ELECTRICAL ACTIVITY OF THE HUMAN BRAIN DURING ARTIFICIAL SLEEP

I. THE CYCLICAL PATTERN OF RESPONSE TO BARBITURATE SEDATION

BY

B. D. WYKE*

From the Nuffield Department of Surgery, Radcliffe Infirmary, Oxford

A wide variety of special techniques is now employed in clinical electroencephalography (Kaufman and Watson, 1949) to unmask latent abnormalities in cerebral electrical activity. One of the most useful of these is clinical and electrical observation of the patient while asleep (Gibbs and Gibbs, 1941, 1947; Wyke, 1949), and this provides information of physiological as well as of direct clinical interest.

As observations during natural sleep are inconvenient, artificial methods of sleep induction have been sought, and such various substances as paraldehyde, sodium amytal, "nembutal," sodium pentothal, sodium evipan, and seconal sodium have been employed to this end. The most satisfactory agent for this purpose in our hands is seconal sodium†, suggested by Gibbs and Gibbs (1949), and our experience with it now embraces 100 cases.

On the basis of this experience the present communication discusses the cyclical changes that this agent induces in the human electroencephalogram. It is restricted to the normal physiological changes. The technique for clinical testing and the abnormal variations are discussed elsewhere.

Method

Preliminary electroencephalographic examinations at rest and during hyperventilation were made on a number of clinically normal individuals, and from these five healthy young adults (with no personal or familial history of neurological disorder) were selected for study for this report because of the clarity and stability of their cerebral electrical activity, and because the dominant alpha frequency lay in the faster bands (10 to 12 c/s). These criteria were chosen to facilitate study of frequency changes.

* Beit Memorial Research Fellow.

† Sodium 5-allyl-5-(1-methylbutyl) barbiturate,

The subjects were put to sleep with graduated doses of seconal sodium, given orally in 1.5 gr. (0.1 g.) absorbable capsules. The final dosage varied with each individual, but in no case did the total amount exceed 4.5 gr. (0.3 g.). This method was used in order to produce a very gradual onset of sleep, so that detailed clinical and electrical studies could be made during the process. Comparison with our other records shows that the response to such graduated sedation does not differ, except in its time relations, from the response produced by the less prolonged induction of sleep employed in routine studies.

Attempts were made to correlate the EEG changes with the depth of sleep by examination of the patient at various stages. The responses to various forms of sensory stimulation (tactile, painful, visual, and auditory) as well as observations of the subject's spontaneous and reflex behaviour were noted as the record was being made. Observations during spontaneous waking as well as during provoked arousal were made in each case.

The subjects were examined lying on a bed in a darkened room. Tracings were made at frequent intervals from all regions of the head (frontal, precentral, postcentral, occipital, and temporal areas). Each test occupied three to four hours, compared with the one and a half to two hours required for routine clinical testing. The technical details, method of electrode placement, and method of recording have been described in detail in separate reports (Wyke, 1949; 1950), but it should be emphasized that each chronological stage of sleep has been examined in both longitudinal and transverse runs, and with and without ear leads.

Results

Comparative analysis of all our records shows that following an adequate dose of seconal sodium each patient passes through a series of stages, from waking to sleeping and back to waking again, that are recognizable clinically and electrically. Each subject varies slightly in various minor details, but, independent of whether the case is clinically normal or abnormal, a basic cyclical pattern of response (Fig. 1-6) is common to all. As in normal sleep, there is no clear transition from one stage to the

FIG. 1.—Normal resting record immediately before administration of second sodium. Occipital alpha rhythm at 11 c/s. Figs. 1 to 5 are successive records from the same subject at one examination. Amplifier characteristics unchanged throughout.

FIG. 2.—Stage 1 of progressive barbiturate sedation: recording 15 minutes after initial oral dose of 2.25 grains (0.15 g.) of second sodium. Subject still awake and alert.

FIG. 4.

FIG. 3.

FIG. 3.—Stage 2 of progressive barbiturate sedation: recording 35 minutes after initial oral dose of 2.25 grains (0.15 g.) of seconal sodium. Subject lightly drowsy.

FIG. 4.—Stage 3 passing into Stage 4 of progressive barbiturate sedation: recording 80 minutes after initial dose of 2.25 grains (0.15 g.) of seconal sodium, and 20 minutes after a further oral dose of 0.75 grain (0.05 g.). Subject asleep.

FIG. 6.

FIG. 5.

FIG. 5.—Stage 5 of progressive barbiturate sedation: recording 110 minutes after initial oral dose of 2.25 grains (0.15 g.) of secenal sodium, and 50 minutes after a second dose of 0.75 grain (0.05 g.). Subject deeply asleep.

