurrence of the disturbances. These phenomena are brought about by a disturbance of homeostasis and the struggle for its restoration.

The electroconvulsive seizure is accompanied by viscero-vegetative phenomena which differ in the normal and the decorticated animals, the latter showing a longer phase of apnoea, a more marked gastric atonia and cardiac phenomena.

### *D. Factors influencing the development of an experimental epileptic seizure*

Among the factors which may influence the development of the epileptic seizure we shall enlarge upon polarization of the cortex and the influence of the reticular formation.

The importance of the radial polarization gradient of the cortex for maintaining its spontaneous activity and for its reactivity was demonstrated by Goldring and O'Leary (1950, 1954) and by Libet and Gerard (1941). A repetitive sensorial stimulation results in summation of certain normal aspects of an isolated sensorial stimulus which gives rise to long-lasting fluctuations of the radial polarization gradient of the cortex. The onset of such slow variations as produced by a sensorial stimulus is marked by a surface positivity, and hence a negativity of the deep structures. Therefore, an epileptogenic repetitive sensorial stimulation may result in the same neuronal polarization gradient as that appearing as a condition of the after-discharge following direct electrical stimulation of the cortex. In both cases, after a sufficiently prolonged activity, the deep somatic extremities of the neurons with a position perpendicular to the surface of the cortex seem to repolarize more slowly than their superficial extremities. The electric field thus created would be the immediate factor of a self-sustained subsequent activity. Further, a continuous depolarization gradient might be one of the factors maintaining a normal spontaneous activity of the cortex (Bremer, 1958).

Burns (1955) showed that the intensity of the after-discharge in the isolated cortex is proportional to the potential gradient voltage. On the other hand, the after-discharge is elicited or facilitated by a continuous electrical current in radial direction from the surface to the depth of the cerebral cortex and the after-discharge focus is suppressed by an opposite depth–surface current.

Cathodic polarization of the cortical motor area may change the type of cortical epileptogenic discharges (Kreindler, Atzev *et al.*, 1959). Experiments were carried out on rabbits, and polarization was produced by means of an electrode placed directly on the motor cortex (active electrode) and by a large electrode placed on the abdomen, the intensity being 70 $\mu$A. Cathodic polarization caused the rhythm of some spontaneous discharges of rapid waves to become slower. It is worth mentioning that cathodic polarization facilitates the convulsive reactivity of the motor cortex when it is produced by electrical stimulation of the homolateral striated area. Hence, the effect of cathodic polarization on propagated phenomena is contrary to that on local, focal ones. The action of polarization might be related to the spreading depression.

As regards facilitation and suppression of the epileptic activity by certain nervous

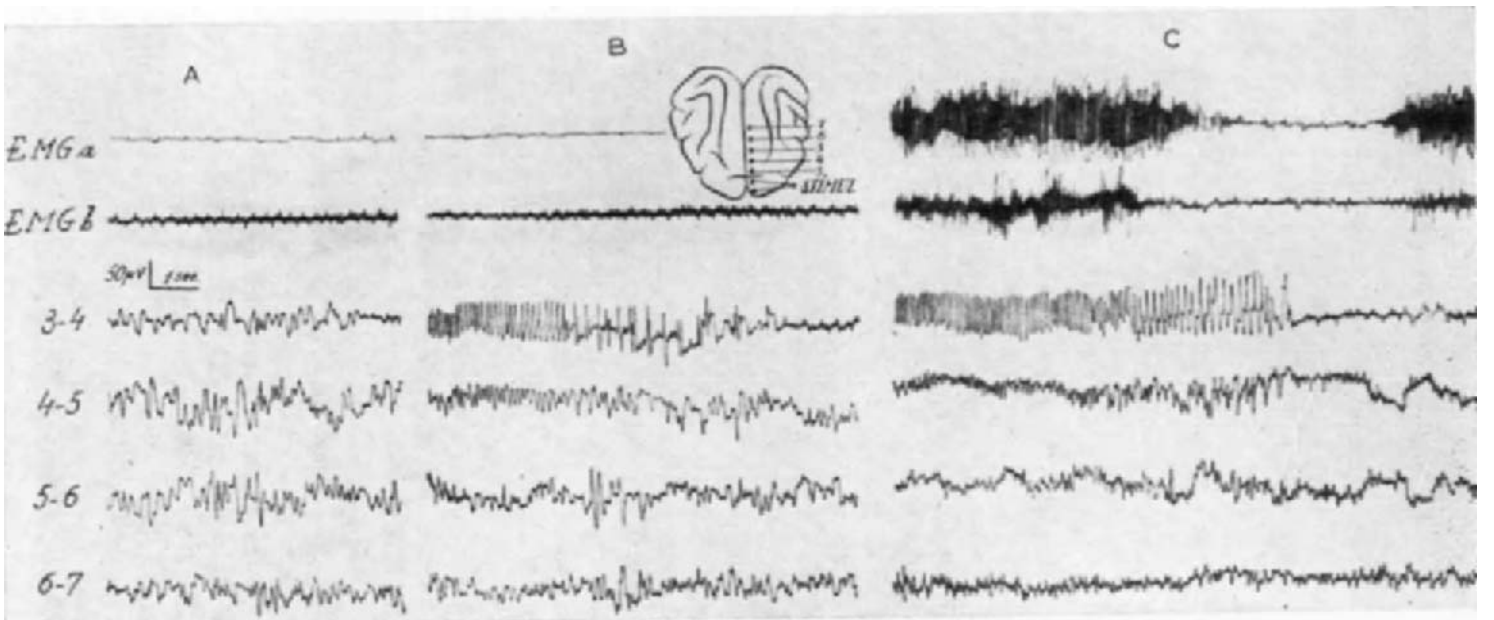


Fig. 64. Facilitation of the after-discharge induced by electrical focal stimulation of the motor cortex in the uncurarized cat by electrical stimulation of the neocerebellum. A = before cortical stimulation; EMGa = electromyogram of the flexors of the right anterior limb; EMGb = electromyogram of the extensors of the right anterior limb; B = electrical after-discharge without clinical phenomena (the electromyogram is silent) induced in the derivation from points 3–4 and 4–5 by focal stimulation of g. sigmoideus anterior (distance between stimulating electrodes 2 mm; 0.8 V; 100 c/s; 5 sec) of a point 3 mm from electrode 3; C = facilitation of the cortical after-discharges by a stimulation of right crus I preceding the cortical stimulation (0.25 mA; 250/s; 0–5 msec). The cerebellar stimulation precedes the cortical one by 3 sec; they then continue together for another 5 sec. Note, at the same time as the facilitation of the after-discharge, an intense activation of the electromyogram and a desynchronization of the cortical tracing. (From Kreindler and Steriade, 1960b.)

structures, Kreindler and Steriade (1960a) and Steriade (1960) showed that only a poorly organized epileptic activity, which characterizes the onset of an electric attack or of a penicillin-induced attack, can be inhibited by stimulating the cerebellum or the diffuse thalamic system. As the seizure tends to become better organized with several circuits involved in a hypersynchronous activity, stimulation of the same structures with the same parameters results in an opposite effect, that is in facilitation.

Kreindler and Steriade (1960a,b) studied the influence of the neocerebellar areas on the focal electrical after-discharge elicited by stimulation of the motor cortex. The stimulation of the cerebellar areas (folium, tuber, ansatus) in the uncurarized cat, contralateral to the stimulated cortical point, results in a facilitation of the cortical after-discharge, manifested as an increase in voltage, prolongation of the duration of the after-discharge and sometimes by a spreading of the electrical phenomena to other cortical leads, far from the stimulated point. The facilitation sometimes manifests itself as a morphological change of the after-discharge waves. This modification corresponds, in the combined cerebellar and cortical stimulation, to the one observed after an isolated cortical stimulation but of a greater intensity than the test one. Generally speaking, the cerebellar facilitation is readily observable in the cortical after-discharge obtained by slightly supraliminal or liminal intensities. Sometimes, however, a similar effect was obtained when a subliminal voltage applied to the motor cortex was transformed into a supraliminal stimulus, if preceded by a stimulation of the contralateral neocerebellar structures (Fig. 64). The cerebello–cortical facilitation is transmitted not only via the cerebello–rubro–thalamo–cortical classical pathways, but also through the diffuse cerebello–reticulo–cortical projections, since there is a general increase in the excitability of the cerebral cortex, manifested in the facilitation of the after-discharge from other cortical regions besides the motor one, not to speak of the homolateral facilitation of the cortical after-discharge. In the neuronal exhaustion phenomenon induced in the motor cortex by an electrical current of great intensity, or one of long duration applied to the cerebellum, it is observed that the focal cortical after-discharge is hindered when the cerebellar stimulation is previously applied. Once the after-discharge has appeared at the level of the stimulated point of the cortex, a further cerebellar stimulation, whatever its strength, is unable to suppress it any more (Fig. 65). Thus, the focal after-discharge evoked by cortical faradization can be inhibited by long and strong cerebellar stimulation applied before and during cortical stimulation; this phenomenon is in contrast to the facilitation phenomenon obtained through a short stimulation at low intensity in the same experiment for the same type of cortical after-discharge.

Whereas in the uncurarized cat the facilitation or inhibition of the cortical focal after-discharge is chiefly related to the parameters of the cerebellar stimulation (probably related to the tonigenic activation degree), in the curarized cat only small after-discharges can be inhibited. In the latter, the facilitation may be expressed only in the cortical after-discharges that exceed a given intensity. Both the dynamogenesis and the inhibition produced by the cerebellum seem to occur at a cortical level, since it is not possible to record these phenomena in the thalamic relay nuclei (VPL and VL nucleus) (Fig. 66).

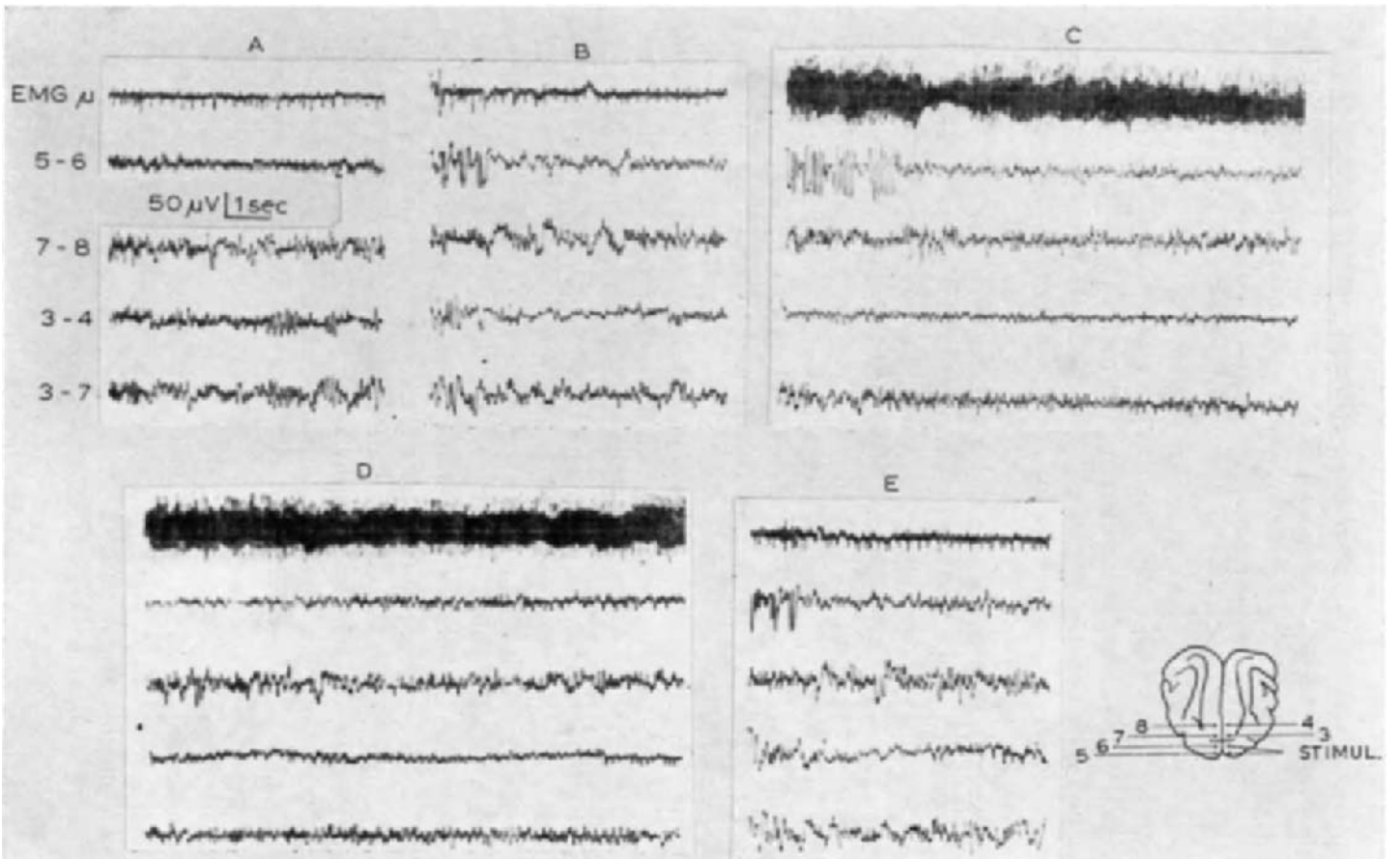


Fig. 65. Uncurarized cat. A = before cortical stimulation; B = electrically-induced after-discharge in the left anterior g. sigmoideus; C = enhancement of the after-discharge by an associated liminal cerebellar stimulation (0.3 mA, preceding the cortical one by 3 sec); D = inhibition of the same after-discharge by an intense supraliminal cerebellar stimulation (1.5 mA, preceding the cortical one by 15 sec); E = control. (From Kreindler and Steriade, 1960b.)

The part of the functional state of the motor cortex in the reversion of the cerebellar effect on the strychnine induced clonic movements has also been pointed out by Moruzzi (1941). The fact that in Moruzzi's experiment the facilitating influence appeared only upon subliminal strychninization of the motor cortex, *i.e.* conversely with the results in the above-mentioned experiments in which facilitation only occurred with a penicillin action exceeding a certain level of cortical excitability, may be accounted for by penicillin and strychnine differing in nature, and the experiments dealing with peripheral events in one case and cortical effects in the other.

The cortical penicillin focus in the cat can also be facilitated or suppressed by cerebellar stimulation (Steriade, 1960). Fast repetitive stimulation of the ansoparamedian lobe and certain vermian lobules induces cessation of the penicillin spikes, in most cases with an after-effect. With increase in the amplitude of the spikes, the effect of cerebellar stimulation is inverted and becomes definitely facilitatory, the facilitatory effect manifesting itself as an after-effect of stimulation. In this phase, diffuse cortical desynchronization obtained by stimulation of the cerebellum is acompanied by accentuation of focal hypersynchrony on the lead recording the penicillin spikes. Sometimes, accommodation to the stimulus becomes evident, as the amplitude of the spikes, facilitated at the beginning, diminishes before stimulation is over. At other times, intrastimulatory suppression is followed by poststimulatory facilitation, a kind of rebound phenomenon (Fig. 67). Sometimes facilitation by stimulation of the cerebellum only occurs at the moment in which the penicillin spikes pass beyond the initial cortical focus and spread to other cortical zones. In that event, epileptic activity may be reawakened by cerebellar stimulation even against a background of complete electrical silence, both the accommodation and the postexcitatory rebound phenomenon appearing. Fast repetitive stimulation of the diffuse thalamic system (nucleus centrum medianum, nucleus reuniens, anterior ventral nucleus etc.) brings about, as in stimulation of the cerebellum, cessation of the penicillin spikes only at their beginning, when they first appear and their amplitude is low. Stimulation of these nuclei using the same parameters facilitates the penicillin spikes when their amplitude increases (Fig. 68).

The enhancement of a penicillin-induced focal hypersynchronia occurs against a background of diffuse desynchronization brought about by cerebellar or thalamic stimulation (Steriade, 1960). This shows that only certain epileptic activities may be abolished by neuronal desynchronization, a phenomenon also noticed by Bremer (1958). The parallelism shown by Kreindler and Steriade's (1958) and Steriade's experiments (1960) to exist between the increasing amplitude and better organization of epileptic accidents, on the one hand, and their facilitation by a desynchronizing ascendent stimulation on the other, might be correlated with some clinical phenomena, *i.e.* with small clinical paroxysms which may be either suppressed or, on the contrary, precipitated by a particular constellation of afferent impulses (Kreindler, Steriade *et al.*, 1958).

Arduini and Lairy-Bounes (1952) studied the action of stimulation of the bulbar reticular formation and of sensory stimulation on the strychnine cortical spikes induced in the 'encéphale isolé' cat.

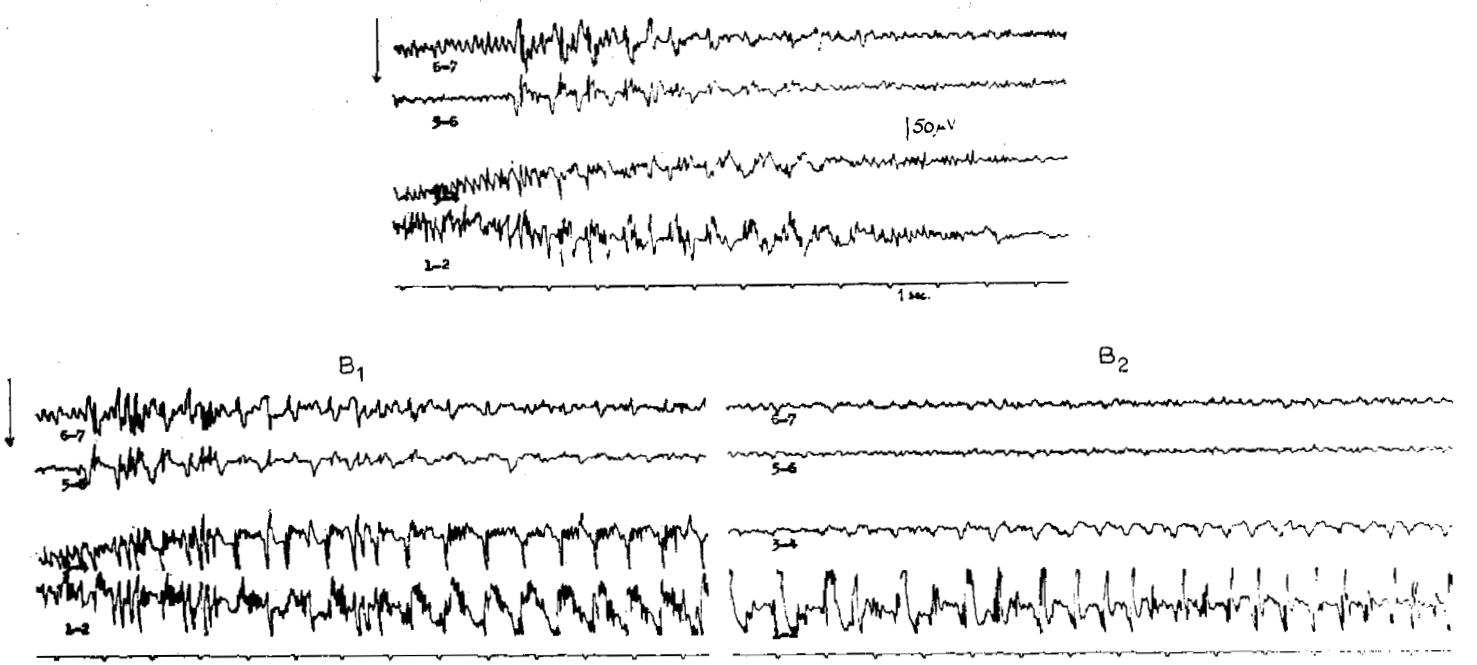


Fig. 66. Curarized cat. Lead 1–2 = left g. sigmoideus; 3–4 right g. sigmoideus; 5–6 VPL thalamic nucleus; 6–7 VL thalamic nucleus. A = cortical after-discharge spreading to VPL and VL; $B_1$ and $B_2$ = facilitation of the cortical after-discharge by association of a cerebellar stimulation. Note the facilitation only of the cortical after-discharge without any influence of the propagated thalamic potentials. Between $B_1$ and $B_2$ is an interval of 5 sec. (From Kreindler and Steriade, 1960b.)

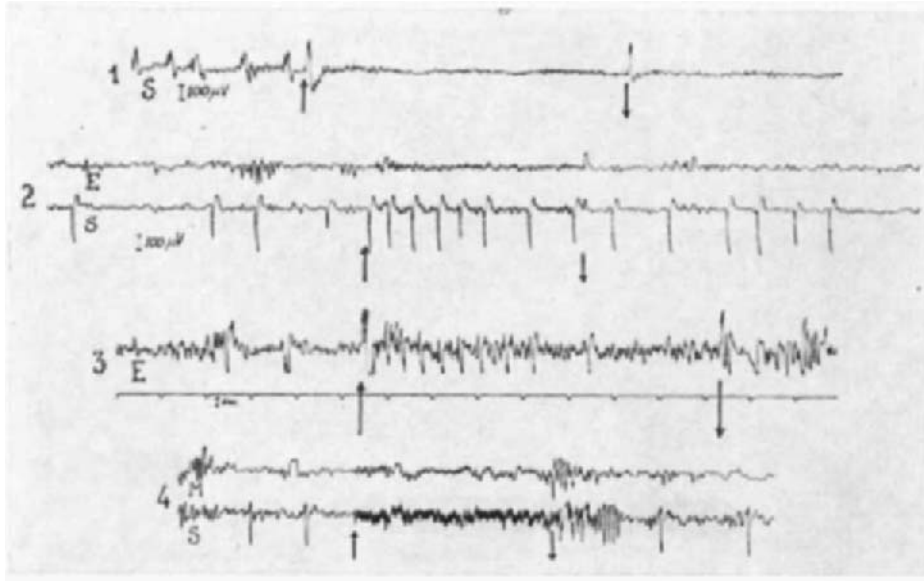


Fig. 67. Effect of cerebellar stimulation on cortical penicillin spikes. 1 = small amplitude spikes, immediately after the application of penicillin to sigmoid gyrus, stopped during the stimulation (between arrows) of the right anterior lobe (0.25 mA) and as its post-effect. 2 = the same animal as in 1. The stimulation with the same parameters of the same cerebellar point determines, parallel with the diffuse desynchronization, a facilitation of the penicillin spikes reaching an advanced phase of greater amplitude. 3 = another animal. Facilitation by stimulation of the right paramedian lobe (0.3 mA) with accommodation under stimulus. 4 = another animal. Arrest of spikes during the stimulation of the right anterior lobe (0.3 mA) with post-excitatory rebound. S = g. sigmoideus; E = g. ectosylvius; M = g. marginalis. (From Steriade, 1960.)

Smith and Purpura (1960) studied the influence of stimulation of non-specific afferent pathways on focal discharges. Weak low-frequency stimulation of midline thalamic nuclei or of the brain stem reticular formation did not affect the discharge characteristics of epileptogenic lesions in the posterior sigmoid or anterior suprasylvian gyrus. In contrast, high frequency stimulation of these structures often exerted marked effects on epileptogenic lesions which depended primarily on the character of the spontaneous paroxysmal activity present in the latter. Inhibition of low-frequency discharges and facilitation of higher frequency activity was most commonly observed. Short bursts of high-frequency stimuli were effective in triggering single spikes or driving an area of epileptogenic cortex in sustained seizure.

Stimulation of the reticular formation and midline thalamic nuclei (Kreindler and Steriade, 1961) preceding by a few seconds and/or simultaneously with the electrical stimulation inducing a focal cortical after-discharge, causes in the 'encéphale isolé' cat a marked enhancement of after-discharge. This may be manifested by an increase in voltage, by a prolongation of the duration of after-discharge and, sometimes, by a spread of the electrical phenomena to other cortical leads, far from the stimulated point (Fig. 69). Generally the reticular and midline thalamic facilitation is readily observable in the cortical after-discharge obtained by slightly supraliminal or liminal intensities. However, a similar effect was sometimes obtained when a subliminal

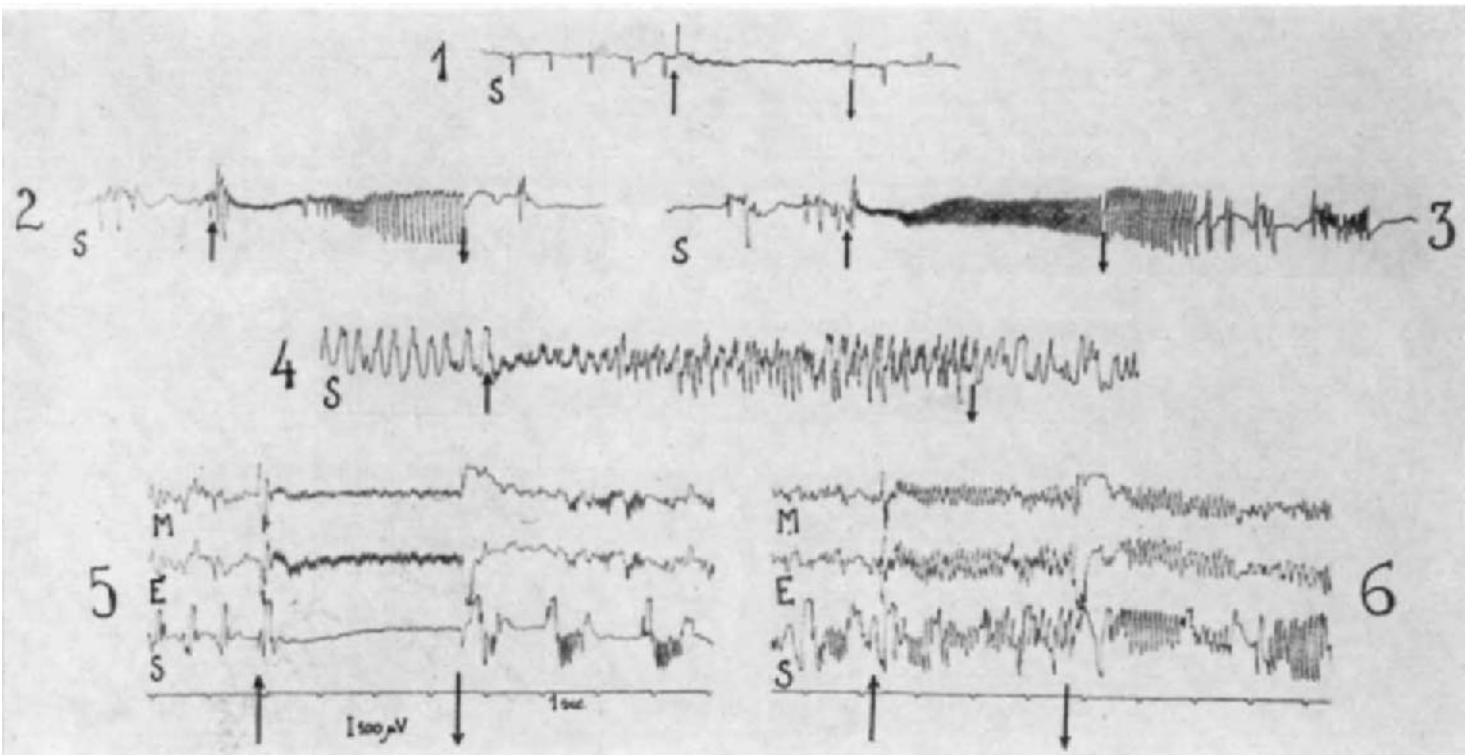


Fig. 68. For legend see p. 147.

voltage applied to the cerebral cortex was transformed into a supraliminal stimulus if preceded by a stimulation of the reticular formation or midline nuclei (Fig. 70).

The increase in focal cortical *hypersynchrony*, an expression of reticular and thalamic facilitation, occurs within the frame of a diffuse desynchronization in the form of arousal reaction, characteristic of fast repetitive stimulation of activating systems.

Reticular or midline facilitation is diffusely exerted, at cerebral cortex level, on anterior after-discharges (gyrus sigmoideus) as well as on posterior ones (gyrus marginalis), with no topographic differentiation.

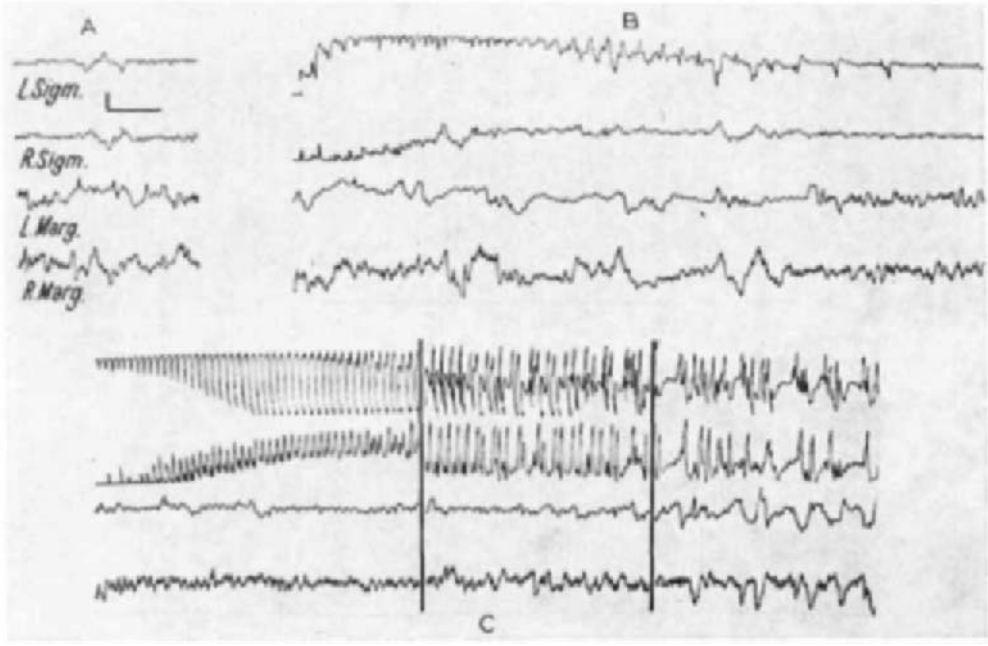


Fig. 69. Facilitatory effect of reticular stimulation on neocortical after-discharge. A = background activity; B = after-discharge induced by stimulating the left sigmoid gyrus; C = marked increase in sigmoidal after-discharges associating the neocortical stimulation to a fast-repetitive reticular stimulation (vertical bars indicate a lapse of 5 sec). (From Kreindler and Steriade, 1961.)

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Fig. 68. Effect of stimulation of diffuse thalamic system on penicillin cortical spikes. 1 = small amplitude spikes stopped by the stimulation (0.32 mA) of the left centromedian nucleus. 2 = the same animal in a later phase, the spikes reaching greater amplitude are facilitated during the stimulation with the same intensity (0.35 mA) of the same thalamic point. 3 = the same animal. A more intense stimulation (0.5 mA) of the centromedian nucleus determines the facilitation with an important post-effect. 4 = the same animal. The generalized cortical seizure (the graph reproduces only the lead from g. sigmoideus) is modified showing an increase in the frequency and a growth in the amplitude of waves during the stimulation of the same thalamic nucleus (0.35 mA). 5 = another animal. Note the inhibition of penicillin spikes in g. sigmoideus during the stimulation of the left n. reuniens (0.3 mA) and the post-excitatory rebound formed of rapid waves, which includes both the area to which the penicillin crystal had initially been applied and remote cortical areas (g. marginalis and g. ectosylvius). 6 = the same animal as in 5. When in a more advanced phase the penicillin spikes come to assume the aspect of a well-organized focal crisis, the stimulation with the same intensity (0.3 mA) of n. reuniens determines a pronounced intensification of the seizure with a generalization in the leads of g. marginalis and g. ectosylvius. (From Steriade, 1960.)

