ELECTRICAL ACTIVITY OF THE HUMAN BRAIN DURING ARTIFICIAL SLEEP

2. REGIONAL DIFFERENTIATION OF RESPONSE TO BARBITURATE SEDATION

BY

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As Berger's (1933-36) original studies on the electrical activity of the brain were made with only two electrodes on the head, he was led to suppose that the brain functioned as a whole in this respect. This impression has persisted almost unchanged, except for sporadic attempts at more detailed analysis, and criticisms of this unitary theory have received little acceptance, especially in the field of human physiology.

In spite of Tönnies' (1933) early objections to Berger's conclusions, and the demonstration by Adrian and Matthews (1934) and Adrian and Yamagiwa (1935) of the special electrical characteristics of the occipital lobe, contemporary workers, for example, Foerster and Altenburger (1935), continued to support the unitary view. Then Rubin (1938) reported that the two cerebral hemispheres may beat asynchronously, and also that differences in the frequency of the resting rhythm may be observed between the anterior and posterior parts of the same hemisphere. At the same time Jasper and Andrews (1938) found that faster (beta) frequencies were more particularly associated with the frontal region.

More recent studies (Walter and Grey Walter, 1949; Hill, 1950a and b; Hill and Parr, 1950) indicate a possible relation between the temporal lobe and the production of slower (theta) frequencies, and between the frontal lobe and fast frequencies. Also to be considered from this point of view are studies on the maturation patterns of cerebral electrical activity in growing children (Lindsley, 1938; Smith, 1938, 1939, 1941; Barnes, 1946) which indicate that the acquirement of the adult pattern of brain rhythms is not a uniform process throughout the cerebral cortex.

Occasional studies on animals have also thrown the unitary concept into question, although the validity of some of the results reported remains in

doubt. For example, Kornmüller (1933, 1935, 1937) claimed to recognize rhythms characteristic of various cytoarchitectural areas of the rabbit brain. Somewhat similar observations were made by Rheinberger and Jasper (1937) on anaesthetized cats, but the regional differences were not consistently apparent in unnarcotized animals. Clark and Ward (1945) also described area differences in the electrical activity of the cat's brain during the onset of natural or induced sleep. More recent studies (Swank and Foley, 1948; Swank, 1949; Swank and Cammermeyer, 1949; Garvin and Amador, 1949; Bailey, von Bonin, and McCulloch, 1949) indicate that regional differences may also be observed in dogs, monkeys, and chimpanzees during narcosis.

As no specific study along these lines is yet available for man, the opportunity has been taken, in the course of observations on the cyclical changes in brain potentials during barbiturate-induced sleep (Wyke, 1949, 1950b), to utilize a regionally distributed electrode pattern (Wyke, 1950a) for analysis of the cycle of changes in different areas of the human brain. It emerges that while only the crudest and most variable regional differences are apparent in the electrical activity of the waking human brain, serial recording during advancing barbiturate sedation discloses a course of events which appears to be individually characteristic for each of the major subdivisions of the brain surface. The method employed precludes any attempt at more precise anatomical correlation than this. Direct cortical and intra-cerebral recordings will have to be undertaken to determine whether architectonic correlations are justifiable.

Method

The material upon which this study is based consists of 100 subjects of all ages from infancy to late middle age, either clinically normal or else suffering from a variety of disorders of the nervous system. Studies made

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on the normal subjects were compared with those on patients with localized and non-localized cerebral lesions, and with those made on cases of psychiatric disorder.

This communication is concerned with normal responses. The variations seen in the different categories of abnormality will be discussed separately. Where possible several records were obtained on the subjects while awake, and in some instances two or three sleep records were made on separate occasions in order to check the consistency of response from time to time in the same subject.

