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THE PSYCHOLOGICAL REVIEW.

STUDIES FROM THE PSYCHOLOGICAL LABORATORY OF THE UNIVERSITY OF IOWA.

ON THE EFFECTS OF LOSS OF SLEEP.[1]

BY PROFESSOR G. T. W. PATRICK AND DR. J. ALLEN GILBERT.

The object of the following experiments was to determine some of the physiological and mental effects of enforced abstinence from sleep. In an address before the International Medical Congress at Rome in 1894, M. de Manacéine reported some experiments upon young dogs on the effects of absolute insomnia. The animals were kept from sleeping, and died at the end of the fourth or fifth day. (*Arch. Ital. Biol.* XXI, 2. PSYCHOLOGICAL REVIEW II, 1, p. 81.) So far as is known to the present writers, no experiments upon human subjects have hitherto been made on enforced insomnia for psychological purposes. The plan of our experiments was as follows: It was proposed to keep the subjects awake continuously for about 90 hours, to make a series of physiological and psychological tests upon them at intervals of 6 hours in respect to reaction-time, discrimination-time, motor ability, memory, attention, etc.; to observe secondly, the general effects of insomnia, and finally to observe the depth, character and amount of sleep following the period of waking. This plan was successfully carried out with three subjects, the depth of sleep being ascertained, however, in the case of only one. The subjects were in each case constantly attended by either one or two watchers.

[1] One of the three experiments described in this article was reported in a paper by Professor Patrick at the December meeting of the American Psychological Association at Philadelphia.

They took their regular meals at 7 a. m., 12.30 p. m., and 6 p. m., the food being normal in character and amount. In addition they ate a very light lunch at 12.30 a. m. The days were spent in occupations conforming as nearly as possible to the usual daily work of the subject. The nights were spent at first in reading or playing light games, and toward the end of the experiments in any way best adapted to keep the subjects awake, such as walking, working upon apparatus, or playing active games. Each set of experiments, however, took nearly two hours, so that this occupation consumed almost one-third of the time both day and night.

We give first a general account of the subjects and experiments. The first subject, J. A. G., is a young man of 28 years, assistant professor in the University. He is unmarried, of perfect health, of nervous temperament, of very great vitality and activity. He is accustomed to about 8 hours of sound sleep from 10 p. m. to 6 a. m. He awoke at his usual time Wednesday morning, November 27, and remained awake until 12 o'clock Saturday night. The second night he did not feel well and suffered severely from sleepiness. The third night he suffered less. The fourth day and the evening following he felt well and was able to pass his time in his usual occupations. During the last 50 hours, however, he had to be watched closely, and could not be allowed to sit down unoccupied, as he showed a tendency to fall asleep immediately, his own will to keep awake being of no avail. The daily rhythm was well marked. During the afternoon and evening the subject was less troubled with sleepiness. The sleepy period was from midnight until noon, of which the worst part was about dawn.

The most marked effect of the abstinence from sleep with this subject was the presence of hallucinations of sight. These were persistent after the second night. The subject complained that the floor was covered with a greasy-looking, molecular layer of rapidly moving or oscillating particles. Often this layer was a foot above the floor and parallel with it and caused the subject trouble in walking, as he would try to step up on it. Later the air was full of these dancing particles which developed into swarms of little bodies like gnats, but colored red,

purple, or black. The subject would climb upon a chair to brush them from about the gas jet or stealthily try to touch an imaginary fly on the table with his finger. These phenomena did not move with movements of the eye and appeared to be true hallucinations, centrally caused, but due no doubt to the long and unusual strain put upon the eyes. Meanwhile the subject's sharpness of vision was not impaired. At no other time has he had hallucinations of sight and they entirely disappeared after sleep.

The period of 90 hours being completed at 12 o'clock Saturday night, the subject was allowed to go to sleep, which he did immediately. He was awakened at intervals of one hour to ascertain the depth of sleep, but fell asleep again at once after each awakening, and slept until half past ten Sunday morning. He awoke then spontaneously, wholly refreshed, felt quite as well as ever, and did not feel sleepy the following evening. He slept, however, two hours later than usual Monday morning.

The special tests made upon this subject, 14 in number, are shown with the results in Table I. They were all repeated every 6 hours throughout the whole period, and repeated again finally after the subject had slept. The results of the latter tests are shown in the last column. In reaction-time and discrimination-time, the effects of practice were eliminated as far as possible by preparatory training preliminary to the experiment. A few words of explanation of methods and apparatus are necessary. The pulse was taken at the beginning of each set of tests and then again at the end immediately after the subject was fatigued by tapping with the forefinger as rapidly as possible for 60 seconds. The subject was weighed the same time after each meal and in the same clothing. Grip was taken with an ordinary hand dynamometer. Pull was taken with the same instrument, the subject using the second finger of each hand.

For reaction-time the stimulus was a telephone click, with signal, the reaction being the release of a key, the subject being in the dark room, away from the recording drum. Each reaction-time given represents the mean value of from 10 to 15 reactions. For discrimination a modification of the same apparatus was used, the subject reacting only to the loud stimulus.

J. A. G.

Table I.

	November 27.			November 28.				November 29.				November 30.				Dec. 1. After Sleep.
	9 a.m.	3 p.m.	9 p.m.	3 a.m.	9 a.m.	3 p.m.	9 p.m.	3 a.m.	9 a.m.	3 p.m.	9 p.m.	3 a.m.	9 a.m.	3 p.m.	9 p.m.	12 m.
1. Pulse	88	89	68	62	81	72	74	74	68	65	63	63	61	72	61	77
2. Temperature (Centigrade)	36.72	36.39	36.17	35.78	36.56	36.67	36.56	35.67	36.44	36.56	36.11	36.28	36.00	36.50	36.39	36.17
3. Weight (Kilograms)	67.70	67.75	68.30	67.78	68.19	68.04	68.52	68.83	68.27	67.99	68.35	68.60	68.41	68.13	68.47	67.39
4. Grip (Kilograms)	48.08	46.95	51.94	47.86	47.17	44.45	40.83		44.91	48.08	47.17	45.36	43.99	49.67	43.77	50.35
5. Pull (Kilograms)	27.22	27.67	28.12	26.31	26.76	25.86	22.68	22.68	26.31	25.86	24.95	23.59	22.68	26.99	23.13	27.67
6. Reaction-time. Mean (Sec.)	.122	.132	.129	.149	.133	.129	.139	.143	.146	.130	.144	.146	.139	.165	.148	.128
Mean Variation.	9	26	28	20	10	16	24	25	21	10	50	21	31	26	20	13
7. Discrimination-time. Mean (Sec.)	.258	.240	.242	.253	.225	.215	.216	.271	.207	.210	.213	.213	.206	.201	.158	.205
Mean Variation	50	56	51	48	38	32	43	67	63	63	40	65	62	36	43	52
8. Sensibility to pain. Lower threshold		3250	3000	3100	2750	3100	2650	2800	3150	2800	2750	2850	3300	3150	3250	3200
Upper threshold		4450	4350	4550	4050	4650	4450	4300	4600	4250	4200	4300	4550	4850	4400	4800
9. Acuteness of Vision (cm.)	137.2	132.1	139.7	134.6	142.2	156.2	150.5	120.6	137.2	143.5	137.2	152.4	148.6	156.8	171.4	125.7
10. Memory (Sec.)		540	260	159	290	330	200	105	240	70	262	290	123	190	545	125
11. Addition of Figures		228	254	248	238	249	223	215	205	216	196	210	200	250	224	277
12. Voluntary Motor Ability	42.2	42.2	40.1	39.0	40.0	41.2	38.6	35.5	39.5	39.0	35.0	38.9	41.0	39.0	39.7	41.3
13. Fatigue. Per cent. of Loss	24.1	24.6	22.6	20.5	18.0	24.0	13.7	12.1	17.0	13.9	11.4	20.6	17.6	17.9	13.6	17.7
14. Pulse after Fatigue	89	81	92	82	75	76	58	59	62	62	54	58	63	59	52	84

Sensibility to pain was tested by a specially prepared algometer, arranged to bring any desired pressure upon the middle of the fingernail of the first finger, the finger being inserted between two horizontal bars, the one pressing upon the fingernail being a very dull wooden knife edge. The figures record the pressure in grams, the lower threshold representing the first feeling of pain, the upper threshold the point at which the pain could no longer be endured. Acuteness of vision was tested in the dark room by finding the greatest distance at which the subject could read a section of a page from Wundt's *Studien* by the light of one standard candle at a distance of 25 cm. The memory test consisted in committing to memory 10 of the Ebbinghaus nonsense syllables. These were used in the ordinary way, but we consider this test of very slight value, for it is impossible not to learn these lists by association, and impossible to get different lists which offer equal ease or difficulty in association. The effects of loss of sleep upon attention and association we attempted also to ascertain by determining the greatest number of figures in prepared columns that could be added in three minutes. Voluntary motor ability was tested by having the subject tap with the forefinger as rapidly as possible upon a key for 5 seconds, using the recording drum and graphic chronometer. He then continued tapping for 60 seconds to fatigue the muscles. The number of taps during the last 5 seconds was then recorded. In the table is given first the number of taps in the first 5 seconds, then the percentage of loss in the last 5 seconds due to fatigue. The results of the special tests may best be studied from the table. Attention is called, however, especially to the following. The steady increase in the subject's weight during the experiment and the sudden decrease in weight after sleep are noteworthy, and apparently not to be accounted for by accidental circumstances. His average weight during the last 24 hours was 18 ounces greater than the average during the first 24 hours, and at 9 o'clock Saturday night the subject weighed 27 ounces more than at 9 o'clock Wednesday morning. During the 10½ hours' sleep, however, which followed the experiment, the subject lost 38 ounces, being 11 ounces more than he had gained during the

experiment. In the tests with the dynamometer the subject lost slightly and gradually in strength of both grip and pull, regaining all after sleep. On Saturday afternoon, however, the subject made what appeared to be a spurt, in view, perhaps, of the approaching end, and gripped and pulled nearly as much as at the beginning. The reaction-time beginning with 122σ increased somewhat regularly, reaching its maximum, 165σ Saturday afternoon, after 81 hours without sleep, and dropped back to the normal immediately after sleep. The discrimination-time appears to decrease, but as it does not increase after sleep the result cannot in this case be attributed to loss of sleep. The acuteness of vision uniformly *increased* throughout the experiment, falling below the normal after sleep. The slight retardation in the increase in the second night corresponds with the period of slight sickness at that time. There is a significant decrease in voluntary motor ability. The decrease in this subject's pulse-beat after fatigue by tapping is abnormal and apparently a result of loss of sleep.

The above experiment upon J. A. G. was regarded as somewhat preliminary. It was, therefore, decided to repeat the experiment upon two other subjects, making such modifications in the special tests and apparatus as seemed to be desirable. The second subject, A. G. S., was a young man of 27 years, instructor in the University, unmarried, quiet and of excellent health. The third subject, G. N. B., was a young man of 24 years, instructor in the University, unmarried, of German parentage, stout and perfectly healthy. At the time of the experiment, A. G. S. was accustomed to 9 hours of sound and regular sleep; G. N. B. to 8 hours. These two subjects entered upon their sleep fast at 7 o'clock, Tuesday morning, March 17, 1896. 90 hours was again the period determined upon. On Friday night, March 20, at 11.15, the last set of experiments being completed, they were allowed to retire, so that their waking period was actually 88¼ hours. In the case of these two subjects there was no illness, no hallucinations of sight, and no serious suffering or discomfort. A. G. S. became very sleepy during the last 24 hours and had to be watched constantly. On Friday, at 9 p. m., after a brisk walk in

the cool air, his temperature sank to 35.3° Cent. (95.6° F.), but in 15 minutes rose to 36.3° Cent. (97.3° F.). Of the three subjects he was the only one who apparently could not have prolonged the experiment beyond the period of 90 hours without danger. G. N. B. had less trouble in keeping awake and showed outwardly but slight effects of the abstinence from sleep. Both subjects slept immediately upon retiring at 11.15 p. m., Friday. They both slept uninterruptedly until 10.30 a. m., Saturday. They both awoke then for a few moments and slept again, A. G. S. until 11.15 a. m., G. N. B. until 2.40 p. m. They both felt wholly refreshed upon awaking, required no further extra sleep, and felt no ill effects from the experiment.

The special tests made upon these two subjects are shown with the results in Table II. and Table III., and exhibited, in part, in graphic form in the subjoined curves. They were as before, repeated every 6 hours. To eliminate, as far as possible, the effects of practice, the tests were begun two or three days before the beginning of the sleep fast. The first three sets of results in the tables, being taken the first day before any loss of sleep, should represent the normal reaction of the subject. These, taken together with the results of the tests made after awaking shown in the last column of the tables, make a fairly adequate standard for comparison with the results obtained during the sleep fast. The tests in respect to pulse, temperature, weight, grip, reaction-time, discrimination-time, sharpness of vision, voluntary motor ability, and fatigue, were the same as described above for the first subject. The strength of pull was taken with an ordinary lift dynamometer, the subject, standing upon a small platform with bent knees and straightened back, lifting his utmost by means of two handles connected by ropes with a large spring balance. In the memory test, the nonsense syllables were discarded and 18 figures substituted. 18 small squares of cardboard were provided upon which were printed the 9 figures, each figure thus appearing twice. For each experiment a random order of these figures was made, and then modified, if necessary, to prevent adjacence of same figure and suggestive combinations. The subject, timed with a stop

watch, committed to memory the list, the watch being stopped when the subject announced his readiness to recite the list. Each experiment consisted in committing to memory three such lists. The tables show in seconds the average of these three trials in each case. No. 11 was a test in adding numbers. The sheets of figures used by Miss Holmes in studying fatigue in school children and described in the Pedagogical Seminary, Vol. III., No. 2, were used. The subject was required to add each set of 40 figures by twos, setting down the results. He then added the results and then added the original figures in a different order. Any variation recorded in the two results indicated errors. The tables give the time required for the whole process. Test No. 12 was designed to determine the subject's facility in seeing and naming letters. A page from THE PSYCHOLOGICAL REVIEW was used; the subject reading the lines backward merely named the letters as fast as possible. The tables record the number of letters, average of two trials, named in one minute. Test No. 9 was designed to show the acuteness of hearing by discrimination of the intensity of two sounds. The sounds were vibrations of a tuning fork heard in a telephone in the silent room, the intensity being varied by a resistance board, only one telephone being used. The results in the tables have only relative value, indicating the number of divisions upon the resistance board by which the resistance had to be increased to enable the subject to detect the difference in the intensity of the sounds.

We may call special attention to a few of the results. In both subjects we again observe an increase in weight throughout the experiment with decrease after sleep. But with these subjects the decrease is less than the increase. In strength of lift both subjects lose quite regularly and seriously, but regain nearly all after sleep. In the memory tests, the results are very marked, especially with G. N. B. His average time in normal condition for committing the 18 figures was 134 seconds. No remarkable increase in this time was observed until the expiration of 72 hours. At 9 a. m. Friday the subject required 960 seconds to commit the first set of figures and failed entirely to commit the third set, working at it for *20 minutes*. At 9

A. G. S.

TABLE II.