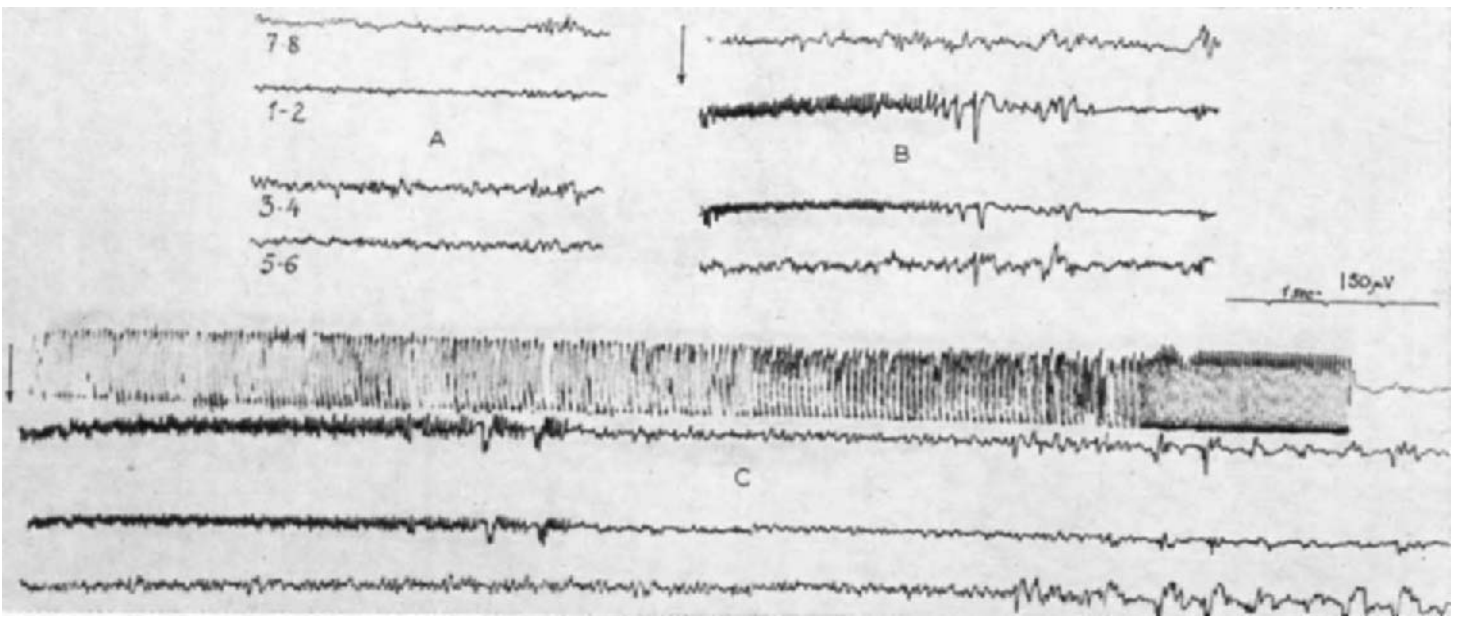


Fig. 70. Facilitatory effect of midline thalamic stimulation on neocortical after-discharge. A = background activity; B = after-discharge induced by stimulating the left sigmoid gyrus; C = autonomous after-discharge in the thalamic lead (7–8) and simultaneous facilitation of neocortical after-discharge by associating the neocortical stimulation to a fast repetitive stimulation of the left midline thalamic nuclei. 1–2, 3–4 and 5–6, same legend as for Fig. 69. 7–8 = points in the left midline thalamic nuclei. (From Kreindler and Steriade, 1961.)

No phenomena of cortical suppression could be observed such as occurred in our previous experiments on cerebello-cortical relationships (Kreindler and Steriade, 1960a).

The mescaline focus induced in the gyrus sygmoideus of the cat was enhanced by stimulation of the mesencephalic reticular formation. The spread of epileptical spikes to the contralateral ectosylvian gyrus as well as to the deep structures was facilitated by the stimulation of the mesencephalic reticular formation. The focal discharges were depressed by intravenous injection of chlorpromazine (Fig. 71).

Stimulation of the reticular formation modified the neocortical excitability to direct electrical stimulation, thereby facilitating the transition from normal to convulsive activity (Kreindler *et al.*, 1964 unpublished data, Crighel, Kreindler *et al.*, 1963). The direct cortical response (DCR) either to single liminal or supraliminal shock did not change or showed an irregular alteration during reticular formation stimulation. A constant effect consisted of the disappearance of the late positive potential (Fig. 72). DCRs evoked by rhythmic stimuli were markedly altered and, at formerly inefficient stimulation parameters, after-discharges were sometimes observed during the concomitant stimulation of the mesencephalic reticular formation. In fact, the positive primary phase, elicited under such circumstances, was greatly amplified and a late biphasic positive–negative wave developed. The latency of this second wave increased gradually from 20 to 60–80 msec. Sometimes cortical stimulation continued simultaneously with the reticular one, and DCRs resumed their initial patterns. In some of these experiments the resuming of the initial aspect of the DCRs was preceded by a period of disorganization of the DCRs. In some other instances, an after-discharge appeared. The same alterations also affected the transcallosal potential (Fig. 73).

In contrast to diffuse facilitation obtained by stimulating the reticular formation and the midline thalamic nuclei, stimulation of the ventral anterior thalamic nucleus (VA) exerts characteristic topographically localized effects on cortical after-discharge according to the ventrally or dorsally stimulated area of this nucleus (Kreindler, Steriade *et al.*, 1960a). Facilitation of after-discharge in the sigmoid gyrus is obtained by stimulating the ventro-medial area of VA, while facilitation of after-discharge in the gyrus marginalis occurs when stimulating the dorso-lateral area of the same nucleus. Such localized effects can only be obtained at liminal voltages, and they appear more regularly in the 'cerveau isolé', than in the 'encéphale isolé' preparation (Fig. 74).

In the framework of the baso-lateral amygdala of the cat, Kreindler and Steriade (1964) found two mechanisms controlling the cortical electrogenesis. A high-rate stimulation of the dorsal amygdaloid structures (A.c.l., nucleus and dorsal areas of the A.a. and A.l. nuclei) resulted in a reticular-like desynchronizing reaction ('arousal' of the cortical rhythms), while stimulation of ventral amygdaloid structures (A.b.p. nucleus and ventral portions of A.a. and A.l. nuclei) with the same parameters resulted in a synchronization of neocortical activity ('sleep' patterns). Such reactions depended neither on desynchronizing nor on synchronizing structures of the lower brain stem, as they had been found to persist in the 'cerveau isolé' preparation.

Investigating the dorsal and ventral portions of the basolateral amygdaloid com-

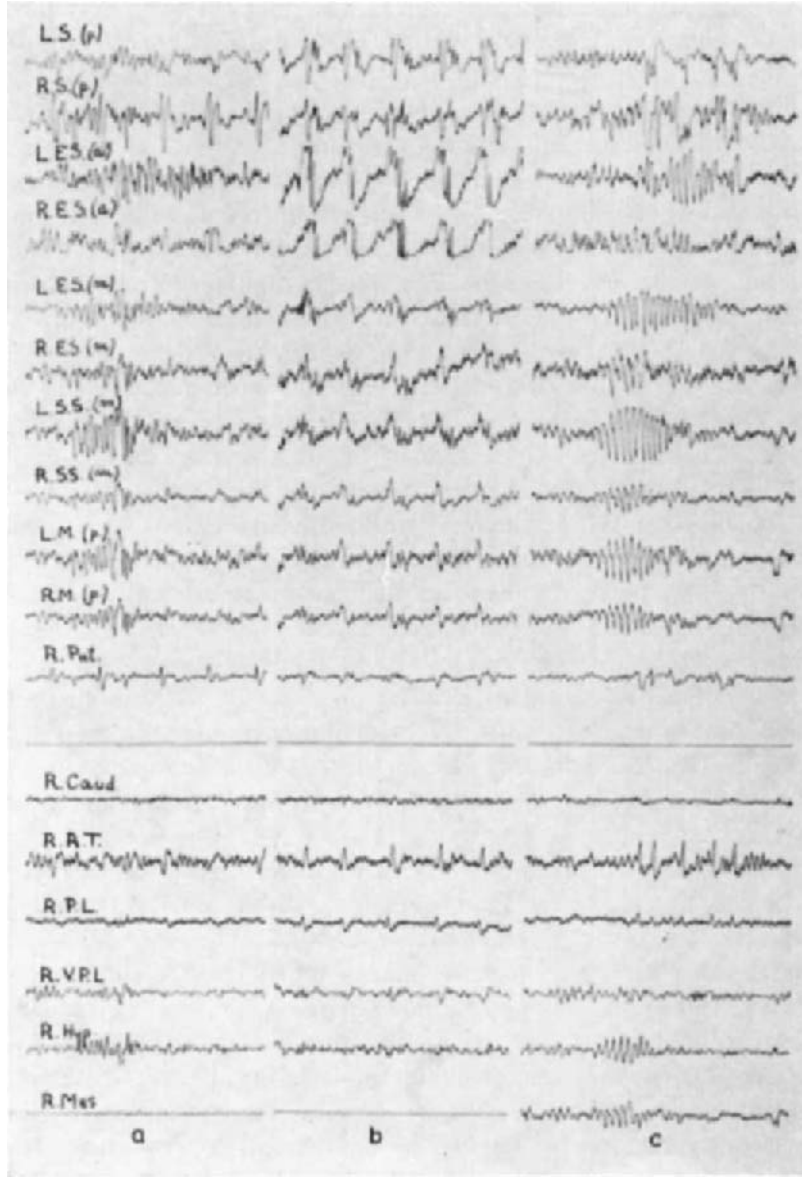


Fig. 71. The mescaline focus induced in the g. sigmoideus of the cat is enhanced by stimulation of the mesencephalic reticular formation. a = control; b = immediately after suppression of the stimulation of the reticular formation; c = soon after the cessation of the generalized seizure induced by stimulation of the reticular formation. (From Crighel and Stoica, 1961.)

plex in the same experiment, we found that the capacity to organize epileptic waves during (D) and after (AD) electrical stimulation differed at each level (Kreindler and Steriade, 1963b). No epileptic-type discharges occurred during the desynchronizing reaction to stimulation of the dorsal amygdaloid nuclei; we only noticed an AD after cessation of the epileptogenic electrical stimulation. In contrast with dorsal amygda-

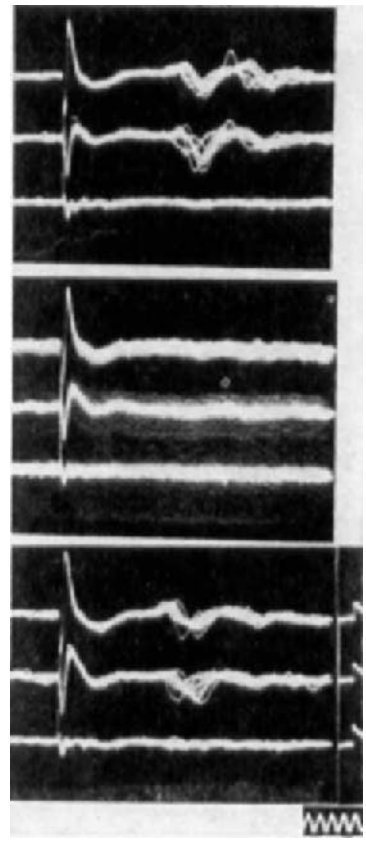

Fig. 72. Disappearance of the late positive potential of the direct cortical response during stimulation of the mesencephalic reticular formation. Top record = control; the late positive potential appears in both homolateral leads with a latency of 180 msec. Middle record = disappearance of the late potential during MRF stimulation. The direct cortical response is slightly enhanced. Bottom = re-appearance of the late potential 30 sec after cessation of MRF stimulation with a latency of only 160 msec. First trace is recorded 2 mm from the stimulating point; second trace, 5 mm and third trace, controlaterally. (From Kreindler and Steriade, 1964.)

loid nuclei, the A.p.b. nucleus, when stimulated with the dorsal amygdaloid nuclei, and the A.b.p. nucleus, when stimulated with the same parameters, caused the epileptic discharges to become organized from about the first second of stimulation.

The appearance of the AD only after cessation of the dorsal amygdaloid stimulation might be due to the suppression of the organizing epileptic discharges by stimulation. This suppressing effect can be explained by the fact that the stimulation evoking the epileptic paroxysm applies to a structure desynchronizing *per se* the epileptogenic effects and therefore inducing their self-arrest. On the other hand, the greater epileptogenic capacity of the A.b.p. nucleus compared with the A.c. l. nucleus (Steriade, 1963), and the possibility that the ventral amygdaloid areas can organize an epileptic paroxysm from the first second of electrical stimulation, are perhaps due to the synchronizing effects exerted by the stimulation of such areas on spontaneous cortical rhythms.

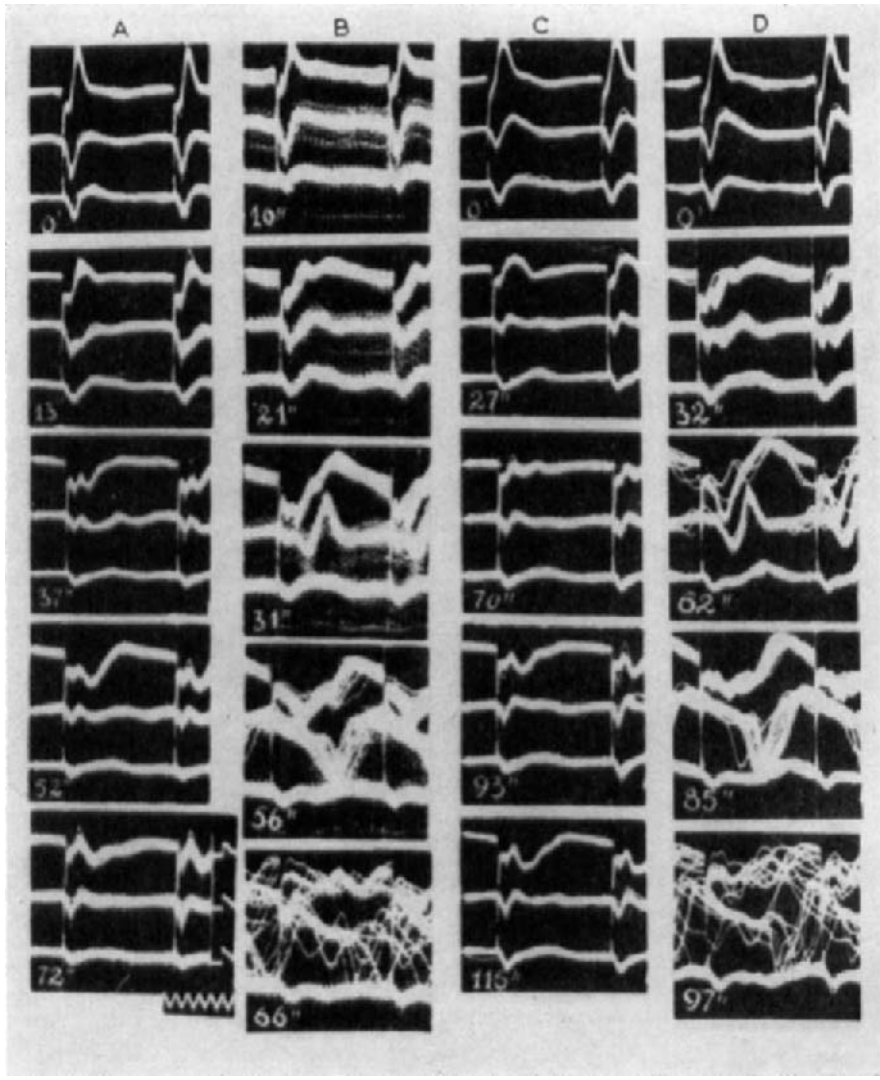


Fig. 73. Stimulation of the MRF during direct cortical stimulation. A = several superimpositions of evoked potentials at different time intervals (noted at each record) during a 10/sec continuous supraliminal stimulation of the g. suprasylvius; B = the same during concomitant stimulation of the MRF; C = control; D = long lasting alteration of the cortical excitability following repeated stimulation of the MRF; the alteration of the direct cortical response is the same during a concomitant MRF stimulation. Trace 1 = at a distance of 2 mm from the stimulated cortical point; trace 2 = at 5 mm from this point; trace 3 = contralateral to the stimulated point. Calibration 10 msec; 200 $\mu$V. (From Kreindler and Steriade, 1964.)

The course of an attack is influenced by subcortical lesions. Kreindler, Voiculescu *et al.* (1956a) observed in the cat with chronic thalamic lesions the appearance of spontaneous convulsant seizures following an electroconvulsive attack. These 'spontaneous' seizures showed certain peculiar characteristics in the animals with thalamic lesions. In a cat whose left centrum medianum was destroyed and with a small lesion

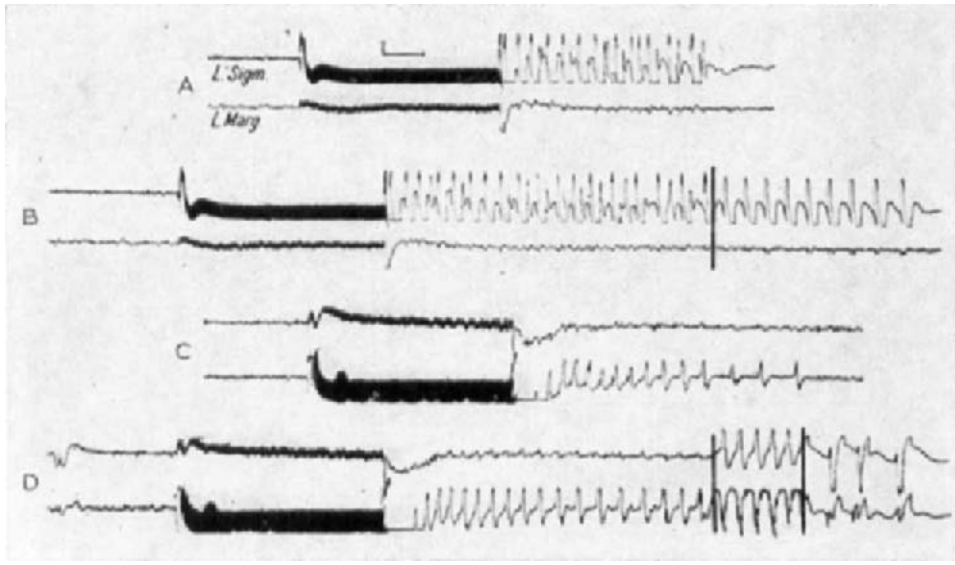


Fig. 74. Selective potentiation of neocortical after-discharge by stimulating various levels in the nucleus ventralis anterior (VA). A = test after-discharge by stimulating the left sigmoid gyrus; B = increase in sigmoid after-discharge associating the neocortical stimulation to a fast repetitive stimulation of the ventral area of VA nucleus. The stimulation of the dorsal area in the same nucleus has no effect on the test after-discharge from A. C = test after-discharge by stimulating the left marginal gyrus; D = marked increase in marginal after-discharge by associating the neocortical stimulation with a fast repetitive stimulation of the dorsal area of VA nucleus. The stimulation of the ventral area in the same nucleus has no effect on the test after-discharge from C. (From Kreindler, Steriade *et al.*, 1960a.)

in the neighbouring part of the posterior lateral nucleus, the attack began on the left with ample spikes having a frequency of 12/sec on the subcortical leads which were propagated only after 10–15 sec to the subcortical leads on the right. Progressively, large slow and irregular waves spread over the right subcortex then involved the left cortex and only much later (20 sec after the others) the right cortex, *i.e.* the side opposite to the lesion. Generalization therefore occurred earlier on the side of the thalamic lesion. The clinical seizure set in with some delay, namely 65 sec after involvement of the right cortex.

Kreindler and Steriade (1964, unpublished data) conducted experiments on unanaesthetized cats ('cerveau isolé' and 'encéphale isolé' preparations) in order to study the effects of amygdaloid lesions on the threshold of seizures induced by allocortical stimulation.

The lesion of the dorsal part of the basolateral amygdaloid complex (D. — 2.5 to D. — 3.5) induces the synchronization of the background neocortical activity. At the same time, the threshold of epileptic after-discharges obtained in the hippocampus by stimulating the ventral part (D. — 6 or D. — 7) of the amygdaloid complex is lowered (Fig. 75). This observation confirms previous results of the authors concerning the occlusive effect exerted on epileptogenesis by fast repetitive stimulation of the dorsal amygdaloid regions.

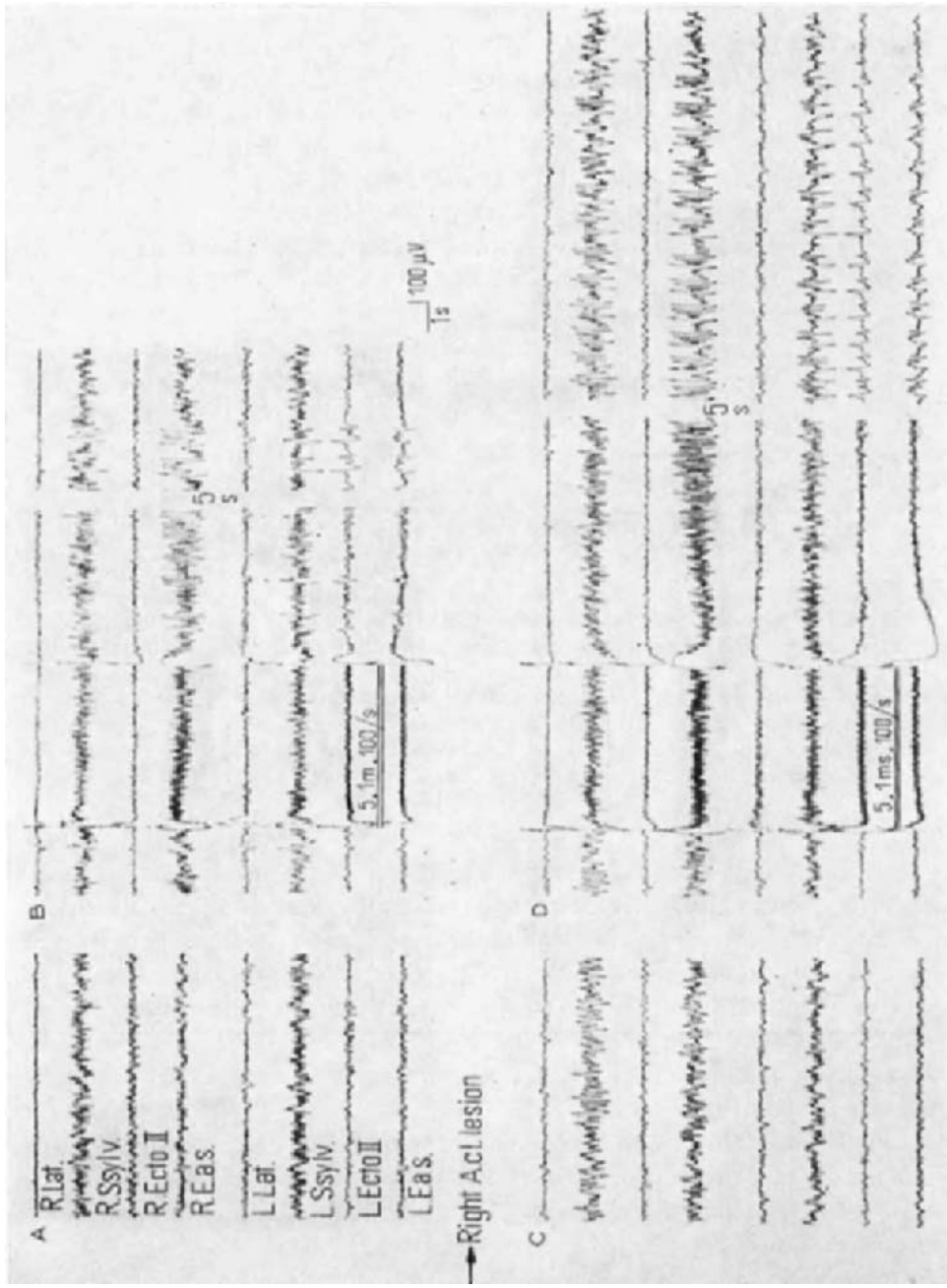


Fig. 75. Cat. 'Encéphale isolé'. Stimulation of the left nucleus amygdalae centro-lateral (A.c.l.). A and B = before the lesion of the right A.c.l. C and D after this lesion. A = before stimulation; B = after stimulation of the left nucleus A.c.l. during 5 sec, 1 msec duration 100/s. C = after the lesion of the right A.c.l. there is a hypersynchrony of the homolateral tracing; D = stimulation of the left nucleus A.c.l. after lesion of the right A.c.l. with the same parameters as in B induced an after-discharge of much longer duration. From above: g. lateralis right, g. suprasylvius right, g. ectosylvius II right, g. ectosylvius anterior superior right, g. lateralis left, g. suprasylvius left, g. ectosylvius II left, g. ectosylvius anterior superior left. (From Kreindler and Steriade, 1964 unpublished graph.)

Lesions of the rostral mesencephalic reticular formation reduce the capacity of the cerebral cortex to respond with a sustained hypersynchronous activity to electric shock. Such lesions do not appreciably modify metrazol convulsions, but reduce the intensity and duration of hypersynchronous activity determined by this substance. When the cortex is isolated from the mesencephalic reticular formation, it loses its capacity to respond with high voltage hypersynchrony, whatever the means employed to induce the seizures (Freedman and Ferris, 1956).

### *E. The post-paroxysmal electrical silence*

The electrical pattern of the convulsive seizure has a different termination depending on the peculiarities of the seizure trigger and development. The generalized seizure, however, is always followed by a period of electrical silence of several seconds duration.

According to Gastaut (1954) an epileptic centre shows two distinct tendencies, that is to increase the amplitude and decrease the frequency progressively. The decreasing frequencies are believed to express a process of fatigue partly due to the increasingly long duration of the refractory period of neurons brought about by the lessening of the energetic reserves, relative asphyxia and toxicity of the acid metabolites.

Voinescu *et al.* (1957) have investigated the way an electroconvulsive seizure ceases. Most frequently the arrest of the clinical seizure was preceded by that of the electrical seizure in the cerebral cortex with the exception of the gyrus splenialis where ammonian-type convulsive waves persisted as long as the clinical seizure. On the contrary, arrest of the electrical seizure before the clinical one was never seen in the mesencephalon, and only rarely in the thalamus. Persistency of convulsive waves after cessation of the clinical seizure was frequent in the thalamus and mesencephalon and rare in the mesencephalic reticular formation. The lateral ventral nucleus of the thalamus is characterized especially by this tendence of the electrical attack to persist for a long time. Moreover, it is in the ventral thalamic nuclei that the electrical activity reappears earlier than anywhere in the thalamus following the post critical electrically silent period.

After an electroconvulsive seizure the electrical activity progressively returns to normal; when the post paroxysmal electrical silence period is over the first to reappear are small waves which increase gradually. This return is somewhat late in the sigmoid cortex and earlier in the occipital and temporal cortex; this return is extremely precarious as it affects the gyrus splenialis, mesencephalon and thalamic ventral nuclei. As a rule, the dorsomedian nucleus displays such activity later. The midline thalamic nuclei, Ammon's horn and the dorsal lateral nucleus of the thalamus hold an intermediary position.

It appears that such differences as exist between the isocortex on the one hand, and the posterior splenial gyrus and Ammon's horn on the other, are due to the latter's display during the attack of a peculiar electrical activity (the 'comb rhythm', the 'Ammonian rhythm') which propagates into other structures during the seizure.

The end of the seizure is usually marked by a progressive decrease in the frequency of waves. Sometimes, however, the decrease is not progressive as, following an arrest of 1–2 sec, high voltage waves reappear usually synchronous with the clonic movements.

Electrical silence in the corticogram is accompanied by hyperpolarization of the neurons (Sawa *et al.*, 1963) which points to the existence of an active inhibitory process at cell level.

Jung and Tönnies (1950), studying cortical repetitive stimulation, relate the disappearance of the dendrites' superficial negative response at the onset of the seizure, to some pathogeneic significance in the sense that the negative superficial response would signify an inhibitory homeostatic process normally opposed to convulsive activity. This activity would appear upon extinction of this frenatory wave ('Bremswelle').

That the electrical silence is not due to a total exhaustion of all the neurons of the brain is also supported by the findings of Kreindler *et al.* (1961b) showing that responses in the gyrus marginalis can still be evoked during the postparoxysmal electrical silence by a repetitive photic stimulus. Hence, while the dendritic, superficial recordings show the exhaustion of some neurons, other neurons continue to respond to photic stimuli during the period of electrical silence. Exhaustion does not involve all the cortical neurons equally. It has been noticed in leads from deep structures that some post-ictal electrical silence occurs while there are still rapid wave discharges occurring for a few additional seconds in certain subcortical structures and particularly in the hippocampus and some thalamic nuclei.

By using a method for measuring the latency of the response to each stimulus from a burst of photic repetitive stimuli, Crighel and Neştianu (1957b) found during the first 20–30 sec after the cessation of the convulsive bioelectrical manifestations — and hence during the electrical silence period — only a decrease in mean latencies.

During the period of postparoxysmal motor inhibition which, from the viewpoint of electrical activity, is marked by electrical silence, the defence reflex to a nociceptive stimulus is much decreased in the rat in which a generalized convulsive seizure has been induced by repetitive focal stimulation of the motor cortex. Immediately after the end of the seizure the reflex is strong and polyphasic, and it only displays a smaller amplitude from the third second onwards after the end of the seizure (Kreindler and Zuckermann, 1957).

The characteristics of the inhibition period following the generalized convulsive seizure were studied in the rat in which a generalized cortical focal seizure was induced by repetitive stimulation of the motor cortex (Kreindler and Zuckermann, 1956). After the generalized convulsive fit the duration of the refractory period was established, *i.e.* the length of time during which it is not possible to induce another convulsive fit. At first the refractory period follows a seizure induced by a threshold stimulus, and later, seizures induced by stronger stimuli than this threshold. With the threshold stimulus the refractory period lasts 2 min on average. If we try again to induce a seizure by the threshold stimulus after this period, the attack is then much shorter than the initial one.

The restoration period of the convulsive circuits may be studied by applying the

threshold stimulus at varying intervals after the refractory period is over; the duration of the attack will be found to be longer and longer until, at an interval of about 5 min, the attack regains the duration of the initial seizure.

If, during the refractory period, we apply a repetitive stimulus whose intensity exceeds the threshold stimulus that triggered off the first attack, we shall find that at this more intense stimulus, another attack may be evoked even during the refractory period. However, during the first 10 sec following the development of a seizure to a liminal stimulus there is a period during which any repetitive stimulus, no matter how intense, is unable to trigger off another attack. We may thus distinguish an absolute refractory period from a relative refractory period.

In the same animal, the convulsive attacks are followed by a refractory period that is longer when there is an intensity in excess of the threshold intensity of the repetitive stimulus used for inducing the seizure. Animals with a long-lasting seizure at the threshold intensity display a short postconvulsive refractory period and *vice versa*.

An interesting fact is that the direct motor response, *i.e.* the motor response of some muscle groups to the focal stimulation of the motor cortex, has a much shorter refractory period than that of the convulsive fit: what happens is that despite the impossibility of triggering off a new convulsive seizure during the latter period, it is possible to elicit the motor response of a muscle group to cortical stimulation. Hence it may be inferred that the neuronal chains participating in producing the direct motor response are other than those involved in the convulsive fit, and that this is determined by a reverberation in longer neuronal chains which is also the cause of its longer refractory period.