Sleep was induced according to the method previously described (Wyke, 1949, 1950b), seconal sodium being administered orally in doses usually of 1.5 to 3 gr. (0.1 to 0.2 g.) for adults. Children received smaller doses by mouth or by rectum. Some subjects were given repeated small doses in order to induce a protracted onset of sleep (Wyke, 1950b), but no subject received more than 4.5 gr. (0.3 g.) as a total dose.

The technique of electrode placement is a critical factor in studies such as this, and the method, apparatus, and recording technique are described in detail in another communication (Wyke, 1950a). Using this technique, the activity of each major brain region has been studied at each stage of sleep in runs orientated in two planes at right angles to one another. The activity of each area is thus compared with that of adjacent regions, emphasis being placed on the differences between their patterns of electrical behaviour by virtue of the bipolar recording technique.

After initial trials with ear (or more remote) electrodes as reference points and of bipolar methods, the latter system was selected as giving a convenient and adequate representation of regional differences in electrical activity. However, ear leads (with the electrode inserted into the external auditory meatus) continued to be used as part of the longitudinal and transverse bipolar runs, and this arrangement proved to have special value for the examination of temporal lobe activity. The technical aspects of the bipolar method are fully discussed elsewhere (Grey Walter, 1938; Williams and Gibbs, 1939; Gibbs and Gibbs, 1941; Hill and Parr, 1950; Offner, 1950). Suffice it to say that this method tends to cancel out potential changes common to two electrodes linked together, thereby more or less isolating the differences in local activity existing beneath them, and in addition, a study of phase relations and focal activity becomes possible.

Results

The overall sequence of changes in human cerebral electrical activity induced by barbiturate sedation has already been described (Wyke, 1950b). In the course of that study it became apparent that the pattern of events differed in various regions of the brain, and the present paper describes the cycle of events in terms of the individual regions of the brain in which they occur. The classification of the stages of sleep is that given in the paper referred to above, in which the concomitant somatic changes

are also discussed. Although the cycle is described here for each anatomical region in turn, it will of course be apparent that all regions transverse their particular sequence of changes simultaneously, and with a certain degree of overlap from region to region. The nomenclature of brain rhythms employed in this discussion follows that given by Hill and Parr (1950).

Frontal.—In the frontal lobes (Figs. 1, 5, and 7) the most obvious change is a steadily progressive shift down the beta frequency spectrum during the early stages of sleep. During stage 1 there is usually little alteration in activity in frontal leads, except perhaps a slight but gradually progressive increase in the voltage of the waking beta rhythm, when present. Throughout stage 2 this increase in amplitude becomes more pronounced, while towards the end of the period episodic slowing of the beta activity becomes apparent. This slowed beta (16 to 18 c/s) activity gradually occupies more and more of the frontal frequency spectrum as stage 3 begins, and as this period develops short spindles of 16 c/s waves form while the faster frequencies disappear. Towards the end of stage 3 further slowing to 14 c/s occurs, and this latter activity gradually increases in amplitude and amount as stage 4 begins, a change first apparent near the vertex.

During stage 4 almost steady firing of 14 c/s waves occurs in long spindles, of greatest amplitude near the midline, and at higher voltage in children than in adults. At the same time random slow (about 6 c/s) waves usually appear near the vertex, becoming more obvious as stage 5 begins, while the 14 c/s activity shows occasional slowing to 12 c/s, appearing first and remaining more apparent in inferior, rather than superior frontal regions.

As stage 5 develops, 14 c/s activity tends to disappear in the inferior frontal leads, leaving short spindles of 12 c/s waves interposed between irregular theta (4 to 6 c/s) waves. Near the midline low voltage runs of 14 c/s activity may persist even in deep sleep, but late in stage 5 the principal feature of frontal lobe activity is steady firing of slow (4 to 6 c/s) activity at varying amplitude, with occasional superimposition of 12 c/s activity. This slow activity may focus in one or other superior frontal region, the focus appearing as stage 4 passes into stage 5.