	March 17.			March 18.				March 19.				March 20.				Mar. 21. After Sleep.
	9 a. m.	3 p.m.	9 p.m.	3 a.m	9 a.m.	3. p.m	9 p.m.	3 a.m.	9 a.m.	3 p.m.	9 p.m.	3 a.m.	9 a.m.	3 p.m.	9 p.m.	1 p. m.
1. Pulse	74	68	75	61	73	73	72	71	79	62	67	61	74	68	63	76
2. Temperature (Centigrade)	37.11	36.39	36.78	37.11	37.00	37.22	36.89		36.89	36 44	36 56	36.33	37.06	36.67	35.33	37.22
3. Weight (Kilograms) . . .	67.02	67.47	67.47	67.24	66.68	67.24	67.13	66.68	67.02	67.36	67.47	67.59	67.02	67.36	67.59	67.24
4. Grip (Kilograms) . . .	33.56	39.92	30.39	33.11	33.56	29 03	24.04	24.04	28.12	29.48	26 31	26.76	29.03	30.39	27.22	33.56
5. Pull (Kilograms) . .	155.58	163.30	140.62	117.94	150.60	113.40	127.00	81.65	107.05	89.36	88.45	49.44	49.44	95.26	92.99	131.54
6. Reaction-time. Mean	.121	.134	.138	.134	.141	.138	.143	.154	.147	.150	.141	.146	.143	.148	.193	.160
Mean Variation	0.6	1.5	0.8	0.9	2.2	1.2	7.1	1.5	1.7	1.9	2.4	1.5	1.9	2.5	4.0	2.9
7. Reaction-time with discrimination and choice. Mean	.158	.200	.310	.175	.202	.201	.182	.162	.188	.280	.189	.170	.222	.176	.311	.231
Mean Var.	5.9	4.2	7.4	4.1	3.5	4.5	2.9	3.6	4.1	8.3	4.7	3.9	5.3	4.3	8.0	6.0
8. Acuteness of Vision (C.M.)		103.8	103.8	113.6	122.3	112.8	96.1	105.1	115.4	116.6	119.2	109.0	119.7	118.0	123.3	119.7
9. Discrimination of Sound .	8.0	12.5	10.0	11.2	11.6	13.0	12.5	31.0	12.5	22.0	21.0	31.0	23.0	18.7	18.0	16.5
10. Memory (Sec.)	115	110	112	143	129	145	102	159	120	152	217	202	139	100	570	88
11. Addition of Figures . . .		85	119	118	105	103	130	192	111	108	185	610	113	190	345	109
12. Naming of Letters	165	160	155	154	162	155	134	113	154	144	127	91	147	135	117	171
13. Voluntary Motor Ability .	38	36	33	37	41	36	30	34	36	36	37	28	39	38	34	42
14. Fatigue. Per cent. of Loss	29.0	13.9	15.1	13.5	29.3	16.6	13.3	26.5	19.4	25.0	21.7	0.00	20.5	23.7	26.5	21.4
15. Pulse after Fatigue . . .	80	69	69	66	79	71	77	65	72	75	64	62	70	64	61	83

G. N. B.

Table III.

	March 17.			March 18.				March 19.				March 20.				Mar. 21 After Sleep.
	9 a.m.	3 p.m.	9 p.m.	3 a.m.	9 a.m.	3 p.m.	9 p.m.	3 a.m.	9 a.m.	3 p.m.	9 p.m.	3 a.m.	9 a.m.	3 p.m.	9 p.m.	4 p.m.
1. Pulse	63	64	63	68	68	67	67	69	70	62	64	68	74	65	73	84
2. Temperature (Centigrade)	36.22	36.44	36.33	37.17	36.78	37.22	36.56	36.67	36.33	36.61	36.56	36.89	37.06	35.78	36.56	37.22
3. Weight (Kilograms) . . .	68.49	69.29	69.29	69.17	69.51	69.74	69.85	69.99	69.85	69.99	70.08	70.08	69.40	69.74	69.85	69.29
4. Grip (Kilograms) . . .	42.64	34.47	38.10	33.11	39.36	43.09	37.65	34.01	37.19	37.65	42.64	43.09	44.45	47.63	44.00	41.73
5. Pull (Kilograms) . . .	118.84	129.28	146.15	138.35	125.19	117.94	106.60	111.13	120.20	113.40	113.40	113.40	113.40	111.13	95.26	117.94
6. Reaction-time. Mean	.145	.148	.157	.130	.142	.143	.134	.187	.136	.137	.141	.123	.139	.141	.142	.124
Mean Variation	1.8	1.3	1.4	0.8	1.1	1.7	1.8	2.9	3.7	1.0	1.7	1.8	1.1	2.9	3.2	1.6
7. Reaction-time with discrimination and choice. Mean	.167	.170	.200	.140	.185	.177	.214	.170	.178	.147	.158	.133	.153	.143	.175	.166
Mean Var.	3.6	7.2	5.6	1.4	3.7	1.6	5.5	4.6	6.8	1.8	2.7	3.7	2.3	1.2	2.3	4.0
8. Acuteness of Vision . . .		110.3	115.4	141.0	132.1	134.6	127.4	129.5	134.6	119.2	137.2	126.9	130.9	128.7	135.9	134.6
9. Discrimination of Sound .	12.8	20.0	12.5	24.8	14.0	15.0	20.5	17.5	24.5	30.0	23.0	20.0	22.5	21.0	32.0	21.5
10. Memory	170	133	128	206	170	135	273	143	112	353	169	201	820+	645	900+	106
11. Addition of Figures . . .		120	125	141	135	122	140	141	135	120	118	115	118	123	130	109
12. Naming of Letters	177	180	169	165	183	163	158	158	156	165	154	156	157	148	117	188
13. Voluntary Motor Ability .	41	37	38	39	41	42	34	39	39	39	40	44	42	42	40	40
14. Fatigue. Per cent. of Loss	19.5	16.2	26.3	28.2	29.3	28.6	14.7	28.2	25.6	33.3	25.0	34.1	26.2	26.2	35.0	22.5
15. Pulse after Fatigue	70	69	60	69	79	63	64	69	79	64	55	64	77	69	70	96

p. m. he could not commit the figures, and having made no progress after 15 minutes he desisted. The attention could not be held upon the work. A kind of mental lapse would constantly undo the work done. With both subjects an energetic 'waking up' by means of brisk walking and fresh air was often necessary during the latter time in order to address themselves to these mental tasks. After sleep, A. G. S. easily committed the figures in 88 seconds, and G. N. B. in 106 seconds, this being in both cases the shortest time in which the work was done. In respect to the number of letters named in one minute, there is with both subjects a steady decrease with the progress of the insomnia, with immediate return to the normal after sleep. In adding numbers similar results appear in a marked form in the case of A. G. S., but with G. N. B. adding time was affected but slightly. Reaction-time increases with A. G. S., as with J. A. G., but the reaction-time of G. N. B. is not lengthened. In respect to reaction with discrimination and choice the results are irregular and unsatisfactory. There is an irregular increase with A. G. S., but an actual shortening of time with the other two subjects.

Attention should be called to the length of sleep following the sleep fast and its relation to the whole amount of sleep lost. A. G. S. found it necessary to make up but 16 % of the lost sleep, as measured by time; J. A. G. 25 %; G. N. B. 35.3 %; As restoration was in each case apparently complete, explanation must be sought in one of two hypotheses or in both. The first is that, owing to the greater 'depth' of sleep after the sleep fast, the anabolism accompanying restoration was more rapid. The second is that the partial restoration which normally accompanies the waking period was, in the case of this long waking, greater than usual; that the subjects, in other words, although apparently awake and, indeed, as wide awake as they could be kept, were nevertheless at times partially asleep. There are reasons to believe that the results depend upon both of these causes. Our subjects well illustrated the fact that sleep is a matter of degree. All that could be done both by objective diligence and subjective effort to keep the subjects wide awake was done. If the subject, contrary to his own intention, closed

his eyes, although he immediately opened them in response to his watcher's command, still there was time for a short and, perhaps, refreshing 'nap.' Again, one of our subjects, who was kept jogging about the streets during a sleepy period at 5 a. m., afterwards could remember little about the walk. Another subject, standing with eyes open, reflectively gazing at a piece of apparatus upon which there were some pieces of rope, suddenly reported that he had had a dream about a man being hung. With our first subject we undertook to test the delicacy of the muscle sense by means of lifting weights. These weights were small tin pails loaded with graded weights and lifted by a detachable handle. Lifting these pails was found to be very monotonous and sleepy work. The subject was not permitted to let his attention wander, and yet he reported at least four dreams. For instance, he lifted two pails, carefully judged their relative weight, and as he set the second one down, instead of saying that No. 1 or No. 2 was the heavier, he said 'trimmings,' evidently having fallen asleep as he was lifting or setting down the pails and dreamed that they contained trimmings. It must be understood that these dreams were instantaneous and the subject as wide awake as he could be kept, but these facts reveal a cerebral condition related to sleep. This hypothesis alone, however, would not seem to account fully for the small proportion of sleep made up. And, indeed, a study of our special tests shows that restoration took place chiefly during the profound sleep following the sleep fast, and took place rapidly. That this sleep was actually more profound and that the profound part of it was longer than usual was shown by our experiments in depth of sleep in the case of J. A. G. reported below.

The depth of normal sleep for the consecutive hours of the night has been studied by Michelsen and by Kohlschütter, and the results presented in the so-called sleep curves. The depth of sleep was determined by these observers by the intensity of sound necessary to awaken the sleeper. Their results show the greatest depth of sleep at the end of the first hour. After the first hour the curve drops abruptly and rapidly. Already at the end of the second hour sleep is light and continues slowly

to become lighter until morning. In the case of our first subject, J. A. G., we attempted to ascertain the relative depth of sleep for the consecutive hours of the profound sleep following the sleep fast, for the sake of comparing our results with the normal sleep curve. As a sound stimulus would not be practicable, for the reason that, the experiments all being made in the same period of sleep the sleeper would soon become accustomed to it, we substituted a pain stimulus. An electric garter, to which the subject had become accustomed by wearing it for some nights preceding the sleep fast, was attached to the sleeper's ankle and connected with an induction coil in an adjoining room, and so arranged that the current could be closed for a constant time, viz., .334 sec., by means of a pendulum, and that the strength of the current could be varied by means of a resistance tube. It was agreed that the sleeper should announce his awaking by means of an electric button at his bedside. The current was turned on at intervals of one hour. Unfortunately the least resistance that could be arranged with the resistance tube failed to awaken the sleeper at the first three periods, so that it was necessary to cut out the tube and the pendulum and apply the direct current and measure it roughly by the time the circuit had to be closed. Our results, therefore, lack the exactness necessary for the construction of a curve or table, but still show plainly the relative depth of sleep for the consecutive hours. The deepest sleep was found at the end of the second hour, when the subject could not be aroused sufficiently to ring the bell, but responded by a cry of pain. The next deepest sleep was found at the end of the first hour and the next at the third hour. The current used at these three times was one which it was altogether out of the question for the subject to endure when awake. At the end of the second hour, just after the experiment, we entered the sleeper's room and attempted to awaken him by speaking to him in a loud voice without avail. At the fourth hour the sleep was less deep, and continued to become lighter regularly until awaking, but the decrease in depth was very much less rapid than in the normal sleep curves reported above. At 10 a. m. a very slight current awakened the sleeper, and at 10:30 he awoke spontaneously as stated.

The tendency of our subjects to have short semi-waking dreams suggested to us that in enforced insomnia there would be offered a good opportunity for a study of dreams. This, of course, was incompatible with our purpose, but in the cases of A. G. S. and G. N. B., at the end of the sleep fast and before allowing the subjects to retire, we undertook a few experiments in dreams. We allowed the subjects to sit with head supported behind, and to sleep for periods of 30 seconds, one

TABLE IV.

J. A. G.	2d day before experiment.	1st day before experiment.	1st day of experiment.	2d day of experiment.	3d day of experiment.	4th day of experiment.	4th day of experiment. (Sleep.)	1st day after experiment.	2d day after experiment.
Hours			24	24	24	14	11¾	24	
Total amount urine (ccm.)			1475	1370	1270	805	400	950	
Grams N. per hour . . .			0.901	0.929	0.667	0.723	0.490	0.723	
Grams P_2O_5 per hour . .			0.1327	0.1438	0.1105	0.1304	0.0564	0.0888	
Relation P_2O_5 to N. . . .			1: 6.8	1: 6.5	1: 6.0	1: 5.5	1: 8.7	1: 8.1	
A. G. S.									
Hours	38		24	24	24	13½	12¾	24	24
Total amount urine (ccm.)	1308		1510	1700	1420	750	525	1000	1240
Grams N. per hour . . .	0.655		0.661	0.628	0.745	0.661	0.414	0.6175	0.761
Grams P_2O_5 per hour . .	0.0765		0.0708	0.0791	0.1011	0.1000	0.0674	0.0907	0.1023
Relation P_2O_5 to N. . . .	1: 8.6		1: 9.3	1: 7.9	1: 7.4	1: 6.6	1: 6.1	1: 6.8	1: 7.5
G. N. B.									
Hours	24½		24	24	23	13½	16½	24½	24
Total amount urine (ccm.)	920		1240	1205	1730	650	365	705	705
Grams N. per hour . . .	0.4853		0.7094	0.6270	0.6123	0.5195	0.3390	0.5020	0.4765
Grams P_2O_5 per hour . .	0.0574		0.0802	0.0931	0.0826	0.0815	0.0435	0.0616	0.0613
Relation P_2O_5 to N. . . .	1: 8.5		1: 8.8	1: 6.7	1: 7.4	1: 6.4	1: 7.8	1: 8.1	1: 7.8

minute, three minutes, etc., then awakening them and asking for their dreams. No dreams were obtained in any case. If the period was less than one minute the subject sometimes had a hazy memory of something like a dream which could not be put into words. If the sleep was longer it was apparently profound and dreamless. These rough experiments confirm, of course, the generally accepted opinion that dreams are the product of light sleep, representing indeed the reinstatement of consciousness after the early and profound sleep.

Through the kindness of Dr. E. W. Rockwood, of the University, a chemical analysis of the urine was made throughout the experiments in the case of each of the subjects. The object of the analysis was to determine the influence of continued waking upon the relative amounts of nitrogen and phosphoric acid respectively excreted. The results are fully exhibited in Table IV. as compiled by Dr. Rockwood. Considered in relation to the fact that each subject increased in weight during the insomnia, the results are significant. They show not merely that there was an increase in the excretion of both nitrogen and phosphoric acid during the period of insomnia, but that relatively more phosphoric acid was excreted than nitrogen. A certain amount of support is thus given to the theory of a special connection between mental activity and the katabolism of the phosphorized bodies of the nervous system.

STUDIES ON THE PHYSIOLOGY OF SLEEP

I. The Effects of Prolonged Sleeplessness on Man

NATHANIEL KLEITMAN

From the Hull Physiological Laboratory of the University of Chicago

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Most investigators of the physiology of sleep, in reporting their findings, remind their readers, by way of apology, of the tremendous importance of the subject for the advancement of our knowledge of physiology as a science, as well as for the rational treatment of insomnia. They also like to record the fact that the average individual spends more than a third of his life in sleep, has been doing this from time immemorial, and raise the question whether eight hours or more of sleep a day really constitutes the minimum penalty for keeping awake the rest of the time. It seems reasonable to suspect that as in the case of protein consumption, there is a large "factor of safety" in the amount of sleep we are getting, and that it could be considerably reduced without impairment of health or loss of efficiency. This and other questions related to industrial physiology, especially physiology of fatigue, can be answered only by a thorough systematic study of the subject. But curiously enough, there are scarcely a dozen investigators engaged at any one time in the study of this great physiological mystery, and most of these workers are psychologists. It seems that because animals are not very well adapted for this work and the human beings that are available cannot be dissected, physiologists have allowed the psychologists to tackle this problem as best they could. Present day textbooks of physiology contain but a few short references to the subject, usually antiquated, and some texts (Starling's, for example) ignore the subject entirely. Luciani's four-volume work is the only textbook that treats the subject adequately, but unfortunately it is not in general use as a manual. Thus most medical students first encounter sleep in their study of pharmacology, and there they learn several easy ways of putting a person "to sleep." In this manner the "practical" aspect of the problem for them at least is solved. If we recall that textbook writers generally do not peruse psychological literature in bringing out their new editions, it will be readily understood why the work of many able investigators has not been brought to the attention of our students.