The re-establishing of the cerebral functions after an epileptic seizure comes about gradually in three different steps, *i.e.* at three different functional levels. First of all, certain elementary synaptic processes are re-established; this is manifested by the resumption of normal values of latencies of responses to repetitive photic stimulation. In fact, Crighel *et al.* (1959) showed that the latency of the response to each stimulus of a repetitive train of photic stimuli undergoes large variations in the normal unanaesthetized cat. After an epileptic seizure induced by electroshock these latency variations were very small. The latency curve resumes the initial pattern 8 min after the cessation of the seizure. This latency change to each stimulus of a repetitive photic stimulation following a convulsive seizure points to the occurrence of synaptic disturbances at the level of some cortical neuronal complexes.

In the second place, the peculiar wakefulness state of the cerebral cortex is again re-established after an epileptic attack. A return to normal reactivity to stimuli a short time later is also found in subcortical structures. This process develops in an undulating manner in the sense that at a given moment the state of wakefulness may already exist over the cortex but will be absent over some subcortical structures and *vice versa*, that is, at certain moments it may be absent in the cortex and present in some subcortical structures. Restoration of the state of wakefulness is effected by the ascendent reticular system that resumes its control over more rostral structures, and particularly over the cerebral cortex.

The last to return to normal are the orientating and the conditioned reflexes. The

re-establishing of all these elementary functions occurs in an oscillating manner, *i.e.* during the process of resumption of the normal state, there are moments when these functions having returned, again disappear and thus come and go several times during the post-ictal period.

After an electroconvulsive attack an important disturbance may be noticed in the alimentary and defence-conditioned reflexes; sometimes a stable conditioned reflex reappears only several hours after the electroconvulsive attack. The latency period of the conditioned reflex is increased after the seizure, and the disturbances of the differentiation process persist for a long while. During the process of restoration of the unconditioned and conditioned reflexivity, the vegetative component of the conditioned defence reflexes (for instance, the respiratory component) reappears earlier than the motor component; in a similar manner its differentiation is restored sooner. The unconditioned reflexes appear before the conditioned reflexes while the conditioned reflexes that are more thoroughly established reappear before those that are less. Optical conditioned reflexes reappear later than the acoustic ones. The process of inhibition does not subside simultaneously in each of several structure affected (Ungher *et al.*, 1952, 1954).

There are alternate periods of disappearance and transient restoration of the conditioned reflexes during the postparoxysmal period. Restoration of the equilibrium between the periods of excitation and of inhibition, comes about by successive passages through phasic states in which the reappearance of the excitation process displays, at first, long latency periods, and ends with the prevalence of the excitation process and disappearance of the elaborated differentiation (Kreindler, 1957). Immediately after a convulsive attack, the projection of the nonspecific system over the cerebral cortex is the first to be re-established, which results in the restoration of wakefulness accompanying the reappearance of unconditioned reflexes. The specific projection is re-established later concomitantly with the reappearance of the elementary reflexes of orientation. Much later the temporary connections are re-established which underlie conditioned reflexivity. This is shown by a much finer orientation, much better adapted to the environment (Kreindler, 1957).

The specific and the nonspecific afferent pathways are concomitantly involved in the conditioning process. The specific afferent pathways of the conditioned stimulus run directly to the cerebral cortex while the unspecific one, running through the reticular formation can do one of two things: on the one hand, the stimulus can go to the brain cortex where it maintains a state of wakefulness; or, on the other hand, it can go to the neighbouring vegetative structures where it determines the vegetative reactions accompanying any process of conditioning. Kreindler, Ungher *et al.* (1955) showed that after a convulsive attack, during the period in which consciousness and environmental orientation are regained, there is a dissociation between these two aspects of conditioned reflexivity in that the vegetative component of conditioning reappears before the motor component in the conditioned defence-reflex.

The reappearance of the arousal reaction after a convulsive attack furthermore has an undulant inconstant character, *i.e.* at certain moments it is quite marked, disappears or greatly diminishes in intensity for a few seconds, only to reappear again.

Kreindler, Voiculescu *et al.* (1959) investigated the manner in which the arousal reaction reappears following a nociceptive stimulus after an electroconvulsive seizure in the curarized cat. During the first 10 sec after the end of the attack the arousal is absent from both in the cortical leads and in the subcortical ones and is progressively re-established within the following 3–5 min; in the ecto- and suprasylvian centres it appears somewhat earlier than in the other. The arousal reaction is expressed either by desynchronization having either rapid waves with a low voltage or waves with a diminished voltage but no change in frequency, or by hypersynchrony consisting of a short burst of high voltage waves; the latter can also be manifested merely by a potential evoked at the time the stimulus is applied (Tables I and II).

TABLE I

NUMBER OF AROUSAL REACTIONS OBTAINED TO 100 STIMULATIONS APPLIED BEFORE AN ELECTROCONVULSIVE SEIZURE IN THE CAT AND AT DIFFERENT INTERVALS AFTER ITS DEATH. THE 'AROUSAL' WAS PRODUCED BY A BLAST OF AIR ON THE CORNEA

| *Before the seizure* | *After the seizure (sec)* | | | | |
|---|---|---|---|---|---|
| | *0–10* | *21–50* | *51–100* | *101–200* | *201–500* |
| 70 | 48 | 40 | 57 | 62 | 68 |

TABLE II

NUMBER OF AROUSAL REACTIONS TO 100 STIMULATIONS IN DIFFERENT REGIONS OF THE CORTEX

| *Region* | *Before the seizure* | *After the seizure (sec)* | | |
|---|---|---|---|---|
| | | *0–50* | *51–100* | *101–200* |
| Frontal | 80 | 35 | 63 | 52 |
| Temporal | 77 | 54 | 62 | 77 |
| Occipital | 52 | 36 | 54 | 56 |

As regards the subcortical structures, the arousal reaction is little visible over the anterior nuclei of the thalamus both before and after the convulsive attack, while the midline and hypothalamic nuclei have a much better reactivity. As a rule, however, alterations in the arousal reaction following an attack are very varied, resembling the variability of conscious disturbances after an attack in man. The arousal reaction in the shape of bursts of slow high-voltage waves resembles the type of hypersynchronous arousal described by Kellaway (1957) in the 1–3-year-old child.

Therefore it seems that at certain moments centres bringing desynchronization are those inducing a gradual increase in the amplitude of cortical discharges (Dempsey and Morrison, 1942) which are situated above the intra-laminar, midline nuclei and the anterior nuclei, while those exhibition states of excitation are than situated above the thalamic reticular formation (Starzl *et al.*, 1951).

# CHAPTER V

# ARREST OF THE EPILEPTIC ATTACK

The arrest of an epileptic attack is not only an exhaustion phenomenon but also the result of the coming into play of an active arresting mechanism. Jung (1949) asserted that the caudate nucleus intervenes as an inhibitory structure in the active arrest of the convulsive seizure, for towards the end of the attack regular slow waves may be collected from here and this coincides with the episode of relaxation of the clonic movements interposed between the fast rhythms recorded in the thalamus and the cortex. Gastaut and Hunter (1950a,b) and Starzl *et al.* (1953) have recorded the same slow waves in the intralaminar nuclei and the midline thalamic nuclei.

On the basis of microelectrode studies on afferent cortical areas, Jung (1957) believes it is possible to distinguish three anti-convulsive braking mechanisms of neurons which prevent the development of the convulsive activity in the normal brain: (1) the stabilizing activity of the A-neurons which are not influenced by afferent stimuli; (2) the balance of excitation and inhibition in the activity of the neurons influenced by afferent stimuli through simultaneous and mutual stimulation and inhibition of some antagonistic neurons or through the pre- or poststimulatory inhibition of one and the same neuron; and (3) the inhibition or over-excitation characterized by diminution of the discharge-frequency of the neurons at high-rate afferent stimuli.

After an electrical stimulation different reactions may be observed for afferent stimuli at high or low rate. Single stimuli or stimuli below 8/sec regularly bring about inhibitory pauses with secondary activation but do not provoke epileptic discharges of the neuron. Stimuli at 10–100/sec render it possible for the neurons to discharge also during the inhibitory pause and are apt to elicit an epileptic discharge in any normal brain. Before the convulsive stage the microrhythms display a prolongation of the primary wave and the isolated neurons show repetitive discharges without prolonged inhibitory breaks.

The administration of strychnine prolongs the primary wave intensifying the secondary waves while the isolated cell shows the transition from a single discharge or a coupling of two discharges, to repetitive discharges. The single electrical stimulus brings about a short-lasting facilitation and a more prolonged inhibition whereas the inhibitory mechanism becomes exhausted at repetitive stimuli and is paralysed by strychnine.

According to Gastaut (1958b) several factors are concerned in the arrest of the epileptic seizure, two of which have prime importance: in the first place there is a progressive fatigue and final exhaustion of the neurons due to some metabolic factors

that bring about a gradual slowing down of the discharges; and secondly, there is an active inhibitory mechanism in which a thalamo-caudate system plays an important role. The slow waves generated by the latter system exert an inhibitory action. The clonic phase is attributed to this mechanism, which is why only the convulsions involving the telencephalon and the diencephalon have a clonic phase.

Gastaut *et al.* (1956) believe a thalamo-caudate inhibitory system exists in the unspecific thalamo-cortical projection system which not only actively inhibits the reticular formation of the thalamus as well as the caudate reticular formation of the brain stem, but at the same time prevents the discharge of cortical spikes as well as peripheral contractions. The existence of connections between the head of the caudate nucleus and the unspecific structures of the thalamus was demonstrated by Shimamoto and Verzeano (1954). The thalamo-cortical discharge of the major convulsive attack, which is responsible both for the cortical spikes and for reticular de-inhibition (with its consequent tonic phase) is at the same time responsible for the coming into play of the inhibitory system, *i.e.* the slow waves which rhythmically interrupt the discharge of spikes. The slow wave is not a convulsive wave but represents a genuine state of neuronal depression connected with a phenomenon of active inhibition.

According to Gastaut and Fischer-Williams (1959) petit mal seizures are accounted for by the existence of a particularly efficient inhibitory system in which each spike immediately puts into action the inhibitory system as manifested by the appearance of slow waves. The discharge is inhibited immediately after its appearance. The end of each slow inhibitory wave permits the renewed appearance of a thalamic discharge which furnishes an explanation for the rhythmicity of the repetition.

Jasper (1955) considers that it is only the nervous tissue actively participating in the epileptic process that is exhausted, and suggests a period of 'neuronal exhaustion', a characteristic consequence of the discharge of the primary focus. Hence, after its epileptic discharge, Jasper believes, there arises a process of exhaustion at the site of the focus. The focus relays its discharge and its consequent exhaustion only to those areas with which it is connected through 'concentrated neuronal pathways', *i.e.* structures by which are understood dense bundles of fibres, such as for instance the uncinate mamillo-thalamic fascicle, optic radiations, etc.

Kreindler (1955) distinguishes two kinds of active mechanism for arresting the convulsive attack, *i.e.* extracerebral and cerebral ones.

The extracerebral mechanisms of arrest of the convulsive seizures are manifold. Kreindler, Ungher *et al.* (1955; 1963) have investigated three different aspects of these mechanisms:

*(1) The latency of the nociceptive spinal reflex* in the cat increases considerably after a convulsive attack, *i.e.* from its normal value of 13 msec to 26-27 msec (Kreindler, Ungher *et al.*, 1955). Sometimes the latency of the spinal nociceptive reflex decreases for a little while after a convulsive attack, after which it increases and passes into a state of absolute refractoriness for one or several minutes. In this event it is unlikely that we have to deal with a postparoxysmal inhibition process, for a very intense tetanization of the same group of muscles involved in the spinal reflex whose length exceeds that of the convulsive attack, does not cause the latency of the nociceptive

spinal reflex to increase. The increased latency of the nociceptive spinal reflex which arises immediately after a generalized convulsive seizure is probably the consequence of the alteration of some dynamic processes at the level of the central nervous system; in this way it is proved that there exists a peripheral ring of the mechanism arresting the attack. The very state of strong excitation during a convulsive attack creates a peripheral barrier by itself, by means of an active physiological phenomenon.

It has recently been demonstrated that at the end of an attack and during the electrical silence period in the cerebral cortex, the monosynaptic reflex at the lumbar level of the spinal cord is deeply depressed (quoted from Fernandez-Guardiola *et al.*, 1962) while in the meantime the structures of the mesencephalic reticular formation in the neighbourhood of the red nucleus present high-frequency discharges.

*(2) The role of certain interoceptive stimuli.* During a convulsive attack a violent discharge takes place both at the level of the central nervous system and at its periphery, as well as a veritable viscerovegetative storm which discharges violently along the organovegetative system. Spread of the excitation to the entire vegetative system brings about a state of strong excitation of the interoceptors and of all vegetative afferent pathways, this causing the strong excitation of the organovegetative system to be relayed to the cerebral cortex, *i.e.* to the cortical projection extremity of this system. An intense stimulation of the interoceptors causes an alteration in cortical excitability, such as for instance the intense stimulation of the carotid sinus in the dog, which causes a marked change in cortical electrical activity; in all likelihood this effect is mediated by the reticular formation of the brain stem, as is proved by the diffuse character of this alteration (Kreindler, 1946). On the other hand, the excitability of the cortical centres in relation to the autonomic system following a convulsive attack is restored before the ecxitability of the cortical centres related to the somatomotor system (Kreindler, Voiculescu *et al.*, 1955b). Thus, the excitability of the cortical centre of pupillo-dilatation after a convulsive attack returns to normal after an average time of 150 sec whereas the excitability of the motor area only returns to its normal value after 207 sec.

The projection of interoceptors at the level of the subcortical centres and of the cerebral cortex probably triggers neuronal mechanisms which play a part in arresting the epileptic seizure.

Exteroceptive stimuli, some of which, being of a rather peculiar nature, may also play a role in arresting an epileptic seizure. Thus, Efron (1957) described a case in which the uncinate seizures were extinguished by strong and unpleasant olfactory stimuli. In the same patient the attacks could also be arrested by conditioning stimuli; by associating inhibitory olfactory stimuli with an unconditioned optic stimulus, after a certain number of associations, the optic stimulus acquired inhibitory properties and could by itself arrest the seizure. The attack could be stopped not only by the optic stimulus, but also by those central neural processes induced in the mental representation of these stimuli.

*(3) Biochemical alterations* associated with the convulsive seizure may also play a role in its active arrest. (See the following chapter.)

It has been asserted that the anoxia reduces the seizure development, likewise plays

a role in its arrest. Thus, Gellhorn and Yesinick (1941) showed that anoxia exerts a depressant action on the convulsive phenomena, and Ruf (1951) showed that the administration of oxygen prolongs the duration of the convulsive attack. Voiculescu and Broşteanu (1960) studied the effect of asphyxia on the electroconvulsive attack in the curarized cat by temporarily arresting artificial respiration. Asphyxia shortens the duration of the electroconvulsive seizure and diminishes the amplitude of the wave discharges; moreover the shape of the waves changes, in that instead of high voltage waves lasting an average 100 msec they become spikes.

A fact against determining an exact role of anoxia in arresting an attack is that the attack ceases while artificial respiration is being continued in the animal. The manner in which artificial respiration overcomes hypoxia still remains in doubt, however. Jasper and Erickson (1941) and Davies *et al.* (1944) have shown that local cortical hypoxia may occur after a convulsive attack regardless of any disturbance in pulmonary respiration.

The cerebral arresting mechanisms of an epileptic seizure are connected with the existence of some suppressing neuronal chains and circuits which become activated by an epileptic discharge and lead to its cessation. An important role in activating such cerebral depressor circuits is probably carried out by the migration phenomenon of epileptic activity (see page 132), *i.e.* the successive passing of epileptic discharges, during the development of the attack, from one brain structure to another. During this migration epileptic activity comes to involve intracerebral depressor circuits as well.

The existence of circuits abolishing convulsive activity in the strychninized spinal cord has been demonstrated by Terzuolo (1954), who showed that it is possible to inhibit completely the strychnine tetanus of the curarized cat by electrical stimulation of the bulbar inhibitory centre or of the inhibitory area of the anterior lobe of the cerebellum. These inhibitory supraspinal systems exert a moderating tonic action on the spinal cord in typical strychnine epilepsy. The spinal tetanic rhythm is at any moment slowed down by the inhibitory action of the supraspinal mechanism.

Branch and Martin (1958) assert that the arrest of the epileptic seizure by electrical stimulation is due to the fact that this stimulation brings into action the inhibitory intercalary neurons of the cortex.

An argument in favour of the intervention of an active abolishing mechanism of the attack is that it ends suddenly and simultaneously over the cortex and in a great many subcortical leads. Only in the hippocampus and in some thalamic nuclei does it still persist for a couple of seconds after the sudden termination in the other structures. If we had to deal merely with an exhaustion process it would be difficult to accept the concurrent exhaustion of neurons with such different functional values. The experiments of Voiculescu and Broşteanu (1960) show that the cortical cells, being more sensitive to anoxia, are those in which the convulsive activity becomes first extinguished during asphyxia. The different sensitivity to anoxia of the newer levels is well known, particularly from the investigations of Ward (1947b), in which he used animals poisoned with sodium cyanide. An actual difference exists between the various structures in their resistance to a type of exhaustion other than that due

to the convulsive attack. It is therefore likely that the sudden and simultaneous cessation of the electric attack over a great many structures is not only the result of an exhaustion phenomenon.

The epileptic attack progresses by continuously recruiting new reverberating circuits. Its arrest probably occurs when the epileptic discharge tends to migrate from one structure to another, at a given moment penetrating a circuit having desynchronizing properties and hence extinguishing the attack. An important process in arresting an epileptic attack seems to occur in certain thalamic and cerebellar abolishing circuits in the thalamus and cerebellum.

Kreindler, Voiculescu *et al.* (1956a) showed that a lesion in an area located in the posterior part of the median thalamus in the cat, comprising the nucleus centrum medianum and the neighbouring areas of the posterior lateral nucleus, greatly prolongs the duration of an electroconvulsive attack (from an average of 25–40 sec to 290–400 sec). Lesions in other nuclei, even if they are bilateral, do not entail such a prolongation of the attack (Table III).

TABLE III

DURATION OF ATTACKS ACCORDING TO THE SITE OF THALAMIC LESION

| | *Lesion* | *Duration of attack in sec* | *Type of seizure* |
|---|---|---|---|
| Cat 442 | The whole n. posterior lateralis, almost all the centrum medianum and the n. parafascicularis | 1st attack 400<br>2nd ,, 200<br>3rd ,, 200 | Tonicoclonic |
| Cat 434 | Wholly destroyed centrum medianum, n. posterior lateralis, n. centralis lateralis, n. parafascicularis | 1st attack 115<br>2nd ,, 150<br>3rd ,, 70 | Tonicoclonic |
| Cat 304 | Wholly destroyed centrum medianum, n. centralis medialis, n. parafascicularis, n. anterior dorsalis, n. dorso-medialis | 320 | Tonicoclonic |
| Cat 16 | N. posterior lateralis ventralis (anterior part), n. ventralis partially destroyed, n. reticularis (partially) | 25 | Tonicoclonic |

The tonic seizures occur three times more often in animals with hypothalamic lesions than in those with an intact hypothalamus. Hence, in animals with thalamic injuries the average duration of an attack is four times as long. The duration of the purely clonic attacks in animals with hypothalamic lesions and in normal animals, are of virtually equal duration whereas in animals with thalamic damage the attack is generally somewhat longer.

An argument in support of the assumption that some thalamic structures play a part in the arrest mechanism of the epileptic seizure is adduced by Kreindler, Voiculescu *et al.* (1956a); in cats with chronic thalamic lesions in the area of the nucleus centrum medianum they observed spontaneous convulsive attacks often following an electroconvulsive seizure. Thus, in an animal (cat 304) with total lesion of

the n. anterior dorsalis, dorso-medialis, centrum medianum, centralis medialis, parafascicularis and also with lesions in the n. ventralis lateralis and ventralis posterior — all located in the left thalamus — a series of subintrant spontaneous convulsive seizures lasting 4 h occurred within 15 min after an electroconvulsive seizure induced 2 months after the operation; these attacks subsided only after general ether narcosis.

Several minutes after the cessation of the electroconvulsive seizure large waves are seen which tend to become generalized within a few minutes and finally develop into a generalized clinical seizure. In some animals, the first high-voltage waves occur in the deep leads, in others in the cortex. At first, the waves have a high frequency and display a spike-like pattern. Hence, in these spontaneous seizures the electric attacks in general precede the onset of the clinical attack by several minutes. Such spontaneous seizures after an electroconvulsive attack have never been noticed in a normal animal without thalamic lesions.

The electrical pattern of the seizure in the animal with thalamic seizures differs from that of the normal animal in that the portions of asynchronism between the epileptic waves in the various structures are much larger. Thus, whereas 55% of the tonicoclonic seizures in normal animals show short periods of asynchronia, in animals with thalamic lesions 87% of them have long periods of asynchronia which appear either between the cortical and subcortical leads or between the interhemispheral leads.

Lesions of some thalamic nuclei may therefore facilitate the appearance of the epileptic attack. Conversely, under certain experimental conditions, stimulation of the medial centre of the thalamus may inhibit the cortical after-discharge at the level of the sigmoid gyrus (Suter *et al.*, 1958).

Stimulation of the cerebellum may depress or, under certain experimental conditions, abolish a focal after-discharge (Kreindler and Steriade, 1960) (see page 141).

From these investigations it may be seen that some neuronal chains of the brain are capable of abolishing the epileptic paroxysmal character of a stimulus, such as for instance hypersynchronous focal after-discharges. These neuronal chains are to be found both in the cerebellar system and in the thalamus, and are endowed with peculiar qualities which differentiate them from the facilitating neuronal chains. Activation of the chains to abolish a paroxysm probably takes place during the development of an epileptic attack when, owing to the migration phenomenon of the electrical activity focus, they begin to function and take part in the active arresting mechanism of the epileptic attack.

On the basis of his observations on 'inhibitory attacks' Jasper (1955) believes there are specific cortical areas which, following activation by an epileptic process, may bring about a decrease in the electrical discharge in their immediate neighbourhood, and decrease the electrical activity of large cortical areas in both hemispheres. Green and Shimamoto (1953) on studying both the hippocampal attack and its spread, and on trying to find an explanation for the mechanism of convulsions solely on the basis of certain feedback circuits of microscopical size, maintain that the sudden and simultaneous standstill of epileptic activity is due to an abolishing area, possibly a diencephalic one, since after diencephalic lesions the arrest of the attacks comes about gradually and not suddenly.

Fernandez-Guardiola *et al.* (1962) reached the same conclusions, namely that there was an ever greater likelihood that the end of an epileptic after-discharge is due not solely to exhaustion but to an active inhibition process with a subcortical localization which acts on the brain cortex and produces the repolarization of the cells involved. This inhibitory mechanism was located by Jung (1957), as mentioned above, in the caudate nucleus, and by Gastaut and Fischer-Williams (1959) in the thalamo-caudate system. Other structures may be involved too, such as the reticular formation. Thus, units of this formation situated next to the red nucleus display high-frequency discharges during the period of cortical electric silence. The discharge of cerebellar units towards the end of the clonic phase during the period of depression of electrical activity of the brain is analogous with the discharges of the reticular formation.

The conclusion reached by Fernandez-Guardiola *et al.* (1962) is that it is logical to correlate the increased electrical activity of the cerebellum observed during their experiments, with the striking inhibitory process which is noticed towards the end of the seizure. The cerebellum may therefore play an important part in preventing and terminating cerebral attacks. It is not excluded that this effect may be exerted through the intermediary of some other subcortical structures which may also play a similar role.

An inhibitory motor phenomenon may occur under certain experimental conditions of electrical stimulation of the brain cortex. Thus Kreindler and Zuckermann (1956) observed that stimulation of the motor cortex of the rat by means of a repetitive weak stimulus (50/sec) abolishes during the time of stimulation any spontaneous movements in the animal. The phenomenon is determined by the amount of stimulation regardless of the stimulated areas. The process involves the entire motor area since the spontaneous movements of all limbs are concurrently abolished.

Another phenomenon observed by Kreindler and Zuckermann (1956) during their experiments of repetitive stimulation of the motor cortex in the rat, is that of *intrastimulatory accommodation* of the motor effect, *i.e.* the movements of the limbs appear immediately after the stimulus is applied, but after it has persisted for some 2–3 sec they disappear and the animal remains motionless although stimulation continues.

Both results quoted above show that a cortical stimulus may set certain abolition mechanisms in motion, the effect being an abolition of the peripheral motor phenomena. The existence of abolition phenomena following repetitive stimuli is therefore revealed not only in electrical phenomena but also in motor phenomena. On the other hand, we consider it of interest to relate this phenomenon of intrastimulatory accommodation of the motor effect to the phenomenon of intrastimulatory electrical discharge as observed in the repetitive stimulation of some amygdalo-hippocampal structures (Kreindler and Steriade, 1963b).

Kreindler and Zuckermann (1956) showed that a convulsive attack, brought about in the rat by repetitive stimulation of the motor area with a threshold intensity, exhibits a refractory period during which it is impossible to bring about a second convulsive attack. There is an inverse relation between the duration of the refractory period and the attack itself, whereby the shorter the period, the longer the attack and *vice versa*. Post-convulsive refractoriness is not the manifestation of a state of neuronal

exhaustion for if this were so the relationship would be reversed, *i.e.* the longer the attack the longer the refractory period. In all likelihood the post-ictal refractoriness is due to the development of an inhibition process: the stronger the latter as compared with the stimulation, the shorter the period of convulsive manifestations and the longer the refractory period.

The postcritical refractoriness to repetitive stimuli of the motor cortex may be attributed to a phenomenon of parabiotic inhibition. If a repetitive focal threshold stimulation is produced during the post-ictal refractory period, the attack will not appear but this stimulation will result in the prolongation of the refractory period. Hence, it is not a question of the non-excitability of some neuronal chains but of the fact that stimulation causes another effect, *i.e.* it prolongs an inhibition state instead of producing an excitation phenomenon. It is well known that a stimulus applied to the focus of parabiotic inhibition intensifies this inhibition. Zurabashvili (1952) too attributes a certain role to parabiotic inhibition in the development of the electro-convulsive seizure.

If the duration of the repetitive stimulation of the motor cortex is extended beyond its optimal duration in order to trigger a generalized motor attack in the rat, the inhibition state is intensified, which shortens the duration of the self-sustained convulsions and lengthens the period of postparoxysmal inhibition.

The arrest of the bulbo-pontine subcortical attack does not take place in the same way as the cortical attack; instead of the sudden cortical cessation occurring concomitantly in all the limbs of the rat in which a generalized convulsive seizure had been evoked by focal repetitive stimulation of the motor area, the bulbopontine attack produced by repetitive stimulation at this level ceases first in the posterior limbs. Fine and rapid clonic movements sometimes persist in a single limb after the convulsions have ceased in the other limbs (Kreindler and Zuckermann, 1956).

CHAPTER VI

# BIOCHEMICAL ASPECTS OF THE SEIZURE IN CONVULSIVE DISORDER

Although there is still a lack of certainty about the chemical events underlying the convulsive reactivity of the brain or the various forms of manifestation of the seizure, the existing data may serve as a starting point for further investigations.

In the following pages we shall review some biochemical aspects of the seizure related to its trigger, development and arrest as well as to some features of convulsive reactivity.

## *Interparoxysmal disturbances*

The knowledge of such biochemical processes in the central nervous system as occur during the interparoxysmal period in both experimental and chronic epilepsy as well as in epileptic disease, is of particular importance. What is the substratum of convulsive potentiality and what are the intrinsic conditions by which the convulsive manifestations are triggered?

A number of investigations *in vivo* and *in vitro* have been carried out to seek answers to these questions.

Oxygen consumption in the brain *in vivo* during the interparoxysmal periods does not differ from the normal, either in experimental chronic epilepsy induced by aluminium hydroxide injection or in human epileptic foci (Schmidt *et al.*, 1945; Tower, 1960).

Studies *in vitro* carried out on tissue slices either from animals with epileptogenic foci induced by application of alumina cream or injections of methionine sulphoximine, or from patients who had suffered chronical epileptogenic foci and from whom these had been surgically excised, have shown no changes in oxygen consumption or glycolysis (McIlwain, 1955; Elliott, 1955). Thus, the oxidative metabolism of the cerebral cortex shows no 'chronic' or persistent disturbances demonstrable *in vitro*. The disturbances *in vivo* of oxidative metabolism brought about by convulsions appear to be limited to the paroxysmal period, and tend to disappear when the seizure is over.

Investigations carried out by Mison-Crighel *et al.* (1962) have detected interparoxysmal tissue oxidation disturbances. Thus, EEG and biochemical exploring of the cortical scar in the cat showed that electrographic elements of lesion and convulsion at the periphery of the scar were associated with a decrease both in cytochrome oxidase and succinic dehydrogenase activities.

Acetylcholine glutamate and electrolyte metabolism is greatly altered during the

interparoxysmal period. Thus, an increased cholinesterase activity and an incapacity to bind acetylcholine were found in the human epileptogenic temporal lobe cortex. The same metabolic defect was encountered in the cortices of monkey, dog and rabbit when convulsive seizures were induced by methionine sulphoximine or megimide (Tower, 1958b).

The acetylcholine binding defect may be corrected *in vitro* by the addition of glutamine and asparagine to samples collected from patients anaesthetized before the removal of the specimen. The values of the bound acetylcholine were found to be higher (Tower and Elliott, 1953), which suggests that it is not the speed of acetylcholine production that undergoes a change but merely the form in which it is produced, as free acetylcholine exists in excessive amounts in the epileptogenic tissue.

Slices of cerebral cortex from animals with thiosemicarbazide-induced convulsions (Tower, 1960) showed decreased glutamic and $\gamma$-aminobutyric acid, but normal glutamine values. It has been possible to correct the metabolic defects by adding pyridoxal phosphate or GABA. The same metabolic defects were found in cortical samples collected from cats with seizures induced by megimide (3-methyl-3-ethylglutarimide) or methionine sulphoximine. Partial or complete correction could be achieved by adding GABA and, in the case of methionine-sulphoximine-induced convulsions, by the addition *in vitro* of L-asparagine or L-methionine. Pyridoxal phosphate could not correct the metabolic defect in the specimens from the cat with methionine-sulphoximine-induced seizures.

In the cerebral scar at the periphery of which graphic elements with a convulsive pattern were found, the activity of glutamic oxaloacetic transaminase was found to be decreased (Mison-Crighel *et al.*, 1962).

While the formation of ammonia in the specimens and incubating medium was not found to differ, the electrolyte metabolism was altered, showing a tissue-potassium loss and replacement by an equivalent amount of sodium both in human samples and in brain tissue slices from cats with methionine-sulphoximine-induced convulsions. No anomalies in electrolytes were noticed with thiosemicarbazide-induced convulsions.

The acetylcholine binding defect, the glutamic acid loss and the deficiency of intracellular-potassium conservation could be corrected by the addition *in vitro* of L-asparagine, ATP or GABA. None of these metabolism-correcting substances had any effect whatever on glutamine synthesis; hence, the inhibition of glutamine synthesis is not considered to have a direct connection with epileptogenicity (Tower, 1960). Such anomalies, called 'chronic' because they persist after the excision, are regarded as the components of a biochemical lesion that might facilitate the convulsive mechanisms.

One fact can be established about the cell-membrane during a state of hypoxia in the cat. In contrary to the human, during this state addition *in vitro* of L-asparagine or ATP is able to overcome acetylcholine binding and the glutamic decrease, although it does not affect K incorporation. Therefore this indicates impairment in the cell membrane integrity during the reduction of the oxygen supply. Studies *in vivo* have yielded similar results. It has been demonstrated that administration of methionine

(Reiner *et al.*, 1950) and injection of L-asparagine and glutamine (Tower, 1960) prevents the convulsive attacks induced in mice through methionine sulphoximine and that previous treatment with GABA or asparagine arrests seizures induced by megimide, metrazol (Hawkins and Sarett, 1957), or by strychnine (McLennan, 1957).