FIG. 6.—The stages in progressive barbiturate sedation as seen in longitudinal leads. Amplifier characteristics constant throughout. Different subject from Figs. 1 to 5. Initial dose of secenal sodium 3 grains (0.2 g.) followed by 1.5 grain (0.1 g.) 60 minutes later. Recording times given in Table I.

TABLE I

Stage	Mins. after 1st dose	Mins. after 2nd dose
1	15	—
2-3	50	—
3	70	10
4	100	40
5	135	75
Awake (spontaneous)	150	90

next, a waxing and waning of changes superimposed upon a general trend into progressively deeper sleep being the usual picture.

Any subdivision of the processes of natural or induced sleep is therefore arbitrary, but the description to follow embodies those subdivisions which seem to have practical significance. The details of the present analysis are described from the records of the five patients specially selected for protracted sleep study; but all the stages may be identified, however briefly, in each of the records in which a more rapid survey has been carried out.

Stages in the Second Sleep Cycle

Stage 1 (Figs. 2 and 6).—During the first 10 to 20 minutes, under our conditions of graduated dosage, as the subject lies quietly with his eyes closed, there begins a slowly developing instability of the resting rhythm. This becomes apparent first in the temporal regions, and a little later in the occipital leads. At the same time there is a gradual increase in the voltage of the beta (16–30 c/s) activity from the frontal regions, and sometimes a transient increase in the amplitude of the occipital activity also occurs.

During this period the subject undergoes no apparent subjective or objective change. He is fully alert, able to perform calculations and reply to questions in normal fashion, and makes fairly frequent spontaneous movements as he settles down into a comfortable position.

Towards the end of this period some shortening of the duration of the alpha spindles is noticeable, and alpha suppression in response to visual stimulation becomes less crisp than normal.

Stage 2 (Figs. 3 and 6).—Over the next 15 to 20 minutes, the instability of the resting rhythm becomes progressively more pronounced.

More marked in the temporal regions, this instability is always more advanced in these areas than the corresponding changes in the occipital leads. In the latter, the duration of the alpha spindles is further decreased, and the gradually lengthening intervals between them are occupied by mixed alpha frequencies from 8 to 12 c/s with

a voltage about half that of the spindled alpha activity which remains at the dominant frequency of the waking record. This latter activity is also gradually reduced in amplitude as the subject passes through this stage, after the initial transient increase in voltage that occurs in some subjects. In the frontal regions the beta activity shows periodic slowing to 16 c/s, so that the normal mixture of beta frequencies begins to be interrupted by short runs of 16 c/s activity.

During this period the subject gradually becomes quieter, his respiration slows a little, and he makes fewer and fewer spontaneous movements. Initially, there is a subjective feeling of relaxation, during which there is occasional yawning, and this passes into a stage of light drowsiness during which the subject may lose contact with his environment for brief moments. However, he is readily roused by a conversational voice or a light touch, although replies to questions are now definitely slowed and sometimes a little confused. Application of any of these stimuli quickly reverses the brain potential pattern through the preceding stages, but the gradually progressing stages of sedation re-establish themselves quickly as soon as the subject is allowed to quieten down.

Stage 3 (Figs. 4 and 6).—As the rest of the first hour elapses, alpha spindling (at the waking dominant frequency) gradually disappears, and slower components of the alpha band become more apparent. Thus the 10–12 c/s activity characteristic of the waking alpha spindles of these subjects is gradually replaced by 8–9 c/s activity, the admixture of 10–12 c/s frequencies becoming less and less, so that towards the end of this period activity in the occipital leads consists of a diffuse mixture of frequencies at 8 to 12 c/s, with the slower components of this band gradually increasing in amplitude and amount. At the same time the faster components of the beta band disappear frontally, the residual 16 c/s activity increases in voltage, becomes more apparent in the temporal leads, and begins to be replaced by 14 c/s activity in both frontal and temporal areas. Also, in the latter regions, frequencies in the theta band (4–7 c/s) are increasingly represented, appearing first as random 6 c/s waves and then as short runs lasting up to 0.5 second. Similar changes occur in the pre- and post-central regions, although these tend to lag behind and to have a lower amplitude than the temporal areas.

The subject is now definitely drowsy, and respiration is slower and deeper. He occasionally makes a slow spontaneous movement of one or other limb, and this is generally accompanied by a

FIG. 7.—Reversal phenomena during progressive barbiturate sedation (same subject as Fig. 6).

FIG. 7A. Induced arousal reaction in early part of Stage 4. Auditory stimulus (single loud handclap) at arrow, followed by K complex and then a spontaneous movement (artefact at A), following which the processes of deepening sedation are re-established.