In this paper references will be made to both physiological and psychological literature. One of the best books ever written on the subject of sleep is Piéron's *Le Problème Physiologique du Sommeil* (1), which besides embodying the results of original research on sleep from the histological, biochemical and physiological standpoints (this by a psychologist!) contains a valuable and exhaustive bibliography brought up to 1912. To save space references will be given only to those papers which appeared after 1912, or have not been included in Piéron's bibliography; others referred to as (P) will be found in Piéron's bibliography.

Sleep should be studied not only in man, but in animals as well. Little work has been done on the comparative physiology of sleep, and at present we have no good criterion for determining whether an animal is asleep or not. Thus some people endow even plants with the ability to sleep, while others restrict sleep to animals with a nervous system, "no matter how rudimentary" (8). In these studies experiments were made on men and dogs, and this, the first paper of the series, contains a report of the results obtained on the human subject.

METHODS. The method of experimental insomnia appeared to be best suited as a beginning, for two reasons. In the first place, it should enable us to study the behavior and reactions of a subject deprived of sleep for a number of days, the concomitants of prolonged wakefulness and, if possible, to see whether all the changes that the various theories of sleep postulate actually occur; and in the second place, it should permit us to observe the concomitants of deep dreamless sleep, such as we could expect the subject to lapse into at the end of the period of experimental insomnia. The first to use this method on man were Patrick and Gilbert (P) who in 1896 kept three persons awake for a period of 90 hours. They performed a number of psychological and physiological tests during the experiment and on the day following the completion of the experiment, but had no normal control with which to compare their results. The test was made only once, and the individual findings will be referred to in various places in the course of this and following papers. In 1916 Smith (3) performed a number of psychological tests upon herself, studying primarily the effects of fatigue. On some occasions she studied the effects of the loss of one night's sleep. More recently Robinson and Herrmann (4) reported results obtained on three subjects who had been subjected to a period of experimental insomnia lasting 65 hours. They tested the subjects' muscular strength (Smedley's hand dynamometer), steadiness, aiming, ability to name letters and to do mental arithmetic. In this case the period of sleeplessness was preceded and followed by normal periods of observation of some days' duration (11 to 26 before and 4 to 5 after the test). They likewise performed the insomnia experiment only once.

In this study we employed six subjects, all young adults, male students at the University of Chicago. Each of these went through one or more sleepless periods. The duration of the experimental insomnia varied in different tests from 40 to 115 hours. Thus as regards the number of subjects used, the number of periods of insomnia and the maximum duration of sleeplessness, this method has been considerably extended by our experiments. Most of the work that involved long periods of normal control testing was done on the writer, who went through more than a dozen sleepless periods himself. The other subjects were used to check the results obtained on him.

The original intention was to keep conditions as uniform as possible and to have only one variable—absence of sleep. The subject was supposed to undress and go to bed at the usual hour, to relax his muscles, and keep awake throughout the night. This was found impossible of accomplishment, because the subject always fell asleep some time during the night. Attempts to keep awake by sitting in a reclining chair were likewise unsuccessful. The only method that was found to work consisted in having the subject keep moving throughout the night, with short periods of rest sitting down. Even in that case he would fall asleep shortly after he sat down, and he therefore had to be watched continually throughout the period of insomnia, especially at night-time. On some occasions even this method was only partially successful, because the subject would fall asleep as soon as he was awakened, and unless the observer made him walk it was impossible to keep him awake. For these reasons the experiments were not *strictly* insomnia tests, but insomnia plus a certain amount of muscular activity during the night, activity that a person would not engage in if asleep. The results obtained and reported below may be partly at least due to this increased muscular work. But from the standpoint of intoxication theories of sleep this could not be considered a drawback. On the contrary, the intoxication, if present, should only be accentuated by the products of muscular activity. On the other hand, the perpetual falling asleep during certain hours of the night might be looked upon as short almost momentary "naps," and it might be argued that they would have some restorative power, and would enable the subject to go without sleep longer than he could otherwise. The method then is not perfect, but it is the best we could devise at this time.

For the determinations of the pulse, temperature, respiratory rate and blood pressure, the subject was allowed to lie completely relaxed for at least 15 minutes, and in measuring basal metabolism, for at least 30 minutes. Only in one series of tests were the measurements taken with the subject in the sitting position, and this for purposes of comparison. All these determinations were made daily at 7 a.m. The

pulse was counted by ordinary palpation of the radial artery, the count being made after the subject's hand had been held for over one minute. Respiratory rate was determined by observing the movements of the pointer on the cylinder of the spirometer at a time unknown to the subject. Temperature was measured by a one-minute certified clinical thermometer, which was kept under the tongue for at least five minutes. For blood pressure we used the Tycos sphygmomanometer, making all determinations in duplicate. Basal metabolism was measured by means of the Benedict portable respiration calorimeter (5), using as a basis oxygen consumption only. Analysis of the blood was usually made late in the afternoon. For the red and white blood count we used the Neubauer counting chamber. Hemoglobin was determined by means of Sahli's hemoglobinometer, using Dare's hemoglobinometer as a check. For blood sugar determinations the Folin-Wu method was used, and the alkaline reserve of the blood or the plasma was determined by the Van Slyke method. The percentage of corpuscles was determined by the hematocrit method.

In our urine work we partitioned the 24-hour sample into two parts. What we call the day urine is a 16-hour sample from 6 a.m. to 10 p.m.; the night urine, an 8-hour sample from 10 p.m. to 6 a.m., the period devoted to sleep. All previous workers divided the 24-hour urine into two 12-hour samples, their "night urine" including not only the urine excreted during the eight hours of sleep, but also that of four hours of wakefulness. Thus the data we present show the activity of the kidney during wakefulness and during sleep, normally and during the hours usually devoted to sleep in our periods of experimental insomnia. We also studied the activity of the kidney during periods of "reversed routine," that is, sleep during the day and wakefulness at night. Campbell and Webster (6) have recently reported similar experiments on the secretory activity of the kidney on a reversed routine, but they allowed their subjects to eat at night, thus introducing new factors. In our experiments in which two subjects were used for many weeks, the meal hours were fixed at 8 a.m., 12 m. and 9:30 p.m., so that the subject on "reversed routine," sleeping from 1 p.m. to 9 p.m. did not have to change his meal hours. No attempt was made to keep the diet absolutely uniform, and these are to be regarded not as metabolism experiments, but as a test of the secretory rhythm of the kidney and its possible persistence or change during changed conditions. In the urine analysis, for total nitrogen the modified Kjeldahl method was employed; for creatinine the Folin method, using pure creatinine solution as a standard; chlorides were determined by the ordinary Vollhard method; phosphates by the uranium acetate method; and total acidity by the Folin titration method.

In the tests made during the sleep following insomnia the heart rate, respiratory rate, temperature and blood pressure were determined as above. The pupillary reflex and the position of the eyes were examined by gently spreading the eyelids with the fingers, and flashing a light from a pocket flashlight. The skin of the face was stimulated by touching it with sharp pieces of paper, and the reflex movements of the arms and hands on both sides were observed. The plantar reflex was determined by passing a pencil along the inside and outside aspects of the soles, the foot being illuminated by a flashlight. The subjects very rarely woke during these tests, and their general reflex behavior was observed during the several determinations.

RESULTS: *Subjective observations during insomnia.* While there were differences in the subjective observations of the subjects in the course of the experimental insomnia, they were so slight that a common description for them all will suffice. During the first night the subject did not feel very tired or sleepy. He could study or read or do laboratory work, but felt an attack of drowsiness between 3 and 5 o'clock in the morning. There were some itching or burning sensations in the eyelids during the night. In the morning the subject felt as usual, except for a slight indisposition which always appeared when the subject sat down to rest. As long as he kept moving, and especially if he engaged in laboratory work, he did not feel any urgent desire to sleep. On the second night he felt sleepier much earlier, or else felt a peculiar "buzzing in the head," or else a sensation of emptiness, not only in the head but in the entire body. Similar sensations were described by the subjects of Patrick and Gilbert and of Robinson and Herrmann. It was more difficult to keep awake during the second night, and the dryness of the eyes often became very unpleasant. It was found impossible to read or to study, because sitting would cause the subject to fall asleep. However, even during the second night work requiring manipulations and movement from place to place could be carried on with great ease and had the effect of banishing the desire for sleep. On the day following the longing for sleep subsided again, and the person could perform routine work as usual. He had great difficulty, however, in keeping awake at lectures. Even if he did not fall asleep while listening to the monotone of the lecturer, he had difficulties in taking notes. After a few words had been written in the correct fashion, his hand would begin to slip in executing the delicate movements of writing, would slide across the paper, and instead of words there was unintelligible scribbling. A new effort would make the hand write properly, but only for a short time. The lecture hour was a trying one for every one of our subjects. On the third night the desire for sleep was still more accentuated, but on the day following the subject again felt much better. On this day

taking lecture notes was entirely impossible, as the pencil would fall out of the subject's hands after he had been sitting for a short while. Laboratory work was possible, as on previous days. Attempts to count one's own pulse were almost always unsuccessful, because the subject would lose trend of the count after he had reached twenty or thereabouts, or else would become extremely drowsy. Only one subject (N. K.) kept awake for a fourth night, and he reported momentary dreams during the night, whether walking, standing or sitting. No hallucinations had been experienced by any of our subjects. The subjective feeling of drowsiness was not any worse after 115 than after 60 hours of wakefulness, and if the subject was engaged in an interesting conversation, he felt no desire for sleep at any time during the experiment. Likewise, a trip to an "all-night" café proved to a number of our subjects that interest in their surrounding had a powerful effect in dispelling all the subjective symptoms of drowsiness and depression. Lying down had the effect of inducing immediate sleep. This was observed on the subject whose basal metabolism was measured every morning during the period of insomnia, and who had to relax completely for this purpose. The observer had to keep a very close watch over him, and even so he managed to fall asleep while his companion determined his blood pressure (this may partially account for some of the low blood pressure values obtained). Usually on lying down for a minute or so the eyelids drooped without closing (relaxation of the levator palpebrae super.), and the subject saw double because of the divergence of the eyeballs. Shortly after that the eyes closed, unless the subject was disturbed. If the subject was aroused as he was falling asleep in the horizontal position, it was a matter of seconds before he was asleep again. We may sum up by stating that subjectively all the individuals tested felt sleepier during the night than during the day following; that drowsiness could be dispelled by any form of muscular activity and sleepiness accentuated by inactivity; that it was more difficult to stay awake while sitting than while standing and entirely impossible while lying; that at times the subject felt a greater need to sit down or lie down and rest than to sleep. None of the subjects employed experienced any loss or even diminution of appetite during the period of insomnia.

Objective observations during insomnia. In appearance the victim of experimental insomnia did not differ from his fellows. In fact no observer could tell a person who had not slept for several nights from a normal individual. This was true, however, only of the subject who was engaged in some kind of activity. When he sat down, one could see that he was extremely sleepy, even in the daytime. At night the observer had to watch the subject very closely. It was amusing to note that some subjects used ruses to escape the watchful eye of the observer. After being roused many times they pretended to get up for a stroll in the corridors of the building, but would actually walk over to some corner, sit down and fall asleep almost immediately. On other occasions the subjects would become irritable and resent being aroused every few minutes. They would pretend that they were not falling asleep, would roundly deny the fact. However, in all cases a short walk would restore the subject's good disposition and banish his drowsiness. The mental power of the subject was normal so far as could be determined. We performed a few tests on letter naming and on mental arithmetic, but our results were negative, confirming Robinson and Herrmann (4). Only in the subject who was kept awake for more than four days could some deficiency in mental power be observed. This consisted in temporary semi-dreaming states. In one case, early in the morning of the fifth day of insomnia, the subject was looking up logarithms of some numbers as they were called off by the observer. After some time the latter noticed that the subject's movements became mechanical and began to watch him as he looked up the various logarithms. He found that the subject invariably located the logarithms and called them off correctly, but once in response to a number whose logarithm he had located, instead of calling off the latter, said: "It is because they are against the system." On being questioned the subject admitted that all the time he was looking up the logarithms he had been under the impression that he was having a heated argument with the observer on the subject of labor unions. It is interesting to note that one of Patrick and Gilbert's subjects went through a similar experience during a weight lifting experiment, when instead of saying "number one," said "trimmings," and afterwards admitted to have dreamt during the experiment.

Our quantitative results will be found summarized in three tables. Patrick and Gilbert found a progressive increase in weight of their subjects during insomnia. We could not confirm this. Blood sugar and whole blood and plasma CO_2 determinations were made on two subjects (N. K. and M. P.). No variations that did not fall within the diurnal curve could be detected. Likewise, erythrocyte and leucocyte counts, percentage of hemoglobin and percentage of corpuscles, studied in one subject during several sleepless periods, showed no deviation from the normal. The absence of any change in the alkaline reserve of the blood is significant in that it shows that no toxic acid product accumulated in the blood during sleeplessness. The values for the heart rate, respiratory rate, temperature, blood pressure and basal metabolic rate, all obtained on subject N. K., are given in table 1. The normal days include the period preceding and following sleeplessness

tests, and the figures constitute the average of all the daily observations made. Besides the several periods of sleeplessness there was one 5-day period of complete fasting (4 observations) which was introduced mainly as a check on the accuracy of the basal metabolism determinations. In series 1, with the subject in the horizontal position, the average heart rate at 7 a.m. for 33 days was 74 per minute. The average obtained during three periods of insomnia (7 observations) was 62. In series 2, with 14 normal days and one period of insomnia of 4 days, the values are 75 and 62. The heart rate during insomnia was 17 per cent

TABLE 1

Showing the effect of insomnia and fasting on the average heart rate, respiratory rate, temperature, systolic and diastolic blood pressure and basal metabolism

NUMBER OF DAYS	CONDITION OF SUBJECT	HEART RATE	RESPIRATORY RATE	TEMPERATURE	BLOOD PRESSURE		BASAL METABOLISM
					Systolic	Diastolic	
			Series 1				
				°C.			calories
33	Normal	74	14	36.15	110	72	1491
7	Insomnia	62	14	36.07	105	67.5	1500
4	Fasting	80	14	36.20	114	77	1648
			Series 2				
14	Normal	75	14	36.50	107	72.5	1527
4	Insomnia	62	12	36.43	101	67	1569
			Series 3				
15	Normal	85	15	36.83	110	83	
4	Insomnia	79	13	36.80	116	88	

Subject N. K.; observations made daily at 7 a.m. In series 1 and 2 subject was in the lying position, in series 3 subject was seated.

lower than normal, and individual counts were as low as 56 per minute. In series 3, comprising 14 normal days and one 4-day insomnia period, with the subject in the sitting position, the decrease in heart rate resulting from sleeplessness was 6 beats per minute, or 7 per cent. During the fasting period the heart rate increased about 8 per cent. Respiratory rate showed no change in series 1, and a decrease of two respirations per minute in series 2 and 3. The temperature showed no change either during sleeplessness or during fasting. An interesting observation as regards the temperature variation, when it was recorded every two or three hours in several subjects during a number of tests, was the noticeable "damping" of the diurnal temperature wave. A good example of this is shown in figure 1, which respresents the temperature curve during a 115-hour period of insomnia. The reader will note that the difference between the temperatures taken at 1 p.m. and 1 a.m. following was 1.38 degrees on the first day, 1.12 on the second, 1.00 on the third, 0.85 on the fourth and 0.68 on the fifth. While not all our temperature curves are as nearly diagrammatic as the one plotted, they all show the same tendency for the temperature to be equalized, indicating that the diurnal temperature rhythm is dependent upon sleep for its persistence.