Good results (checked by EEG) were likewise obtained in the clinic by oral administration of L-asparagine alone or associated with other drugs, or by administering GABA.

The occurrence, development and nature of the convulsive seizure greatly depend on the state of excitability during the preconvulsive period, and on the integrity of the biochemical and homeostatic mechanisms. It could be demonstrated that the duration of the seizures, the prevalence of one or another phase and the changes in brain metabolism that ensue after the electroshock differ according to the preconvulsive functional condition. In rats injected with large (20 and 40 mg) caffein doses producing a state of inhibition with a dominant tonic phase of the seizure, the duration and intensity of the seizure were increased, and the seizures sometimes became subintrant with a concomitant blood sugar increase and maintenance of the glycogen storage. The state of excitation produced in the brain by small (4 mg) caffein doses seems to limit the duration and intensity of the seizure, causing the cerebral glycogen to increase and the cerebral glucose to fall (Mison-Crighel *et al.*, 1959; Constantinescu, as yet unpublished).

The injection of the relaxant myocaine (glycerol ester of guaiacol) before an electroshock prevents the dysfunction of carbohydrate metabolism, restricts the splitting of phosphocreatine after cardiazol and picrotoxin, and after electroshock and amidopyrine it facilitates phosphocreatine synthesis (Mison-Crighel, 1957). Similarly, alkaline phosphatases no longer decrease after an electroshock if myocaine has previously been injected (Appel *et al.*, 1957).

The electroshock-induced convulsive seizure in the rabbit with hyperglycaemia produced by intravenous injection of glucose, has a prolonged duration and the activities of cytochrome oxidase and succinic dehydrogenase no longer undergo the alterations brought about by electroshock in normal animals (Lascăr, 1958).

Previous anaesthesia in animals prevents the onset of chemical alterations in the brain (Gershoff *et al.*, 1949; Elliott *et al.*, 1950; Mison-Crighel, 1957) and masks the alterations that could otherwise be revealed on the specimen removed from animals with epileptogenic foci induced by aluminium hydroxide (Elliott and Henderson, 1948).

### *Biochemical changes preceding the onset of convulsions*

Although the numerous experimental data that are available afford some indications as to certain biochemical processes preceding convulsions, no absolute evidence has so far been furnished about the mechanisms that are directly responsible for the trigger of convulsive activity.

The relation between the ammonia level and the degree of cerebral excitability was inferred by Richter and Dawson (1948) and Benitez *et al.* (1954) from the fact

that the administration of ammonium salts induced convulsions in animals and that the ammonia level in the brain tissue increases rapidly during the preconvulsive and the convulsive phases of the electroshock- or picrotoxin-induced seizure. These authors, as well as Sapirstein (1943), consider ammonia to be capable of inducing convulsions. Moreover, Torda (1953) believes that ammonia is increased as a consequence of cerebral hyperactivity which precedes detectable convulsions. These data however have not yet been correlated with EEG data. Other investigators (Takahashi *et al.*, 1961) demonstrate that the rat brain ammonia level and the cerebral excitability changes are not correlated, and that the ammonia increase does not precipitate the convulsive activity but is the metabolic consequence of the functional excitation of the nervous tissue. Besides, ammonia is a normal metabolite of cellular transaminations that are particularly active in the brain (Meister, 1954), and represents a normal constituent of active neurons (Torda, 1953). Ammonia might be metabolized into an abnormal 'convulsant' product, guanidinobutyric acid (Waelsch, cited by Tower, 1960): this assumption, however, needs further investigation.

Another mechanism which appears to participate in the trigger of convulsions is that of the splitting and synthesis of acetylcholine (ACh).

ACh as present in the brain *in vivo* is to be found in the insoluble bound form, and its concentration depends on the speed of its synthesis and the liberation of free ACh. The convulsive activity is associated with an accelerated release so that ACh decreases. Re-synthesis is very fast when the content decreases. Richter and Crossland (1949) noticed that within a few tenths of a second after the application of the electrical stimulus, the level of acetylcholine, particularly of bound acetylcholine in the rat brain, dropped rapidly. Only when the brain recovered its initial ACh level did the convulsions induced by the electrical current begin. Possibly, an appreciable amount of ACh is necessary not only for cerebral activity but for convulsive activity as well (McIlwain, 1955). The convulsions come to a standstill when the ACh content falls to 40% of the normal value.

Similar results were obtained in metrazol (Crossland, 1953) or picrotoxin (Stone *et al.*, 1945) convulsions, but the fall of ACh was not noticed before the onset of convulsions. Takahashi *et al.* (1961) reached the conclusion that, apart from other factors, an increased ACh level is necessary for the trigger of convulsive activity. The metabolism of electrolytes is closely related to ACh anomalies. Woodbury *et al.* (1958b) noticed an increase in intracellular $Na^+$ which appears to precede the convulsive activity induced by arresting the inhalation of $CO_2$ in anaesthetic doses. Changes in the acid–base balance suggest that pH, bicarbonate and carbonic acid concentrations may be closely related with the convulsive process. The changes in cation distribution that cause the membrane excitability to alter (partial depolarization) are believed to bring about repeated discharges. An increase in intracellular sodium is believed to decrease the membrane potential, and the membrane now responds to minimal or small stimuli which do not affect a normal membrane. In this way an explanation could be furnished for the hyperexcitability and repetitive activity characteristic of epileptic areas (Tower, 1960).

It may, of course, be argued that the data so far obtained do not afford evidence

as to the participation of the electrolytes in the interior of the neurons in relation to the non-neuronal electrolytes.

What should be borne in mind is the interrelation between the anomalies of ACh and the metabolism of electrolytes. The liberation of an increased quantity of ACh may contribute to ion alterations. ACh increases the permeability for $Na^+$ and $K^+$ at the postsynaptic membrane level, and this effect might be a cause of cation re-distribution. The cations, in turn, by decreasing the membrane potential difference and increasing the intracellular $Na^+$ close to a critical threshold level, make it possible for a quantity of ACh smaller than that normally liberated to generate an effective postsynaptic potential. The earlier responses of the epileptogenic areas are more a matter of degree than of difference in response. According to Shanes (1958) these mechanisms involve the cell membrane and therefore the permeability for cations.

Woodbury *et al.* (1958a) adduced arguments in favour of the hypothesis that the cation concentration change is a factor preceding the onset of convulsions. For instance, after adrenalectomy, cerebral excitability is noticed to increase, EEG waves to slow down and intracellular $Na^+$ concentration to increase; the administration of adrenocortical hormones brings about reverse phenomena.

There is believed to be an interrelation between cerebral amino acids and $Na^+$ alterations, namely the glutamic acid : glutamine ratio varies in direct proportion with the cerebral excitability and inversely with the extracellular $Na^+$ : intracellular $Na^+$. The GABA concentration is considered to vary according to cerebral excitability. This hypothesis it seems, is only upheld for methionine sulphoximine-induced convulsions, as in most convulsions the glutamic acid decreases. When convulsions are due to ammonia toxicity, the glutamic acid : glutamine ratio decreases by an increase in glutamine, *i.e.* in a direction contrary to this hypothesis. According to Tower (1960) glutamine is not directly concerned in the mechanism of convulsions. Although the exact interrelation between amino acids of the glutamate group and electrolytes has so far not been clearly established, numerous data point to its existence (Terner *et al.*, 1950; Woodbury, 1958b; and others).

Gershenovitsch *et al.* (1963) found that both the glutamine and glutamine-synthesis increase during the preconvulsive stage of oxygen poisoning when the preconvulsive condition lasted for less than 10 min. Mison-Crighel *et al.* (1964) found a significant fall in glutamic acid and glutamine and an increase in glutaminase within 2 min after the topical application of mescaline, *i.e.* before the triggering of the convulsive activity. Kolousek and Jiracek (1959b) observed that methionine sulphoximine inhibits glutamine formation in the preparoxysmal state by the reaction of glutamic acid $\rightarrow$ glutamine $NH_3$, which causes disturbances in the cerebral function and leads to the appearance of convulsions. The same disturbances are found by Kolousek *et al.* (1959a) in adult rat brain susceptible to audiogenic seizures, thus confirming the hypothesis of Vrba (1955, 1957) that the functional activity of the brain depends on a certain level of the glutamic-acid–glutamine $NH_3$ cycle.

From the results discussed above it may be inferred that the various factors participating in the triggering of the seizures are directly or indirectly connected with oxidative metabolism. The fact that convulsions may be induced also in states of

hypoxia, hypoglycaemia and cyanide poisoning permits the inference that disturbances of the oxidative metabolism may be one of the primary causes of convulsions (Elliott *et al.*, 1950). Most alterations that take place before the convulsions begin are due to enhanced metabolic requirements as regards neuronal hyperactivity. The production of energy through oxidative metabolism must be maintained at a certain level above the critical one for the convulsions to take place.

### *Alterations during the development of the seizure*

A great number of investigators are concerned with the biochemical events which accompany the convulsive seizure caused by different physical (electrical stimulation) or chemical (metrazol, picrotoxin, caffeine, etc.) agents in the acute, semichronic (methionine sulphoximine, megimide, electroshocks repeated at certain intervals) or chronic (injection of alumina gel and the production of cerebral scars) experiments. From the existing data it may be inferred that the most radical chemical alterations take place after the onset of convulsions, which coincides with an enhanced energy requirement of neuronal hyperactivity. The divergent conclusions that were reached in regard to one or other of the disturbed mechanisms have been partly due to the different methods of investigation, such as the experimental model — *e.g.* the use of different convulsant agents — and the method of investigation itself — investigations *in vitro* or *in vivo* — and partly to the different stage during the course of the seizure at which the chemical processes were observed: the beginning of the fit, the clonic phase or the end of the clonic phase.

Although it seems that there is no unitary or specific mechanism, a 'biochemical lesion' that is common to all seizures, the facts so far observed show that there is a direct or indirect relationship of the epileptic seizure to the various stages of oxidative metabolism. According to Elliott and Penfield (1948), as well as to the great majority of authors, a convulsive mechanism cannot be conceived without the direct or indirect involvement of energetic metabolism. On the other hand, it is well known that the brain may maintain its excitability by metabolizing its structural compounds (proteins, amino acids, nucleic acids, phospholipids) which may undergo important changes during the period of the convulsions.

Numerous investigations have shown that the increase of cerebral circulation rates during the convulsive activity is probably due to dilatation of the cerebral vessels by increased tissular acidity owing to additional formation of $CO_2$ and lactic acid, and perhaps to the release of acetylcholine and other active substances (Elliott, 1955).

Oxygen consumption increases during an epileptic seizure, oxygen being necessary for maintaining convulsivity. Its lack determined an arrest of electrical activity in the cerebral cortex (Jasper and Erikson, 1941; Gibbs *et al.*, 1947; Kreindler *et al.*, 1963b; Mison-Crighel *et al.*, 1963).

The essential expression of a disturbed cerebral metabolism following lack of oxygen, is the disintegration of the energy-rich phosphorus compounds. The production of ATP is absolutely necessary for maintaining functional energy for the biosynthesis of peptide bonds, the renewal of amino acids, the synthesis of phospho-

lipids, of ACh and of glycogen (Palladin, 1954; Strickland, 1956). The exclusive dependence of the brain tissues on glucose as an energy source, and the possibility of energy deficiency have focused the attention of investigators in this direction.

In generalized convulsions induced by absinth oil, camphor, picrotoxin, caffeine, metrazol, strychnine, coramine, sulphopyridine, or electrical stimulation, the cerebral glucose and glycogen (Klein and Olsen, 1947) as well as the cerebral glucose:blood glucose ratio were found to decrease. On the other hand the cerebral lactic acid increased which is probably due to the decreasing pH during the period of convulsive activity. The requirements of oxygen and glucose exceed their supply, which leads to the decrease in energy-rich compounds, *i.e.* phosphocreatine and ATP (Gurdjan *et al.*, 1947; Mison-Crighel, 1957).

Energy-rich substances are used up at the beginning of the convulsive activity, whereby the tissular reserves are exhausted and this may be observed in parallel with the characteristic electric pattern (Dawson and Richter, 1950). Determinations were made according to electrical impulses lasting from 1 to 5 sec. Changes in phosphocreatine and ATP occurred during the first 15 sec after which these compounds returned to normal.

Immediately after the cessation of convulsions induced by electroshock (a 70-V current with only a 4-sec passage time), picrotoxin, cardiazol or amidopyrine, an increase in lactic acid and a decrease in phosphocreatine was found in animals that had not been anaesthetized previously (Mison-Crighel, 1957).

Studies *in vitro* on cerebral cortex slices could only achieve a qualitative reproducibility; only by direct electrical stimulation (Gore and McIlwain, 1952) in the presence of an increased concentration of $K^+$ ions in the incubating medium, were alterations observed *in vivo*, *i.e.* an increase in the consumption of oxygen and glucose and in the splitting of phosphocreatine; picrotoxin, metrazol or caffeine failed to cause any changes in oxidative metabolism (Anguiano and McIlwain, 1951). Evidently the agents listed above do not affect the oxidative metabolism *in vivo* either.

Immediately after the convulsive attack induced by electroshock an inhibition of cellular oxidation takes place, expressed by a decreased cytochrome oxidase activity and an increased succinic dehydrogenase activity in the rabbit motor cortex (Lascăr and Pintilie, 1955); these changes are similar to those found by Albaum *et al.* (1946) at the end of cyanide-induced convulsions. The inhibition of the oxidative processes probably leads to the modification of other compounds (glycogen, energy-rich compounds, the accumulation of inorganic phosphorus).

Another metabolism involved in normal cerebral as well as in convulsive activity, is that of acetylcholine. But whereas acetylcholine may be maintained at a constant level during normal activity, the cellular activity which is much more intense during the convulsions leads to the splitting of this substance. The intermittency of convulsive seizures is believed to be due to the alteration in the splitting and synthesis of ACh. The time intervals between acetylcholine splitting and its resynthesis are similar to those of phosphocreatine cleavage and resynthesis which precede and accompany the convulsions, with one quantitative difference, namely the amount of phosphocreatine that is transformed is 500 times greater than that of ACh (McIlwain, 1955).

After parenteral administration of methionine sulphoximine in cat, dog and rabbit, typical epileptiform anomalies in the EEG observed are without histophathological alterations. Cortex specimens collected after the onset of convulsions (within 18 to 24 h after administration) show the same metabolic anomalies as those of epileptogenic cerebral tissue specimens in humans, *i.e.* the incapacity to bind acetylcholine.

The experiments of McIntosh and Oborin (1953) pointed to close correlations between the brain ACh level and cortical electrical activity; those of Feldberg (1957) pointed to the correlation between the latter and the liberation of acetylcholine in the brain.

As is known, the ACh system is concentrated and active in the cerebral cortex and subcortical nuclei, *i.e.* areas where a convulsive activity is possible. Further evidence for the involvement of ACh in convulsions is the enhanced activity of cholinesterase in the epileptogenic foci as compared to the non-epileptogenic cerebral cortex (Pope *et al.*, 1947; Tower and Elliott, 1952a,b). The increase in cholinesterase in epileptogenic foci could be interpreted as a compensation phenomenon probably resulting from the increased amount of free ACh during the convulsive activity.

Pope *et al.* (1947) found the cholinesterase activity to be increased in the mirror foci which appear in cortical homologous areas that are contralateral to the primary experimentally-induced foci. This activity of cholinesterase returns to normal after removal of the primary focus and arrest of focal mirror activity. Uzunov *et al.* (1961) and Atzev (1962) found the convulsant action of atebrine to be due to its anticholinesterasic effect.

Picrotoxin and metrazol *in vitro* may stimulate ACh synthesis (McLennan and Elliott, 1951).

Numerous studies have shown the relationship between acetylcholine and $K^+$. Although the extrusion of $K^+$ from the cell seems to be facilitated by acetylcholine, supplementary studies are required in order to confirm the involvement of this mechanism and of others in the maintenance of a balance between intra- and extracellular K in normal and epileptic neurons. The same problem is raised also as regards $Na^+$.

Colfer and Essex (1947), who used the micro incineration technique, found that, during convulsions induced by electrical stimulation, metrazol or audiogenous stimuli in the rat and rabbit, intracellular K decreases as compared with the normal brain specimens. The return to normal takes place within about 3 h. The studies of Cicardo (1945), Adams *et al.* (1952), Mison-Crighel *et al.* (1955) have furnished indirect arguments to the effect that there is a fall of intracellular $K^+$ during generalized convulsions. Pappius and Elliott (1954) have not found significant differences between the $K^+$ and $Na^+$ contents in the human epileptogenic and non-epileptogenic cortex specimens, nor have Mison-Crighel *et al.* (1964) found them in the epileptogenic cat cortex resulting from the topical application of mescaline as compared with the normal cortex. Woodbury *et al.* (1958a,b) underline the importance of electrolytes in the development of the convulsive seizure. They did not find the extracellular: intracellular $K^+$ ratio in epileptic animals to be modified as compared with the controls, but have found a decrease in the extracellular $Na^+$ : intracellular $Na^+$ ratio, reflecting the increase of $Na^+$ in the intracellular space.

As shown before, although the intimate interrelations between electrolytes and amino acid metabolism are not as yet known, experimental results allow us to deduce the existence of these connections, particularly with the glutamate–GABA system.

In epileptogenic lesions in the cat cortex induced by freezing a small surface with ethyl chloride, glutamic acid, glutamine and glutathione in the lesion decrease during paroxysmal electrical activity, whereas the level of $\gamma$-aminobutyric acid remains constant (Berl *et al.*, 1959). A 50% decrease in glutamic acid coincides with the onset of convulsive activity in the EEG. In strychnine-induced convulsions (Haber and Saidel, 1948) and in fluoro-acetate-induced convulsions (Dawson, 1953) the concentration of glutamic acid fell.

In the epileptogenic focus induced by the topical application of mescaline, important alterations are noticed in the glutamate–GABA system that are not specific to the epileptic activity in the focus since the same alterations were found over the entire neocortex (Mison-Crighel *et al.*, 1964). Glutaminase was found to recover its initial activity at the 10th min of epileptogenic discharge and to increase significantly at 30 min after topical application of mescaline (Mison-Crighel *et al.*, unpublished).

Immediately after an epileptic seizure total amino nitrogen in the brain decreases, and it increases after 10 epileptic seizures when qualitative differences were found (Wertheimer-Luca, 1957, 1958).

According to Vrba (1955, 1957) cerebral activity stimulated by prolonged muscle movements is associated with a fall in amino nitrogen in the brain proteins and concomitant increases in free glutamine and glutamic acid. The changes are reversible. During the convulsions similar changes are apt to occur (Hydén, 1943).

At the end of the electroshock-induced seizure, Pintilie (1959) found a significant decrease in the glutathione level with a return to the initial values within 15 min of the cessation of the convulsions; there also occurred a significant increase in ascorbic acid.

The involvement of the glutamate system in convulsive states is better illustrated in the convulsions caused by the dietetic deficiency of pyridoxine (vitamin $B_6$). Pyridoxine is essential — as the coenzyme pyridoxal phosphate — for the metabolism and function of the central nervous system, and is primarily connected with amino acid metabolism. The antagonists of pyridoxine, deoxypyridoxine, metoxypyridoxine and some other chemical compounds act by blocking or inhibiting the action of the coenzyme pyridoxal phosphate. These compounds are thiosemicarbazide, semicarbazide and isoniazide (Biel and Vilter, 1954) and penicillamine (Kuchinskas and Du Vigneaud, 1957). Killam (1957) demonstrated that the effect of hydrazides is due particularly to the blocking of glutamic acid decarboxylase which results in the reduction of the amount of GABA. The hydrazides are believed to act by forming complex hydrazones with pyridoxal phosphate which they inactivate. This is believed to be due to excitation of the combination between the apoenzyme (the protein part of the enzyme) and the coenzyme. Transaminases are more resistant to pyridoxine deficiency.

Pogodaev (1963) found that during the electroconvulsive seizure there was an increase in non-protein nitrogen, in the activity of proteolytic enzymes and an intensification in the renewal of proteins (measured by the speed of inclusion of labelled

tyrosine and methionine into the brain proteins). Geiger *et al.* (1960) similarly found an acceleration in the renewal of the cerebral proteins during metrazol-induced convulsive activity. Nevertheless, there appear to be homeostatic mechanisms which tend to keep the levels of amino acids constant despite all protein alterations.

The degree of intensification of the $^{32}P$-incorporation into the tissue submitted to electroshock — a manifestation of the degree of intensification of cerebral metabolic activity during convulsive paroxysms — was taken as an index in estimating the strength of the convulsive activity (Volanschi *et al.*, 1961). It was found that in adult cats submitted to electroshocks an important and significant increase in $^{32}P$-incorporation had been obtained in most of the cortical (anterior and posterior cortex) and subcortical (caudate nucleus, cerebellum, hypothalamus and mesencephalon) formations explored, with maximum values in the motor cortex and mesencephalon.

In recently-born (two-week-old) kittens submitted to electroshock, no significant change in $^{32}P$-incorporation as compared to controls was found in most of the cortical (anterior and posterior cortex) and subcortical (caudate nucleus, Ammon's horn, cerebellum) structures explored, which denotes a low convulsive capacity of these formations. Only in the mesencephalon and hypothalamus, these being phylogenetically older and ontogenetically earlier formations, was a significant increase noticed, even though reduced $^{32}P$-incorporation value.

Histochemical researches on the development of acid and alkaline phosphatases in the brain of newborn and adult cats have shown that the metabolic functions of the acid phosphatases in the nerve cell are underdeveloped in the immature cat brain especially at the neuropil level.

Both in adult and newborn guinea-pigs (known to present from birth an advanced degree of cerebral histomorphological maturation), the electroshock acted by significantly and considerably increasing the $^{32}P$-incorporation into the cortical and subcortical structures explored.

Other metabolic anomalies related with convulsions were likewise found to exist. Thus, convulsions due to electroshock cause an increase in serotonin (Laborit *et al.*, 1947; Bertaccini, 1959) and copper (Costa-Foru, 1961) levels in the brain. Metrazol convulsions are followed by an intensified metabolism of lipids and nucleic acids (Geiger, 1957).

### *The arresting mechanisms of the convulsive seizure*

Some important factors in the active arrest of a convulsive seizure are the biochemical processes in the central nervous system and at the periphery which are reflected on the central nervous system.

Alterations in cortical and cortico-subcortical dynamics during the convulsive attack lead to disturbances in cerebral metabolism and in that of the various organs. These metabolic disturbances may in turn play the part of an active factor in the arresting mechanism of the seizure, both by their direct action on the upper nervous structures and by their action on effector organs; they sometimes profoundly alter the reactivity of these organs.

Some local biochemical alterations determined by the convulsive activity of the neurons might contribute to the arrest of the convulsions. Thus, Torda (1953) demonstrated an accumulation of ammonium ions, and Davies *et al.* (1944) detected polarographically an important fall in the $O_2$ pressure in the grey matter of the cortex. The latter could probably be traced to an intensified oxygen consumption which is not compensated by an increased cerebral blood flow owing to elevated arterial pressure and local vasodilatation.

During the attack, oxygen pressure in the cortex falls and attains a minimum at the end of the clonic phase (Ward *et al.*, 1948). Hence the seizure is accompanied by an intensive metabolic activity which not even the increased blood supply is able to correct; consequently an oxygen-deprived metabolism sets in which leads to the accumulation of acids. At the cessation of the seizures the cortex with excess acids consumes large amounts of oxygen for the utilization of the lactic acid and the restoration of the bound phosphorus compounds. It is likely that the accumulation of $CO_2$, particularly during the period of apnoea, plays an important role in arresting the seizure. $CO_2$ is a normal metabolite which, if present in excessive amount in neurons, lessens the influx of sodium and therefore reduces the excitability of the membrane. $CO_2$ inhibits the convulsions caused by most convulsants (Pollock and Bain, 1950; Gellhorn and Yesinick, 1942) but potentiates the action of mustard gas and agenized proteins (Pollock and Bain, 1950). Gellhorn and Heymans (1948) have also found that hypercapnia facilitates the convulsive potentials induced by the topical application of convulsants to the cerebral cortex. Hence, the inference that biochemical alterations are not the same, since the anticonvulsant effect is not the same in every kind of seizure. $CO_2$ may depress spontaneous and evoked activity in the fornix–hippocampal complex which has a very low threshold for epileptic discharges and which therefore seems to be connected with epileptiform phenomena (Dunlop, 1957 a, b). According to Roberts and Eidelberg (1960) there may be a connection between the anticonvulsant effect of $CO_2$ and the GABA system.

In fact it has been demonstrated (Roberts *et al.*, 1958) that the relative activities of glutamic acid decarboxylase (GAD) and of GABA transaminase (GABAT) may be changed by modification of the intracellular pH. Acidification is believed to exert an untoward influence on GAD activity and GABA increase, whereas alkalinization is supposed, on the contrary, to increase GABAT activity and to decrease GABA. Some authors ascribe an 'anticonvulsant' effect to $\gamma$-aminobutyric acid (Tower, 1960), although this may play a metabolic part in arresting the convulsive attack. Apnoea, or the reduction of oxygen to 4%, arrests the convulsive activity which begins again as soon as oxygenation is re-established (Jasper and Erickson, 1941; Gurdjan *et al.*, 1947).

Among the other biochemical processes that may contribute to the phenomena of arresting convulsive activity at the level of the cerebral cortex is the peculiar cholinergic pattern found during the last seconds of the convulsive attack; this is characterized by a fall in the amount of free acetylcholine which returns to normal values, and by an increase in bound acetylcholine which at times attains three times its initial value (Kreindler, Voiculescu and Crighel, 1957). It is possible that this may represent a

compensation phenomenon which contributes to the mechanisms of arrest of the seizure in the cerebral cortex. The end of the seizure is believed to occur when the ACh reserves are exhausted (Elliott, 1955). ACh synthesis is achieved by the energy derived from carbohydrate metabolism requiring the presence of ATP. ATP, derived from carbohydrate metabolism, may be used in acetylation.

Another link in the self-arresting mechanism of the convulsive attack seems to be represented by a humoral component. Mison-Crighel *et al.* (1955) showed that the $Mg^{2+}$ increases considerably after a convulsive seizure in the renal veins and in the splenic vein. This points to the massive elimination of magnesium (an ion that activates many enzymic systems and a co-enzymic constituent of others such as cholinacetylase, glutamo-transferase, phosphorylating enzymes etc.) as a factor in the seizure-arrest mechanism. The synthesis of glutamine from glutamic acid + $NH_3$ comes about in the presence of ATP and $Mg^{2+}$. In fact, its sedative role in nervous processes is well known. As early as 1908 Marinescu showed that the Mg ion acts at the nerve cell and synapse level. Injections of Mg salts were used to overcome convulsions. Gordon and Waelsch (1955) believe that during the passage of a nervous impulse $Ca^{2+}$ is liberated from the surface of the lipidic membrane and that its restoration is necessary for the return of a stable condition of rest. They think that Mg is apt to replace calcium at the surface of the membrane where the latter is not capable of inducing anesthesia in many organisms. Flink (1956) has shown that, when Mg is deficient, convulsive attacks occur and that blood magnesium is low in epileptics.

Other substances which are normally found in the brain in relatively large concentrations might likewise play a role in the self-arresting mechanisms of the convulsive attack. Waelsch (1961) raises the problem of the importance of certain free or bound metabolites, in an active or immobilized form. Little is known about such forms of glutamic acid and $\gamma$-aminobutyric acid, but there is evidence on the storage in particles or vesicles of ACh, cholinacetylase, acetylcholinesterase (De Robertis *et al.*, 1963) and catecholamines (Hebb *et al.*, 1956, 1958).

Other compounds, namely asparagine and pyridoxine, that are found in the brain in normal conditions have proved to be efficient in arresting experimental convulsive seizures also in man. A more thorough study of the mechanism by which these compounds (particularly the former) come into play might contribute towards the elucidation of the problem of the active intervention of certain metabolic factors in the self-arresting process of convulsive attacks.

In order to appreciate exactly the arrest mechanism of the epileptic seizure, one should bear in mind that the maximal activity of the entire nervous system or a part of it can only develop intermittently. After a short period of activity, processes of restoration set in which are slower than those that accompany the activity (McIlwain, 1955).

Despite the accumulation of numerous data concerning the cerebral biochemistry during the preconvulsive period as discussed above, no valid inferences may be drawn as to the causes underlying the appearance of a convulsive activity and its biochemical substrate. There is no irrefutable evidence that a certain metabolic disturbance is the cause of the convulsions. These disturbances are more likely the expression of

a convulsive activity, and may possibly be correlated with the clinical pattern (tonic or clonic), with the duration and intensity of the convulsion and with the cerebral structure on which the convulsive agent acts.

The question arises whether there are permanent metabolic disturbances which render the brain more liable to convulsions. A number of investigations have shown that certain permanent metabolic anomalies may play a part in the onset of convulsions. The incapacity to bind acetylcholine, the disturbance of amino acid and electrolyte metabolism are only links in much more complex metabolic chains which probably converge for the maintenance of neuronal hyperactivity.

In the triggering mechanism of the convulsive seizure a number of factors are believed to play a part, such as the accumulation of free acetylcholine through anticholinesterases, the imbalance between free and bound acetylcholine, the glutamic acid and glutamine metabolism disturbances, the interference with the Krebs' cycle, the low concentration of intracellular $K^+$. The excess of free acetylcholine and the interference with the re-entrance of $K^+$ into the cell affect the polarization of the cell membrane in the sense of discharge and hyperactivity.

Among the factors which may give rise to convulsive activity those might be listed that are believed to interfere with the stage of decarboxylation of glutamic acid and its transformation into $\gamma$-aminobutyric acid. The splitting of the latter would lead to a fall in the oxygen consumption, as it has been demonstrated *in vitro* that the $\gamma$-aminobutyric acid is an important substrate for oxidative metabolism. It is hard to accept this hypothesis only, since pyridoxine deficiency that may cause this disturbance is rarely met with in man.

The biochemical changes observed during the convulsions are rather the consequence of convulsive activity; the disturbances of the oxidative metabolism do not precede the onset of the convulsions, while the blood flow, the oxygen consumption, the energy-rich phosphates, begin to return to normal at the end of the convulsions. The production of energy derived from oxidative metabolism must be maintained above a critical level for the convulsions to occur; yet the participation both of energy-production and of the oxidative metabolism in initiating the convulsions may be considered as primary, as for instance in cyanide poisoning, in hypoglycaemia and in hypoxia (Elliott, 1955).

In insulinic hypoglycaemia, when the carbohydrate metabolism is inadequate because of the lack of a substrate (glucose), glutamic acid and GABA are resorted to in order to maintain the carbohydrate metabolism (Dawson, 1953). The decreasesin glutamic acid and $\gamma$-aminobutyric acid *in vivo*, or in epileptogenic brain speciment *in vitro*, may be the result of excessive requirements of the substrate for the oxidaive metabolism or of a deficiency in the normal utilization rate of the substrate with a secondary decrease in these amino acids.

The disturbance of glutamate metabolism may be connected with general disorders in nitrogen metabolism, since glutamate is a keystone in the transfer and metabolism of ammonia and of the amino groups. During the convulsions other non-carbohydrate substrates apart from amino acids may be used, *i.e.* proteins and lipids.

It has been proved that the metabolism of protein, of nucleic acids and of lipids

participates in neuronal activation, and that these 'structural' compounds are rapidly split and resynthesized after stimulation at a certain intensity. Hence, Geiger (1957) supposes that the passing of an impulse at adequate strength would leave a trace through the chemical alteration of the nerve cell. The question may be asked whether this metabolic 'trace' on the background of an enzymic deficiency or a general metabolic deficiency does not in some way concur in the preparation or appearance of a convulsive activity.