FIG. 7B.—Spontaneous arousal reaction late in Stage 3. A is artefact due to the spontaneous movement.

transient reversal of the electrical changes in all leads, particularly posteriorly (Fig. 7b). He fails to respond to questions asked in an ordinary voice, grunts, yawns or makes an unintelligible reply to louder questions, and requires a stronger tactile or brighter visual stimulus than before to rouse him. However, he is still easily and quickly awakened by such stimuli, and this arousing is accompanied by well-defined reversal of the electrical changes in all regions of the brain, this time most apparent in the fronto-temporal leads. Also, during this stage, stimuli produce trains of complex wave forms in all regions of the head (Fig. 7a) which resemble the "K complexes" identified in natural sleep by Loomis, Harvey, and Hobart (1938).

Stage 4 (Figs. 4 and 6).—Over the next 30 minutes the outstanding feature is the rapidly increasing prominence of 14 c/s activity in all leads. This is always more marked in the fronto-temporal regions, where frequencies of 16 c/s or more have almost disappeared, but it is also increasingly apparent in the parietal and occipital leads. In the latter it first appears as low voltage activity superimposed on the *mélange* of slowed alpha activity which characterizes the beginning of this stage. Later, prominent 14 c/s waves appear in short bursts in the intervals between the developing spindles of slowed

(8 to 9 c/s) alpha activity, together with random 5 or 6 c/s waves which appear towards the end of this stage. This 14 c/s activity builds up in the fronto-temporal leads to form spindles lasting 1.0 to 1.5 seconds, with a maximum peak-to-peak amplitude of 50 to 60 microvolts; in children it is even higher, reaching 100 microvolts on some occasions.

The proportion of theta components in the temporal leads also steadily increases during this period, and short runs of 4 or 6 c/s activity, as well as many random waves in this band, are evident between the 14 c/s spindles. This theta development spreads out from the temporal regions into the frontal areas, then shows up in the pre- and post-central leads, and finally occupies a gradually increasing proportion of the spectrum displayed in the parietal and occipital leads. All the spindled 14 c/s and theta activity is bilaterally synchronous, while the random activity is mainly so, but may be partly asynchronous in the two hemispheres.

During this stage, the deepening drowsiness of Stage 3 seems to pass into light sleep, for now the subject is even more difficult to rouse, and respiration is still slower and deeper. Towards the end of Stage 3 isolated twitches or jumps of one limb or part of a limb may be seen, but these are no longer

apparent in Stage 4. Also, spontaneous organized movements are hardly seen during this latter period. The electroencephalogram shows more transient and less marked reversal phenomena on stimulation than before, even when quite strong stimuli are applied; and although "K complexes" can still be elicited, they are less and less developed as this stage is transversed. It is during this stage that dreaming and sleep talking appear to be most common in both normal and abnormal subjects: and in the latter quite elaborate phantasies may be expressed vocally.

Stage 5 (Figs. 5 and 6).—In the frontal leads there is now little activity apparent except low voltage 14 c/s activity, which occasionally slows to 12 c/s. In the temporal leads, as elsewhere in the brain, there is progressive flattening of all frequencies, including the 12 to 14 c/s activity, and the latter now fires almost continuously at low voltage with brief intervals occupied by 3 to 6 c/s waves. This slow activity is now increasingly represented in the posterior leads as well, and in the occipital leads it may become the dominant frequency at low voltage mixed with a residuum of slowed alpha components.

This appears to be a period of steadily deepening sleep, marked by the complete inertness and relaxation of the subject, with very slow stertorous respiration and snoring at times. There is outward divergence of the eyeballs, constriction of the pupils, and diminution of the tendon reflexes. The plantar reflexes are either sluggishly flexor or absent by now.

Sleep continues to deepen throughout this stage, and the period of deepest sleep (reached in about 120 to 150 minutes with protracted sedation) is characterized by a diminution in voltage of all frequencies everywhere except in the anterior temporal regions, where the most prominent feature is steady bilaterally synchronous discharge of theta activity, mainly at 4 c/s. The 12 to 14 c/s activity disappears as the 4 c/s activity becomes prominent; while in the occipital leads 3 to 6 c/s activity appears superimposed on low voltage waves represented by slow oscillation of the base line with a period of 0.5 to 1 sec. In very deep sleep some 2 to 3 c/s activity may appear in the temporal leads in addition to theta activity, but this is not common under the conditions described above.

At this stage the patient responds only to very intense and repeated stimulation, and that very slowly and sluggishly. The mouth usually falls open, saliva dribbles from it, and the skin becomes flushed and warm and is often covered with a fine sweat. The pupils show marked constriction, and either do not react to light or else display hippus.

The tendon reflexes disappear, as do the abdominal reflexes, and the plantar response is usually extensor, especially in children.