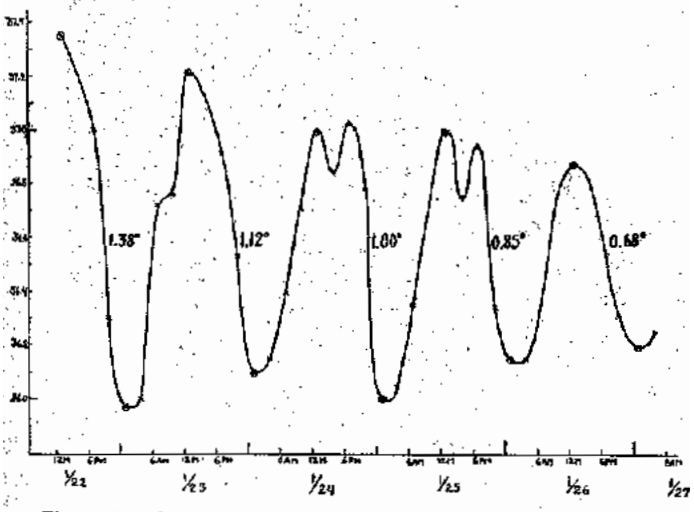

Fig. 1. Diurnal temperature curve during a 115-hour insomnia period. Circles on the curve indicate temperatures at 1 p.m. and 1 a.m. It will be noted that the differences between the temperatures taken at 1 p.m. and 1 a.m. becomes progressively smaller.

The blood pressure, both systolic and diastolic, was lower during the insomnia periods, when it was taken with the subject in the horizontal position; with the subject seated, it showed a rise. It also rose during fasting. The basal metabolic rate did not vary with lack of sleep. This may be only apparent, because the subject would continually fall asleep during the determination, and be continually awakened by the production of sharp metallic sounds. The momentary spells of sleep might have lowered the consumption of oxygen, while the awakenings involving as they do increased muscular tension, might have tended to

increase it. Comparative respiration curves on normal days and on sleepless days are shown in figure 2. On the whole there was a slight rise in basal metabolism during insomnia in both series 1 and 2. During

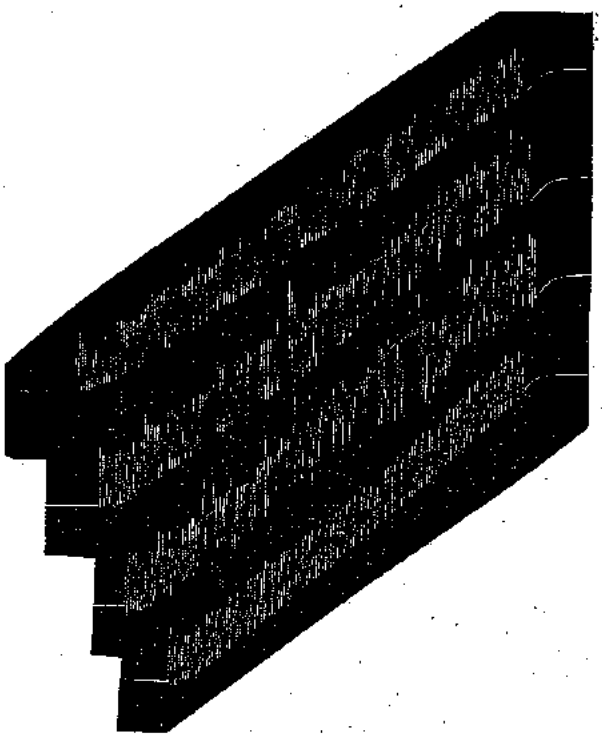

Fig. 2. Respiration tracings secured by means of the Benedict portable respiration calorimeter. Upper tracing taken on a day preceding the period of insomnia. The middle two tracings were taken on the third and fourth days of insomnia. The lowermost tracing was taken on the morning following the termination of the insomnia test. Reduced twice.

fasting the basal metabolic rate was markedly increased, which is in agreement with the results obtained by Kunde (7) under similar conditions.

Observations during sleep following insomnia. The subject of the insomnia experiment, at the end of the period, usually retired at 10 or 11 o'clock in the evening. The observer visited his bed-chamber at about 1 a.m. and again at 4 a.m. It was the invariable impression of the observers (as judged from general reflex irritability) that their subjects slept more deeply on the second visit than on the first. The values of the heart rate, respiratory rate, systolic and diastolic blood pressure and temperature taken during the first sleep following the period of insomnia in one subject are given in table 2. They show that

TABLE 2

Observations on the heart rate, respiratory rate, temperature and blood pressure during sleep following period of insomnia

DATE	HEART RATE	RESPIRATORY RATE	TEMPERATURE	BLOOD PRESSURE		DURATION OF INSOMNIA
				Systolic	Diastolic	
First call—1 a.m.						
			°C.			hours
12- 3-22	71	12	35.60	97	62	64
12-13-22	63	12	35.80	98	66	90
1-27-23	68	12	36.20	94	62	115
2-13-23	66	12	36.10	103	76	65
2-24-23	75	14	36.00	98	76	115
Average.....	69	12.5	35.95	98	68	
Second call—4 a.m.						
12- 3-22	60	11	35.70	96	64	
12-13-22	62	14	35.90	96	64	
1-27-23	63	12	36.25	95	65	
2-13-23	66	12	36.10	103	76	
2-24-23	72	12	36.10	101	74	
Average.....	64.5	12	36.00	98	68.5	

the respiratory rate was about the same at both hours, but that the heart rate was lower at 4 o'clock. In other subjects the respiratory and heart rates varied, sometimes being lower on the second observation, sometimes higher. The temperature did not vary from 1 to 4 a.m. The blood pressure was low, but not much lower than the pressure shown in the morning during the insomnia periods. The general behavior of the subject varied with the amount of sleep lost and with the usual depth of the person's sleep. Thus the sleep of one subject (N. F.) was normally much deeper than that of other subjects after two or three sleepless nights. But as a rule the sleep was deeper the greater the loss

of sleep during the preceding period of insomnia. The unavoidable sounds made by the observer rarely aroused the sleeper, but occasionally seemed to disturb him. The eyes were always found rolled up and out, but sometimes returned to their normal position wher the eyelids were spread apart. The pupils were frequently but not always found markedly constricted, but in one subject (S. L.) they were widely dilated. Every one of our subjects showed a positive pupillary reflex, but the response was very slow, it sometimes taking several seconds for the pupil to contract. There was no resistance to the insertion of the thermometer into the subject's mouth. The sleeper never closed his mouth tight enough to break the thermometer. The application of the sphygmomanometer cuff in some cases aroused the subject, but he always fell asleep before the reading was taken, as was evidenced by resumed snoring. Brushing the cheek with a rolled piece of tissue paper from the ear to the corner of the mouth often elicited a facial grimace and a movement of the hand, intended to scratch the stimulated spot. There was no strict homolaterality about this response. As a rule, the right hand would respond when the right cheek was stimulated, but if this hand was under cover and the left hand exposed, the latter would respond instead. In a few cases both a direct and a crossed reflex were elicited by this method. Plantar stimulation *invariably* elicited a positive Babinski in every one of our subjects during the sleep following insomnia, and in the deep sleeper referred to above (N. F.) during an ordinary night's sleep. Not only was there an extension but also a spreading of all the toes. This reflex could be obtained any number of times, provided a suitable interval (15 to 20 seconds) was allowed between successive stimulations. If the sole was scratched at shorter intervals, several extensor responses were followed by an extension-and-flexion, later by flexion of the toes, and either an attempt to rub the sole with the other foot or a flexion of the leg upon the thigh. On several occasions a crossed as well as direct Babinski was observed. Stroking the surface of the posterior tibial region from the tendo Achilles to the fossa of the knee usually resulted in a prompt flexion of the knee. All these tests were made without waking the sleeper, and if they did not follow each other too closely, without disturbing him. The duration of sleep following a period of insomnia was not much greater than normal.

Analysis of urine. In our urine work we first studied the excretion of total nitrogen in one subject (N. K.). The period covered 45 days of normal routine which preceded and followed two sleepless periods of 65 hours each, and one fasting period of 5 days. The normal average excretion of nitrogen was 14.477 grams in 24 hours, 9.911 grams for the day (16 hours) and 5.066 for the night (8 hours), or 0.619 gram and 0.633 gram per hour respectively. During the insomnia period the average was 15.323 grams in 24 hours, 10.538 grams for the day and 4.785 grams for the night, or 0.659 gram and 0.598 gram per hour. There was then a slightly greater excretion of nitrogen in the daytime during insomnia, but the difference is not great enough to make it significant. During the fasting period 11.805 grams of nitrogen were excreted in 24 hours, 7.730 grams for the day and 4.075 for the night (0.483 gram and 0.509 gram per hour respectively).

In a second series of experiments we used two subjects, N. K. and M. P. The results obtained are summarized in table 3. Both subjects had supposedly normal kidneys, and their urines showed neither albumen nor sugar. But when they were tested by means of the phenolsulphonephthalein excretion method, M.P.'s kidney function was found to be perfectly normal, whereas N.K.'s kidneys seemed somewhat below par. We are presenting the results obtained in both subjects, but as N.K. appears to be slightly nephropathic, more weight will be given to the figures obtained on M.P. From the table it will be seen that N.K. secretes more urine at night than in the daytime. That this increased secretion is dependent upon sleep can be seen from the fact that on a reversed routine he secreted more in the daytime than at night. M.P. secretes much more urine during the waking hours than while asleep, and the rate of the hourly secretion during the day was decreased on a reversed routine. During insomnia N.K. secreted less urine at night, further indicating that the increased night secretion under normal conditions was due to sleep. From these results it will be seen that the excess night secretion of urine by the nephritic or nephropathic kidney is connected not with the time of day, but with the condition of sleep. The phosphate excretion per 24 hours was almost twice as great in N.K. as in M.P. In either case, however, there was a slight diminution of phosphates on a reversed routine, and a slight increase during insomnia. N.K. excreted slightly less P at night than in the daytime, but this difference is greatly magnified (from 3.5 to 13.5 mgm. per hour) on a reversed routine. M.P. normally excretes much more P during the night, and this condition is strikingly changed on a reversed routine. The results obtained on both subjects show that a certain amount of the phosphate excreted bears a *direct* relation to sleep. The excretion of phosphates during the sleepless nights is less than normal in both subjects, confirming this conclusion. The same results were obtained by Campbell and Webster (6) on their 3- and 4-day periods of reversed routine, but, as stated above, in our experiments sleep was the only variable. Practically the same relations hold true for total acidity as for phosphates, confirming the observation of Campbell and Webster on the parallelism between the excretion of

TABLE 8

The secretory activity of the kidney on a normal routine, "reversed" routine, and during experimental insomnia

SUBJECT	TYPE OF TEST	NUMBER OF DAYS	AVERAGE FOR 24 HOURS	AVERAGE FOR "DAY"		AVERAGE FOR "NIGHT"	
				16 hours	1 hour	8 hours	1 hour
1. Volume of urine, in cubic centimeters							
N. K.	Normal	45	1063	680	43	383	48
	Reversed	4	1054	749	47	305	38
	Insomnia	8	1009	700	44	309	39
M. P.	Normal	35	1498	1173	73	325	41
	Reversed	12	1422	1090	68	332	42
2. Phosphates, in milligrams of P							
N. K.	Normal	45	1063	728	45.5	335	42
	Reversed	4	1027	808	50.5	219	27
	Insomnia	8	1121	821	51	300	37.5
M. P.	Normal	35	581	339	21	242	30
	Reversed	12	528	433	27	95	12
	Insomnia	2	647	418	26	229	29
3. Total acidity in cubic centimeters of N/10 acid							
N. K.	Normal	45	546	366	23	180	23
	Reversed	4	482	354	22	128	16
	Insomnia	8	530	360	23	170	21
M. P.	Normal	35	269	165	10	104	13
	Reversed	12	232	168	11	64	8
	Insomnia	2	217	104	7	113	14
4. Chlorides, in grams of Cl							
N. K.	Normal	45	6.01	4.47	0.280	1.54	0.193
	Reversed	4	5.40	3.54	0.221	1.86	0.233
	Insomnia	8	4.92	3.55	0.222	1.37	0.171
M. P.	Normal	35	6.57	5.07	0.317	1.50	0.188
	Reversed	12	4.65	3.19	0.200	1.46	0.183
	Insomnia	2	6.58	5.59	0.350	0.99	0.124
5. Creatinine, in milligrams							
N. K.	Normal	45	1988	1334	32	646	80
	Insomnia	8	2064	1438	90	626	78
M. P.	Normal	35	1862	1276	80	586	74
	Reversed	12	1934	1378	86	556	70

phosphates and the total acidity of the urine. Chlorides were excreted in greater quantities in the daytime than at night in both subjects tested. This rhythm persisted during insomnia, but there was a tendency toward reversal on the changed routine. This could not be due to a change in the ingestion of chlorides, as all meals were taken at fixed hours whether the subject slept at night or during the day. The figures for creatinine excretion are significant in that they show that more creatinine was excreted per hour in the daytime than at night, on the normal routine, reversed routine and during insomnia. It is the only substance of those we studied in reference to which the kidney shows a more or less fixed diurnal rhythm.

Effects of muscular relaxation. A number of tests were made on the effects of complete muscular relaxation. The subjects were asked to lie down and to relax their muscles. They were blindfolded and their ears were plugged with cotton. As a rule, after 30 minutes in this condition, the subject was found asleep. The observer did not return before 30 minutes so as not to unduly disturb the subject who could still hear somewhat with his ears plugged. Sidis (P) and Coriat (8) have reported similar experiments on children and adults respectively, and our results confirm theirs, although we are inclined to agree with Coriat's rather than Sidis' interpretation. But this will be taken up in the next section.

DISCUSSION AND THEORY. What is sleep? We must first agree as to the facts, or the so-called concomitants of sleep, and only then attempt to interpret them. The definitions given by most workers agree with each other pretty closely, and the one proposed by Piéron (1) seems to be the best. According to this investigator, sleep is a suspension of the sensori-motor activities that bring the living being into relation with its environment. It is characterized by *a*, marked diminution of muscular tonus in general (with the exception of sphincters and a few other muscles) and the loss of the power of equilibrium; *b*, almost complete abolition of "spontaneous" activity; *c*, raising of the threshold of reflex irritability and general sensibility; and most important, *d*, complete absence of critical reactivity, which normally involves analysis of sensations. All other rest states seen in animals, whether diurnal or seasonal, could not be looked upon as sleep, but, together with hypnosis, coma, etc., as sleep-like conditions.