Until the end of stage 4 most activity is bilaterally synchronous in the two frontal lobes, but beyond this point more and more activity becomes asynchronous, until, in deep sleep, the two frontal regions seem to be functioning with almost complete electrical independence. Similar observations apply to other regions of the brain in this respect.

Precentral.—In the precentral (Figs. 2, 5, and 7) regions the initial change as sedation begins is the development of gradually increasing instability of the resting rhythm. This rhythm, in cases with occipital alpha frequencies in the upper limits of the alpha band, is often 1 to 1.5 cycles slower than the occipital rhythm, and its gradual loss of stability usually precedes similar changes in the posterior regions of the brain.

Sometimes frontal beta activity spreads back into the precentral regions as it increases in amplitude during the later part of stage 1 and throughout stage 2. In any case runs of 14 to 16 c/s activity rapidly build up in the precentral regions during stage 2, so that by the beginning of stage 3 high voltage (60 to 80 μ V) spindles of 14 c/s activity become prominent, especially near the midline. In many cases this 14 c/s activity focuses in one or other superior precentral region at this stage, or occasionally in both superior precentral regions. Towards the end of stage 3 and in the early part of stage 4 this 14 c/s activity ceases to focus and then slows, at first at random and then in episodes of gradually increasing duration, to 12 c/s, appearing in short spindles near the vertex, and mixed with 14 c/s and 6 to 7 c/s waves in the inferior precentral regions.

By the end of stage 4, 14 c/s waves have almost disappeared, except for occasional random activity, and lower voltage 12 c/s activity dominates the whole region, mixed with 6 to 7 c/s waves which gradually spread upwards from the inferior precentral regions towards the vertex. During stage 5 this latter activity increases in voltage and slows further to 4 to 6 c/s, producing spindles of theta activity separated by short runs of 12 c/s (occasionally low 14 c/s activity) near the midline. These theta spindles at first are bilaterally synchronous, but as stage 5 develops this synchrony is gradually lost. In deepest sleep random waves at 3 c/s may appear in the precentral regions, usually in inferior rather than in superior leads and often focusing on one or other side. This change is accompanied by an increase in the duration of the theta spindles, which now show little bilateral synchrony. Little or no activity appears in the faster frequency bands in the deeper levels of stage 5.

Postcentral.—In the postcentral (Figs. 3, 5, and 7) and parietal areas the sequence of changes is intermediate between the precentral and occipital regions, but on the whole tends to conform to the pattern of the latter, rather than the former.

In stage 1 and during the early part of stage 2 little alteration can be seen, except some shortening in duration of the alpha spindles. As stage 2

develops the resting rhythm becomes unstable, and there is a fairly abrupt decrease in amplitude of all frequencies towards the end of this period. At the same time faster frequencies build up from the background of unstable alpha activity, so that 12 c/s and then 14 c/s waves appear—a picture the reverse of that in anterior leads. Thus a 10 c/s alpha rhythm in the waking record first becomes unstable, then decreases in voltage and finally gives place to 12 to 14 c/s activity. By the end of stage 3 14 c/s activity is firing bilaterally in long spindles, of higher amplitude near the midline than in more inferior regions.

As stage 4 is traversed this 14 c/s activity decreases in amplitude, while slower waves (at 4 to 6 c/s) make their appearance. These appear first at random and then in short runs, bilaterally synchronous and of increasing amplitude, as stage 5 begins. As this latter period evolves the faster frequencies become less prominent again, while the theta frequencies are more and more evident. In the deepest levels of sleep all that remains is a slow oscillation of the baseline interrupted by random 4 c/s waves and with a superimposed low voltage ripple occurring episodically at about 14 c/s.

Occipital.—It is in the occipital (Figs. 4, 5, and 7) and in the anterior temporal regions that the earliest electrical signs of barbiturate sedation are manifest. The initial change in the occipital lobes is a gradual shortening of the duration of the waking alpha spindles, or the appearance of spindling in those subjects whose waking records show an uninterrupted rhythm. This occurs early in stage 1, and in some subjects there may be, at the same time, an increase in amplitude of the spindled activity which is usually evanescent, but may sometimes persist into the early part of stage 3.