The above-mentioned metabolic disturbances might be assumed as being intimately connected with the convulsive process since they were seen only in the tissues identified by all available criteria as epileptogenic foci, and not in the adjacent tissues (Tower, 1960). Yet the same alterations were sometimes also observed in adjacent tissues and those contralateral to the focus (Mison-Crighel *et al.*, 1964). It seems that not all types of convulsions display the same type of biochemical lesion.

It is common knowledge that drugs do not act on the same nervous structures and that their effect in the different animal species varies, while others act through metabolic interference — fluorinated compounds block the Krebs' cycle and lead to the accumulation of citric acid and ammonia; pyridoxine deficiency, hydrazides, or methionine sulphoximine exert and effect on certain stages in the metabolism of amino acids.

Moreover, a series of metabolic disturbances is described which appears to be common to all types of convulsive attacks: the increase in lactic acid and ammonia, the rapid splitting of creatine phosphate and the fall in acetylcholine storage. On the other hand, a series of similar biochemical changes — such as the decrease in labile phosphates — is observed in insulinic hypoglycaemia which from the electrographic viewpoint is wholly different from other convulsive manifestations.

Kreindler has shown (1955, 1957) that the arrest of the convulsive attack is an active process which is due to some factors that act both at the level of the central nervous system and at the periphery. The accumulation of $CO_2$, the peculiar cholinergic pattern caused by the increase in bound acetylcholine, and the humoral factors including the participation of Mg, probably form only part of the active mechanism. According to McIlwain (1955) the convulsive activity seems to be an unorganized return of activity in the brain, rather than a response to impulses.

The chemical changes to be found after the cessation of the convulsions likewise show that the metabolic interrelation between the brain and the blood or the cerebrospinal fluid are altered. In the venous blood of the brain a number of alterations are observed to occur which express the tissular metabolic disturbances. Other alterations reflect the influence of the periphery on the central nervous system. The increase in blood sugar following the convulsions, the liberation of ascorbic acid from the adrenal glands — probably for supplementing the oxidative requirements of the brain after electroshock — the rise of potassium and particularly of magnesium in the renal veins, are but some of the evidence of mutual metabolic relations between the central nervous system and the other organs.

## SUMMARY

*After-discharge* is a self-sustained reverberating discharge and may therefore be considered as the elementary pattern of epileptic seizure. Sensioral after-discharge represents a particular phenomenon of reverberating discharge induced by afferent stimuli and its characteristics express the tendency towards autorhythmical activity of central neurons.

The characteristics of the after-discharge produced by electrical stimulation differ according to the structure stimulated. The neocortical after-discharge induced by a direct cortical stimulus is manifested by changes in the relationship between positive and negative response-phases, and a stronger stimulation results in the change of a local inhibitory mechanism. Topical application of amino acids (*e.g.* aspartic acid) to the cortex modifies the neocortical after-discharge by depressing the inhibitory function of inhibitory superficial layers. Neocortical after-discharge is accompanied by characteristic progressive changes in the spike discharges of the neurons, activated by each electrical impulse. Within the neocortex there are regional variations in characteristics of the after-discharge.

*Allocortical after-discharge* (amygdaloid) differs in the dorsal and ventral regions of the basolateral amygdaloid nucleus as well as in the basolateral amygdaloid nucleus and the nucleus centralis lateralis. The spread of an after-discharge produced by stimulating particular formations of the brain stem gives rise to brain stem seizures with sharply distinct electro-clinical characteristics.

Electrical stimulation produces *intrastimulatory and poststimulatory discharges* which are two different effects. In general, intrastimulatory discharge is suppressed by stimulation of a suppressive circuit. During allocortical stimulation (amygdala) there is a possibility of studying the features of these two phenomena, *i.e.* intra- and poststimulatory discharges.

The experimental pattern most frequently used for creating an *epileptogenic focus* is topical application of certain drugs. The *strychnine* spike may attain one or more millivolts and is the consequence of hypersynchronia. The strychnine spike is followed by an after-discharge. Low concentrations of topically applied strychnine to the cortex increase the amplitude of recruiting sequences and higher concentrations induce a decrease in amplitude if indirectly activated.

The *penicillin* focus produces spike discharges which gradually build up into large high-voltage discharges and is followed by rhythmical after-discharges. Propagation from a penicillin focus in the centrum medianum of the thalamus differs from that in the nucleus lateralis thalami and gives rise, with small amounts of penicillin, to synchronous bursts of slow paroxysmal high-voltage waves in the thalamus.

The *mescaline* focus remains localized for a long time, and then spreads to the symmetrical contralateral cortex and later to subcortical structures.

*The epileptic neuron* has two main functional characteristics: abnormally great potentials in the soma and dendrites, and a high frequency of the potential spreading to the axon. It appears that the interparoxysmal after-discharges are confined to dendritic layers. In an epileptic population there is a very close relation between slow outbursts and unit activity: the majority of unit elements in the area fire at least one spike and often numerous repetitive spikes at a very high frequency. There is a close relationship between dendritic depolarization and epileptic discharge, the epileptic spikes being generated by apical dendrites of the cerebral cortex. The autonomous activity which characterizes the 'epileptic' neuron is due to a relatively persistent dendritic depolarization with a resultant difference in potential between the cell body and its dendrites.

During prolonged stimulation at high frequency and high intensity, in most cortical and hippocampal neurons, the intracellular records show progressive decrease of the hyperpolarizing wave, progressive prolongation of the depolarizing wave and temporal summation of the depolarizing wave.

*The genesis of an epileptogenic focus* is one of the main problems in epilepsy. Synchronization of the discharge plays an important role. It depends not only on recruitment of an increasingly large number of neurons, but also on the frequency of neuronal discharges. Since the epileptic neuron represents a summation of the depolarizing activity of the dendrites, synchronization must take place at this level. Another synchronization mechanism would be that of the effect of the electrical field. The glia may be assumed to interfere in the synchronization mechanism. Another likely mechanism is that of isolation of an area of the cortex. Around an experimental epileptogenic focus the units fire spontaneously in the inter-ictal periods in greater number than in the more distant cortical tissue. During an epileptic seizure produced in the monkey by an epileptogenic focus with alumina cream, in some cells of this focus all activity ceases during the paroxysm, in others there is an intense activity at high rate discharges. Although the 'epileptic' cell sometimes spontaneously fires high frequency bursts, there is no relation between this activity of the soma (perikaryon) and dendritic activity recorded by the pial electrode. The onset of seizure discharges is accompanied by massive dendritic depolarization. The epileptogenic focus has a lower threshold for the after-discharge induced by electrical stimulation; and epileptogenic lesions localized in one hemisphere are always accompanied by a state of diffuse hyperexcitability of the neurons.

*Peculiarities of epileptogenic foci in different cerebral structures.* The epileptogenic focus in the unspecific thalamic nuclei induces synchronous discharges in the ipsilateral hemisphere. We cannot speak of a centrencephalic focus, where a centrencephalic seizure would be due to neuronal system disturbances. Topical cortical application of penicillin to the gyrus cinguli induces synchronous discharges on the convexity of both hemispheres. The seizure in the gyrus cinguli spreads to the hippocampal system only when supraliminal stimuli are used. Alumina cream injection into the anterior part of the temporal lobe determines motor automatism seizure and

corresponding electroencephalographic alterations. Stimulation of the median supracallosal cortex induces 16–20/sec rhythmic discharges in the gyrus suprasplenialis, and in the anterior and posterior limbic area.

Chronic epileptogenic lesions produced in the subcortical zone by alumina cream injections may induce severe generalized convulsions. Injection into the amygdala may induce seizures similar to those of psychomotor epilepsy in man; injection into the hippocampus may induce spontaneous bilateral phasic and continuous discharges and slow asynchronous spikes of Ammon's horn.

*Pharmacological drugs, asphyxia and epileptogenic foci.* The cortical epileptogenic focus is, as a rule, little influenced by the known anticonvulsant substances. Asphyxia leads to disappearance of epileptic activity in all formations of a penicillin focus; however, discharges sometimes persist in certain subcortical formations after cessation of cortical activity. The paroxysmal discharges induced by topical applications to the cerebral cortex become rarer, their voltage diminishes and the complex discharges become simpler and simpler. It appears that asphyxia would suppress in a first phase only the dendritic potentials, leaving intact the axon potentials.

*Epileptogenic focus and evoked activity.* The superficially evoked cortical response increases in amplitude and duration before, and sometimes after, a spontaneous discharge induced by an epileptogenic lesion. In the cortical focus induced by topical application of mescaline the evoked responses in acoustic and cortical areas are characterized by high amplification of the negative phase. In deep barbiturate sleep there is an inversion of the polarity of the evoked potentials after topical application of mescaline. The organization of an epileptic cortical discharge also requires the participation of the deep layers. During the various phases of focal discharge, differences are observed in the organization of the synaptic systems that intervene in the production of the surface-negative, dendritic postsynaptic potential. The response evoked by a single stimulus applied to the sciatic nerve cannot be made evident during 8–10 sec after focal electrical stimulation of the specific sensory area. Epileptogenic stimulation of the nucleus lateralis posterior does not prevent the appearance of photically evoked potentials in the visual area. Whereas in the somesthetic area the specific sensory response disappears for several seconds following an after-discharge, in the visual area this response persists even during the after-discharge. The electroconvulsive seizure alters the capacity of different subcortical structures to follow the photic stimulation rhythm. The direct cortical response to an electrical stimulus shows changes after a metrazol induced seizure. The topical application of mescaline induces an amplification of the negative response and lengthening of the duration of the direct cortical response. The first to interfere in the organization of the after-discharge of an experimental epileptogenic focus are the intracortical circuits. On the other hand, the experimental epileptogenic focus modifies the reactivity of large areas of the cerebral cortex.

*Triggering of the epileptic seizure.* Explosive self-recruitment due to lowered neuronal excitability threshold, synaptic or ephaptic interactions, and alteration of the recovery cycles may be a factor in triggering the activity of an epileptogenic focus. A sharp and iterative depolarization of a large number of units producing high fre-

quency bursts of variable duration may be the functional substrate of epileptic disturbances. Triggering of a seizure by injection of cardiazol shows that in the precritical period of 1 to 3 min there are changes in the reactivity of the cortex to intermittent photic stimulation. Preconvulsive activity is manifested by a slight increase in latency of the responses to intermittent photic stimulation. Convulsive activity varies with the degree of maturity of the cerebral cortex. Electrical shock produces in the newborn kitten a tonic seizure with cortical and subcortical spindles of 5–13 c/s. In immature cats the direct cortical stimulation elicits a response with long latency.

The efficiency of the epileptogenic focus depends upon the morphofunctional features of the different cerebral structures.

Triggering of a *focal seizure* depends upon the characteristics of the stimulus. Both the direct motor response and the self-sustained seizure with features of an afterdischarge are not only the expression of stimulation of the efferent neurons, but also of stimulation of certain closed neuronal circuits. Lengthening of the convulsive focal repetitive stimulus applied to the motor cortex exercises a suppressive action on triggering of the convulsive seizure. Using various parameters of stimulation one can induce certain changes in morphology of the amygdala-hippocampally evoked responses.

Triggering of *generalized seizures* by cardiazol-induced discharges from the whole of the cerebellar and cerebral cortex and from subcortical structures. Sensitivity to convulsive drugs varies in the animal scale. Largactyl prevents the appearance of epileptic seizures induced by convulsive drugs. Convulsive drugs differ from one another as to the various thresholds at which they give rise to convulsive discharges in the brain (cortex, cerebellum etc.).

Experimental epilepsy induced by methionine sulphoximine is of particular interest through its ability to induce, analogously to human epilepsy, spontaneous seizures interrupted by periods of apparently normal behaviour. The seizures resemble certain types of psychomotor epilepsy in man, associated with spiking activity, diffuse bilaterally synchronous bursts of slow waves and $\theta$ frequency as background rhythms.

*Triggering by sensory stimulation* is of interest for clinical applications. The 'epilepsy of Amantea' and musicogenic epilepsy are examples of such a triggering. 'Reflex' facilitation of convulsive activity appears to be due to a breakdown of the equilibrium between the unspecific systems. Repetitive stimulation of certain sensory influxes may trigger an epileptic seizure. Audiogenic epilepsy of the rat induced by an intensive acoustic stimulus is due to a motor dominant with electroencephalographic correlation, with ample synchronous waves in the hippocampus and pyriform gyrus. Triggering of an epileptic seizure by association of cardiazol and photic stimulation may be due to a hypersynchrony of several neuronal complexes or only of the neurons of a certain neural complex.

Sinocarotic afferent impulses may perhaps also play a role in triggering a convulsive seizure, since mechanical stimulation of its baroreceptors produces a hypersynchrony of the cortical waves.

Conditioning stimuli may induce a convulsive activity by associating, for instance, an interoceptive stimulus to a convulsive drug, or by associating an acoustic stimulus to an electrical stimulation of the motor cortex in the dog. Generalized hypersyn-

chronous discharges induced by chronic epileptogenic lesions can be conditioned, the conditioning stimulus being a weak sound, the unconditioning a repetitive photic stimulus. In the dog, association of repetitive photic stimulation and electrical shock produces hypersynchronous discharges to photic stimulation alone, similar to those produced by the electric shock. Human pathology provides examples of an epileptic seizure that can be triggered by an extero-, proprio- or interoceptive stimulus.

The triggering mechanism is extremely complex, being the result of an 'afferent constellation' that is difficult to define in each separate case.

*Development of the epileptic seizure.* In this development we can distinguish several phases: the spread or propagation, the generalization, the peak, and finally the electrical silence.

*The propagation of epileptic activity* is sometimes ephaptic. An axo-somatic spread exists also. Cortical propagation of an after-discharge develops along a zone of cortical contiguity, and the size of the invaded area depends upon the parameters of the stimulus. Local spread of the after-discharge seems to be preceded by the progressive appearance of surface-negative waves in the cortex surrounding the focus of paroxysmal activity.

A chronic cortical focus may produce secondary functional alterations in subcortical or cortical structures ('mirror focus'). A chronic epileptogenic focus in the sensory-motor region produces recurrent, spontaneous discharges in the caudate nucleus, the globus pallidus, the putamen and the nucleus centralis posterior lateralis. Propagation takes place along certain pre-established pathways or connections of functional projection, but the anatomical connections alone cannot account for the preferential routes of propagation of the epileptic discharge. Propagation may also take place from a subcortical focus to the cortex. Propagation that takes place along the neuronal circuits is arrested by interruption of these circuits. Repetitive stimulation, prolonged so as to produce at the end a seizure which leads to its propagation, has the following intracellular effects: progressive decrease of the hyperpolarization wave, progressive lengthening of the depolarization wave and then temporal summation of the depolarization. It is possible that a phenomenon analogous to 'spreading depression' interferes in the mechanism of propagation of the epileptic discharge. Spread of the epileptic activity from different cerebral structures shows certain characteristics of a preferential order. Motor cortex stimulation in cat induces after-discharges at the symmetrical points of the contralateral hemisphere before the occurrence of epileptic potentials at the adjacent points of the homolateral hemisphere. There are differences between propagation of a sigmoid penicillin focus and an ectosylvian focus to subcortical structures. The epileptic activity of different thalamic nuclei depends strictly upon the activity of the cortical regions with which these nuclei are connected. However, there can be intense paroxysmal discharges in the thalamic nuclei whose cortical projection zone showed no epileptic activity. Propagation of the discharges from a focus on the ectosylvian gyrus takes place first towards the ventrolateral ectosylvian gyrus, then to the sigmoid gyrus and the homolateral lateral gyrus. The propagation of discharges from a temporal focus occurs early in the thalamic nuclei. Electrical stimulation of the *temporal cortex* in the monkey brings about a discharge in almost

the entire homolateral temporal cortex and in the nucleus amygdalae and hippocampus. The propagation of an epileptogenic focus is preferentially directed towards the homotopic areas of the contralateral hemisphere and then towards the central subcortical stuctures. Subcortical structures play an important part in the propagation of discharges from a cortical penicillin focus. Penicillin foci in the diffuse thalamic system and in the lamina medullaris interna have peculiar characteristics of propagation. There are differences of latencies and propagation between a thalamic penicillin focus and a cortical one, the hippocampal propagation from the thalamus to the hippocampus having a greater amplitude and occurring earlier.

*Propagation from the amygdalo-hippocampal complex* most frequently involves the ipsilateral septum, the hypothalamus and the mesencephalic tegmentum. Stimulation of the parvocellular basal amygdaloid nucleus induces a rhythmic intrastimulatory discharge both in the hippocampus and in the lateral central amygdaloid nucleus. Stimulation of this central nucleus causes intrastimulatory discharges in the parvocellular basal amygdaloid nucleus. There is a two-way relationship between these two nuclei, and between the parvocellular basal amygdaloid nucleus and the hippocampus. The neocortical propagation of amygdaloid after-discharges is particularly directed towards areas homologous with the insular and temporal lobe. There are propagations of amygdaloid discharges to the fornix and the supra-optic anterior hypothalamic area, to the habenula, and to the nucleus medialis dorsalis.

After stimulation of the hippocampus the threshold of the activating reaction evoked by the mesencephalic reticular formation is 2–3 times higher. Discharges from the hippocampus propagate to the temporal cortex, to the fimbria, fornix and gyrus splenialis posterior, and disappear after ablation of the hippocampus.

During the full development of an epileptic seizure, convulsive activities may be recorded in the cerebellum, pontine reticular formation, the hippocampus, globus pallidus, putamen, thalamus and amygdala. The epileptic generalization comes about essentially by intra- and intercortical propagation, but the subcortical structures play an important part. It may be that this generalization is due to the disturbance of the equilibrium between excitation and inhibition processes. Sometimes the electrical characteristics of generalized seizure activity appear to be the result of the primary effect of a focus plus the secondary reactivity of each of the local areas activated by the focus. Direct recording sometimes shows considerable independence of electrical patterns in areas of anatomical proximity.

The generalized electroconvulsive seizure is characterized by the perfect synchrony of a great number of cortical and subcortical structures. Spontaneous generalized epileptic seizure in man, however, shows some neuronal chains that are not involved in its development. The generalized seizure provoked by stimulation of 'non-motor' areas brings into action convulsive chains which have other characteristics of excitability than those put into action by a repetitive stimulation of the motor area. During the first stages of development of the generalized motor convulsive seizure induced by repetitive stimulation, a state of refractoriness is observed at the stimulated point. During a convulsive attack some neuronal chains undergo a phenomenon of occlusion or suppression while others do not.

*Rapid rhythms* in the subcortical structures, namely in the hippocampus and the thalamus, are seen during the development of a convulsive seizure. The hippocampal rapid rhythm may not follow the general cerebral synchrony and may outlast the duration of the discharge in the cortex. Chronic bilateral lesions of the hippocampus cause all the fast rhythms to disappear. In the thalamus there is during the attack a very regular rapid rhythm ('comb rhythm') which has some peculiarities with regard to its amplitude, frequency and propagation.

*The spike and wave complex* is met during the development of an electroconvulsive attack most frequently in the cortical leads. It represents a kind of reaction common to many cerebral areas during the phenomenon of paroxysmal synchronism, and must not be identified with petit mal epilepsy. The spike may have an origin other than the wave.

The *migration phenomenon* of epileptic activity during the attack is characterized by passing of the discharge from one structure to another. Shifting of rapid rhythms, the spike and wave complex and phase opposition are observed during an attack.

*Electroclinical correlations.* In the phylogenetic scale there is a predominance of the tonic pattern in the lower animals. There are differences in convulsive aptitude between rat and cat. Extrapyramidal pathways play a dominant part in the mechanism of generalized convulsions.

There seems to exist a correlation between the site of the discharge focus and the clinical type of the epileptic fit. An epileptogenic focus in the cortex alters the conditioned reflexes, the memory and learning processes.

The convulsive seizure is accompanied by a rich viscero-vegetative symptomatology pointing to a spread of excitation to central vegetative structures (changes in blood pressure and excitability of vegetative nerves etc.). There are marked disturbances in the function of viscera (gastric movements, respiration, heart function, renal volume etc.).

*Factors influencing the development of an experimental epileptic seizure.* Polarization of the cortex may change the type of cortical epileptogenic discharges. Poorly organized epileptic activity can be inhibited by stimulating the cerebellum or the diffuse thalamic system. As the seizure tends to become better organized, stimulation of the same structures with the same parameters results in an opposite effect, *i.e.* facilitation. There are differences in this respect between curarized and uncurarized animals. The cortical penicillin focus can also be facilitated or suppressed by cerebellar stimulation. Stimulation of the reticular formation and midline thalamic nuclei causes a marked enhancement of cortical after-discharge. The cortical mescaline focus is enhanced by stimulation of the mesencephalic reticular formation, and stimulation of this formation modifies the neocortical excitability to direct electrical stimulation facilitating the transition from normal to convulsive activity. In contrast to diffuse facilitation obtained by stimulation of the reticular formation and the midline thalamic nuclei, stimulation of the nucleus ventralis anterior of the thalamus exerts characteristic topographically localized effects on the cortical after-discharge according to the ventral or dorsal stimulated area of this nucleus. Investigation of the dorsal and ventral portions of the basolateral amygdaloid complex has shown that

the capacity of organizing epileptic discharges during and after electrical stimulation differs at each of these levels.

The course of an attack is influenced by subcortical lesions (centrum medianum of the thalamus, amygdala and reticular formation).

The *postparoxysmal electrical silence* follows a generalized seizure. Electrical silence is accompanied by hyperpolarization of the neurons which points to the existence of an active inhibitory process at the cell level. The electrical silence is not due only to a total exhaustion of all the neurons of the brain. The restoration period of the circuits which were involved in the epileptic activity passes gradually through different phases of refractoriness. Three different functional levels are gradually re-established after an epileptic seizure. After an electroconvulsive seizure there are alterations of the orienting reflex and the alimentary and defence conditioned reflexes. The reappearance of the arousal reaction after a convulsive attack has an undulant inconstant character.

*The arrest of the epileptic attack* is not only an exhaustion phenomenon but also the result of an active arrest mechanism. Such mechanisms may be situated in the cortex, in a thalamo-caudate system. The extracerebral mechanisms of arrest of the convulsive seizures are manifold: increase in latency of the nociceptive spinal reflex; violent excitation of certain intraceptive afferents due to the viscero-vegetative storm which accompanies the generalized convulsive seizure; excitation which, mediated through the reticular formation, exerts its influence on numerous cerebral structures; biochemical alterations such as anoxia and increase in the magnesium content of the blood. The cerebral arresting mechanisms may be due to bringing into action certain inhibitory internuncial cortical neurons, or certain inhibitory circuits, where certain lesions of the thalamus (centrum medianum) are able, by causing such circuits to be interrupted, to prolong the duration of an epileptic attack. Inhibitory circuits may involve also the cerebellum. Inhibitory motor phenomena may occur under certain experimental conditions of electrical stimulation of the brain cortex. The postcritical refractoriness to repetitive stimuli of the motor cortex may be attributed to a phenomenon of parabiotic inhibition.

*Biochemical aspects* of convulsive disorders have different aspects in the interparoxysmal period, in the preparoxysmal period, during the seizure and immediately after it. In the interparoxysmal period there are disturbances of tissular oxygenation, acetylcholine glutamate and electrolyte metabolism being much altered. In the cerebral epileptogenic scar the activity of glutamic oxaloacetic acid transaminase is decreased. Alkaline phosphatases no longer decrease after an electroconvulsive seizure if myocaine has previously been injected. Previous anaesthesia prevents the onset of chemical alterations in the brain.

*Biochemical changes preceding the onset of convulsions* could give us some inferences about the triggering of the seizure. It is possible that ammonia may play a role by being metabolized into an abnormal 'convulsive' product. Another mechanism of triggering could be the splitting and synthesis of acetylcholine. The cation concentration change was incriminated as a factor preceding the onset of convulsions. The GABA concentration and its variations may account for variations in cerebral

excitability. Both the glutamine and glutamine-synthesis were found to increase during the preconvulsive stage.

*Alterations during the development of the seizure* are related to the direct or indirect involvement of energetic metabolism. Oxygen consumption increases. The lack of oxygen determines a disintegration of the energy-rich phosphorus compounds. Glucose and glycogen decrease and cerebral lactic acid increases. Immediately after a generalized convulsive seizure there is an increase in lactic acid and a decrease in phosphocreatine, an inhibition of cellular oxidation shown by a decrease in cytochrome oxidase activity and increased succinic-dehydrogenase activity. The cellular activity which is much more intense during the convulsions leads to the splitting of acetylcholine. There is a close correlation between the brain acetylcholine level and cortical electrical activity. The activity of cholinesterase is enhanced in the epileptogenic foci.

Intracellular $K^+$ decreases during a convulsive seizure. In the epileptogenic mescaline focus important alterations are noticed in the glutamate–GABA system. At the end of an electroconvulsive seizure there is a significant decrease in glutathione level. In newborn kittens no significant change in $^{32}P$-incorporation occurs after an electroconvulsive seizure as compared to controls.

In the *arresting mechanism of a convulsive seizure* biochemical processes play a role. Local biochemical alterations (oxygen-deprived metabolism which leads to the accumulation of acids, excess of $CO_2$, alterations of the GABA-system, etc.) may interfere with this mechanism. A humoral component may be the increase of $Mg^{2+}$ in the renal veins and the splenic vein after a convulsive seizure.

# REFERENCES


ABDULLAH, A. F., AND MAGOUN, H. W., (1957); Effect of induced seizure discharge upon evoked cortical potential. *Fed. Prod.*, **16**, 1.

ADAMS, J. E., AIRD, R. B., AND GAROUTTE, W., (1952); Fluid and electrolyte exchange in the brain in experimental convulsions. *Trans. Amer. neurol. Ass.*, **77**, 34.

ADRIAN, E. D., (1936); The spread of activity in the cerebral cortex. *J. Physiol. (Lond.)*, **88**, 127–161.

ADRIAN, E. D., (1941); Afferent discharges to cerebral cortex from peripheral sense organs. *J. Physiol. (Lond.)*, **100**, 159–191.

ADRIAN, E. D., AND BUYTENDIJK, F. J. J., (1931); Potential changes in the isolated brain stem of the gold fish. *J. Physiol. (Lond.)*, **71**, 121.

ADRIAN, E. D., AND MORUZZI, G., (1939/1940); Impulses in the pyramidal tract. *J. Physiol. (Lond.)*, **97**, 153–199.

AIDA, S., (1956); Experimental research of the function of the amygdaloid nuclei in psychomotor epilepsy. *Folia psych. neurol. jap.*, **10**, 181–207.

AJMONE MARSAN, C., (1961); Electrographic aspects of 'epileptic' neuronal aggregates. *Epilepsia (Amst.)*, **2**, 22–38.

AJMONE MARSAN, C., (1963); Unitary analysis of 'projected' epileptiform discharges. *Electroenceph. clin. Neurophysiol.*, **15**, 197–208.

AJMONE MARSAN, C., AND MAROSSERO, F., (1950); Electroencephalographic and electrocardiographic study of convulsions induced by cardiazol. *Electroenceph. clin. Neurophysiol.*, **2**, 133–142.

AJMONE MARSAN, C., E MAROSSERO, F., (1953); Studio sperimentale di attività elettriche provocate a livelli diversi del sistema nervoso. *Sist. nerv.*, **5**, 174–189.

AJMONE MARSAN, C., AND STOLL, J., (1951); Subcortical connections of the temporal lobe in relation to temporal lobe seizures. *Arch. Neurol. Psychiat. (Chic.)*, **66**, 669–686.

ALBAUM, H. G., TOPPERMAN, J., AND BODANSKY, O., (1946); The *in vivo* inactivation by cyanide of brain cytochrome oxidase and its effect on glycolysis and on the high energy phosphorus compounds in brain. *J. biol. Chem.*, **164**, 45.

AMANTEA, G., (1921); Über experimentelle beim Versuchtier infolge afferenter Reize erzeugte Epilepsie. *Pflügers Arch. ges. Physiol.*, **188**, 287–297.

ANDY, O. Y., BONN, P., CHINN, R., AND ALLAN, M., (1959); Blood pressure alterations secondary to amygdaloid afterdischarges. *J. Neurophysiol.*, **22**, 51–60.

ANDY, O. Y., CHINN, R., AND BONN, P., (1957a); Electrical stimulation of cingulate gyrus. *Electroenceph. clin. Neurophysiol.*, **9**, 181.

ANDY, O. Y., CHINN, R., SPRINGER, P., GILLIS, S., AND BONN, P., (1957b); Mesencephalic and hypothalamic influence on seizure duration in the cat. *Electroenceph. clin. Neurophysiol.*, **9**, 171.

ANDY, O. Y., AND MUKAWA, J., (1960); Amygdaloid propagation to the brain stem. *Electroenceph. clin. Neurophysiol.*, **12**, 333–343.

ANGUIANO, G., AND MCILWAIN, H., (1951); Convulsive agents in the phosphates of the brain examined *in vitro*. *Brit. J. Pharmacol.*, **6**, 444–453.

APPEL, E., HORNET, TH., MISON-CRIGHEL, N., ŞI UNGHER, J., (1957); Actiunea anticonvulsivantă a miocainei. *Stud. Cercet. Neurol.*, **2**, 505–513.

ARANA-INIGUEZ, P., REIS, J. D., NAQUET, R., AND MAGOUN, H. W., (1955); Propagation of amygdaloid seizures. *Acta neurol. lat.-amer.*, **1**, 109–122.

ARDUINI, A., ET LAIRY-BOUNES, G., (1952); Action de la stimulation électrique de la formation réticulaire du bulbe et des stimulations sensorielles sur les ondes strychniniques corticales chez le chat. *Electroenceph. clin. Neurophysiol.*, **4**, 503–512.

ATZEV, E., (1962); *Ognistschina Epilepsia*. Sofia, Meditzina i Fizcultura.

BARRON, D. H., AND MATTHEWS, B. H. C., (1938); The interpretation of potential changes in the spinal cord. *J. Physiol. (Lond.)*, **92**, 276–321.

BARUCCI, M., MESSINA, C., E MORI, F., (1954); Demonstrazione EEG ed electrocorticografica di accessi epilettici spontanei. *Riv. Pat. nerv. ment.*, **75**, 221–247.

BAUMGARTNER, G., (1954); Microelectrode recordings from single cortical neurons in the normal state and during epileptic discharges. *Electroenceph. clin. Neurophysiol.*, **6**, 520–521.

BAUMGARTNER, G., UND JUNG, R., (1955); Hemmungsphänomene an einzelnen corticalen Neuronen und ihre Bedeutung für die Bremsung convulsiver Entladungen. *Arch. Sci. biol. (Bologna)*, **39**, 474–486.

BELEHOVA, M. G., (1963); O vliianii sheinovo simpatitcheskovo nerva na sudorojnuiu aktivnosti kory bolshih polusharii golovnovo mozga koshki. *Fiziol. Jurn. (SSSR)*, **49**, 164–172.

BENITEZ, D., PSCHEID, G. R., AND STONE, W. E., (1954); Formation of ammonium ion in the cerebrum in fluoracetate poisoning. *Amer. J. Physiol.*, **176**, 488.

BENTLEY, H. R., AND WHITEHEAD, J. K., (1950); Dimethylsulfoximine. *J. chem. Soc.*, **3**, 2081–2085.

BERGMANN, F., COSTIN, A., AND GUTMAN, J., (1963); A low threshold convulsive area in the rabbit's mesencephalon. *Electroenceph. clin. Neurophysiol.*, **15**, 683–690.

BERITASHVILI, I., BREGADZE, A., AND TSKIPURIDZE, L., (1958); Paroxysmal bioelectrical discharges of the cerebral cortex. V.S. Rusinov and M. Y. Rabinovitch, Editors. *Electroencephalographic researches in the laboratories and clinics of the Soviet Union. Electroenceph. clin. Neurophysiol.*, Suppl. 8.

BERL, S., PURPURA, D. P., GIRADO, M., AND WAELSCH, H., (1959); Amino acid metabolism in epileptogenic and nonepileptogenic lesions of neocortex (cat). *J. Neurochem.*, **4**, 211–217.