Piéron divides the numerous theories of sleep into "partial" and "complete" theories. By a partial theory he means one that attempts to explain the mechanism of going to sleep, or of the onset of sleep, without attempting to explain the biological necessity of sleep in higher animals; complete theories "explain" not only how we fall asleep, but also why we sleep at all. This division is not very appropriate, because

a theory that explains quite adequately why we sleep, may not have a reasonable explanation of the mechanism of the onset of sleep. Besides, since sleep involves loss of consciousness and of critical reactivity to our surroundings, it would seem that until we know everything concerning the *physiology* of consciousness as contrasted with its psychology, i.e., the chemical and nervous mechanism we shall not know what the loss of consciousness is. For this reason those parts of our present so-called "complete" theories which explain the cause of sleep are not susceptible of experimental confirmation or refutation, and the main concern of an author of such a theory is that it should be in harmony with as many known facts about sleep as possible, and not in glaring contradiction with the rest. On the other hand, "partial" theories, or those parts of the complete theories dealing only with the mechanism of the onset of sleep, can be easily challenged experimentally. These theories are of immediate practical importance in the solution of that type of insomnia which is characterized by the patient's inability to fall asleep. A good "partial" theory should also explain the mechanism of awakening.

Of the theories of the mechanism of the onset of sleep Piéron discusses and criticizes half a dozen groups, and we shall merely touch upon the vasomotor theories of which Howell (P) is a proponent in this country. These theories assume that at the end of the day's activities the vasomotor center becomes fatigued, and this periodic loss of tone of the center is responsible for the inadequate circulation through the brain. This theory is partly based on Mosso's statement (P) that the brain is anemic during sleep. Shepard has recently brought forward evidence to show that during sleep there is a plethora of the brain (9). In our experiments we could not detect any loss of tone of the vasomotor center even after 115 hours of wakefulness, or 7 times the normal 16-hour period. The low blood pressure obtained during the insomnia periods was partly due to a slowed heart, and both the slowed heart and low blood pressure were due to muscular relaxation in the lying position, and were absent when the subject was seated. The facts that it was impossible to keep awake while lying down, in which position the demands on the vasomotor center are small, and that it was easy to keep awake while very active are against this theory. As Shepard says, the vasomotor change, be it anemia or plethora, may just as well be considered a consequence as a cause of sleep. We dwelt on this theory at some length because it is so "popular."

Another outstanding theory is that of auto-intoxication with the products of wakefulness. Piéron reports a number of remarkable experiments on dogs, which we will discuss in a subsequent paper. He discovered a substance, "hypnotoxin," which can be found in the

cerebro-spinal fluid of dogs kept awake for a number of days or weeks and which, when injected into the fourth ventricle of a normal dog will produce somnolence and later sleep. Piéron does not claim, as textbooks maintain, that at the end of a normal day enough "hypnotoxin" accumulates to cause the animal to fall asleep. At best, he thinks, this substance developed during the intensive activity of the nervous centers which preside over the extremely complex sensorimotor functions brings on sleep by reflex inhibition of these centers and *not* by direct toxic action on the cellular elements. The briskness of the onset and cessation of sleep led him to adopt Brown-Séquard's view (P) of the onset of sleep as an inhibitory reflex. This is a very reasonable supposition because the onset of sleep which involves firm closing of the eyelids, a rolling of the eyes up and out and a number of other motor adjustments could not be considered a purely *negative* phenomenon, merely a lack of consciousness. But he does not suggest how this reflex is liberated. It is well known that certain conditions such as deliberate preparation for sleep, absence of noise, horizontal posture, voluntary closing of the eyes, and so on, help to induce sleep, but they cannot be considered the actual liberators of the reflex, but as contributory elements only. As to the actual exciting cause of this reflex, opinions vary. Claparède in his "biological" theory of sleep first proposed in 1905 (P) and amplified in 1912 (10) declares that the onset of sleep is due to a reaction of momentary disinterest in one's surroundings. We fall asleep because we are not interested in what is going on around us, but this is facilitated by fatigue and the possible presence of toxic substances in the blood. Claparède did not do any experimental work. According to Shepard (9), "as we go to sleep, we become absorbed in a mass or complex of fatigue sensations. These tend strongly to inhibit other processes, especially motor activity and consciousness of strain sensations from the muscles." While it is true that fatigue will accelerate the onset of sleep, a person can fall asleep when not fatigued at all, and idlers have no difficulty in falling asleep at the usual hour, or at any hour. Pavlov and his co-workers, in their study of the conditioned reflexes, found that their animals frequently fell asleep during the experiment (11), (12). They found that as a result of prolonged action of a uniform excitant their animals invariably fell asleep. The complete data of their experiments have not been published as yet, but in a personal communication to the writer Pavlov states that their results indicate that sleep and the so-called internal inhibition of a conditioned reflex are identical phenomena, the former being diffuse and the latter localized. Another proponent of the uniform or monotonous stimulus effect is Sidis (P) who adds to this limitation of voluntary movements. This is nearer the truth because

an animal usually ceases all voluntary movements when it is going to sleep, and lack of noise or a monotonous sound does help to precipitate sleep. Coriat (8) challenged the work of Sidis, and performed experiments to show that neither limitation of voluntary movement nor a monotonous stimulus are sufficient to induce sleep. He holds that when the subject did not relax his musculature he did not fall asleep under these conditions. Our experiments, while not contradicting Sidis' findings, tend to confirm Coriat's in that relaxation will usually induce sleep under ordinary conditions, but will invariably do so under conditions of prolonged loss of sleep. In our study of basal metabolism under normal conditions the daily determinations were made at 7 a.m. within one hour after the subject got up, and he often fell asleep while lying completely relaxed for 30 minutes. Similar observations were made by Benedict (5) who in describing his new respiration calorimeter warned the prospective users of a tendency of the patient to fall asleep during the test (although instructed to keep awake), and advised gentle tapping on the metal pipe to wake him up. This powerful influence of muscular relaxation was especially striking during our insomnia experiments. All our subjects could keep awake while working or walking or standing, but when under the same external conditions they sat down in a comfortable chair, and especially if they lay down, they fell asleep immediately. Various discordant noises could not prevent the onset of sleep under these conditions, but quiet favored it.

It is now commonly conceded that consciousness is maintained by incoming afferent stimuli. As early as 1876 Heubel (P) working on lower animals came to the conclusion that "mental activity depends on the incoming peripheral sensory stimulations; where such peripheral sensory stimulations are absent, mental activity is in obeyance and sleep results." While we are all aware of visual, auditory and tactile stimuli, few of us are conscious of muscle sense. Indeed, it was not till 1832 that Sir Charles Bell discovered this "sixth" sense, and it was not accepted universally till the end of the 19th century. Due to the numerical preponderance of proprioceptive fibers, the majority of stimuli pouring into the brain come from the muscles, tendons and joints. When a person lies down, the visual sensations soon become monotonous, and muscular relaxation, removing the greater part of the proprioceptive impulses, precipitates what we call sleep. Fatigue favors the relaxation of the sore musculature, and it induces sleepiness by lowering the stream of proprioceptive impulses. Extreme fatigue is known to prevent the onset of sleep, and this will be readily understood if we recall that such fatigue is painful, and painful stimuli pouring into consciousness tend to keep the person awake. Pain is one of the commonest causes of insomnia. All the criticisms advanced against the

vasomotor and intoxication theories, namely, the effect of darkness, silence, horizontal posture, the ability to postpone the onset of sleep in interesting surroundings,—fail in the case of the muscular relaxation theory. This theory also explains the comparatively long sleep of young animals and children, and helps us to understand why people fall asleep amid loud din and racket, if they are so tired that they have to relax their musculature. No one fell asleep during the recent "dancing Marathons." It would be very interesting to study the behavior of blind and deaf persons.

There is one point which all theories of sleep fail to explain. Granted that there is a raising of the threshold for sensory stimulation, how is this brought about? In 1890 Mauthner (P) developed the conception of a blocking of sensory impulses in sleep. Up to date there is no experimental evidence of such blocking, although the idea of increased synaptic resistance is sound. There is some evidence, however, of such an increased synaptic resistance on the motor side. We refer to the positive Babinski sign. An extension of the toes on plantar stimulation during sleep was observed long before the Babinski sign was discovered (by Rosenbach, in 1879; quoted from Piéron). It was subsequently confirmed by Goldflam (P) and Bickel (P). The latter observer found that the reflex became negative on awakening. He also saw a positive Babinski during the early stages of chloroform anesthesia (before all reflexes disappear). The positive Babinski sign, although its nature is not understood, is clinically found in adults only in case of organic pyramidal lesions. In paralysis of hysteria the reflex is negative. It is safe to assume that in the majority of cases it indicates an interruption between the cerebral cortex and the lower motor neurons. However, it was only a year ago that Haberman (2) in a purely theoretical paper on sleep first interpreted the positive Babinski of sleep as does the present writer. Haberman speaks of a cerebrospinal functional break or a shunting off of some part of the cortex. But the rest of his argument is very obscure. If such a switching off of a whole cable can take place on the motor side, why not on the sensory? These functional breaks would not only tend to produce complete muscular rest, but would also prevent impulses from reaching the higher centers and thereby waking the sleeper. This point will be discussed below in connection with the physiology of dreaming. In our experiments every subject showed a positive Babinski during the sleep that followed insomnia, and with remarkable regularity this reflex would be reversed on continued stimulation at very short intervals, confirming the assumption that it was originally due to an *increased synaptic resistance;* this flexion reflex of the big toe obeys the rule for summation of subminimal stimuli, because these stimuli, although strong enough to

elicit the positive Babinski, are too weak to elicit the flexion reflex. The reversal of the Babinski was usually obtained without arousing the sleeper, indicating that the stimuli had not reached the highest centers, but this latter could be accomplished by continued stimulation. On allowing the subject to lapse into slumber after having been awakened, the positive Babinski could be obtained again and again. The same applies to subject N.F. under normal conditions, because he is a deep sleeper.

For the further interpretation of this finding we shall have to pass over to the discussion of the so-called complete theories. We shall not stop to review all the theories based on internal secretions (hypophysis, thyroid), dehydration, exhaustion of intramolecular oxygen, and the various intoxication theories (lactic acid, cholesterol, CO_2, leucomains, urotoxins, neurotoxins, etc.). An admirable criticism of all of them can be found in Piéron's book. We may mention that the intramolecular oxygen theory was based mainly on the lowering of the respiratory quotient during sleep. But in the light of modern knowledge, it is clear that this is not due to a storage of oxygen, but to a decreased oxidation of carbohydrates, brought about by muscular relaxation. It is well known that severe muscular exercise will bring the quotient up to unity. The intoxication theories are just as "popular" as are the vasomotor theories, but have the distinction of being "complete" in that they explain at one stroke the cause of sleep, and the mechanism of the onset. It was mainly to test these theories that we undertook the experiments on experimental insomnia, and it is our conclusion that there are no evidences of a general intoxication. During a prolonged abstinence from sleep, there was no change in the CO_2 capacity of the blood or the plasma, in the red or white blood count, blood sugar, heart rate, respiration, basal metabolic rate and temperature. After 115 hours of wakefulness the intoxication, if present, was too mild to produce any change in the above and our urinary findings were also negative. Could we then postulate an intoxication at the end of 16 hours of wakefulness? All the arguments brought forward to refute the intoxication idea in the discussion of the partial theories, hold good here. Piéron himself was too cautious to advocate such a theory. What then is the cause of sleep? Among other accepted theories is that of the psychologist, Claparède (10). He decided that sleep was an instinct: "Le sommeil est une fonction de défense, un instinct qui a pour but, en frappant l'animal d'inertie, de l'empêcher de parvenir au stade d'épuisement; ce n'est pas parce que nous sommes intoxiqués, ou épuisés, que nous dormons, mais nous dormons pour ne pas l'être." Such is the power of a phrase that both Sidis and Coriat readily embraced this doctrine in their search for a complete theory of sleep. Yet, Coriat himself remarks that

"any theory of sleep must be based upon sound physiological data, because sleep is a physiological phenomenon." To say that we sleep not because we are intoxicated but in order not to become intoxicated, is no more an explanation of sleep than is to say that we breathe in order not to become intoxicated. As a matter of fact, one can no more commit suicide by refusing to fall asleep than by holding his breath: the reflex will break through in either case. Hunger and thirst have long ago been taken out of the category of "instincts," and put on a sound physiological basis. Nothing will be gained by calling sleep a defensive function. Just as explaining the onset of sleep as being advantageous for the animal at a given moment, Claparède explains waking by saying that it is of greater advantage for it to wake up in the morning than to continue to sleep. In short, there is no "complete" theory of sleep that is in agreement with the majority of facts.

The writer does not claim any originality for the complete theory of sleep he is about to propose. It is merely an attempt to synthesize the many ideas advanced at one time or another by various investigators. As a basis for this theory we shall adopt the doctrine of "levels" in the central nervous system as first advanced by Hughlings Jackson in 1898 (13). He held that "the most complex nervous arrangements, centers and levels are the least organized; the simple, the most organized." A good example of a low level is the respiratory center which is most completely organized and functions in exactly the same manner from birth to death. The highest mental centers are the least organized and are therefore very modifiable, and this enables the animal to learn and establish associations. These highest levels, being the youngest phylogenetically, are much more susceptible to fatigue, intoxication or any kind of injury than are the lower levels. Thus a small dose of alcohol will affect only the highest centers or levels, which exert an inhibitory influence on the natural talkativeness of a person. A larger dose may not only interfere with the ability to make after-dinner speeches, but with his facility in walking properly, and a very large dose is required to paralyze his respiratory center. Likewise in increased intracranial pressure from tumors, granulomata, etc., it is the highest centers that suffer first, and the initial symptoms are described by Osler and McCrae (14) as follows. "The patient may act in an odd unnatural manner, or there may be stupor and heaviness. The patient may be emotional and silly, and there are symptoms resembling hysteria." In our experiments as well as in those of Patrick and Gilbert (P) the only definite effect of insomnia was the depression of the activity of the highest centers that are concerned in analyzing sensations and in solving problems. All our subjects found that they could not study after one night of wakefulness, although they could do ordinary routine

laboratory work fairly successfully throughout the entire period of insomnia. The temporary dissociation of consciousness observed in subject N.K. and in one of Patrick and Gilbert's subjects points in the same direction. It is reasonable to suppose that continued mental activity resulting from wakefulness affects those highest centers first, because they are the least organized and because their metabolism is known to be very active. Whether this fatigue of the higher levels is due to the exhaustion of some nutritive substance in the nerve cells or to an accumulation of the products of cell metabolism cannot be answered at present. On the histological side Piéron reports that he found definitely localized changes in the brains of dogs killed after prolonged periods of sleeplessness, and this indicates that these higher levels have definite localizations in the cortex. In the course of evolution those animals that developed the ability to give these highest centers a rest, could use them to their greatest advantage and won in the struggle for existence. The changes of day and night favored the development of this function. The savages of Central Africa retire with sundown, and speak of nights as so many "sleeps." When it rains and they are forced to remain idle, they sleep. In other words, the periodic cessation of activity due to nightfall (nocturnal animals excepted), coinciding as it did with the end of a day's hunting or fishing, when the animal or primitive man were tired and had to lie down to relax their musculature, gradually developed a switching off of both the afferent and efferent connections of these higher centers, and the phenomenon of sleep was the result. When this procedure was repeated day after day, something in the nature of a conditioned reflex could easily develop, and sleep could thus be set off "precipitously." The highest centers gradually lose their irritability after a day's activity, and this irritability is restored during the night's sleep. Just what happens during sleep is at present unknown, but the results of Campbell and Webster (6) as well as our own show that there is an increased excretion of acids and phosphates in the urine in connection with sleep, whether night or day sleep. However, all this applies to the highest cortical levels whose function is to correctly analyze and interpret the incoming stimuli, to make new associations (learn), and to react in what we call an intelligent manner. But there are lower centers which may not be so fatigued (because of their somewhat better organization), and these may continue to function during sleep, especially light sleep. They are concerned with dreaming. Sensations that are prevented from reaching the highest centers by the increased synaptic resistance, may get to these lower centers, and, while rarely correctly interpreted, start what is known as the dream process. These sensations need not be exteroceptive; they may originate in the viscera. The main characteristic of a dream