Early in stage 2 random slowing of the alpha rhythm begins, producing a picture of increasing instability of the basic rhythm. As this period passes the increasing intervals between the shortening alpha spindles (which remain for the present at the waking dominant frequency) are occupied by mixed frequencies in the lower limits of the alpha band. During stage 3 alpha spindling at the normal dominant frequency steadily diminishes, while the mixture of alpha frequencies between them comes to contain an increasing proportion of slower components (but still within the limits of the alpha band). In some subjects low voltage 14 c/s waves may be seen superimposed occasionally on the slower frequencies during this period. But by the early part of stage 4 most subjects show such activity, which, towards the end of this period, occurs in short runs between the slower frequencies.

As stage 4 ends alpha frequencies gradually disappear, being replaced at first by 6 c/s, and then 4 c/s waves occurring at random. In most subjects the activity near the midline tends to be slower than that in the inferior parieto-occipital regions. As stage 5 begins still slower frequencies (2 to 4 c/s) dominate the picture, while faster frequencies soon disappear. Finally the amplitude of all frequencies diminishes, and a slow periodic oscillation of the base line is disturbed only by random waves at 2 to 4 c/s as the deepest level of sleep is attained. In cases where an alpha focus is identifiable in the occipital lobes, such a focus disappears towards the end of stage 2 or the beginning of stage 3, and no focusing at any frequency is seen in the occipital regions thereafter until the cycle is reversed on waking.

Temporal.—Changes in the temporal (Figs. 2, 3, 6, and 7) lobes seem to usher in the cyclical changes of progressive barbiturate sedation. In most subjects the dominant frequency in this region is 1 to 1.5 c/s slower than that in the occipital leads, and this rapidly loses its stability quite early in stage 1. At the same time faster frequencies (within the beta band) are increased in amplitude. These rapidly slow towards the end of stage 1, so that by the beginning of stage 2 short runs of 16 c/s activity are apparent against the background of slower frequencies.

As stage 2 elapses spindles of 7 to 8 c/s activity develop in the anterior temporal regions, while the beta (mainly 16 c/s) spindles are further increased in amplitude. By the end of stage 2 these high voltage beta spindles are replaced by runs of 14 c/s activity which steadily increase in duration during stage 3, and usually focus in one or other fronto-temporal region. During this latter period 6 c/s waves appear, at first at random and then in bilaterally synchronous runs. Seen first in the anterior temporal regions, this theta activity spreads backwards into the temporo-parietal region, while the faster frequencies in the former areas decrease in amplitude.

By the time stage 4 is well established activity in the anterior temporal regions consists of a mixture of 5 to 7 c/s waves, interrupted by runs of lower voltage 14 c/s waves. As the rest of stage 4 elapses there is further slowing throughout the temporal lobes, the frequencies in the anterior temporal lobes being slower than those in the mid-temporal and temporo-parietal regions. At the same time the amplitude of these slow waves increases gradually, while the 14 c/s activity decreases in voltage and slows at times to 12 c/s.

By the beginning of stage 5 the dominant frequency in the temporal lobes is about 4 to 5 c/s,

and the proportion of 4 c/s activity increases gradually thereafter, while faster frequencies fall off in amplitude until they are represented merely by a low voltage ripple at 12 to 14 c/s superimposed on the slow waves. As stage 5 is traversed slowing becomes more rapid posteriorly than in the anterior temporal regions, so that in deepest sleep the latter regions show only a low voltage oscillation of the baseline at 4 c/s with a superimposed ripple of 12 to 14 c/s waves on the slow waves, while the mid- and posterior temporal regions show higher voltage irregular discharges at 3 to 4 c/s. Thus in deep sleep the anterior temporal lobes never display the degree of slowing apparent more posteriorly, although in the earlier stages of sleep diminution of frequency is more rapid in the former than the latter regions.