BERTACCINI, G., (1959); Effect of convulsant treatment on the 5-hydroxytryptamine content of brain and other tissues of the rat. *J. Neurochem.*, **4** 217–222.

BICKFORD R. G., (1954); Sensory precipitation of seizures. *J. Mich. med. Soc.*, **53**, 1018.

BICKFORD, R. G., DODGE, JR., H. W., SEM-JACOBSEN, C. W., AND PETERSEN, M. C., (1953); *Proc. Mayo Clin.*, **28**, 175–180.

BIEL, J. P., AND VILTER, R. W., (1954); Effects of isoniacid on pyridoxine metabolism. *J. Amer. med. Ass.*, **156**, 1549–1552.

BINGEL, A., (1957); Reading epilepsy. *Neurology (Minneap.)*, **7** ,752–756.

BISHOP, G. H., (1954); Evaluation of activation in the electroencephalogram. *Electroenceph. clin. Neurophysiol.*, Suppl. **4**, 91–92.

BISHOP, G. H., (1956); Natural history of the nerve inpulse. *Physiol. Rev.*, **36**, 376–399.

BISHOP, G. H., (1958); The dendrite: receptive role of the neurone. *Electroenceph. clin. Neurophysiol.*, Suppl. **10**, 12–21.

BISHOP, G. H., AND CLARE, M. H., (1953); Responses of cortex to different electrical stimuli applied to different dephts. *J. Neurophysiol.*, **16**, 1–19.

BONNET, V., ET BREMER, F., (1956); Analyse des modifications préconvulsives de la réaction cérébrale à un stimulus direct répété. *J. Physiol. (Paris)*, **48**, 399–403.

BONVALLET, M., DELL, P., ET HIEBEL, G., (1954); Tonus sympathique et activité électrique corticale. *Electroenceph. clin. Neurophysiol.*, **6**, 119–144.

BONVALLET, M., ET HUGELIN, A., (1961); Influence de la formation réticulaire et du cortex cérébral sur l'excitabilité motrice au cours de l'hypoxie. *Electroenceph. clin. Neurophysiol.*, **13**, 270–284.

BRANCH, C. L., AND MARTIN, A. R., (1958); Inhibition of Betz cell activity by thalamic and cortical stimulation. *J. Neurophysiol.*, **21**, 380–390.

BRAZIER, M. A. B., (1955); Neuronal structure, brain potentials and epileptic discharge. *Epilepsia (Amst.)*, **4**, 9–18.

BRAZIER, M. A. B., SCHROEDER, H., CHAPMAN, V. P., FAGER, C., POPPEN, J. L., SOLOMON, H. C. AND YAKOVLEV, P. I., (1954); Electroencephalographic recordings from depth electrodes implanted in the amygdaloid region in man. *Electroenceph. clin. Neurophysiol.*, **6**, 702.

BREMER, F., (1941); Le tétanos strychninique et le mécanisme de la synchronisation neuronique. *Arch. int. Physiol.*, **51**, 211–260.

BREMER, F., (1943); Etude oscillographique des réponses de l'aire acoustique corticale chez le chat. *Arch. int. Physiol.*, **53**, 103.

BREMER, F., (1949); Considérations sur l'origine de la nature des ondes cérébrales. *Electroenceph. clin. Neurophysiol.*, **1**, 177–193.

BREMER, F., (1958); Le processus d'excitation et d'inhibition dans les phénomènes épileptiques. *Bases Physiologiques et Aspects Cliniques de l'Épilepsie*. Th. Alajouanine, Editor. Paris, Masson (pp. 1–35).

BREMER, F., ET BONNET, V., (1950); Interprétation des réactions rythmiques prolongées des aires sensorielles de l'écorce cérébrale. *Electroenceph. clin. Neurophysiol.*, **2**, 389–400.

BREMER, F., BONNET, V., ET TERZUOLO, C., (1954); Étude électrophysiologique des aires auditives corticales du chat. *Arch. int. Physiol.*, **62**, 390–428.

BRENNER, CH., AND MERRITT, H., (1942); Effect of certain cholin derivation on electrical activity of the cortex. *Arch. Neurol. Psychiat. (Chic.)*, **48**, 382–395.

BROȘTEANU, R., ȘI VOINESCU, I., (1958); Modificările reactivitătii creierului la stimularea luminoasă intermitentă produse de accesul convulsiv experimental. *Stud. Cercet. Neurol.*, **3**, 57–68.

BUREŠ, J., AND BUREŠOVÁ, O., (1960); Activation of latent foci of spreading cortical depression in rats. *J. Neurophysiol.*, **23**, 225–236.

BURNS, B. D., (1949); Some properties of the cat's isolated cerebral cortex. *J. Physiol. (Lond.)*, **110**, 9.

BURNS, B. D., (1950); Some properties of the cat's isolated cerebral cortex, *J. Physiol. (Lond.)*, **111**, 50–68.

BURNS, B. D., (1951); Some properties of the isolated cerebral cortex in the unanesthetized cat. *J. Physiol. (Lond.)*, **112**, 156–175.

BURNS, B. D., (1954); The production of after-bursts in isolated unanesthetized cerebral cortex. *J. Physiol. (Lond.)*, **125**, 427–446.

BURNS, B. D., (1955); The mechanism of after-bursts in cerebral cortex. *J. Physiol. (Lond.)*, **127**, 168–188.

BURNS, B. D., GRAFSTEIN, B., AND OLSZEWSKI, J., (1957); Identification of neurogenes giving burst response in isolated cerebral cortex. *J. Neurophysiol.*, **20**, 200–210.

BUSCHE, K. A., (1957); Die krampferregenden Eigenschäften des Penicillins bei unmittelbarer Einwirkung auf die nervöse Substanz. *Acta neurochir. (Wien)*, **5**, 391–457.

CARRERAS, M., MARCHI, G., ANGELERI, F., AND URBANI, M., (1955); The results of a group of electrophysiologic research on the rhinencephalon. *Electroenceph. clin. Neurophysiol.*, **7**, 440.

CHANG, H. T., (1950a); Dendritic potential of cortical neurons as produced by direct electrical stimulation of the cerebral cortex. *J. Neurophysiol.*, **13**, 1–21.

CHANG, H. T., (1950b); Repetitive discharge of cortico-thalamic reverberating circuit. *J. Neurophysiol.*, **13**, 235–258.

CHANG, H. T., (1951); Changes in excitability of cerebral cortex following a single shock applied to cortical surface. *J. Neurophysiol.*, **14**, 95–112.

CHANG, H. T., (1952); Cortical neurons with particular reference to the apical dendrites. *Cold Spr. Harb. Symp. quant. Biol.*, **17**, 189–202.

CHANG, H. T., (1953); Similarity in action between curare and strychnine on cortical neurons. *J. Neurophysiol.*, **16**, 221–233.

CHANG, H. T., (1955a); Cortical response to stimulation of medullary pyramid in rabbit. *J. Neurophysiol.*, **18**, 332.

CHANG, H. T., (1955b); Activation of internuncial neurons of pyramidal fibres of cortical level. *J. Neurophysiol.*, **18**, 452–471.

CHANG, H. T., (1959); The evoked potentials. *Handbook of Physiology*. Sect. I, V. I. J. Field, Editor. Washington, American Physiological Society (pp. 299).

CHATFIELD, P. O., AND DEMPSEY, E. W., (1942); Some effects of prostigmine and acetylcholine on cortical potentials. *Amer. J. Physiol.*, **135**, 633.

CHATRIAN, G. E., AND PETERSEN, M. C., (1960); The convulsive patterns provoked by Indoklon, Metrazol and electroshock. Some depth electrographic observations in human patients. *Electroenceph. clin. Neurophysiol.*, **12**, 715–725.

CHIVU, V., ȘI STERIADE, M., (1952); Conditionarea unui proces epileptic provocat la cîine prin excitarea electrica directa a scoarfei motorii. *Stud. Cercet. Fiziol.*, **3**, 249–255.

CHOW, K. L., AND OBRIST, W. D., (1954); EEG and behavioral changes on application of $Al(OH)_3$-cream on preoccipital cortex of monkeys. *Arch. Neurol. Psychiat. (Chic.)*, **72**, 80–87.

CHUSID, J. G., KOPELOFF, L. M., AND KOPELOFF, N., (1953); Experimental epilepsy in the monkey following multiple intracerebral injections of alumina cream. *Bull. N.Y. Acad. Med.*, **39**, 898–904.

CICARDO, V. H., (1945); Physico-chemical mechanisms. *J. nerv. ment. Dis.*, **101**, 527.

CLARE, M. H., AND BISHOP, G. H., (1955); Dendritic circuits: the properties of cortical paths involving dendrites. *Amer. J. Psychiat.*, **111**, 818–825.

CLARE, M. H., AND BISHOP, G. H., (1957); Action of strychnine on recruiting responses of dendrites of cat cortex. *J. Neurophysiol.*, **20**, 254–274.

CLARK, G., AND WARD, J. W., (1949); Responses elicited by combined stimulation of pairs of fixed electrodes in unanesthetized monkey. *Amer. J. Physiol.*, **158**, 474–477.

CLEMENTI, A., (1929); Stricninizzazione della sfera corticale visiva ed epilessia sperimentale da stimuli luminosi. *Arch. Fisiol.*, **27**, 356–387.

COLFER, H. F., AND ESSEX, H. E., (1947); Distribution of total electrolyte, potassium and sodium in cerebral cortex in relation to experimental convulsions. *Amer. J. Physiol.*, **150**, 27.

COLLE, Y., MUSSIN, Y., MEULDEES, M., ET GYBELS, J., (1957); Étude comparative de l'EEG et de l'activité électrique des nerfs somatiques, respiratoires et végétatifs au cours des crises convulsives expérimentales. *Rev. Neurol.*, **96**, 470–474.

COSTA-FORU, D., (1961); Modificarile cuprului din creier, ficat, rinichi, splina şi sînge determinate de accesul convulsiv experimental la şobolani. *Stud. Cercet. Neurol.*, **6**, 125–129.

CREPAX, P., AND FADIGA, E., (1958); Electrographic observations on the mechanism of predisposition to reflex epilepsy. *Arch. Sci. biol. (Bologna)*, **42**, 385–406.

CRIGHEL, E., (1959); *Cercetari asupra Reactivitatii Corticale*. Bucharest, Acad. R.P.R.

CRIGHEL, E., BROŞTEANU, R., ŞI NEŞTIANU, V., (1956a); Cercetari electroencefalografice asupra reactivitatii corticale. Actiunea clorpromazinei. *Comunicarile Academiei R.P.R.*, **6**, 959–963.

CRIGHEL, E., BROŞTEANU, R., ŞI NEŞTIANU, V., (1956b); Cercetari electroencefalografice asupra reactivitatii corticale în starile de excitabilitate. *Comunicarile Academiei R.P.R.*, **6**, 1401–1406.

CRIGHEL, E., BROŞTEANU, R., ŞI NEŞTIANU, V., (1957); Cercetari electroencefalografice asupra reactivitatii corticale. *Stud. Cercet. Neurol.*, **2**, 53–67.

CRIGHEL, E., KREINDLER, A., AND SOTIRESCU, N., (1963); Investigations concerning positive delayed potentials induced by direct cortical stimulation. *Rev. Sci. med. (Buc.)*, **8**, 19–24 (in Russian).

CRIGHEL, E., AND MANOLESCU, J., (1965); Intracortical mechanisms regulating the neocortical excitability. *Electroenceph. clin. Neurophysiol.*, **18**, 641

CRIGHEL, E., ŞI NEŞTIANU, V., (1957a); Cercetari electroencefalografice asupra reactivitatii corticale a preparatului 'creier izolat' la pisica. *Stud. Cercet. Neurol.*, **2**, 515–521.

CRIGHEL, E., ET NEŞTIANU, V., (1957b); Recherches électrographiques sur le mécanisme de déclenchement de l'activité convulsive de l'écorce. *Rev. Neurol.*, **96**, 526–527.

CRIGHEL, E., SOTIRESCU, N., AND MARCOVICI, N., (1965); Reactivity of cat immature neocortex to direct stimulation. *Rev. roum. neurol.*, **2**, 45–51.

CRIGHEL, E., ŞI STOICA, E., (1961); Cercetari asupra focarului mescalinic sigmoidian. *Stud. Cercet. Neurol.*, **6**, 547–556.

CRIGHEL, E., ŞI STOICA, E., (1962); Cercetari asupra rolului unor sisteme aferente în declanşarea activitatii unui focar convulsiv. *Stud. Cercet. Neurol.*, **7**, 173–181.

CRIGHEL, E., STOICA, E., ŞI GLINKA RZEZNICKA, Z., (1962); Actiunea mescalinei asupra raspunsurilor evocate primare şi a celor secondare din cursul somnului barbituric profund. *Stud. Cercet. Neurol.*, **7**, 41–48.

CRIGHEL, E., ET TUDOR, I., (1963b); Quelques données expérimentales sur le mécanisme de facilitation de la postdécharge épileptiforme du néocortex. *Rev. Neurol.*, **108**, 180–181.

CRITCHLEY, M., (1937); Musicogenic epilepsy. *Brain*, **60**, 13–27.

CROSSLAND, J., (1953); The significance of brain acetylcholine. *J. ment. Sci.*, **99**, 247.

DAVIES, E. W., MCCULLOCH, W. W., AND ROSEMAN, E., (1944); Rapid changes in the $O_2$ tension of cerebral cortex during induced convulsion. *Amer. J. Psychiat.*, **100**, 805–829.

DAWSON, R. M. C., (1953); Cerebral amino acids in fluoroacetate poisoned, anesthetized and hypoglycemic rats. *Biochim. Biophys. Acta (Amst.)*, **11**, 548.

DAWSON, R. M. C., AND RICHTER, D., (1950); Effect of stimulation on the phosphate esters of brain. *Amer. J. Physiol.*, **160**, 203–211.

DELGADO, J. M. R., AND HAMLIN, H., (1958); Direct recording of spontaneous and evoked seizures in epileptics. *Electroenceph. clin. Neurophysiol.*, **10**, 463–486.

DELL, M. B., BONVALLET, M., ET DELL, P., (1951); Evolution corticale des crises épileptiques provoquées chez le chat. *Rev. Neurol.*, **84**, 595–602.

DEMPSEY, E. W., AND MORRISON, R. S., (1942); The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. *Amer. J. Physiol.*, **135**, 293–300.

DE ROBERTIS, E., DE LORES ARNAIZ, R. G., SALGANIKOFF, I., PELLEGRINO DE IRALDI, A., AND ZIEHER, L. M., (1963); Isolation of synaptic vesicles and structural organisation of the acetylcholine system within brain nerve endings. *J. Neurochem.*, **10**, 225–235.

DOLIN, A. O., (1939); Uslovnyi epileptitcheskii pripadok. *Arch. Sci. biol. (Bologna)*, **4**, 1.

DOW, R. S., FERNANDEZ-GUARDIOLA, A., AND MANNI, E., (1962); The production of cobalt experimental epilepsy in the rat. *Electroenceph. clin. Neurophysiol.*, **14**, 399–407.

DUNLOP, C. W., (1957a); Effect of carbon dioxide on deep structures of temporal lobe of brain in the marsupial phalanger. *Amer. J. Physiol.*, **190**, 172.

DUNLOP, C. W., (1957b); Effect of carbon dioxide in the rhinencephalon on the marsupial phalanger. *Amer. J. Physiol.*, **191**, 200–202.

ECCLES, J. C., (1951); Interpretation of action potentials evoked in the cerebral cortex. *Electroenceph. clin. Neurophysiol.*, **3**, 449–464.

ECCLES, J. C., (1957); *The Neurophysiology of Nerve Cells.* Baltimore, John Hopkins Press.

ECCLES, J. C., (1959); Neuron physiology. *Handbook of Physiology, Sect. I, Neurophysiology, V.I.* Baltimore, Waverley Press.

ECHLIN, F. A., (1959); The supersensitivity of chronically isolated cerebral cortex as a mechanism in focal epilepsy. *Electroenceph. clin. Neurophysiol.*, **11**, 697–722.

ECHLIN, F. A., ARNETT, V. AND ZOLL, J., (1952); Paroxysmal high voltage discharges from isolated and partially isolated human and animal cerebral cortex. *Electroenceph. clin. Neurophysiol.*, **4**, 147–164.

ECHLIN, F. A., AND MCDONALD, J., (1954); The supersensitivity of chronically isolated and partial isolated cerebral cortex as a mechanism in focal cortical epilepsy. *Trans. Amer. neurol. Ass.*, **79**, 75–79.

ECTORS, L., (1956); An experimental study of the effect of barbiturates on cortical epilepsy. *Acta Neurol. Psychiat. Belg.*, **56**, 138–152.

ECTORS, L., cit. from BREMER, E., (1958); *Bases Physiologiques et Aspects Cliniques de l'Épilepsie.* Paris, Masson.

EFRON, R., (1957); The conditioned inhibition of uncinate fits. *Brain*, **82**, 251–262.

EIDELBERG, E., AND FRENCH, J. D., (1961); Dendritic mechanisms. *Epilepsia (Amst.)*, **2**, 39–41.

EIDELBERG, E., KONIGSMARK, B., AND FRENCH, J. D., (1959); Electrocortical manifestations of epilepsy in monkey. *Electroenceph. clin. Neurophysiol.*, **11**, 121–128.

ELLIOTT, K. A. C., (1955); *Chemical Studies in Relation to Convulsive Conditions in Neurochemistry.* K. A. C. Elliott, J. H. Page and J. H. Quastel, Editors. Springfield, Thomas (p. 677).

ELLIOTT, K. A. C., AND HENDERSON, N., (1948); Metabolism of brain tissue slices and suspensions from various mammals. *J. Neurophysiol.*, **11**, 473.

ELLIOTT, K. A. C., AND PENFIELD, W., (1948); Respiration and glycolysis of focal epileptogenetic human brain tissue. *J. Neurophysiol.*, **11**, 485.

ELLIOTT, K. A. C., SWANK, R. L., AND HENDERSON, N., (1950); Effects of anesthetics on acetylcholine content of brain. *Amer. J. Physiol.*, **162**, 469–474.

ENOMOTO, T. F., AND AJMONE MARSAN, C., (1959); Epileptic activation of single cortical neurons and their relationship with electroencephalographic discharges. *Electroenceph. clin. Neurophysiol.*, **11**, 199–218.

ERICKSON, T. C., (1940); Spread of the epileptic discharge. An experimental study of the after-discharge induced by electrical stimulation of the cerebral cortex. *Arch. Neurol. Psychiat. (Chic.)*, **43**, 429–452.

ERICKSON, T. C., GILSON, W. E., ELWEHJEN, C. A., AND NEWELL, G. W., (1947); Wheat gluten as a convulsant. *Ass. Res. nerv. Dis. Proc.*, **26**, 164–178.

FAETH, W. H., WALKER, A. E., AND ANDY, O. J., (1954); The propagation of cortical and subcortical epileptic discharge. *Epilepsia (Amst.)*, **3**, 37–48.

FAETH, W. H., WALKER, A. E., AND WARNER, W. A., (1956); Experimental subcortical epilepsy. *Arch. Neurol. Psychiat. (Chic.)*, **75**, 548–562.

FELDBERG, W., (1957); Acetylcholine. *Metabolism of the Nervous System.* D. Richter, Editor. Oxford, Pergamon Press (pp. 493).

FERNANDEZ-GUARDIOLA, A., ALCARAZ, M., AND GUZMAN, F. C., (1961); Inhibition of convulsive activity by the reticular formation. *Acta neurol. lat.-amer.*, **7**, 30–36.

FERNANDEZ-GUARDIOLA, A., MANNI, E., WILSON, J. H., AND DOW, R. S., (1962); Microelectrode recording of cerebellar and cerebral unit activity during convulsive discharge. *Exp. Neurol.*, **6**, 48–69.

FERRARI, E., E GALASSO, G., (1957); Contributo sperimentale allo studio delle vie preferenziali di diffusione dell'attività epilettica corticale. *Acta neurol. (Napoli)*, **12**, 145–157.

FESSARD, A., (1951); Aspects électrophysiologiques de la transmission synaptique. *Arch. int. Physiol.*, **59**, 605–618.

FESSARD, A., (1958); Les mécanismes de synchronisation interneuronique et leur intervention dans la crise épileptique. *Bases Physiologiques et Aspects Cliniques de l' Epilepsie.* Th. Alajouanine, Editor. Paris. Masson (pp. 37–60).

FISCHER-WILLIAMS, M., AND COOPER, R. A., (1963); Depth recording from the human brain in epilepsy. *Electroenceph. clin. Neurophysiol.*, **15**, 568–587.

FLINK, E. B., (1956); Magnesium deficiency syndrome in man. *J. Amer. med. Ass.*, **160**, 1406–1409.

FORSTER, F. M., (1945); Action of acetylcholine on motor cortex. *Arch. neurol. Psychiat. (Chic.)*, **54**, 391.

FREEDMAN, D. A., AND FERRIS, G. S., (1956); Effect of mesencephalic lesions on metrazol-induced cortical activity. *Neurology (Minneap.)*, **6**, 173–178.

FRENCH, J. D., GERNANDT, B. E., AND LIVINGSTONE, R. B., (1956); Regional difference in seizure susceptibility in monkey cortex. *Arch. neurol. Psychiat. (Chic.)*, **75**, 260–274.

GALAMBOS, R., ROSE, J. E., BROMILEY, R. B., AND HUGHENS, J. R., (1952); Microelectrode studies on medial geniculate body of cat. II. Responses to clicks. *J. Neurophysiol.*, **15**, 359–380.

GANGLOFF, H., AND MONNIER, M., (1957); The action of anticonvulsivant drugs tested by electrical stimulation of the cortex, diencephalon and rhinencephalon in the unanaesthetized rabbit. *Electroenceph. clin. Neurophysiol.*, **9**, 43–58.

GÄNSHIRT, H., POECK, K., SCHLIEP, H., VETTER, K., UND GÄNSHIRT, L., (1959); Durchblutung und Sauerstoffversorgung des Gehirns im Elektrokrampf bei Katze und Hund. *Arch. Psychiat. Nervenkr.*, *198*, 601–621.

GARCÍA-AUSTT, JR., E., ARANA, R., MIGLIARO, E., SANDE, M. T., AND SEGUNDO, J. P., (1954); Changes in the EEG and in the tendon jerks induced by stimulation of the fornix in man. *Electroenceph. clin. Neurophysiol.*, **6**, 653–661.

GARNER, J., AND FRENCH, J. D., (1958); Regional differences in seizure susceptibility in cat cortex. *Arch. Neurol. Psychiat. (Chic.)*, **80**, 675–681.

GASTAUT, H., (1950); Combined photic and metrazol activation of the brain. *Electroenceph. clin. Neurophysiol.*, **2**, 263–275.

GASTAUT, H., (1954); *The Epilepsies. Electroclinical Correlations.* Springfield, Thomas.

GASTAUT, H., (1958a); Discussion. *The Reticular Formation of the Brain.* H. Jasper *et al.*, Editors. Boston, Little (pp. 361–362).

GASTAUT, H., (1958b); The physiopathology of grand mal seizures generalized from the start. *J. nerv. ment. Dis.*, **127**, 21–33.

GASTAUT, H., AND FISCHER-WILLIAMS, M., (1959); The physiopathology of epileptic seizures. *Handbook of Physiology.* Sect. I, V. I. J. Field, Editor. Baltimore, Williams and Wilkins (pp. 329–363).

GASTAUT, H., ET GASTAUT, Y., (1958); Etude électroencéphalographique et clinique des convulsions anoxiques de l'enfant. Leur situation dans le cadre des convulsions infantiles. *Rev. Neurol.*, **99**, 100–116.

GASTAUT, H., ET HUNTER, J., (1950a); Le phénomène de l'alternance dans les rythmes induits par la stimulation lumineuse intermittente sur le cortex optique strychninisé. *J. Physiol. (Paris)*, **42**, 592–596.

GASTAUT, H., AND HUNTER, J., (1950b); An experimental study of the mechanism of photic activation in idiopathic epilepsy. *Electroenceph. clin. Neurophysiol.*, **2**, 263–287.

GASTAUT, H., NAQUET, R., ET ROGER, A., (1952); Etude des postdécharges électriques provoquées par stimulation du complexe nucléaire amygdalien. *Rev. Neurol.*, **87**, 224–231.

GASTAUT, H., NAQUET, R., ET VIGOUROUX, M., (1953a); Un cas d'épilepsie amygdalienne expérimentale chez le chat. *Electroenceph. clin. Neurophysiol.*, **5**, 291–294.

GASTAUT, H., NAQUET, R., VIGOUROUX, R., ROGER, A., ET BADIER, M., (1953b); Etude électrographique chez l'homme et chez l'animal des décharges épileptiques dites 'psychomotrices'. *Rev. Neurol.*, **88**, 310–354.

GASTAUT, H., REGIS, H., DONGIER, S., AND ROGER, A., (1956); EEG conditioning of epileptic discharges and the concept of reflex-conditioned epilepsy. *Electroenceph. clin. Neurophysiol.*, **8**, 720.

GASTAUT, H., ET ROGER, A., (1955); *Les Grandes Activités du Lobe Temporal.* Masson. Paris (p. 83).

GASTAUT, H., TOGA, M., AND NAQUET, R., (1958); Clinical electrographic and anatomical study of epilepsy induced in dogs by the ingestion of agenized proteins. M. Baldwin and P. Bailey, Editors. *Temporal Lobe Epilepsy.* Springfield, Thomas (pp. 268–278).

GASTAUT, H., VIGOUROUX, M., ET NAQUET, R., (1952); Lésions épileptogènes amygdalo-hippocampiques provoquées chez le chat par injection de 'crème d'alumine'. *Rev. Neurol.*, **87**, 607–609.

GEIGER, A., (1957); Chemical changes accompanying activity in the brain. *Metabolism of the Nervous System.* K. Richter, Editor. Oxford, London, Pergamon Press (p. 245).

GEIGER, A., HORVATH, N., AND KAWAKITA, Y., (1960); The incorporation of $C^{14}$ derived from glucose into the proteins of the brain cortex at rest and during activity. *J. Neurochem.*, **5**, 311–322.

GELLHORN, E., (1953); *Physiological Foundations of Neurology and Psychiatry.* Minneapolis, Univ. of Minnesota Press (p. 141).

GELLHORN, E., AND HEYMANS, C., (1948); Differential action of anoxia, asphyxia and carbon dioxide on normal and convulsive potentials. *J. Neurophysiol.*, **11**, 261–274.

GELLHORN, E., AND YESINICK, L., (1941); The effect of oxygen lack and inhalation of carbon dioxide on chemically induced convulsions. *Amer. J. Physiol.*, **133**, 290.

GELLHORN, E., AND YESINICK, L., (1942); The significance of carotid sinus reflexes for the effects of anoxia and carbon dioxide on convulsions. *Amer. J. Physiol.*, **137**, 404–408.

GERARD, B. W., AND LIBET, B., (1941); Steady potential field and neuronal activity. *J. Neurophysiol.*, **4**, 435.

GERIN, P., (1960); Microelectrode investigations of the mechanism of electrically induced epileptiform seizures (afterdischarge). *Arch. ital. Biol.*, **98**, 21–40.

GERSHENOVITSCH, Z. S., KRICHEVSKAYA, A. A., AND KOLOUSEK, J., (1963); The effect of raised oxygen pressure and of methionine sulfoximine on the glutamine synthetase activity of rat brain. *J. Neurochem.*, **10**, 79–82.

GERSHOFF, S. N., NEWELL, G. W., AND STONE, W. E., (1949); Chemical studies of the brain in dogs with 'running fits'. *Arch. Biochem.*, **21**, 74.

GIBBS, F. A., AND GIBBS, E. D., (1936); The convulsive threshold of various parts of the cat's brain. *Arch. Neurol. Psychiat. (Chic.)*, **35**, 109.

GIBBS, F. A., MAXWELL, H., AND GIBBS, E. L., cited by J. H. Quastel and D. M. J. Quastel (1961); *The Chemistry of Brain Metabolism in Health and Disease*, Springfield, Thomas, p. 7.

GLOOR, P., (1954); Subcortical and cortical responses to stimulation of the amygdaloid nucleus of the cat. *Electroenceph. clin. Neurophysiol.*, **6**, 711.

GLOOR, P., VERA, C. L., SPESTI, L., AND RAY, S. N., (1961); Investigations on the mechanisms of epileptic discharges in the hippocampus. *Epilepsia (Amst.)*, **2**, 42–62.

GOLDIE, L., AND GREEN, J. M., (1959); A study of the pathological factors in a case of sensory reflex epilepsy. *Brain*, **82**, 505–518.

GOLDRING, S., AND O'LEARY, J. L., (1950); Experimentally derivates between EEG and steady cortical potential. *J. Neurophysiol.*, **13**, 275–288.

GOLDRING, S., AND O'LEARY, J. L., (1954); Correlation between steady transcortical potential and evoked response. *Electroenceph. clin. Neurophysiol.*, **6**, 189–200.

GOODFELLOW, E. E., AND NIEMER, W. T., (1961); The spread of afterdischarge from stimulation of the rhinencephalon in the cat. *Electroenceph. clin. Neurophysiol.*, **13**, 710–721.

GOODWIN, J. E., KORR, W. K., AND LAWSON, F. L., (1940); Bioelectric responses in metrazol and insulin shocks. *Amer. J. Psychiat.*, **96**, 1389–1405.

GORDON, M. T., AND WAELSCH, H., CITED BY KEYNES, R. D., AND LEWIS, P. R., (1955); Electrolytes and nerve function. *Neurochemistry*. K. A. C. Elliott, J. H. Page and J. H. Quastel, Editors. Springfield, Thomas (p. 440).

GORE, M. B. R., AND MCILWAIN, H., (1952); Effects of some inorganic salts in the metabolic response of section of mammalian cerebral cortex to electrical stimulation. *J. Physiol. (Lond.)*, **117**, 471–483.

GRAFSTEIN, B., AND SASTRY, P. B., (1957); Some preliminary electrophysiological studies on chronic neuronally isolated cerebral cortex. *Electroenceph. clin. Neurophysiol.*, **9**, 723.

GREEN, J. D., (1958); Behavior of single cells during seizure activity (Ammon's horn). *Electroenceph. clin. Neurophysiol.*, **10**, 361.

GREEN, J. D., AND ADEY, W. A., (1956); Electrophysiological studies of hippocampal connections and excitability. *Electroenceph. clin. Neurophysiol.*, **8**, 245–262.

GREEN, J. D., DUISBERG, H., AND MCGRATT, W. B., (1951); Electrocorticography in psychomotor epilepsy. *Electroenceph. clin. Neurophysiol.*, **3**, 293–299.

GREEN, J. D., AND NAQUET, R., (1957); Étude sur la propagation locale et à distance des décharges épileptiques. *IVe Congr. int. EEG Neurophysiol. (Bruxelles)*. Acta Medica Belgica (pp. 225–249).

GREEN, J. D., AND SHIMAMOTO, F., (1953); Hippocampal seizures and their propagation. *Arch. Neurol. Psychiat. (Chic.)*, **70**, 687–702.

GROSSMAN, C., (1954); Relationship of form and frequency of experimental epileptic discharges to age. *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 43–46.

GRUNDFEST, H., (1957); Electrical inexcitability of synapses and some of the consequences in the central nervous system. *Physiol. Rev.*, **37**, 337–361.

GUALTIEROTTI, T., MARTINI, E., AND MARMORATI, A., (1950); Electronarcosis. Inhibition of cortical electrical activity following local application of pulsed stimuli. *J. Neurophysiol.*, **13**, 4–8.

GUILLAUME, J., MASARS, G., ET MASARS, Y., (1953); Indications chirurgicales dans les épilepsies dites temporales. *Rev. Neurol.*, **88**, 461.