is lack of *critical* analysis of events. The dreamer meets people that should be known to him to be in remote regions of the globe, and he is not at all surprised at seeing them. Knight Dunlap (15) in an interesting paper on sleep and dreams speaks of the low integration of dreams as contrasted with the high integration of consciousness. But he holds that the law of association of ideas applies in cases of low integration as well, and this is in agreement with everybody's dreaming experience. Dunlap considers that one of the most characteristic symptoms of disposition to normal sleep is the abolition of the learning process, or of high integration. "Momentary impressions may be made; and a series of perceptions produced: but they do not 'stick'." As an example of the persistence of low integration (our lower "level") he uses a violinist who "may play his part in an orchestra very well, when so sleepy (or so drunk) that he has a very confused notion of what is going on; provided, of course, the composition is very familiar, and played as he is accustomed to play it." This is very much like the behavior of the subject N.K. who dreamt of engaging in a heated argument while he was looking up and calling off correctly logarithms of numbers. We should not have touched the subject of dreaming at all but for the detection of the reversal of the Babinski sign during sleep which seems to show how external or internal stimuli by being frequently repeated will overcome the synaptic resistance and reach these lower levels, producing a dream by low-grade uncritical association of ideas. Should these stimuli become stronger, they will reach the highest levels as well, waking the sleeper. The literature of the subject is full of accounts of how a trivial external happening was misinterpreted by the dreamer and a curious dream built around it. A hot bottle placed under the sleeper's feet may make him dream of walking on the hot lava of Vesuvius. In the absence of external stimuli, internal sensations, hunger, thirst or sexual stimuli may start a dream. Distended seminal vesicles will give rise to an erotic dream, but the powerful stimulus of ejaculation is necessary to overcome all synaptic resistances and waken the sleeper. Generally, however, the dreamer may imagine himself walking about, without actually moving a muscle. The "switching off" of the pyramidal tracts which gives rise to the positive Babinski prevents the efferent impulses from reaching the muscles and thereby protects the sleeper from being aroused by the powerful proprioceptive impulses that would in such event be sent up from the muscles. Sleepwalkers apparently lack the ability to completely shunt off the pyramidal tracts, especially after an exciting evening, and their dreams give rise to actual movements. Why these movements do not wake the sleeper through proprioceptive impulses from the muscles cannot be explained, but in normal individuals this is undoubtedly the case (walking during

a nightmare). This theory also explains adequately a phenomenon which no other theory has been able to elucidate, namely, why the subject, once having fallen asleep, wakes up. It is well known that even in the absence of all external stimuli the sleeper will wake up eventually. Our theory explains this on the basis of internal stimuli of thirst, hunger contractions of stomach, distention of the bladder or rectum, which may become so powerful after some hours of sleep that they overcome all synaptic resistances and reach the highest levels, waking the sleeper.

In this connection a word may be said concerning the periodicity of sleep. Why is it easier to sleep at night than in the daytime, and why will a person accustomed to get up at, say, 6 a.m., wake up at the usual hour, whether he goes to bed early or late? This is a part of the general problem of physiological rhythms which are at present not very well understood, but which are possibly conditioned reflexes. Thus the hunger sensation is periodic; yet it does not appear, in man at least, at definite equal intervals of time, but rather at certain hours, the usual meal hours. Some diurnal rhythms are established early in life, as shown by the activity of the lachrymal glands which ceases at the usual bedtime hour in children ("the advent of the sandman"). Many of the so-called diurnal rhythms are dependent upon sleep for their establishment and maintenance. A good example of this is the temperature rhythm. Benedict (16) found a more or less inverted diurnal temperature curve in a night watchman, but was unable to accomplish this experimentally during an 11 to 12 day period of reversed routine. Toulousse and Piéron (1), however, did succeed in inverting the temperature curve by continuing the reversed routine for 5 or 6 weeks, showing that it was due to sleep, or to the inactivity brought about by diurnal sleep. Our experiments also tend to show (fig. 1) that complete insomnia for several days, involving continuous activity, has the effect of progressively flattening the diurnal temperature curve. Some diurnal rhythms can be inverted much sooner, as shown by the change in the secretory activity of the kidney on a reversed routine.

In conclusion the writer wants to state that this theory is provisional and is to be used only as a working hypothesis. As Piéron says: *Une théorie n'est pas la solution d'un problème, c'est contraire l'énoncé d'un problème à résoudre.*

SUMMARY

1. Experiments were performed to study the effects of experimental insomnia in man, the duration of complete sleeplessness being from 40 to 115 hours.

2. Subjectively the persons employed could easily keep awake while engaged in some sort of activity, but felt very drowsy when sitting, and fell asleep immediately on lying down.

3. Muscular relaxation induces sleep under normal conditions (confirming Coriat), but practically precipitates sleep under conditions of experimental insomnia.

4. Blood sugar, alkaline reserve of the blood and plasma, percentage of hemoglobin, percentage of corpuscles, red and white blood cell count, body weight, basal metabolic rate, appetite, temperature, ability to name letters and to do mental arithmetic, all of these showed no variations from normal during the period of sleeplessness.

5. Respiration, heart rate, blood pressure showed a marked decrease in insomnia, but this decrease was mainly due to greater muscular relaxation of the sleepy subject.

6. Numerous reflexes were found to be present in sleep following insomnia, but the response was somewhat sluggish. Sleep seemed to be deeper six hours after its onset than at the end of two hours.

7. A positive Babinski reflex could be elicited in every subject tested during the sleep that followed insomnia. It is interpreted as indicating a functional block of the pyramidal system of fibers.

8. This reflex could be reversed by rapidly repeated stimulation of the sole. The depth of the sleep decreased at the same time. This indicates that a number of subminimal stimuli overcome the synaptic resistance and produce a flexion of the great toe.

9. There is a greater excretion of phosphates and acids at night; but on reversed routine, with the subject sleeping in the daytime, this condition is reversed, indicating that the increased excretion is due to sleep (confirming Campbell and Webster).

10. There is a greater excretion of chlorides in the daytime; the same is true in insomnia; but there is a tendency to reversal in the subject that sleeps during the day.

11. The excretion of total nitrogen and of creatinine shows little diurnal variation, and is unaffected by either insomnia or reversed routine.

12. There is some evidence that the diurnal temperature variation is due to the alternation of sleep and wakefulness, and the temperature wave tends to be effaced during prolonged insomnia.

13. The onset of sleep is probably due to complete muscular relaxation, voluntary or involuntary.

14. A provisional theory is proposed based on the conception of "levels" in the central nervous system, as first elaborated by Hughlings Jackson. Sleep may be due to fatigue of the highest centers of consciousness, and dreaming to the persistence of the activity of the lower centers.

I wish to express my thanks to my colleagues in the laboratory for the help they rendered me in this work. Especial thanks are due to Mr. Charles C. Adams and Mr. Mark T. Phy whose genuine interest and splendid loyalty made this research possible. I shall always cherish the memory of the many sleepless nights we spent together.

I am greatly indebted to Dr. A. J. Carlson for the many helpful suggestions and criticisms in the course of the work, and for the revision of the manuscript.

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COMPTES RENDUS HEBDOMADAIRES

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surtout par l'ensemble de la symptomatologie clinique et plus particulièrement des lésions cutano-muqueuses (y compris les lésions oculaires) (9) qu'il est apte à produire.

(*Institut d'hygiène et de bactériologie de l'Université de l'Etat, à Gand.*)

Cerveau « isolé » et physiologie du sommeil,

par Frédéric Bremer.

Les recherches faisant l'objet de la présente note sont parties de l'hypothèse de travail que le sommeil chez les Mammifères, qu'il s'agisse du sommeil naturel, toxique (barbiturique) ou pathologique (narcolepsie), comporte dans son déterminisme immédiat la déafférentation plus ou moins complète du télencéphale.

Si cette hypothèse est exacte, la déconnexion du télencéphale par une section interrompant l'afflux incessant de tous les messages sensitifs somatiques et viscéraux, doit déterminer un état fonctionnel du cerveau très semblable, sinon identique à celui qui caractérise le sommeil. C'est, effectivement, ce que je crois pouvoir démontrer dans cette communication préliminaire.

L'expérience, qui a été répétée déjà une vingtaine de fois avec un résultat constant, consiste essentiellement à faire, chez le chat éthérisé, la transsection du tronc cérébral au niveau de l'union du mésencéphale et du pont, en laissant en place le télencéphale pourvu de son irrigation normale par le tronc basilaire, respecté grâce à l'emploi d'un instrument mousse, et par les carotides ; celles-ci, de même que les vertébrales ne sont comprimées qu'au moment même de la transsection. La technique est en principe très simple : une large trépanation découvrant le pôle postérieur du lobe occipital permet, après incision en étoile de la dure-mère, d'introduire le long de la tente osseuse du cervelet une spatule étroite jusqu'au tronc cérébral. L'hémostase, déjà naturellement bonne chez le chat, est accélérée par l'application locale d'un extrait de plaquettes. Aussitôt la transsection faite, la compression des vertébrales est relâchée et la narcose à l'éther définitivement supprimée. Quelques minutes plus tard les carotides sont libérées à leur tour.

Lorsque l'expérience réussit, ce qui est actuellement le cas le plus fréquent, l'aspect du cortex découvert ne diffère en rien

(9) *C. R. de la Soc. de biol.*, 1929, t. *102*, p. 951.

(irrigation, saillie, battements) de son aspect d'avant la transsection.

Le télencéphale ainsi séparé du reste du névraxe garde un moyen d'expression naturel de son état fonctionnel : les yeux, par les fibres oculo- et pupillo-motrices de la III^e^ paire, dont les noyaux et les racines sont situés en avant du plan de section. D'autre part, on peut enregistrer oscillographiquement son activité électrique et la comparer à celle du sommeil barbiturique. Ces deux témoignages concordent : ils indiquent nettement que le télencéphale isolé est le siège d'une activité considérable et que cette activité, absolument spontanée et automatique, est celle du sommeil.

Aspect de l'œil. — Immédiatement après la transsection les pupilles commencent à se rétrécir. La contraction irienne s'accélère lorsque, quelques minutes plus tard, cesse la compression des carotides. Elle devient bientôt extrême. Au bout d'une demi-heure à une heure, les pupilles sont littéralement filiformes, leur ouverture n'est plus que virtuelle. En même temps que s'accomplit ce rétrécissement pupillaire, les globes oculaires exécutent un mouvement de bascule progressif vers le bas. La contraction des orbiculaires palpébraux de même que le relâchement de la membrane nictitante sont évidemment fonction de l'état du segment caudal du névraxe sectionné et, pas plus que les autres manifestations réflexes et toniques (rigidité d'extension), ils ne diffèrent de ce que l'on observe sur la préparation décérébrée classique.

Cet aspect de la pupille et cette attitude du globe oculaire sont tout à fait semblables à ceux du sommeil profond, naturel ou barbiturique. Ils se maintiennent indéfiniment. Je les ai observés pendant trois jours consécutifs.

Le myosis est l'expression du déficit d'une activité cortico-nucléaire pupillo-dilatatrice, car il persiste inchangé après l'ablation des hémisphères cérébraux ; et l'excitation électrique en des points déterminés du diencéphale ainsi isolé provoque une my-

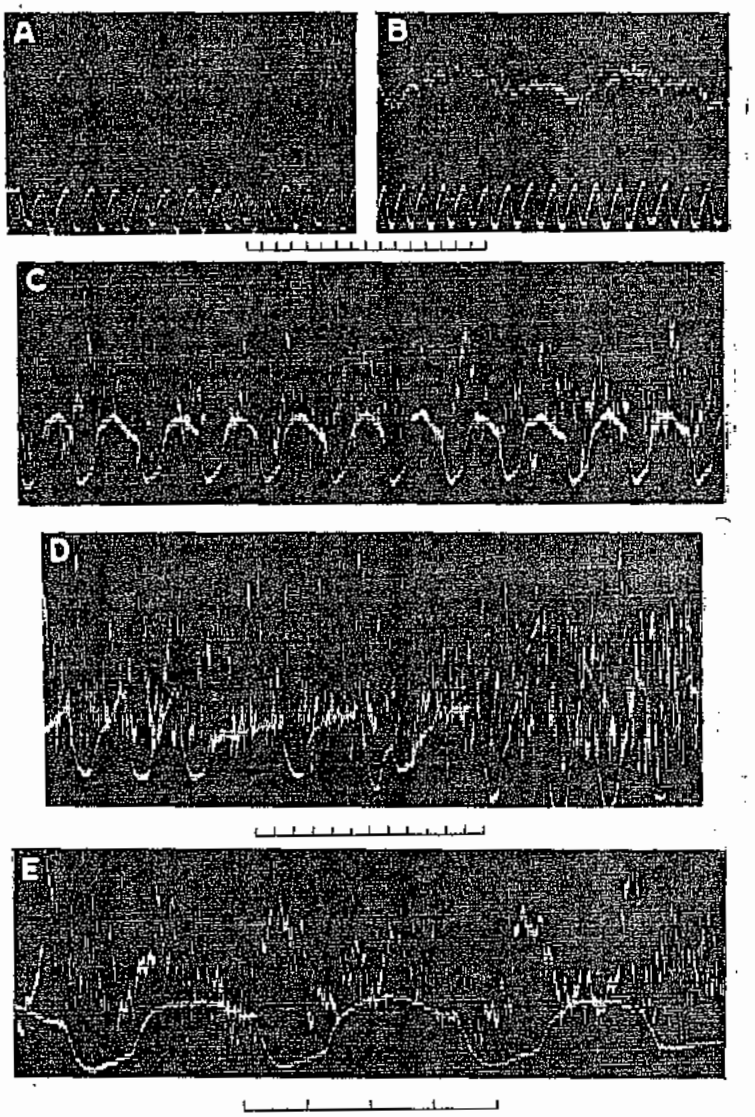
Légende de la figure ci-contre.

Fig. 1. — Potentiels d'action du cortex cérébral du chat, enregistrés à l'oscillographe de Matthews. De haut en bas : oscillogramme (10 mm. = 60 microvolts sur l'original), pneumogramme, (inspiration vers le haut), temps en secondes ; réduit de 1/3.

A. Cerveau intact, éther, narcose très légère. — B. Même animal, narcose plus profonde. — C. Cerveau « isolé » (autre animal). — D. Même préparation qu'en C : inhalation d'acétone marquée par la perturbation de la respiration. — E. Même préparation qu'en C : vitesse plus grande de la plaque. Autres explications dans le texte.

driase, qui ne peut se produire que par inhibition du tonus constricteur.

Il existe d'autres symptômes d'inertie fonctionnelle corticale.



Aréflexie corticale optique et olfactive. — Tant que la contraction pupillaire n'est pas maximale, le réflexe constricteur photomoteur est en général très net, ce qui témoigne de l'intégrité des mécanismes réflexes diencéphalo-mésencéphaliques. Par

contre, l'animal ne présente aucune réaction opto-cinétique, et les stimuli olfactifs qui déterminent une dilatation pupillaire chez l'animal normal ou légèrement narcotisé sont sans effet sur l'œil.