Discussion

Studies of the cyclical changes in electrical activity in different areas of the brain induced by barbiturate narcosis make it apparent that the brain does not respond as a whole under such conditions. While the changes in each region are by no means independent of those in other areas, there is sufficient dissimilarity in the time course and pattern of response between the various areas to permit their individual identification at most stages of sedation. These observations apply to both natural and barbiturate-induced sleep, the similarity of which has been indicated before both in animals (Bremer, 1937; Clark and Ward, 1945) and man (Berger, 1931; Gibbs, Gibbs, and Lennox, 1937; Brazier, 1949; Wyke, 1950b).

Workers with various animal species have previously noted lack of uniformity in the cerebral electrical response to barbiturate sedation. Thus Clark and Ward (1945) described area differences in the electrical activity of the cat's brain, observing that these differences were more prominent and followed a specific sequence in each region during the onset of natural or induced sleep. Swank and Foley (1948) found that during progressive narcotization of dogs with sodium amytal and nembutal slowing and finally suppression of electrical activity was apparent in posterior regions before it appeared in precentral regions. More detailed area differentiation in dogs was reported by Swank and Watson (1949) in a comparative study of the effects of ether, pentothal, nembutal, and amytal, and Garvin and Amador (1949) found that significant area differences appeared in the macaque monkey during dial narcosis. The latter authors state that similar observations in chimpanzees under dial have been made by Bailey, von Bonin, and McCulloch (1949) and indicate that electrical activity is correlated with general brain regions and not with detailed

FIG. 2.

FIG. 1.

FIG. 1.—The succession of changes during the stages of progressive barbiturate sedation, as seen in transverse frontal leads. Figs. 1 to 4 are all from the same subject.

FIG. 2.—The succession of changes during the stages of progressive barbiturate sedation, as seen in transverse precentral leads.

FIG. 4.

FIG. 3.

FIG. 3.—The succession of changes during the stages of progressive barbiturate sedation, as seen in transverse postcentral leads.

FIG. 4.—The succession of changes during the stages of progressive barbiturate sedation, as seen in transverse occipital leads.

FIG. 6.

FIG. 5.

FIG. 5.—Representative stages in the cycle of progressive barbiturate sedation, as seen in parasagittal leads. Different subject from Figs. 1 to 4.

FIG. 6.—Representative stages in the cycle of progressive barbiturate sedation, as seen in longitudinal temporal leads. Different subject from Figs. 1 to 4 and 5.

FIG. 7.—Diagrammatic representation of the frequency distribution in different regions of the brain during each of the stages of progressive barbiturate sedation. The various ratios were calculated on a percentage time basis.

cytoarchitectonic areas, as claimed by Kornmüller (1937). As their studies were not made during progressive narcosis, detailed comparison of their results with those reported here is not possible.

Detailed studies of the area differences in electrical activity during barbiturate narcosis in man have not previously been reported, although generalized analyses of the overall changes in cerebral electrical activity due to various barbiturates have been presented from time to time (Berger, 1931; Gibbs, Gibbs, and Lennox, 1937; Cohn and Katzenelbogen, 1942; Brazier and Finesinger, 1945; Lennox, 1946; Isbell, Altschul, Kornetsky, Eisenman, Flanary, and Fraser, 1950; Greville and Heppenstall, 1950). Brazier and Finesinger in the course of their study of the effects of intravenously injected barbiturates, noted that high voltage fast activity appeared in the frontal regions before becoming apparent elsewhere and that recovery of normal patterns occurred first in occipital leads and appeared more slowly in anterior leads. These observations are confirmed in the studies reported in this and the preceding paper. But the present experiments hardly support Brazier's contention that the fast frequencies constitute a "new" rhythm, suggesting rather that they are derived from the beta rhythm. Lennox and Coolidge (1949) made recordings from several areas of the head during injection of pentothal, but reported only on the distribution of 12 to 15 c/s activity. They suggested that 12 c/s runs during sleep appeared mainly in the frontal regions, while 14 to 15 c/s activity was more diffusely distributed but tended to be most prominent in the paracentral leads. The present findings agree with this in general, but emphasize that the frequency distribution depends on the stage of narcosis at which the electrical activity is sampled. At certain levels of sleep in all individuals 12 c/s activity is more prominent frontally, but it can be observed in paracentral and parietal regions at deeper levels. Similarly at some levels of narcosis 14 to 15 c/s may appear more prominently in paracentral regions, but at lighter levels it dominates the fronto-temporal discharge. At still deeper levels it may be more apparent in the occipital leads than elsewhere.