GURDJAN, E. S., WEBSTER, J. E., AND STONE, W. E., (1947); Cerebral metabolism in metrazol convulsions in the dog. *Res. Publ. Ass. nerv. ment. Dis.*, **26**, 184.

GUSELNIKOVA, K. G., (1959); The study of the bioelectric activity of diencephalon during epileptiform seizures in the rat. *Problems of Epilepsy*. Moscow, Medgiz (In Russian).

HABER, C., AND SAIDEL, L., (1948); Glutamic acid in neural activity. *Fed. Proc.*, **7**, 47.

HAMPSON, J. L., ESSIJ, C. F., MCCAULEY, A., AND HIMWICH, H. E., (1950); Effects of diisopropyl fluorophosphate on electroencephalogram and cholinesterase activity. *Electroenceph. clin. Neurophysiol.*, **2**, 41–48.

HARRISON, F., MAGOUN, H. W., AND RANSON, S. W., (1938); Some determinations of the thresholds to stimulation with the faradic and direct current in the brain stem. *Amer. J. Physiol.*, **121**, 708.

HAWKINS, JR., J. E., AND SARETT, L. H., (1957); On the efficacy of asparagine, glutamine γ-aminobutyric acid and 2-pyrrolidinone in preventing chemically induced seizures in mice. *Clin. Chim. Acta*, **2**, 481–484.

HAYASHI, T. A., (1952); A physiological study of epileptic seizures following cortical stimulation in animals and its application to human clinics. *Jap. J. Physiol.*, **3**, 46–64.

HAYNE, R. A., BELLINSON, L., AND GIBBS, F. A., (1949); Electrical activity of subcortical area in epilepsy. *Electroenceph. clin. Neurophysiol.*, **1**, 437–445.

HEBB, C. D., AND SMALLMAN, B. N., (1956); Intracellular distribution of choline acetylase. *J. Physiol. (Lond.)*, **134**, 385.

HEBB, C. D., AND WHITTAKER, V. P., (1958); Intracellular distribution of acetylcholine and choline acetylase. *J. Physiol. (Lond.)*, **142**, 187–196

HENRY, C. E., AND PRIBRAM, K. H., (1954); Effect of aluminium hydroxide cream implantation in cortex of monkey on EEG and behavior performance. *Electroenceph. clin. Neurophysiol.*, **6**, 693–694.

HENRY, C. E., AND SCOVILLE, W. B., (1952); Suppression-burst activity from isolated cerebral cortex in man. *Electroenceph. clin. Neurophysiol.*, **4**, 1–22.

HIPPIUS, H., ROSENKATTER, L., UND SELBACH, H., (1957); Untersuchungen zure Verlaufsdiagnostik kortikaler Krampfpotentiale. *Arch. Psychiat. Nervenkr.*, **196**, 379–401.

HUGHENS, J. R., (1959a); Studies on the supracallosal mesial cortex of unanaesthetized conscious mammals. I. Cat. A. Movements elicited by electrical stimulation. *Electroenceph. clin. Neurophysiol.*, **11**, 447–458.

HUGHENS, J. R., (1959b); Studies on the supracallosal mesial cortex of unanaesthetized conscious mammals. I. Cat. B. Electrical activity. *Electroenceph. clin. Neurophysiol.*, **11**, 459–469.

HUNTER, J., AND INGVAR, D. H., (1955); Pathways mediating metrazol induced irradiation of visual impulses. *Electroenceph. clin. Neurophysiol.*, **7**, 39–60.

HYDE, J. S., BECKETT, S., AND GELLHORN, E., (1949); Acetylcholine and convulsive activity. *J. Neurophysiol.*, **12**, 17–27.

HYDÉN, H., (1943); Protein metabolism in the nerve cell during growth and function. *Acta physiol. scand.*, **6**, Suppl. 67.

INGVAR, D. H., (1955a); Reproduction of the 3 per second spike and wave EEG pattern by subcortical electrical stimulation in cats. *Acta physiol. scand.*, **33**, 137–150.

INGVAR, D. H., (1955b); Electrical activity of isolated cortex in the unanesthetized cat with isolated brain stem. *Acta physiol. scand.*, **33**, 151–168.

INGVAR, D. H., (1959); On the patho-physiology of the 3 per second spike and wave epilepsy. *Electroenceph. clin. Neurophysiol.*, **11**, 187.

IWATA, K., AND SNIDER, R. S., (1954); Cerebello-hippocampal influences on the electroencephalogram. *Electroenceph. clin. Neurophysiol.*, **11**, 439–446.

JANZEN, R., MAGOUN, R., UND BECHTER, F., (1951); Tierexperimentelle Untersuchungen über die Ausbreitung der epileptischen Erregung. *Dtsch. Z. Nervenheilk.*, **166**, 223–237.

JASPER, H., (1949); Electrical signs of epileptic discharge. *Electroenceph. clin. Neurophysiol.*, **1**, 11–18.

JASPER, H., (1951); Electrocorticogram in man. *Electroenceph. clin. Neurophysiol.*, **2**, 16–29.

JASPER, H., (1955); Electrical activity in the depths of the cortex as compared to that on the surface. *Res. Trans. Amer. neurol. Ass. (Chic.)*, 21–22.

JASPER, H., (1957); Reflections on the spike and wave complex in cortical and mesencephalic seizures. *Electroenceph. clin. Neurophysiol.*, **9**, 379.

JASPER, H., (1962a); Changing concepts of focal epilepsy. *Round Table Conference on the Surgical Treatment of the Epilepsies and its Neurophysiological Aspects. Smolnice, 1960.* Bratislava, Publishing House Slovak Acad. Sci. (p. 27).

JASPER, H., (1962b); Discussion. *Round Table Conference on the Surgical Treatment of the Epilepsies and its Neurophysiological Aspects.* Bratislava, Publishing House Slovak Acad. Sci. (p. 173).

JASPER, H., AJMONE MARSAN, C., AND STOLL, J., (1952); Cortico-fugal projections to the brain stem. *Arch. Neurol. Psychiat. (Chic.)*, **67**, 155–166.

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

JASPER, H., AND ERICKSON, T. C., (1941); Cerebral blood flow and pH in excessive cortical discharge induced by metrazol and electrical stimulation. *J. Neurophysiol.*, **4**, 333–347.

JENKNER, F. L., AND WARD, A. A., (1953); Bulbar reticular formation and tremor. *Arch. Neurol. Psychiat. (Chic.)*, **70**, 489.

JINNAI, D., YOSHIDA, T., SONYI, T., AND KOSAKA, F., (1950); Experimental studies on the march of spasms during epileptic convulsions. *Acta Med. Okayama*, **8**, 26–29.

JOHNSON, H. C., AND WALKER, A. E., (1952); Response of experimental epileptic foci to intravenous and topical metrazol. *Electroenceph. clin. Neurophysiol.*, **4**, 131–142.

JUNG, R., (1949); Hirnelektrische Untersuchungen über den Elektrokrampf; die Erregungsabläufe in corticalen Hirnregionen bei Katze und Hund. *Arch. Psychiat. Nervenheilk.*, **183**, 206–244.

JUNG, R., (1951); Origine e propagazione di potenziali convulsivi cerebrali nelle ricerche sperimentali negli animali. *Riv. Neurol.*, **21**, 333–347.

JUNG, R., (1957); Conditions for the development of seizure activity in experimental epilepsy. *Electroenceph. clin. Neurophysiol.*, **9**, 352.

JUNG, R., UND TÖNNIES, J. F., (1950); Über Entstehung und Erhaltung von Krampfentladungen. Die Vorgänge am Reizort und die Bremsfähigkeiten des Gehirns. *Arch. Psychiat.*, **185**, 701–735.

KANDEL, E. R., AND SPENCER, W. A., (1961); The pyramidal cell during hippocampal seizure. *Epilepsia (Amst.)*, **2**, 63–69.

KELLAWAY, P., (1957); Ontogenetic evolution of electrical activity of the brain in man and animals. *Proc. First int. Congr. Neurol. Sci., Brussels* (pp. 141–154).

KENDRYCK, F. J., AND GIBBS, A. F., (1958); Interrelations of medial temporal and orbital areas of man revealed by strychnine spikes. *Arch. Neurol. Psychiat. (Chic.)*, **79**, 518–524.

KILLAM, K. F., (1957); Convulsant hydrazides. II. Comparison of electrical changes and enzyme inhibition induced by the administration of thiosemicarbazide. *J. Pharmacol. exp. Ther.*, **119**, 263–271.

KING, R. B., SCHRIKER, JR., J. L., AND O'LEARY, J. L., (1953); An experimental study of the transition from normal to convulsoid cortical activity. *J. Neurophysiol.*, **16**, 286–298.

KIYONO, S., AND MATSUMOTO, J., (1963); Reflex convulsions. *Med. J. Osaka Univ.*, **13**, 387–392.

KLEIN, J. R., AND OLSEN, N. S., (1947); Effect of convulsive activity upon the concentration of brain glucose, glycogen, lactate and phospate. *J. biol. Chem.*, **167**, 746.

KOLOUSEK, J., HERAB, F., UND JIRACEK, V., (1959a); Beitrag zur Kenntnis des Stickstoffmetabolismus des Gehirns der Ratten die auf einem akustischen epileptogenen Reiz gegenüber empfindlich oder unempfindlich sind. *J. Neurochem.*, **4**, 175–177.

KOLOUSEK, J., AND JIRACEK, V., (1959b); Stickstoffmetabolismus des Gehirns und der Leber bei Ratten nach einer Applikation von Methioninsulfoximine. *J. Neurochem.*, **4**, 178–182.

KONIGSMARK, B. W., ABDULLAH, A. F., AND FRENCH, J. D., (1958); Cortical spread of afterdischarge in the monkey. *Electroenceph. clin. Neurophysiol.*, **10**, 687–696.

KOOI, K. A., AND BECK, E. C., (1956); Frequency of photic stimulation as a variable in the activation of experimental convulsions. *Electroenceph. clin. Neurophysiol.*, **8**, 653–663.

KOPELOFF, L. M., BURRERA, E., AND KOPELOFF, N., (1942); Recurrent convulsive seizures in animals produced by immunologic and chemical means. *Amer. J. Psychiat.*, **98**, 881–902.

KOPELOFF, N., KENNARD, M. A., PACELLA, B. L., KOPELOFF, L. M., AND CHUSID, J. G., (1950); Section of corpus callosum in experimental epilepsy in the monkey. *Arch. Neurol. Psychiat. (Chic.)*, **63**, 719–727.

KORNMÜLLER, A. E., (1937); *Die bioelektrischen Erscheinungen der Hirnrindenfelder.* Leipzig, Thieme.

KREINDLER, A., (1946); Recherches expérimentales sur les relations entre le sinus carotidien et le système nerveux central. *Bull. Soc. Sci. Acad. Roum.*, **28**, 448–481.

KREINDLER, A., (1955); *Epilepsia.* Bucureşti, Acad. R. P. R.

KREINDLER, A., (1957); Sur certains mécanismes neurophysiologiques élementaires qui sont á la base de l'état de conscience. *Premier Congr. int. Sci. Neurol., Bruxelles.*

KREINDLER, A., (1960); *Epilepsia. Kliniceskie i Eksperimentalnyie Issledovania.* Moskova, Medgiz.

KREINDLER, A., (1962); Arrest mechanism of the epileptic seizure. *Epilepsia (Amst.)*, **3**, 329–337.

KREINDLER, A., ATZEV, E., ŞI CRIGHEL, E., (1959); Cercetari asupra influentei electrotonusului asupra activitatii convulsive corticale. *Stud. Cercet. Neurol.*, **4**, 89–98.

KREINDLER, A., BROŞTEANU, R., ŞI POILICI, I., (1957); Corelatii electroencefalografice şi vegetative *stud. Cercet. Neurol.*, **2**, 462–476.

KREINDLER, A., CRIGHEL, E., ŞI CALCAIANU, GH., (1961); Modificarile respunsului evocat somestezic produse de descarcarile focale penicilinice şi pentazolice. *Stud. Cercet. Neurol.*, **6**, 347–352.

KREINDLER, A., CRIGHEL, E., ŞI CHIVU, V., (1950a); Modificarile de excitabilitate ale vagosimpati-

cului pentru pragul reflexului inhibitor al respiratiei, reflexului depresor, cord şi stomac dupa accesul epileptic produs prin electroşoc. *Bull. şt. Sec. St. med. Acad. R.P.R.*, **2**, 951–966.

KREINDLER, A., CRIGHEL, E., ŞI SOTIRESCU, N., (1962); Modificarile respunsului cortical direct produs de mescalina şi reserpina. *Stud. Cercet. Neurol.*, **7**, 287–296.

KREINDLER, A., CRIGHEL, E., ET SOTIRESCU, N., (1963a); Recherches électrographiques sur les mécanismes d'organisation des manifestations convulsives focales à la suite d'une stimulation électrique néocorticale. *Rev. Neurol.*, **108**, 181–182.

KREINDLER, A., CRIGHEL, E., ŞI TUDOR, L., (1963b); Mecanisme reflexe şi anoxice în modificarile electrocorticografice produse de insuficienta circulatorie cerebrala acuta. *Stud. Cercet. Neurol.*, **8**, 93–104.

KREINDLER, A., IONESCU, I., ŞI GOLDHAMMER, B. L., (1957b); Studiul clinic şi electroencefalografic al unui caz de epilepsie de trunchi cerebral. *Neurologia (Buc.)*, **2**, 54–62.

KREINDLER, A., MISON-CRIGHEL, N., (1957); Biohimiceskie essledovaniia pri eksperimentalnoi epilepsii. *J. Nevropat. Psihiat.*, **57**, 1205–1209.

KREINDLER, A., OLTEANU, I., CRIGHEL, E., ŞI CHIVU, V., (1950b); Cercetari asupra accesului convulsiv de trunchi cerebral. *Stud. Cercet. Fiziol. Neurol.*, **1**, 91–113.

KREINDLER, A., ET STERIADE, M., (1958); *La Physiologie et la Physiopathologie du Cervelet.* Paris, Masson.

KREINDLER, A., ŞI STERIADE, M., (1960a); *Cerebelul.* Bucureşti, Acad. R.P.R.

KREINDLER, A., AND STERIADE, M., (1960b); Effect of cerebellar stimulation on focal electrical afterdischarge. *Acta neurol. lat.-amer.*, **6**, 119–136.

KREINDLER, A., AND STERIADE, M., (1961); Diffuse and selective facilitation of focal cortical afterdischarges by stimulating the reticular formation and the diffuse thalamic system. *Excerpt. Med. (Amst.), Int. Congr. Ser.*, No. **37**, 23.

KREINDLER, A., ŞI STERIADE, M., (1962); Sootnoşeniia charaktera elektriceskin razreadov posiedeistviia epileptoidnovo tipa i razlicinîh struktur tentralnoi nervoi sistemî. *Struktura i Funktiia Nervnoi Sistemi.* Moskova, Medgiz (pp. 27–34).

KREINDLER, A., AND STERIADE, M., (1963a); The amygdaloid electrical afterdischarge in the cat. I. Excitability parameters. II. Organization of intra-stimulatory discharges. *Electroenceph. clin. Neurophysiol.*, **15**, 535.

KREINDLER, A., AND STERIADE, M., (1963b); Functional differentiation within the amygdaloid complex inferred from peculiarities of afterdischarges. *Electroenceph. clin. Neurophysiol.*, **15**, 811–826.

KREINDLER, A., AND STERIADE, M., (1964); EEG patterns of arousal and sleep induced by stimulating the amygdaloid complex in the cat. *Arch. ital. Biol.*, **102**, 576–586.

KREINDLER, A., STERIADE, M., ŞI CRIGHEL, E., (1961); Relatiile dintre paroxismele focale corticale şi raspunsurile evocate senzoriale. *Stud. Cercet. Neurol.*, **6**, 39–44.

KREINDLER, A., STERIADE, M., AND DEMETRESCU, M., (1960a); Topographic differentiation in nucleus ventralis anterior with respect to facilitatory influences on focal cortical afterdischarges. *Electroenceph. clin. Neurophysiol.*, **12**, 750.

KREINDLER, A., STERIADE, M., ET UNGHER, J., (1960b); Le rôle des afférences dans le déclenchement de l'accès convulsif. *Wld Neurol.*, **1**, 276–285.

KREINDLER, A., STERIADE, M., VOINESCU, I., ŞI BOTEZ, M., (1958); Consideratii asupra unor cazuri de epilepsie reflexa. *Neurologia (Buc.)*, **3**, 203–215.

KREINDLER, A., UNGHER, J., ŞI STOICA, I., (1955); Cercetari asupra componentelor respiratorii şi motorii ale reflexului de aparare şi actiunea accesului convulsiv asupra acestor componente. *Comun. Acad. R.P.R.*, **5**, 761–770.

KREINDLER, A., VOICULESCU, V., BROŞTEANU, R., ET VOINESCU, I., (1956); Activité électrique de l'hippocampe du chat pendant l'accès convulsif expérimental. *Rev. Neurol.*, **94**, 872–876.

KREINDLER, A., VOICULESCU, V., BROŞTEANU, R., ET VOINESCU, I., (1959); La réaction d'éveil après l'accès convulsif. *Electroencephalography and clinical Neurophysiology and Epilepsy.* Vol. III. First int. Congr. Neurol. Sci., Brussels, 1957. London, Paris, Pergamon Press (pp. 248–253).

KREINDLER, A., VOICULESCU, V., BROŞTEANU, R., ET VOINESCU, I., (1960); Recherches sur l'épilepsie expérimentale focale provoquée par l'application de pénicilline sur l'écorce cérébrale. *Arch. ital. Biol.*, **68**, 10–20.

KREINDLER, A., VOICULESCU, V., BROŞTEANU, R., VOINESCU, I., ŞI NEŞTIANU, V., (1953); Tulburarile relatiilor corticosubcorticale în accesul convulsiv experimental studiate prin metoda electroencefalografica. *Stud. Cercet. Fiziol. Neurol.*, **4**, 311.

KREINDLER, A., VOICULESCU, V., BROŞTEANU, R., VOINESCU, I., ŞI NEŞTIANU, V., (1955); Studiul

electrofiziologic al modificarilor reflexului spinal nociceptiv sub influenta accesului electroconvulsiv la pisica. *Bull. şt. Sec. St. med. Acad. R.P.R.*, **7**, 21–37.

KREINDLER, A., VOICULESCU, V., BROŞTEANU, R., VOINESCU, I., ŞI NEŞTIANU, V., (1956a); Studiul electroencefalografic al rolului diencefalului în mecanismul de desfaşurare şi de oprire al accesului convulsiv. *Bull. şt. Sec. St. med. Acad. R.P.R.*, **8**, 71–99.

KREINDLER, A., VOICULESCU, V., BROŞTEANU, R., VOINESCU, I., ET NEŞTIANU, V., (1956b); Recherches électroencéphalographiques sur l'accès convulsif expérimental. *Rev. Neurol.*, **94**, 120–135.

KREINDLER, A., VOICULESCU, V., ŞI CRIGHEL, E., (1957); *Epilepsia.* Bucureşti, Acad. R.P.R. (p. 31).

KREINDLER, A., VOINESCU, I., VOICULESCU, V., ŞI BROŞTEANU, R., (1961a); Cercetari asupra propagarii descarcarilor generate de un focar penicilinic talamic. *Simp. Lanturi şi circuite neuronale, Bucuresti* (pp. 33–35).

KREINDLER, A., VOINESCU, I., VOICULESCU, V., ŞI BROŞTEANU, R., (1961b); Propagarea descarcarilor paroxistice cu punct de plecare din girusul ectosilvian. *Stud. Cercet. Neurol.*, **6**, 45–55.

KREINDLER, A., ŞI ZUCKERMANN, E., (1956); Cercetari asupra mecanismului de declanşare şi de oprire a accesului convulsiv produs prin excitatie focala. *Stud. Cercet. Neurol.*, **1**, 139–179; 180–190.

KREINDLER, A., ŞI ZUCKERMANN, E., (1957); Cercetari asupra mecanismului de declanşare şi de oprire a accesului convulsiv produs prin excitatie focala. *Stud. Cercet. Neurol.*, **2**, 385–412; 563–570.

KREINDLER, A., ZUCKERMANN, E., STERIADE, M., AND CHIMION, D., (1958); Electroclinical features of the convulsive fit induced experimentally through stimulation of the brain stem. *J. Neurophysiol.*, **21**, 430–436.

KRISTIANSEN, K., AND COURTOIS, G., (1949); Rhythmic electrical activity from isolated cerebral cortex. *Electroenceph. clin. Neurophysiol.*, **1**, 265–272.

KRUSHINSKI, L. V., (1959); The physiological mechanism of reflex epilepsy seizures. *Vop. Epilepsii.* Moscow, Medgiz.

KUCHINSKAS, E. J., AND DU VIGNEAUD, V., (1957); An increased vitamin $B_6$ requirement in the rat on a diet containing L-penicillamine. *Arch. Biochem. Biophys.*, **66**, 1–9.

LABORIT, H., BROUSSOLLE, B., ET PERRIMOND-TRONCHET, R., (1947); Essais pharmacologiques concernant le mécanisme des convulsions dues à l'oxygène pur en pression chez les souris. *J. Physiol. (Paris)*, **49**, 963.

LAIRY, G. C., (1956); Déclenchement réflexe de l'activité convulsive. *Electroenceph. clin. Neurophysiol.*, **8**, 73–85.

LAIRY-BOUNES, G. C., PARMA, M., ET ZANCHETTI, A., (1952); Modifications pendant la réaction d'arrêt de Berger de l'activité convulsive produite par l'application locale de strychnine sur le cortex cérébral du lapin. *Electroenceph. clin. Neurophysiol.*, **4**, 495–502.

LASCĂR, E., (1958); Influenta hiperglicemiei provocate asupra modificarilor activitatii citocromoxidazei şi succindehidrazei din cortexul motor al iepurelui dupa accesul convulsiv experimental. *Stud. Cercet. Neurol.*, **3**, 85–91.

LASCĂR, E., ŞI PINTILIE, C., (1955); Modificarea activitatii citocromoxidazei şi succindehidrazei din cortexul motor al iepurelui sub influenta accesului convulsiv experimental produs prin electroşoc. *Bull. şt. Sec. St. med. Acad. R.P.R.*, **7**, 1255–1261.

LEÃO, A. A. P., (1944); Spreading depression of activity in the cerebral cortex. *J. Neurophysiol.*, **7**, 359–390.

LEWEY, F. H., (1950); Neuropathological changes in nitrogen trichloride intoxications of dog. *J. Neuropath. exp. Neurol.*, **9**, 396–405.

LI, C. L., (1959); Cortical intracellular potentials and their responses to strychnine. *J. Neurophysiol.*, **22**, 436–450.

LI, C. L., AND CHOU, J. N., (1960); Inhibitory interneurons. *Inhibition of the Nervous System and γ-Aminobutyric Acid.* New York, Pergamon Press (pp. 147–154).

LI, C. L., CULLEN, CH., AND JASPER, H. H., (1956); Laminar electrode analysis of cortical unspecific recruiting response and spontaneous rhythms. *J. Neurophysiol.*, **19**, 131–143.

LI, C. L., AND JASPER, H., (1953); Microelectrode studies of the electrical activity of the cerebral cortex in the cat. *J. Physiol.*, **121**, 117–140.

LIBERSON, W. T., AND AKERT, K., (1951); Hippocampal seizure state. *Electroenceph. clin. Neurophysiol.*, **3**, 210.

LIBERSON, W. T., AND AKERT, K., (1955); Hippocampal seizure states in guinea-pig. *Electroenceph. clin. Neurophysiol.*, **7**, 211–222.

LIBERSON, W. T., SCOVILLE, W. B., AND DUNSMORE, R. H., (1951); Stimulation studies of the prefrontal lobe and uncus in man. *Electroenceph. clin. Neurophysiol.*, **3**, 1–8.

LIBET, B., AND GERARD, R. W., (1939); Control of the potential rhythm of the isolated frog brain. *J. Neurophysiol.*, **2**, 153–169.

LIBET, B., AND GERARD, R. W., (1941); Steady potential fields and neurone activity. *J. Neurophysiol.*, **4**, 438–455.

LIVINGSTONE, R. B., FRENCH, J. D., KONIGSMARK, B., RICHLAND, K. J., AND ABDULLAH, A. F., Cited from Eidelberg, E., Konigsmark, B., and French, J. D., (1959); Electrocortical manifestations of epilepsy in monkey. *Electroenceph. clin. Neurophysiol.*, **11**, 121–128.

LODIN, Z., (1958); An electroencephalographic study of the changes produced by the administration of methionine sulfoximine in dogs and rats. *Physiol. bohemoslov.*, **7**, 95–103.

LORENTE DE NÓ, R., (1939); Transmission of impulses through cranial nerve nuclei. *J. Neurophysiol.*, **2**, 402–464.

LOUCKS, R. B., (1934); Technique for faradic stimulation of tissues beneath the integument in the absence of conductors penetrating the skin. *J. comp. Psychol.*, **18**, 305–313.

MAGOUN, H. W., (1950); Caudal and cephalic influences of the brain stem reticular formation. *Physiol. Rev.*, **30**, 459–475.

MARINESCO, G., (1909); *La Cellule Nerveuse.* Paris, Doin (pp. 173).

MARKHAM, J. W., BROWNE, K. M., JOHNSON, H. C., AND WALKER, A. E., (1951); Rhombencephalic activity. *Bull. Johns Hopk. Hosp.*, **89** and Suppl. 442–467.

MAROSSERO, F., AND GARRONE, M., (1952); Convulsive activity in the cerebellar cortex. *Electroenceph. clin. Neurophysiol.*, **4**, 230.

MARSHALL, W. H., (1959); Spreading cortical depression of Leão. *Physiol. Rev.*, **39**, 239–279.

MARTIN, A. R., AND BRANCH, C. L., (1958a); Inhibition of Betz cell activity by thalamic and cortical stimulation. *J. Neurophysiol.*, **21**, 380–390.

MARTIN, A. R., AND BRANCH, C. L., (1958b); Spontaneous activity of Betz cells in cats with midbrain lesions. *J. Neurophysiol.*, **21**, 368–379.

MAZZELLA, H., GARCÍA-AUSTT, E., AND GARCÍA-MULLIN, R., (1956); Carotid sinus and EEG. *Electroenceph. clin. Neurophysiol.*, **8**, 155.

MCCULLOCH, W. S., (1949); Mechanisms of spread of the epileptic activity of the brain. *Electroenceph. clin. Neurophysiol.*, **1**, 19–24.

MCCULLOCH, W. S., AND DUSSER DE BARENNE, J. G., (1935); Extinction: local stimulatory inactivation within the motor cortex. *Amer. J. Physiol.*, **113**, 97–98.

MCILWAIN, H., (1955); *Biochemistry and the Central Nervous System.* London, Churchill.

MCINTOSH, F. C., AND OBORIN, P. E., (1953); Release of acetylcholine from intact cerebral cortex. *Abstr. Comm. 19th Int. Physiol. Congr.* (p. 580).

MCLENNAN, H. Y., (1957); A comparison of some physiological properties of an inhibitory factor from brain (factor I) and of gamma-aminobutyric acid and related compounds. *J. Physiol. (Lond.)*, **139**, 79.

MCLENNAN, H. Y., AND ELLIOTT, K. A. C., (1951); Effects of convulsant and narcotic drugs on acetylcholine synthesis. *J. Pharmacol. exp. Ther.*, **103**, 35.

MEISTER, A., (1954); Enzymatic transfer of alpha amino groups. *Science*, **120**, 43–55.

MELLANBY, E., (1946); Diet and canine hysteria. Experimental production by treated flour. *Brit. Med. J.*, **2**, 885–890.

MELLANBY, E., (1948); Role of amino acids in canine epilepsy. *Nutr. Rev.*, **6**, 237–241.

MERLIS, J. K., AND MISRAHY, G. A., (1959/1960); Cortico-spinal mechanisms in experimental seizures. *Epilepsia (Amst.)*, **1**, 527–537.

METTLER, F. A., AND METTLER, C., (1940); Conversion of phasic into tonic mevements by pyramid lesion. *J. Neurophysiol.*, **3**, 527–537.

MEYERS, R., KNOTT, J. R., HAYNE, R. A., AND SWEENEY, D. B., (1950); The surgery of epilepsy. Limitation of the concept of the corticoelectrographic 'spikes' as an index of the epileptogenic focus. *J. Neurosurg.*, **7**, 337–346.

MISON-CRIGHEL, N., (1957); Actiunea miocainei asupra modificarilor determinate de accesul convulsiv experimental în substanta cerebrala. *Stud. Cercet. Neurol.*, **2**, 361–366.

MISON-CRIGHEL, N., CONSTANTINESCU, E., COSTA-FORU, D., AND CRIGHEL, E., (1962); Changes in the activity of some enzyme systems determined in the cortical scar and at the level of secondary degenerative lesions. *Acta. neurol. scand.*, **38**, Suppl. 1, 81.

MISON-CRIGHEL, N., CONSTANTINESCU, E., i. CRIGHEL, E., (1959); Vlianie predconvulsivnovo functionalnovo sostoiania na razvertyvanie sudorojnovo pripadka i byzyvaemye. *Ukr. Biochem. J.*, **31**, 834.

MISON-CRIGHEL, N., CRIGHEL, E., ŞI COSTA-FORU, D., (1963); Actiunea insuficientei circulatorii

cerebrale acute asupra unor leziuni din cortexul cerebral. Corelatii cu date electoencefalografice. *Stud. Cercet. Neurol.*, **8**, 105–115.

MISON-CRIGHEL, N., LAZAR, D., LASCAR, E., ŞI GIOSAN, E., (1955); Modificarile metabolismului mineral şi echilibrului acidobazic determinate de accesul convulsiv experimentae. *Stud. Cercet. Fiziol. Neurol.*, **6**, 373–425.

MISON-CRIGHEL, N., LUCA, N., AND CRIGHEL, E., (1964); Effect of epileptogenic focus induced by topical application of mescaline on glutamic acid, glutamine and GABA in the neocortex of cats. *J. Neurochem.*, **11**, 333–340.

MISON-CRIGHEL, N., PINTILIE, C., AND CRIGHEL, E., (1965); Glutaminase activity and neocortical excitability. *Nature (Lond.)*, **206**, 1257–1258.

MORIN, G., ET CORRIOL, J., (1958); Epilepsie et pression artérielle. Etude des corrélations électro-kymographiques. *Ann. Rech. méd.*, **12**, 503–517.

MOROCUTTI, C., E VIZIOLI, R., (1957); Attività elettrica del cervello ed accessi convulsivi nel *Bufo vulgaris*. *Riv. Neurol.*, **27**, 669–676.

MORRELL, F., (1959); Experimental focal epilepsy in animals. *Arch. Neurol.*, **1**, 141–147.

MORRELL, F., (1961); Microelectrode studies in chronic epileptic foci. *Epilepsia (Amst.)*, **2**, 81–88.

MORRELL, F., AND FLORENZ, A., (1958); Modification of the freezing technique for producing experimental epileptogenic lesions. *Electroenceph. clin. Neurophysiol.*, **10**, 187–188.

MORELL, F., AND NAQUET, R., (1956); Conditioning of generalized hypersynchronous discharges in cats with epileptogenic lesions. *Electroenceph. clin. Neurophysiol.*, **8**, 728.

MORRELL, F., ROBERTS, L., AND JASPER, H. H., (1956); Effect of focal epileptogenic lesions and their ablation upon conditioned electrical responses of the brain in the monkey. *Electroenceph. clin. Neurophysiol.*, **8**, 217–236.

MORRELL, F., AND TORRES, F., (1958); On the nature of epileptic interference. *Electroenceph. clin. Neurophysiol.*, **10**, 764.

MORRELL, F., TORRES, F., AND SANDLER, B., (1960); Excitability of the mirror focus. *Electroenceph. clin. Neurophysiol.*, **12**, 241.