Inexcitabilité électrique du cortex isolé. — Des stimuli faradiques qui, appliqués sur les régions oculo-motrices frontales et occipitales sont efficaces chez l'animal légèrement éthérisé, n'ont aucune action visible lorsqu'on les applique, même avec une intensité notablement plus forte, sur les mêmes régions du cortex isolé.

Activité électrique spontanée du cortex isolé. — Le cortex isolé, en apparence inerte, est en réalité le siège d'une activité électrique rythmique intense, d'une surprenante régularité, et cette activité est indistinguable de celle que présente le cortex de l'animal en état de sommeil barbiturique.

Les figures 1. A et B et 2. A, montrent ce qu'est l'activité du cortex du chat, soumis à une narcose éthérique, d'intensité très légère en 1 A, moyenne en 1. B et 2. A : succession irrégulière de pulsations brèves à la fréquence de 25 à 30 par seconde, ne présentant pas de tendance nette à une variation périodique régulière de leur amplitude. Cette périodicité ne s'observe, ainsi que l'avaient déjà indiqué Bartley et Bishop (1*) et Adrian et Matthews (2*), que lorsque la narcose éthérique (ou chloroforme-éthérique) est si profonde que la respiration est près de s'arrêter, et alors les oscillations brèves sont fort diminuées d'amplitude.

Les oscillogrammes du cortex isolé (fig. 1, C, D, E et figures de la note suivante) ont un aspect très différent des précédents et tout à fait caractéristique et constant : les oscillations brèves sont beaucoup plus amples, leur fréquence est plus lente (10 à 15 par sec.), et surtout elles présentent des alternances parfaitement régulières de croissance et de décroissance, réalisant des

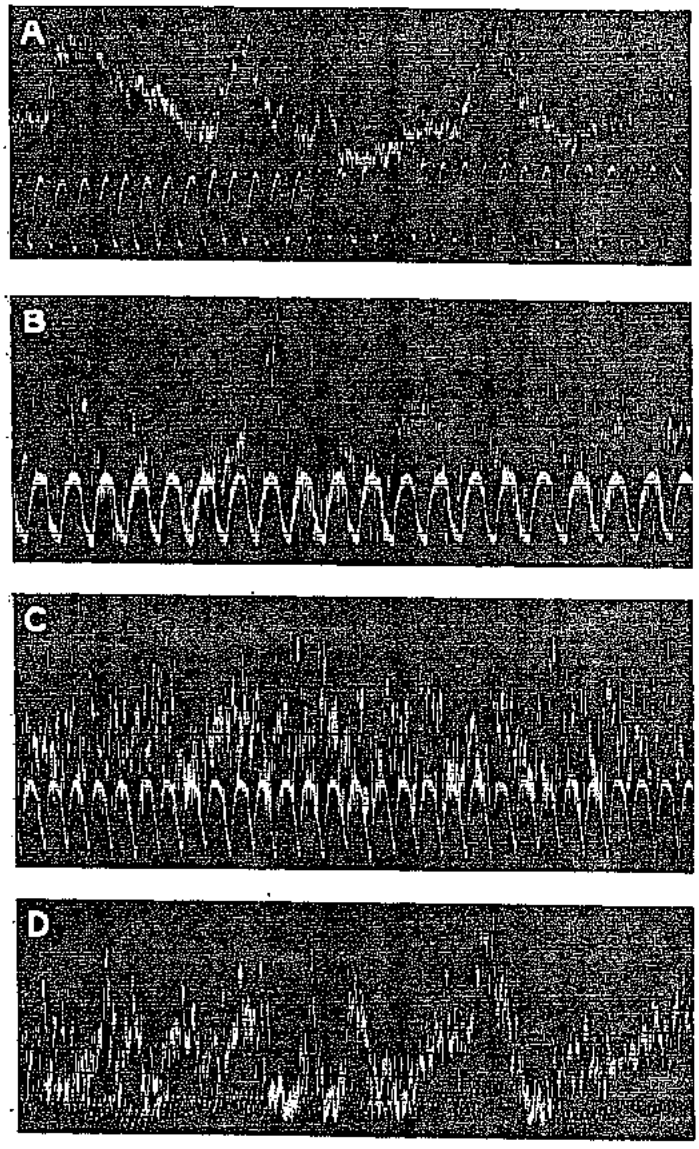
(1*) Bartley et Bishop. *Amer. Journ. of Physiol.*, 1933, t. *103*, pp. 173 et 203.
(2*) Adrian et Matthews. *Journ. of Physiol.*, 1934, t. *81*, p. 440.

Légende de la figure ci-contre.

Fig. 2. — Potentiels d'action du cortex cérébral (intact) du chat. Même technique que pour les oscillogrammes de la figure 1 ; réduit de 1/3.

A. Ether, narcose d'intensité moyenne. — B. Même animal après l'injection intraveineuse, en plusieurs fois, de 4 cgr. de « Dial » par kgr. (éther supprimé) : l'oscillogramme recueilli après 1,5 cgr. de « Dial » seulement était pratiquement identique. — C. Même animal, après l'injection intraveineuse de 1,5 mgr. de sulfate de strychnine : spasmes au moindre choc sans symptômes de réveil. — D. Même animal, 3 h. 1/2 plus tard, quelques minutes après l'injection dans le diencéphale, de 0,4 mgr. de sulfate de strychnine ; symptômes de réveil. Autres explications dans le texte.

périodes d'activité maximales séparées par des périodes de repos relatif. Le rythme de cette alternance est lent : sa période est de 2 à 3 secondes.



Or, cette allure fonctionnelle du cortex isolé est remarquablement semblable à l'activité électrique du cortex du chat en som-

meil barbiturique, ainsi que le montrent les oscillogrammes des fig. 2, B et C, qui ont été enregistrés peu de temps après celui de la fig. 2 A, sur le même animal ayant reçu 4 cgr. de « dial » par kgr. en injection intraveineuse. En C, l'activité corticale est intensifiée par rapport à B, en raison du fait que l'animal a reçu 1,5 mgr. de sulfate de strychnine, en trois injections intraveineuses successives. Il présentait alors des spasmes strychniques au moindre choc et, cependant, ces spasmes n'avaient pas la moindre influence perturbatrice sur l'activité électrique du cortex. Ces faits démontrent, d'une part que le lieu d'action des barbituriques est bien infra-cortical comme le soutient depuis longtemps Pick (3*), d'autre part, que, dans le sommeil barbiturique profond, le cortex cérébral est fonctionnellement déafférenté et présente une activité spontanée intense. La figure 2, D (enregistrée quatre heures après C), dont on notera l'analogie avec 2 A, montre, en ce qui concerne l'activité électrique corticale, l'effet de réveil déterminé par une injection de 0,4 mgr. de sulfate de strychnine dans le diencéphale; ce réveil se manifestait par un redressement de la tête et des yeux, de la dilatation des pupilles, des grognements, des mouvements des pattes, la sortie des griffes.

Il est à remarquer, d'autre part, que l'apparition d'une activité automatique périodique dans le cortex déafférenté est en parfait accord avec les observations de Berger (4*) et celles toutes récentes d'Adrian et Matthews (5*), qui montrent que la suppression du stimulus lumineux fait apparaître le même type d'activité dans le cortex visuel de l'Homme.

Enfin, si le sommeil est la conséquence de la suppression de l'arrivée au cortex des influx de toutes les sensibilités somatiques, le maintien d'une partie de cet afflux corticipète par l'inclusion, dans le bloc télencéphalique déconnecté, des racines et d'une partie de l'appareil nucléaire du trijumeau, doit maintenir un état vigile plus ou moins complet du cerveau. C'est effectivement ce que paraissent indiquer des expériences en cours.

En résumé, la déafférentation complète (nerfs olfactifs et optiques exceptés) du cerveau chez le chat, par une transsection du tronc cérébral en arrière de la III^e^ paire, transsection laissant en place le télencéphale normalement irrigué, détermine immédiatement un état fonctionnel de celui-ci très semblable, sinon identique, à celui du sommeil naturel et barbiturique.

(3*) E.-P. Pick. *Deutsche Zeitschr. f. Nervenheilkunde*, 1928, t. *106*, p. 338.

(4*) H. Berger. *Arch. f. Psychiatrie*, 1933, t. *99*, p. 55 (et nombreux travaux précédents).

(5*) Adrian et Matthews. *Brain*, 1934, t. *57*, p. 355.

Cet état, qui persiste indéfiniment, est caractérisé par un myosis extrême, et une aréflexie corticale olfactive et optique contrastant avec une activité électrique spontanée intense, régulièrement périodique, très différente de celle du cortex de l'animal soumis à un narcotique volatil, ou non narcotisé.

L'étude oscillographique du cortex du chat en état de sommeil barbiturique démontre que ce cortex est fonctionnellement déafférenté.

(*Laboratoire de pathologie générale de l'Université de Bruxelles.*)

QUELQUES PROPRIÉTÉS DE L'ACTIVITÉ ÉLECTRIQUE DU CORTEX CÉRÉBRAL « ISOLÉ »,

par FRÉDÉRIC BREMER.

La méthode du cerveau « isolé » décrite dans la note précédente, permet d'étudier dans des conditions particulièrement favorables l'activité électrique spontanée du cortex, puisque celui-ci, non influencé par un narcotique, est, par ailleurs, soustrait à l'interférence des influx sensitifs. L'immobilité de l'animal facilite d'autre part l'enregistrement oscillographique.

Les potentiels d'action corticaux ont été dérivés au moyen d'électrodes d'argent chloruré, prolongées par des pinceaux d'ouate imbibée de Ringer tiède, distantes d'environ 5 mm. l'une de l'autre et posées en général sur la partie supérieure de la circonvolution suprasylvienne; ils ont été enregistrés sur plaques photographiques au moyen d'un oscillographe de Matthews et d'un amplificateur à 5 étages, constitué de trois étages à couplage direct avec contre-batteries, suivis de deux étages à couplage par capacités. La constante de temps de ces deux derniers étages était telle qu'elle permettait l'enregistrement simultané fidèle de phénomènes lents et rapides. La respiration a presque toujours été inscrite simultanément.

L'action des facteurs suivants a été étudiée.

Vascularisation du cortex. — L'ischémie corticale incomplète produite par la compression des carotides (fig. 1 A) ou par l'excitation du bout périphérique du vague, détermine presque instantanément un affaiblissement très marqué des potentiels d'actions corticaux. Lorsque la compression des carotides est prolongée pendant plus d'une minute, on voit réapparaître partiellement l'activité corticale, parallèlement au rétablissement de la

SPECIAL ARTICLES

OTENTIAL RHYTHMS OF THE CEREBRAL CORTEX DURING SLEEP

ECENT interest in brain potentials has induced us put on record the results of experiments carried out the Loomis Laboratory, Tuxedo Park, in which a w phenomenon in this fascinating field has appeared ost clearly—namely, the very definite occurrence of ins of rhythmic potential changes as a result of nds heard by a human subject during sleep. Since work of previous investigators[1] has emphasized at rhythms which spontaneously appear in a person rest with eyes closed disappear when an object is wed or the attention concentrated, we believe the finite demonstration of a means of inducing rhythmic ain discharges to be of considerable interest. At same time the method of continuous study and rrelation with other body changes over periods of ven hours, described herein, greatly facilitates interetation of results where many factors, difficult to ntrol, are undoubtedly involved. Sleep was selected a condition during which brain activity is at a nimum and physiological conditions most constant. The records are made on paper wrapped on a horiontal drum 8 feet long and 44 inches in circumference volving once a minute. Two high-speed dynamic phon recorders describe a pair of spiral lines one fth inch apart, as they move horizontally parallel to e drum at the rate of one foot per hour. Each heart at, each respiration, each bed movement and any oises in the bedroom are recorded by one pen (red nk) as characteristic marks, while brain potentials are corded by the other pen (green ink). In addition ree rachet devices sum the heart beats, the respiraons and the bed movements each minute, marking e rate per minute on the paper. The drum, driven a synchronous motor, acts as its own clock, and timuli may be sent to the sleeper each minute by lectric contact on the drum, thereby placing a series responses near together on the record and allowing sy comparison with the condition where no stimuli e sent in. The amplitude of the brain potentials re ascertained regularly by calibration with sinusoidal otentials of from 2 to 30 per second frequency and om 10 to 50 microvolts amplitude. The siphon corder records have been checked from time to time the cathode ray oscillograph.

The finished record is a sheet of paper 44 inches high and 8 feet long with vertical red and green lines, each pair representing a minute of time. Changes in the processes recorded can be seen at a glance. Either the red or the green lines can be rendered invisible by viewing the record through a red or green glass and inspection thereby simplified. The single sheet of paper, even though large, is a great improvement over the use of paper tape, which was abandoned because examination of the one half mile of tape necessary for an eight-hour run was too time-consuming.

The subject sleeps in a quiet, electrically screened room, containing a very sensitive microphone and a photo-electric bed movement recorder. Electrodes for detecting the various physiological processes are attached to the subject and the amplified impulses sent through shielded cables to the control room 66 feet away. Details of the apparatus will be described in a later paper. Facial movements, swallowing, clenching the jaws, etc., give rise to muscle potentials which appear on the record, but which are quite characteristic and easily distinguishable from brain potentials, as are also disturbances due to passive movements of the scalp.

Our investigation of the brain potential rhythms during night sleep (brain electrodes on high forehead and crown of head) has led us to the following conclusions:

(1) They are undoubtedly of cortical origin and distinct from muscle potentials and movement artifacts. Different persons show quite different potential records.

(2) In a night record certain hours of sleep show many "spontaneous" bursts of waves, while other hours show relatively few.

(3) They often appear in trains lasting 5 to 12 seconds, at intervals of ½ to 2 minutes.

(4) The frequency is on the average an irregular 10 per second, but frequently very regular bursts lasting 1 to 1½ seconds of 14 per second frequency appear. The amplitude builds regularly to a maximum and then falls regularly so that we have designated these "spindles," because of their appearance in the record. Shorter spindles or "balls" of ¼–½ second duration occasionally appear. Five other types can also be distinguished.

(5) They are not correlated with heart beat nor necessarily with respiration, but at times a definite characteristic potential change has accompanied each respiration.

(6) Regular snoring does not necessarily initiate

[1] Literature in paper by Adrian and Mathews, *Brain*, 7: 355, 1934; also Jasper and Carmichael, SCIENCE, 81: 1, 1935. See H. Berger in *Arch. f. Psychiat.*, 1929–35.

brain rhythms, but an occasional isolated snore may start a train.

(7) When asleep sounds of a certain character, such as rustling paper or coughing by a person in the bedroom, closing a door some distance from the subject or low conversation, which does not wake the sleeper, will quite regularly initiate a train of waves which may last for from 5 to 8 seconds (frequency 9 to 10/seconds) and then die out. Fig. 1 A illustrates this effect from the repeated closing of a door at one-minute intervals and allows comparison with regions where no sound stimuli were sent in. The depth of sleep and the noise level in the room determine whether this "sound response" will appear. One deep sleeper gave no response on closing the door but responded regularly on slamming the door.