Again Brazier (1949) found that there was a shift of focus of maximum activity from the parieto-occipital regions to the frontal lobes during the passage from waking to sleep. Similar observations have been made in the present studies, which also confirm Brazier's identification of a precentral focus of 14 c/s spindles during the development of sleep. Detailed analysis indicates that the occipital focus is usually lost as stage 2 passes into stage 3, while the precentral focus of 14

c/s activity shows up as stage 3 develops. The latter focus varies in its actual site, but is usually somewhere in the fronto-temporal regions, and more often in the superior precentral region than elsewhere. As still deeper sleep supervenes these secondary precentral foci disappear, and a more rostral slow focus appears, so that in deepest sleep no focal activity is usually apparent in any area of the brain surface except the frontal regions.

The point to be emphasized, within certain limits, is that no one frequency is characteristic of any cerebral region at all stages of barbiturate-induced sleep, but that at any given level of narcosis the major cerebral areas differ from one another in their overall frequency spectrum. As the level of narcosis changes, the frequency patterns of the different cerebral areas change also, and the dominant frequency of one region may become dominant in another while disappearing in its original site. But the cycle of response occurs at different rates in the different cerebral areas, so that area differentiation at the various levels of narcosis depends upon differences in the time course of response in the various regional systems. This may be correlated with the progressive changes in behaviour and reflex response which are observed to be associated with the passage from one electrical pattern to another (Wyke, 1950b), and it is not until the deepest levels of narcosis are attained that the spontaneous electrical activity of the brain assumes a more or less uniform pattern and area differentiation melts away into the background of slow activity which characterizes all states of deep unconsciousness of whatever origin, and which shows little differentiation from one subject to another (c.f. Loomis, Harvey, and Hobart, 1938; Knott, Henry, and Hadley, 1939; Henry, 1941).

In short, as the brain falls asleep it does so piecemeal. The activity of the various projection systems is serially depressed in a manner which is reflected in the progressive changes in mental, sensori-motor and reflex behaviour which are observed clinically during the passage from normality to deepest unconsciousness and back again. The results of this investigation lend little support to the theory of depression of function of successively lower "levels" by barbiturates proposed by Etsten and Himwich (1946), which may also be criticized on other grounds (Swank and Cammermeyer 1949), or to the "deafferentiation" theory of Bremer (1935, 1937). Instead, the overall impression conveyed by the present studies corresponds more or less to the picture drawn by Sherrington (1940) in "Man on His Nature". More detailed discussion of the possible mechanisms of these effects is reserved for a succeeding communication.

Summary

The cyclical changes induced in each of the major subdivisions of the human brain surface by progressive barbiturate sedation are described.

Evidence is presented to show that during the onset of sleep the brain does not respond in an overall uniform fashion.

It is suggested that while in the waking human brain different cortical areas do not usually possess well-defined electrical identities, during the onset of sleep they pass through a period when they may assume more or less independent patterns of electrical behaviour, the pattern of electrical activity at each stage of sleep being characteristic of the particular region.

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