Stage 6.—The spontaneous waking period occupies between 15 and 30 minutes, and the electroencephalographic changes are essentially a reversal of those described during the onset of sleep, but with a more rapid time course. There is a gradual increase in voltage of all frequencies which begins in the temporal lobes and sweeps over the rest of the brain. At the same time the dominant frequency increases, more rapidly in the occipital lobes than elsewhere; 14 c/s activity reappears and then disappears, being replaced in the frontal leads by the usual beta frequency band; and theta activity is quickly submerged in the reappearance of normal frequencies, first in the occipital leads and then in the temporal regions.

The patient quickly regains consciousness as the 14 c/s and the theta activity disappear in the temporal leads. He stirs, stretches, yawns or groans and flutters his eye-lids; the pupils enlarge and the eyeballs roll about, while the normal reflexes re-appear. By the time the normal dominant alpha frequency is re-established in the occipital leads he is fully awake, although somewhat confused, and often he does not know, and sometimes strenuously denies, that he has been asleep.

The occipital alpha rhythm may remain somewhat unstable for about an hour after waking, and instability may last even longer in the temporal regions. During this period the subject may be a little lightheaded and somewhat ataxic. He is usually very hungry, even if he had had a full meal shortly before beginning the experiment, and it has been found that oral administration of glucose rapidly relieves this feeling of hunger and dissipates the mild mental confusion and ataxia that follows waking.

As yet there is no adequate series of blood sugar estimations available to permit correlation of these two observations, but it seems that "seconal" sedation may perhaps be followed by a mild hypoglycaemia, such as occurs in normal sleep (Kleitman, 1939) and after barbiturate anaesthesia (Sollmann, 1948), although Tatum (1939) and Goodman and Gilman (1941) state that barbiturates in soporific doses produce no significant changes in blood sugar levels.

Discussion

The sequence of cerebral electrical changes described in this paper presents a close parallel to the stages identified in normal sleep by Loomis and others (1937; 1938), Davis, Davis, Loomis,

Harvey, and Hobart (1938), Blake and Gerard (1937), Blake and Kleitman (1939), although most of these workers used fewer electrodes on the head and so were restricted in their area analysis. Also, the clinical state of our narcotized subjects passes through all the phases characteristic of normal sleep as described by Kleitman (1939) and others, while the correlation between the clinical level of sleep and the cerebral electrical pattern is analogous to that described for normal sleep by these authors. However, under the conditions of the present examination, the subjects seldom pass into the very deep stages of sleep that may be attained by naturally sleeping individuals.

All the stages A, B, C, D, and E of Davis and others (1938) may be identified in the "seconal" records of both normal and abnormal subjects. Thus Stage 1 would correspond to the A period of these authors, and this passes into Stage 2, which resembles their "floating" period. Stage 3 corresponds more or less to period B. But although Davis claimed that this marked the "onset of real sleep", we find that subjects in Stage 3 are only drowsy, and show none of the muscular or reflex changes which seem to indicate "real sleep" (compare Kleitman, 1939). This may be associated with the fact that in period B of Davis' classification the alpha rhythm is lost, whereas in our records the alpha rhythm is still identifiable until almost the end of Stage 4 when sleep really seems to begin. Also, it is during Stage 4 that dreaming seems to be most common, and this is in accord with its other resemblances to period C of Davis and others (compare also Blake, 1939). The most marked resemblance however is the prominence of 14 c/s spindles at this stage, the emergence of which from the normal beta frequency band during the onset of natural sleep has been previously noted by Jasper and Andrews (1938). The later phases of Stage 4 and Stage 5 may be equated with periods D and E of the Davis classification, although, as stated, our subjects usually seemed to stop short of the deepest stages of natural sleep which may be seen in this period. Thus, from a chronological point of view, there appears to be a sufficiently close resemblance between the cyclical response to "seconal" sedation and the devolution of normal sleep to suggest that the responsible mechanism is not vastly different in the two cases. Of special significance in this respect is the fact that the correlation between clinical state and brain potential pattern during "seconal" sedation is practically the same as that described for natural sleep. This close correlation is also emphasized by comparison of "seconal" records with tracings made during natural sleep in some of our own subjects.

Whether "seconal" sedation under these circumstances merely increases the patient's indifference to external stimuli to an extent which permits him to fall into natural sleep when placed in a suitable environment, or whether the barbiturate exerts some specific central action by which it initiates and controls the sleep process is at present uncertain. Our material provides results which suggest the latter as the more likely possibility, and the evidence bearing on this point will be presented in a subsequent communication.

Summary

A method for the induction of artificial sleep in human subjects, using "seconal sodium," is described.

The normal chronological sequence of the cyclical response to such sedation is analysed in terms of changes in cerebral electrical activity and clinical level of sleep.

The similarity between natural sleep and artificial sleep induced in this manner is indicated.

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