MORUZZI, G., (1939); Contribution à l'électrophysiologie du cortex moteur, facilitation, after-discharge et épilepsie corticale. *Arch. int. Physiol.*, **49**, 33–100.

MORUZZI, G., (1941); Convulsioni extrapiramidali ottenute mediante iniezioni endovenose di piccole dosi di stricnina nell'animale in narcosi cloralosica. *Boll. Soc. ital. Biol. sper.*, **16**, 167–169.

MORUZZI, G., (1945); Convulsioni extrapiramidali da stricnina. *Arch. Fisiol.*, **44**, 109–162.

MORUZZI, G., (1950); *L'Epilepsie Expérimentale*. Paris, Hermann.

MORUZZI, G., (1952); The physiologic mechanism of the epileptic discharge. *Acta psychiat. neurol. scand.*, **27**, 317–328.

MORUZZI, G., (1953); General mechanisms of seizure discharges. *Electroenceph. clin. Neurophysiol.*, **4**, 221–232.

MORUZZI, G., (1955); Étude au moyen de microélectrodes de l'influence cérébelleuse sur les unités bulbo-réticulaires. *Proc. Coll. int. CNRS Paris*, **67**, 395–409.

MOSIER, J. M., WHITE, P., FISCHER, J. E., AND TAYLOR, R., (1957); Cerebroautonomic and myographic changes accompanying induced seizures. *Neurology (Minneap.)*, **7**, 204–210.

NAKAO, H., BALLINI, H. M., AND GELLHORN, E., (1956); The role of the sino-aortic receptors in the action of adrenaline, noradrenaline and acetylcholine on the cerebral cortex. *Electroenceph. clin. Neurophysiol.*, **8**, 413–420.

NAQUET, R., (1953); *Décharges Epileptiques Amygdaliennes*. Thèse de Marseille.

NAQUET, R., FEGERSTEN, L., AND BART, J., (1960); Seizure discharges localized to the posterior cerebral regions in man, provoked by intermittent photic stimulation. *Electroenceph. clin. Neurophysiol.*, **12**, 305–316.

NAQUET, R., AND MORRELL, F., (1956); Conditioning of hypersynchronous discharges of the myoclonic type reduced by cardiazol injection into the cat. *Electroenceph. clin. Neurophysiol.*, **8**, 728.

NEWELL, G. W., ERICKSON, T. C., GILSON, W. E., AND ELVEHJEM, C. A., (1947); Effect of wheat gluten diet in the electroencephalogram of dogs. *Proc. Soc. exp. Biol. (N.Y.)*, **65**, 115–119.

NIEMER, W. T., POWELL, E. W., AND GOODFELLOW, E. F., (1960); The subcortex and hypothalamic afterdischarges in the cat. *Electroenceph. clin. Neurophysiol.*, **12**, 345–358.

NÜRNBERGER, J. I., AND GORDON, M. W., (1957); The cell density of neural tissue. Direct counting method and possible application as a biological referent. *Progr. Neurobiol.*, **2**, 100–138.

OBRADOV, S. A., (1946); Propagation of epileptical impulses in the brain. *Arch. Neurol. Psychiat. (Chic.)*, **55**, 663.

PAGNI, C. A., MASPES, P. E., ET CASSINARI, V., (1963); Étude stéréo-électroencéphalographique du

lobe temporal dans sept cas d'épilepsie psychomotrice avec foyer EEG temporal. *Rev. Neurol.*, **108**, 96–106.

PALLADIN, A. V., (1954); *Biochimiia Nervnoi Sistemy*. Izv. Akad. Nauk SSSR.

PAPPIUS, H. M., AND ELLIOTT, K. A. C., (1954); Adenosine triphosphatase electrolytes and oxygen uptake rates of human normal and epileptogenic cerebral cortex. *Canad. J. Biochem. Physiol.*, **32**, 481.

PASSOUANT, P., PASSOUANT-FONTAINE, TH., ET CADILLAC, J., (1958); Sommeil et épilepsie expérimentale hippocampique. *C.R. Soc. Biol. (Paris)*, **151**, 2166–2169.

PAYNE, T. J., CLARK, S. L., WARD, J. W., AND COWDEN, E. F., (1943); Atypical seizures elicited by electrical stimulation of the cerebral cortex in the cat. *Arch. Neurol. Psychiat. (Chic.)*, **49**, 244.

PENFIELD, W., AND JASPER, H., (1947); Highest level seizures. *Res. Publ. Ass. nerv. ment. Dis.*, **26**, 252–271.

PENFIELD, W., AND JASPER, H., (1954); *Epilepsy and the Functional Anatomy of the Human Brain*. Boston, Little, Brown.

PETSCHE, H., (1963); Pathophysiology of spike-wave pattern. *Electroenceph. clin. Neurophysiol.*, **15**, 344–345.

PHILLIPS, C. G., (1956); Intracellular records from Betz cells in the cat. *Quart. J. exp. Physiol.*, **41**, 58–69.

PIETTE, Y., (1958); L'électroencéphalogramme de la crise convulsive de l'électrochoc. *Arch. Neurol. Psychiat. Belg.*, **58**, 219–230.

PINTILIE, C., (1959); Actiunea crizei electroconvulsive asupra continutului în glutation redus şi acid aspargic din emisferele cerebrale, glandele suprarenale şi sînge la şobolani. *Stud. Cercet. Neurol.*, **4**, 283–289.

PINTILIE, C., MISON-CRIGHEL, N., ŞI CRIGHEL, A., (1963); Activitatea glutaminazei în focarul convulsiv produs prin mescalina. *Stud. Cercet. Neurol.*, **8**, 271–276.

POBLETE, R., RUBEN, R., AND WALKER, A. E., (1959); Propagation of afterdischarge between temporal lobes. *J. Neurophysiol.*, **22**, 538–553.

POGGIO, G. F., RIBSTEIN, M., UDVARBELYI, G. B., AND WALKER, A. E., (1957); Subcortical responses to focal epileptic discharges in the monkey motor cortex. *Electroenceph. clin. Neurophysiol.*, **9**, 164.

POGGIO, G. F., WALKER, A. E., AND ANDY, O. J., (1956); The propagation of cortical afterdischarge through subcortical structures. *Arch. Neurol. Psychiat. (Chic.)*, **75**, 350–361.

POGODAEV, K. I., (1963); Patochimia mozga. *Trudy 1-vo Moscovscovo Ordena Lenina Med. Inst. im. Setchenova*, 26.

POLLOCK, G. H., AND BEIN, J. A., (1950); Convulsions in the cerebellum and cerebrum induced by gamma-chlorinated amines. *Amer. J. Physiol.*, **160**, 195–202.

POPE, A., MORRIS, A. A., JASPER, H., ELLIOTT, K. A. C., AND PENFIELD, W., (1947); Histochemical and action potential studies on epileptogenic areas of cerebral cortex in man and the monkey. *Res. Publ. Ass. nerv. ment. Dis.*, **26**, 218.

PRIBRAM, K. H., (1951); *Some Aspects of Experimental Psychosurgery. The Effect of Scarring Frontal Cortex on Complex Behavior. Surgical Forum*. Philadelphia, Saunders.

PROLER, M., AND KELLAWAY, P., (1962); The methionine sulfoximine syndrome in the cat. *Epilepsia (Amst.)*, **3**, 117–130.

PURPURA, D. P., (1959); Nature of electrocortical potentials and synaptic organizations in cerebral and cerebellar cortex. *Int. Rev. Neurobiol.*, **1**, 47–163.

PURPURA, D. P., AND GRUNDFEST, H., (1956a); Nature of dendritic potentials and sympathetic mechanisms in cerebral cortex of cat. *J. Neurophysiol.*, **19**, 573–595.

PURPURA, D. P., AND GRUNDFEST, H., (1956b); Effects of curare and strychnine on components of evoked cortical potentials (cat). *Fed. Proc.*, **15**, 146–147.

PURPURA, D. P., AND GRUNDFEST, H., (1957a); Physiological and pharmacological consequences of different synaptic organisations in cerebral and cerebellar cortex. *J. Neurophysiol.*, **20**, 494–522.

PURPURA, D. P., AND GRUNDFEST, H., (1957b); Paradoxal inhibitory action of convulsivants on evoked cortical activity. *Electroenceph. clin. Neurophysiol.*, **9**, 167.

RADTKE, H., UND DUENSING, F., (1955); Das EEG nach kombinierter Inactin-Succinyl Vorbehandlung des ausgelösten Elektrokrampfes. *Arch. Psychiat. Nervenkr.*, **193**, 544–556.

RALSTON, B. L., (1958); The mechanism of transition of interictal spiking foci into ictal seizure discharge. *Electroenceph. clin. Neurophysiol.*, **10**, 217–232.

RALSTON, B. L., (1961); Cingulate epilepsy and secondary bilateral synchrony. *Electroenceph. clin. Neurophysiol.*, **13**, 591–598.

RALSTON, B. L., AND AJMONE MARSAN, C., (1956); Thalamic control of certain normal and abnormal cortical rhythms. *Electroenceph. clin. Neurophysiol.*, **8**, 559–582.

RALSTON, B. L., AND PAPATHEODORU, C. A., (1960); The mechanism of transition of interictal spiking foci into ictal seizure discharge. *Electroenceph. clin. Neurophysiol.*, **12**, 297–304.

RAYPORT, M., (1960); Patterns of cortical unit activity during electrical afterdischarge. *Electroenceph. clin. Neurophysiol.*, **12**, 242.

RAYPORT, M., AND JASPER, H., (1958); Microelectrode analysis of the cortical strychnine spike. *Electroenceph. clin. Neurophysiol.*, **10**, 764.

REINER, L., MISANI, F., AND WEISS, P., (1950); Studies on nitrogen trichloride treated prolamines. VI. Suppression of development of convulsions with methionine. *Arch. Biochem.*, **25**, 447–453.

RICHTER, D., AND CROSSLAND, J., (1949); Variation in acetylcholine content of brain with physiological state. *Amer. J. Physiol.*, **159**, 247–255.

RICHTER, D., AND DAWSON, R. M. C., (1948); The ammonia and glutamine content of the brain. *J. biol. Chem.*, **176**, 1199.

RINALDI, F., AND HIMWICH, H. E., (1955); The cerebral electrographic changes induced by LSD and mescaline. *J. nerv. ment. Dis.*, **122**, 424–432.

ROBERTS, E., AND EIDELBERG, E., (1960); Metabolic and neurophysiological roles of gamma-aminobutyric acid. *Rev. Neurobiol.*, **2**, 279.

ROBERTS, E., ROTHSTEIN, M., AND BAXTER, C. F., (1958); Some metabolic studies of gamma-aminobutyric acid. *Proc. Soc. exp. Biol. Med.*, **97**, 796.

ROJANSKI, N. A., (1953); Fiziologhitcheskie mehanizmy opytno vyzvannovo epileptitcheskovo pripadka. *Fiziol. Zh. (Kiev)*, **39**, 549–560.

ROSENBLUETH, A., AND CANNON, W. B., (1942); Cortical response to electrical stimulation. *Amer. J. Physiol.*, **135**, 690–741.

ROTH, J. S., WASE, A., AND ERCHEL, H. J., (1953); Studies with methionine sulfoximine. *J. biol. Chem.*, **200**, 647–654.

RUF, H., (1951); Experimentelle Untersuchungen durch Sauerstoff und Adrenalin. *Arch. Psychiat. Nervenkr.*, **187**, 97.

SAGER, O., AND BUTKHUZI, S., (1962); Electrographical study of the relationship between dorsomedian nucleus of the thalamus and the rhinencephalon (hippocampus and amygdala). *Electroenceph. clin. Neurophysiol.*, **14**, 835–846.

SAGER, O., CHIVU, V., MOIŞEANU, M., ET BASILESCO, N., (1957); Le complexe 'pointe-onde' obtenu chez les animaux décortiqués bilatéralement pendant l'accès convulsif métrazolique. *Premier Congr. int. Sci. Neurol., Bruxelles*, V. 3, 111–118.

SAPIRSTEIN, M. R., (1943); Effect of glutamine acid on central action of ammonium ion. *Proc. Soc. exp. Biol. Med.*, **52**, 334.

SAWA, M., NERUYAMA, N., AND KAJI, S., (1963); Intracellular potential during electrically induced seizures. *Electroenceph. clin. Neurophysiol.*, **15**, 209–220.

SCHMIDT, C. F., KETY, S. S., AND PENNES, H. H., (1945); The gaseous metabolism of the brain of the monkey. *Amer. J. Physiol.*, **143**, 33.

SCHMIDT, R. P., THOMAS, L. B., AND WARD, JR., A. A., (1959); The hyperexcitable neuron. Microelectrode studies of chronic epileptic foci in monkey. *J. Neurophysiol.*, **22**, 285–296.

SCHMIDT, R. P., AND TOONE, C. D., (1958); Observations on convulsive responses to sensory stimulation. *Electroenceph. clin. Neurophysiol.*, **10**, 190.

SCHULTE, F. J., BUSCH, G., UND HENATSCH, A. D., (1959); Antriebssteigerung Extensomotoneurone bei Aktivierung der Chemoreceptoren im Glomus caroticum. *Pflügers Arch. ges. Physiol.*, **269**, 580–592.

SCOVILLE, W. B., DUNSMORE, R. H., LIBERSON, W. T., HENRY, C. E., AND PETTE, A., (1953); Observation on medial temporal lobotomy and leucotomy in the treatment of psychotic states. *Ass. Ress. nerv. Dis. Proc.*, **31**, 347.

SEGUNDO, J., NAQUET, R., AND ARANA, R., (1955); Subcortical connections for temporal cortex. *Arch. Neurol. Psychiat. (Chic)*, **73**, 515–529.

SELIKOV, V. N., (1959); O mehanizmah gheneralizatzii strichninovovo i bolevovo vozbujdenii v kore bolshih polusharii. *Fiziol. Zh. (Kiev)*, **45**, 910–915.

SEMIOHINA, A. F., (1959); Study on the bioelectrical activity of motor and auditory analysers during reflex-epilepsy seizure. *Problems of Epilepsy*. Moscow, Medgiz (In Russian).

SERVÍT, Z., (1955); Zur Frage der Wechselbeziehung zwischen Erregung und Hemmung in der Pathophysiologie des epileptischen Anfalls. *Pawlow Z. Nerventätigk.*, **5**, 269–275.

SERVÍT, Z., (1957); A contribution of the phylogenetic development of the symptomatology of epileptic attacks. *Czech. Neurol.*, **20**, 409–415.

SERVÍT, Z., (1958); *Základy Evoluční Patologie Epilepsia*. Prague, Nakladu Ceskoslov. Akad.

SERVÍT, Z., (1959); Audiogenic epilepsy in rats as a model of reflex mechanisms in the pathogenesis of epileptic seizures. *J. exp. med. Sci.*, **3**, 37–44.

SHANES, A. M., (1958); Electrochemical aspects of physiological and pharmacological action in excitable cells. II. The action potential and excitation. *Pharmacol. Rev.*, **10**, 165.

SHIMAMOTO, T., AND VERZEANO, M., (1954); Relations between caudate and diffusely projecting thalamic nuclei. *J. Neurophysiol.*, **17**, 278–288.

SILVER, M. L., (1949); Canine epilepsy caused by flour bleached with nitrogen trichlorid. *J. Neuropath. exp. Neurol.*, **8**, 44–48.

SMITH, G., AND PURPURA, D. P., (1960); Electrophysiological studies on epileptic lesions of cat cortex. *Electroenceph. clin. Neurophysiol.*, **12**, 59–82.

SOTIRESCU, N., AND CRIGHEL, E., (1964); Steady potential shifts and long duration wave alterations elicited by different types of neocortical epileptic foci. *Electroenceph. clin. Neurophysiol.*, **17**, 599.

SPERANSKY, A. D., (1943); *A Basis for the Theory of Medicine*. New York, International Publishers.

SPIEGEL, E. A., AND WYCIS, H. T., (1950); The thalamic origin of petit mal. *Electroenceph. clin. Neurophysiol.*, **2**, 23–27.

SPIEGEL, E. A., WYCIS, H. T., AND REYES, V., (1951); Diencephalic mechanisms in petit mal epilepsy. *Electroenceph. clin. Neurophysiol.*, **3**, 473–475.

STAMM, J. S., AND PRIBRAM, K. H., (1960); Effect of epileptogenic lesions in frontal cortex on learning and retention in monkeys. *J. Neurophysiol.*, **23**, 552–563.

STAMM, J. S., AND WARREN, A., (1961); Learning and retention by monkeys with epileptogenic implants in posterior parietal cortex. *Epilepsia (Amst.)*, **2**, 229–242.

STARZL, T. L., NIEMER, W. T., DELL, M., AND FORGRAVE, P. R., (1953); Cortical and subcortical electrical activity in experimental seizures induced by metrazol. *J. Neuropath. exp. Neurol.*, **13**, 262–276.

STARZL, T. E., TAYLOR, H., AND MAGOUN, H. W., (1951); Organization of the diffuse thalamic projection system. *J. Neurophysiol.*, **14**, 133–146.

STERIADE, M., (1960); Mécanisme de facilitare şi inhibitie în epilepsia penicilinica focala corticala. *Stud. Cercet. Neurol.*, **5**, 463–471.

STERIADE, M., (1963); Développement des réponses évoquées en activité épileptique dans les circuits amygdalohippocampiques. *Rev. Neurol.*, **108**, 182.

STERIADE, M., (1964); Development of evoked responses into selfsustained activity within amygdalo-hippocampal circuits. *Electroenceph. clin. Neurophysiol.*, **16**, 221–236.

STERIADE, M., DEMETRESCU, M., AND MANOLESCU, J., (1962); Remanence phenomena in the cat's auditory cortex. *Electroenceph. clin. Neurophysiol.*, **14**, 571.

STOICA, I., AND MARCOVICI, N., (1960); Influenta exciziilor limitate asupra crizelor cardiazolice limitate. *Stud. Cercet. Neurol.*, **5**, 641–652.

STOLL, J., AJMONE MARSAN, C., AND JASPER, H., (1951); Electrophysiological study of subcortical connections of anterior temporal region in cat. *J. Neurophysiol.*, **14**, 305–316.

STONE, W. E., WEBSTER, J. E., AND GURDJAN, E. S., (1945); Chemical changes in the cerebral cortex associated with convulsive activity. *J. Neurophysiol.*, **8**, 233.

STRICKLAND, K. P., Energetics and cerebral metabolism. *Guy's Hosp. Rep.*, **105**, 108.

SUTER, C., KLINGMAN, W. D., BOGGS, D., MARKS, R. D., KOPLINGER, C. B., AND RANDOLF, V., (1958); Sound-induced seizures in animals: Magnesium deficiency and sound-induced seizures in rats. *Neurology (Minneap.)*, **8**, Suppl. 1, 125–128.

SWANK, R. L., AND BRENDLER, S. J., (1951); The cerebellar electrogram: Effect of anaesthesia, analeptics and local novocaine. *Electroenceph. clin. Neurophysiol.*, **3**, 207–212.

TAKAHASHI, R., NASU, N., TAMURA, T., AND KARIYA, T., (1961); Relationship of ammonia and acetylcholine levels to brain excitability. *J. Neuroch.*, **7**, 103–112.

TASAKI, J., AND CHANG, J. J., (1958); Electric response of glia cells in cat brain. *Science*, **128**, 1209–1210.

TERNER, C., EGGLESTON, L. V., AND KREBS, H. A., (1950); Role of glutamic acid in transport of potassium in brain and retina. *Biochem. J.*, **47**, 139.

TERZIAN, H., E TERZUOLO, C., (1952); Ricerche elettrofisiologiche sull'epilessie fotiche di Clementi. *Arch. Fisiol.*, **51**, 301–320.

TERZUOLO, C., (1954); Influences supraspinales sur le tétanos strychninique de la moelle épinière. *Arch. int. Physiol.*, **62**, 179–196.

THOMAS, L. B., SCHMIDT, R. P., AND WARD, JR., A. A., (1955); Observations on single units in chronic cortical epileptic foci and in normal or strychninized cortex. *Electroenceph. clin. Neurophysiol.*, **7**, 478–480.

TORDA, C., (1953); Ammonium ion content and electrical activity of the brain during preconvulsive and convulsive phases induced by various convulsants. *J. Pharmacol. exp. Ther.*, **107**, 197–203.

TORDA, C., Cit. from F. Bremer, (1958a); *Bases Physiologiques et Aspects Cliniques de l'Épilepsie.* Paris, Masson.

TORRES, F., ZIEGLER, D. K., AND WICOFF, H. S., (1958); Spontaneous and induced activity of the isolated cerebral cortex. *Electroenceph. clin. Neurophysiol.*, **10**, 190.

TOWER, D. B., (1958); The neurochemical substrates of cerebral function and activity. H. F. Harlow and C. N. Woolsey, Editors. *Biological and Biochemical Basis of Behaviour.* Madison, Univ. Wisconsin Press.

TOWER, D. B., (1958a); Discussion. M. Baldwin and P. Bailey, Editors. *Temporal Lobe Epilepsy.* Springfield, Thomas (pp. 288–295).

TOWER, D. B., (1958b); The evidence for a neurochemical basis of seizures. M. Baldwin and P. Bailey, Editors. *Temporal Lobe Epilepsy.* Springfield, Thomas (pp. 301–343).

TOWER, D. B., (1960); *Neurochemistry of Epilepsy.* Springfield, Thomas.

TOWER, D. B., AND ELLIOTT, K. A. C., (1952a); Activity of acetylcholine system in cerebral cortex of various unanesthetized mammals. *Amer. J. Physiol.*, **168**, 747.

TOWER, D. B., AND ELLIOTT, K. A. C., (1952b); Activity of acetylcholine system in human epileptogenic focus. *J. appl. Physiol.*, **4**, 669–676.

TOWER, D. B., AND ELLIOTT, K. A. C., (1953); Experimental production and control of an abnormality in acetylcholine metabolism present in epileptogenic cortex. *J. appl. Physiol.*, **5**, 375.

UNGHER, J., IONASESCU, V., ŞI STOICA, I., (1954); Influenta crizei electroconvulsive asupra activitatii nervoase superioare a cîinelui în conditii de activitate motorie libera. *Acad. R.P.R. Sesiunea largita Sectie St. Med.*, 339–379.

UNGHER, J., ET STERIADE, M., (1960); L'analyse électrographique de l'accès épileptique conditionné. *Acta neurol. psychiat. belg.*, **10**, 923–933.

UNGHER, J., STOICA, I., ŞI STAVRICA, R., (1952); Conditionarea manifestarilor epileptiforme. *Stud. Cercet. Fiziol. Neurol.*, **3**, 233–240.

UTSUMI, S., MURAO, F., TSUJI, S., MATSUCKA, K., HORI, Y., AND MIKI, J., (1957); On the EEG of the cortex and subcortical nuclei by electrically induced focal seizure. *Folia psychiat. neurol. jap.*, **30**, Suppl. 4.

UZUNOV, G., ATZEV, E., I AVRAMOV, S., (1961); Promeni v elektrishnote aktivnost na mozga pri lokalna aplikatzia na atebrin vrhu moztshnata kora na zaitzi. *Soobshch. Nautchn. Sesia EEG klin. Neurofiziol., Dec., Sofia.*

UZUNOV, G., BOJINOV, S., I GHEORGHIEFF, J., (1957); Eksperimentalnoe issledovanie patogheneza epileptiformnovo pripadka. *J. Nevropat. Psihiat.*, **57**, 731–739.

VANASUPA, P., GOLDRING, S., AND O'LEARY, J. L., (1959); Seizure discharges effected by intravenously convulsant drugs. *Electroenceph. clin. Neurophysiol.*, **11**, 93–106.

VARDAPTEAN, G. A., (1963); Bioelektritscheskaia aktivnosti razlychinih urovnei nervnoi sistemy krolikov pri sudorogah vyzvannyh metrazolom. *Fiziol. Zh. (Kiev)*, **49**, 33–41.

VASTOLA, E. F., AND ROSEN, A., (1960); Suppression by anticonvulsivants of focal electrical seizures in the neocortex. *Electroenceph. clin. Neurophysiol.*, **12**, 327–332.

VEDIAEV, F. P., (1961); Analiz korkovo-podkorkovyh otnoshenii pri eksperimentalnoi epilepsii. *Fiziol. Zh. (Kiev)*, **47**, 711–720.

VOICULESCU, V., ŞI BROŞTEANU, R., (1960); Influenta anoxiei asupra accesului convulsiv experimental. *Stud. Cercet. Neurol.*, **5**, 489–496.

VOICULESCU, V., BROŞTEANU, R., AND VOINESCU, I., (1960); Effect of anoxia on experimental convulsive seizures. *Electroenceph. clin. Neurophysiol.*, **12**, 751–752.

VOICULESCU, V., VOINESCU, I., AND BROŞTEANU, R., (1964); Propagation of discharges generated by a thalamic penicillin focus. *Rev. Roum. Neurol.*, **1**, 137–145.

VOINESCU, I., (1960); Comb rhythm, hippocampic afterdischarge and its propagation. *Electroenceph. clin. Neurophysiol.*, **12**, 752.

VOINESCU, I., BROŞTEANU, R., ŞI VOICULESCU, V., (1959); Activitatea electrica a formatiilor subcorticale în timpul accesului convulsiv prin electroşoc la pisica cu leziuni bilaterale ale hipocampului. *Stud. Cercet. Neurol.*, **4**, 405–412.

VOINESCU, I., VOICULESCU, V., BROŞTEANU, R., ET KREINDLER, A., (1957); La réaction d'éveil après l'accès convulsif expérimental. *Premier Congr. int. Sci. Neurol. Bruxelles* (pp. 248–253).

VOLANSCHI, D., (1960); Experimental researches on the convulsive activity of the immature brain. *Electroenceph. clin. Neurophysiol.*, **12**, 753.

VOLANSCHI, D., STERESCU, N., VOICULET, N., ŞI LECCA, M., (1961); Studiul comparativ al capaci-

tatii convulsivante a creierului imatur şi matur (cercetari cu $P^{32}$). *Stud. Cercet. Neurol.*, **6**, 291–303.

VON BAUMGARTEN, R., AND SCHAEFER, K. P., (1957); Synchronization phenomena of neighbouring intracerebral nerve cells. *Electroenceph. clin. Neurophysiol.*, **9**, 353.

VON EULER, C., GREEN, J. D., AND RICCI, G., (1958); The role of dendrites in evoked responses and after-discharges. *Acta physiol. scand.*, **42**, 87–111.

VRBA, R., (1955); A source of ammonia and changes of protein structure in the rat brain during physical exertion. *Nature (Lond.)*, **176**, 117.

VRBA, R., (1957); On the participation of ammonia in cerebral metabolism and function. *Rev. Czecosl. Med.*, **3**, 81.

WADA, J., AND CORNELIUS, L. R., (1960); Functional alteration of deep structures in chronic focal cortical experimental epilepsy. *Electroenceph. clin. Neurophysiol.*, **12**, 243.

WAELSCH, H., (1961); Compartmentalized biosynthetic reactions in the central nervous system. S. Kety and J. Elkes, Editors. *Regional Neurochemistry*. Oxford, London, Pergamon Press (p. 57).

WALKER, A. E., ANDY, O. J., AND FAETH, W., (1954); Physiological studies on the amygdala and hippocampus (monkey and cat). *Electroenceph. clin. Neurophysiol.*, **6**, 712–713.

WALKER, A. E., AND JOHNSON, C., (1948); Normal and pathological discharges from frontal cortex. *Res. Publ. Ass. nerv. ment. Dis.*, **27**, 460–475.

WALKER, A. E., MARSHALL, C., AND BERESFORD, E. N., (1947); Electrocorticographic characteristics of the cerebrum in posttraumatic epilepsy. *Res. Publ. Ass. nerv. ment. Dis.*, **26**, 502–515.

WALKER, A. E., POGGIO, G. F., AND ANDY, O. J., (1956); Structural spread of cortically induced epileptical discharges. *Neurology (Minneap.)*, **6**, 616–626.

WALKER, A. E., AND RICHTER, H. A., (1963); Cerebral peduncle in propagation of convulsions. *Arch. Neurol.*, **8**, 581–590.

WARD, JR., A. A., (1947a); Decerebrate rigidity. *J. Neurophysiol.*, **10**, 89–103.

WARD, JR., A. A., (1947b); Convulsive activity induced by fluoroacetate. *J. Neurophysiol.*, **10**, 105–111.

WARD, JR., A. A., (1959/1960); The epileptic spike. *Epilepsia (Amst.)*, **1**, 600–606.

WARD, JR., A. A., (1961); Epilepsy. *Int. Rev. Neurobiol.*, **3**, 142–186.

WARD, JR., A. A., MCCULLOCH, W. S., AND KOPELOFF, N., (1948); Temporal and spatial distribution of changes during spontaneous seizures in monkey brain. *J. Neurophysiol.*, **11**, 377–386.

WARD, JR., A. A., SCHMIDT, R. P., AND THOMAS, L. B., (1956); Some properties of single epileptic seizures. *Electroenceph. clin. Neurophysiol.*, **8**, 167.

WARD, JR., A. A., THOMAS, L. B., AND SCHMIDT, R. P., (1956); Some properties of epileptic neurons. *Trans. Amer. neurol. Ass.*, **82**, 41–43.

WATANABE, S., AND MIWA, K., (1957); Electrocorticographic studies in isolated brain materials. *Folia psychiat. neurol. jap.*, Suppl. 4, 29–30.

WERTHEIMER-LUCA, N., (1957); Modificarile aminoacizilor liberi din organele de şobolan sub actiunea accesului convulsiv experimental. *Stud. Cercet. Neurol.*, **2**, 413–417.

WERTHEIMER-LUCA, N., (1958); Modificarea aminoacizilor liberi din organele de şobolan sub actiunea accesului convulsiv experimental. Nota II. Cercetari cromatografice. *Stud. Cercet. Neurol.*, **3**, 211–216.

WHIELDON, J. A., AND VAN HARREVELD, A., (1951); Drug effects on the results of minimal cortical stimulation. *Electroenceph. clin. Neurophysiol.*, **3**, 31–35.

WHITE, J. C., EIDELBERG, E., AND FRENCH, J. D., (1960); Experimental assessment of epileptogenesis in the monkey cerebral cortex. *Arch. Neurol.*, **2**, 376–390.

WILLIAMS, D., (1953); A study of thalamic and cortical rhythms in petit mal. *Brain*, **76**, 50–69.

WOODBURY, D. M., KOCH, A., AND VERNADAKIS, A., (1958a); Relation between excitability and metabolism in brain as elucidated by anticonvulsant drugs. *Neurology (Minneap.)*, **8**, Suppl. 1, 113–116.

WOODBURY, D. M., ROLLINS, L. T., GARDNER, M. D., HIRSCHI, W. L., HOGAN, J. R., RALLISON, M. L. TANNER, G. S., AND BRODIE, D. A., (1958b); Effect of carbon dioxide on brain excitability and electrolytes. *Amer. J. Physiol.*, **192**, 79–90.

YOUMANS, J. R., (1956); Experimental production of seizures in the macaque by temporal lobe lesions. *Neurology (Minneap.)*, **6**, 179–186.

ZANCHETTI, A., AND BROOKHART, J. M., (1955); Measurement of electrical responsiveness of corticospinal efferents in cat and monkey. *J. Neurophysiol.*, **18**, 288–298.

ZISLINA, N. N., NOVIKOVA, L. A., I TKACENKO, N. M., (1963); Elektrofiziologhiceskoe issledovanie tormoznîh i vozbujdaiuşcih vliianii. *Fiziol. Zh. (Kiev)*, **49**, 5–15.

ZURABASHVILI, A. D., (1952); K teoretitcheskin osnovam elektroshoka. *J. Nevropat. Psihiat.*, **52**, 15–17.

# SUBJECT INDEX

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