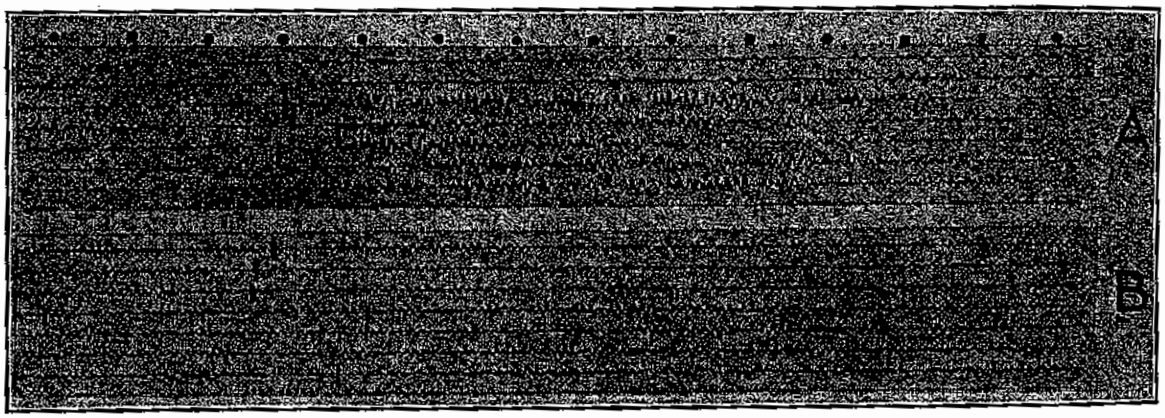


FIG. 1. Sections of brain potential records each taken one minute apart. Read from left to right. At vertical mark sound stimuli sent to subject. Note marked trains of brain rhythms in A when subject asleep but none in B when subject awake, although stimulated by same sound. Time in seconds given by dots at top.

(8) When awake, the same sounds that during sleep initiate a train of waves no longer give rise to them. Fig. 1 B clearly shows this.

(9) During sleep trains of waves appear which can not be correlated with any detectable external stimulus, but which may be connected with internal disturbances of unknown origin. The cause of these very regular bursts is now under investigation.

ALFRED L. LOOMIS
E. NEWTON HARVEY
GARRET HOBART

LOOMIS LABORATORY
TUXEDO PARK

THE CENTRIOLE AND ITS ROLE IN MITOSIS AS SEEN IN LIVING CELLS

THE centrioles in the various genera and families of hypermastigote flagellates[1] range in length from 2 or 3 microns to 80 or more and may be seen easily in living organisms, since they are 1 to 3 microns in width. The achromatic figure and the manner in which it arises from the centrioles also may be seen very clearly in living cells. These protozoa, then, furnish ideal cytological material. Unfortunately, however, there appears to be a tendency among some cytologists to disregard cytological observations on protozoa, although there is no justification for such a tendency, because protozoa are cells, and observations made on them furnish as valuable a basis for generalizations as those made on *Ascaris* eggs, grasshopper testes or other types of classical material. Indeed, most of the Hypermastigina show much more clearly than any other known cells the centrioles, the manner of their duplication, the formation of the achromatic figure from them and the rôle of the achromatic figure in chromosome movement. Furthermore, observations on living material of these organisms show beyond question that the observations on fixed and stained material deal with realities, not artifacts produced by fixation. And the close similarity between the behavior of these hypermastigote centrioles and the centrioles of other cells leaves no room to doubt the general application of the observations on these flagellates to mitosis in both animals and plants.

In some genera, particularly those with short centrioles as in *Joenia*, *Mesojoenia* and other genera of the Lophomonadidae, the achromatic figure arises from the greater portion of the centriole; in other genera, with longer centrioles, it arises only from the distal half or third of the centriole; and in those genera with elongate centrioles, it arises from only a small portion of the centriole, the distal portion. In certain genera, the distal portion of the centriole from which the achromatic figure arises is surrounded by a

[1] The names of the 29 genera and 6 families need not be given here, since they are given in a recent publication to which the reader interested in them is referred (*Mem. Amer. Acad. Arts and Sciences*, Vol. 17, No. 2, 1934).

ELECTRICAL REACTIONS OF THE HUMAN BRAIN TO AUDITORY STIMULATION DURING SLEEP

H. DAVIS, P. A. DAVIS, A. L. LOOMIS, E. N. HARVEY, AND G. HOBART
From the Department of Physiology, Harvard Medical School, Boston, Mass., and The Loomis Laboratory, Tuxedo, N. Y.

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INTRODUCTION

THE SPONTANEOUS electrical activity of the human brain has been described both for the waking state and for sleep by many investigators (see Jasper, 1937, Davis, H., 1939, for references). The modifications of electrical activity as a result of peripheral sensory stimulation in the waking state are slight and have received much less attention. A conspicuous effect in many subjects is the "check," or inhibition, of the 10-cycle "alpha" rhythm which occurs when the eyes are opened. Definite "on-effects," particularly in response to sounds, have been mentioned casually by several investigators and described systematically by one of us (Davis, P. A., 1939, *q.v.* for references).

In sleep one reaction to sensory stimulation is a return of the waking pattern; but three of us have described (Loomis, Harvey, and Hobart, 1938) a more specific disturbance pattern which we designated as the "*K*-complex." The *K*-complex and the waking on-effects are of considerable theoretical importance because of the possibility of identifying them with similar responses of the brains of animals, and thereby coördinating the separate fields of human and of animal investigation. We therefore undertook further investigation of the human *K*-complex in an endeavor to analyze it into its components, and to compare the components with other electrical phenomena in the brains of both man and animals.

METHOD

Twenty-five experiments on sleep were carried out at the Loomis Laboratory in 1938 utilizing the six-channel, ink-writing electroencephalograph and its accessories, described in a previous paper (Loomis, Harvey, and Hobart, 1938). The subjects went to bed either for an afternoon nap or for a full night's sleep. Various types of electrodes (Davis, Davis, Loomis, Harvey, and Hobart, 1939) were employed, including silver, solder, and zinc. Our standard placements were: frontal (at the usual hair-line, 6 cm. to right and left of the midline), central (in the frontal plane of the auditory meatuses, 6 cm. to right and left), occipital (2 cm. above the inion and 5 cm. to right and left), temporal (1 cm. above the tip of the pinna of the external ear). In all cases, recording was by the so-called "monopolar" method. Reference electrodes were placed on one or both ear-lobes or on the mastoid region immediately behind the ears.

RESULTS

On-effects to sounds in the waking state

An earlier series of observations by one of us on the waking on-effect are reported separately (Davis, P. A., 1939). The findings were confirmed in the present experiments. In response to the onset of a steady tone, there is usually a definite diphasic response beginning with a negative wave

(latency 50 to 100 msec.) followed by a slower positive wave (see Fig. 1), in addition to the momentary checking of the alpha rhythm (Fig. 4_1). The diphasic response appears to be a true on-effect. It is widely generalized throughout the cortex and has greater voltage in the central and precentral regions than in the occipital or temporal areas.

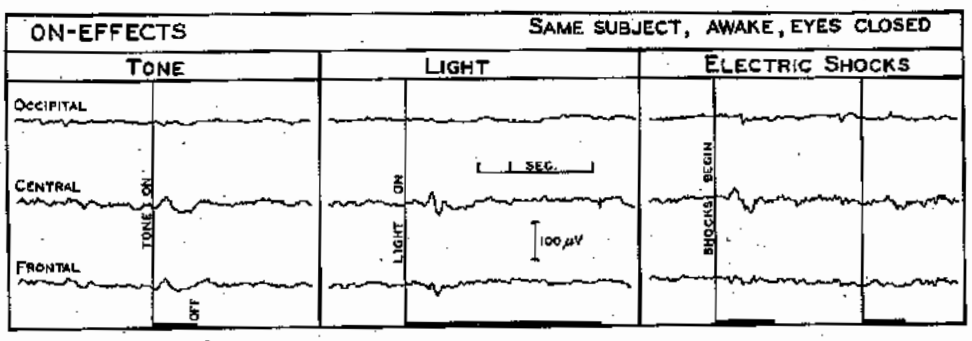

FIG. 1. Waking on-effects to tone of 500 cycles at 70 db above threshold, to indirect illumination of room by a 100-watt incandescent lamp, and to electric shocks delivered to left fourth finger. The subject is a 37-yr.-old man, lying in bed awake, with eyes closed throughout. Noise-level in room at position of sleeper's head, principally from ventilator fan, was 35 to 40 db. Intensity of stimulating tone measured also as a noise-level. Reference electrode on right mastoid region. Scalp electrodes also on right side of head. In this and all subsequent figures an upward deflection represents increasing electrical negativity of the scalp relative to the reference electrode on ear or mastoid region.

It is unnecessary to repeat the detailed description of the auditory on-effect or the conditions favoring its appearance (see Davis, P.A., 1939), but it is significant that neither the check of the alpha rhythm nor the diphasic on-effect is specific for auditory stimulation. Very similar responses have been obtained from visual and also from electrical stimulation. Figure 1 shows clear on-effects from a subject whose interim record was unusually flat. The minor differences in the shape and latency of the on-effects to light (diffuse illumination from a 100-watt bulb seen through closed eye-lids), tone, and electricity (induction shocks to left fourth finger) tended to be characteristic of the particular form of stimulation, but the distribution over the cortex was the same for all three.

The diphasic on-effect and the modification of the alpha rhythm are obviously both of them generalized secondary reactions of the cortex which may be observed under favorable conditions. They should not be interpreted as equivalent to the immediate and localized responses in a particular sensory area which are seen in experiments on the exposed cortex of animals.

The K-complex in sleep

The response which usually follows auditory stimulation during sleep is much larger and much less variable than the waking on-effect. The response is complex, and its characteristics vary systematically with the

stage of sleep. Figure 2 illustrates the *K*-complex as it appears in the *C* stage, recorded simultaneously from six different cortical areas. Shortly after the beginning of the stimulating tone, the scalp becomes electrically negative with respect to the ears by 50 to 100 μV. At about 0.75 sec. the scalp abruptly becomes more positive by 100μV. or more (*S* in Fig. 2). This major positive wave is followed by a slower return to the original electrical level. Fast waves, often sharp and irregular, sometimes in clear and regular 14-per-sec. rhythm and sometimes in slower 8-per-sec. rhythm (as at *F* in

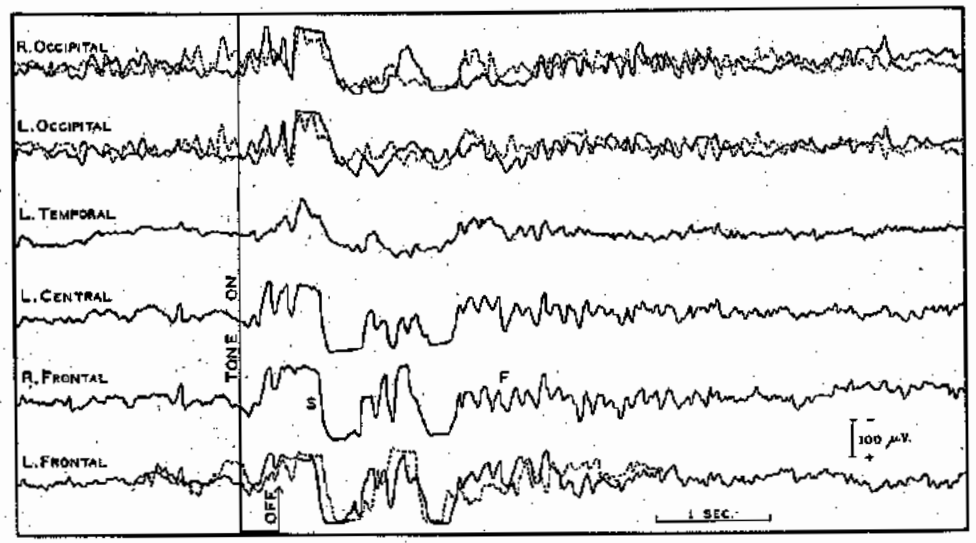

FIG. 2. Typical *K*-complexes in response to tone during *B*-*C* stage of sleep. Afternoon nap, 21-yr.-old man. Tone, 500 cycles at 70 db above threshold. Noise-level as for Fig. 1. Condenser across terminals of loud-speaker to eliminate click at onset of tone in this and subsequent experiments. Reference electrode just above left mastoid. Dotted lines show response at 3 electrodes to a similar stimulus 1.5 min. after the response shown by solid lines. The fast component (*F*) is prominent and is characteristically 8 per sec. in this subject until deep sleep is reached. Note the artificial flattening of the tops and bottoms of the slow waves (*S*) by the current-limiting tube in the output circuit (Loomis, Harvey, and Hobart, 1938).

Fig. 2) are superimposed on the slow waves and may persist for several seconds afterward. The abrupt swing from negative to positive usually occurs at about 0.75 sec., but it may be delayed until more than 1 sec. after the onset of the tone. The first slow negative swing is usually preceded in this subject by waves of medium, that is, 6- to 10-per-sec. frequency. The major features of the pattern are usually closely reproduced in successive trials on the same subject, as illustrated by the dotted lines in Fig. 2. Figure 2 also illustrates a definite tendency of the slow-wave sequence to become rhythmic (note particularly the frontal records). A rhythmic activity of the slow component is highly characteristic of deep sleep (cf. also Fig. $3_{5,5}$).

The distribution of the *K*-complex over the head follows closely the distribution of the waking on-effect. The voltage is regularly greatest in the central and precentral regions, and nearly as great in the frontal. The disturbance is definitely smaller at the occiput and still smaller in the temporal region. The temporal region, however, always gives a low-voltage record for all features (*K*-complexes, on-effects, waking alpha rhythm, etc.), perhaps because of the shunting effect of the soft tissues, notably the temporal muscles, external to the scalp. The *K*-complex may be of higher voltage in the frontal than in the central region, particularly when the major waves are slow and rounded, as in Fig. 4. Very rarely the *K*-complex is most prominent at the occiput.

A characteristic *K*-complex is usually produced by even a rather faint tone (20 db above the noise-level of the room) if the sleeper is in the *B* or *C* stage. The responses are larger and failures of response are fewer if the tone is loud. The pitch of the tone within the range employed (200 to 3000 cycles) is unimportant except that after a series of tests at one pitch, a shift to a new pitch is rather likely to awaken the sleeper. It is possible to initiate typical *K*-complexes by turning on a light in the experimental room or by applying mild electric shocks to the subject's finger, but neither of these stimuli are nearly as effective in evoking *K*-complexes as are sounds.

In one experiment, an effort was made to condition the *K*-complex to electrical stimulation. Electrical stimulation and sound were combined for a number of trials and then the tone was omitted. The response to the electrical stimulation was not clearly greater than it had been previously. There seemed to be some additive effect between the two types of stimulation, as tone plus electrical stimulation gave a somewhat greater proportion of positive responses than did the tone alone. It is difficult to perform satisfactory experiments of this sort, as the responses vary considerably with the depth of sleep and it is difficult to hold the sleeper in a steady state for a long enough time. Usually he either goes too deeply asleep or else, if stimulated too vigorously or too frequently, he awakens.

Spontaneous *K*-complexes are common. Sometimes definite causes can be found for them, the commonest being the sleeper's own breath sounds. It is quite amusing to observe the regular appearance of electrical disturbances with each snore, but it interferes seriously with systematic experimentation. For many *K*-complexes, however, we have found no assignable external cause.

Relation of the K-complex to the stage of sleep

The description of the *K*-complex thus far has been based on the responses of sleepers in the *C* stage of sleep. It is in this stage that the *K*-complex appears most clearly. The genesis of the typical *K*-complex with the onset and progress of sleep is illustrated in Fig. 3. In this experiment the subject (a 14-year-old boy) was instructed to turn off the tone whenever he heard it, by squeezing a rubber bulb placed in his hand. The waking

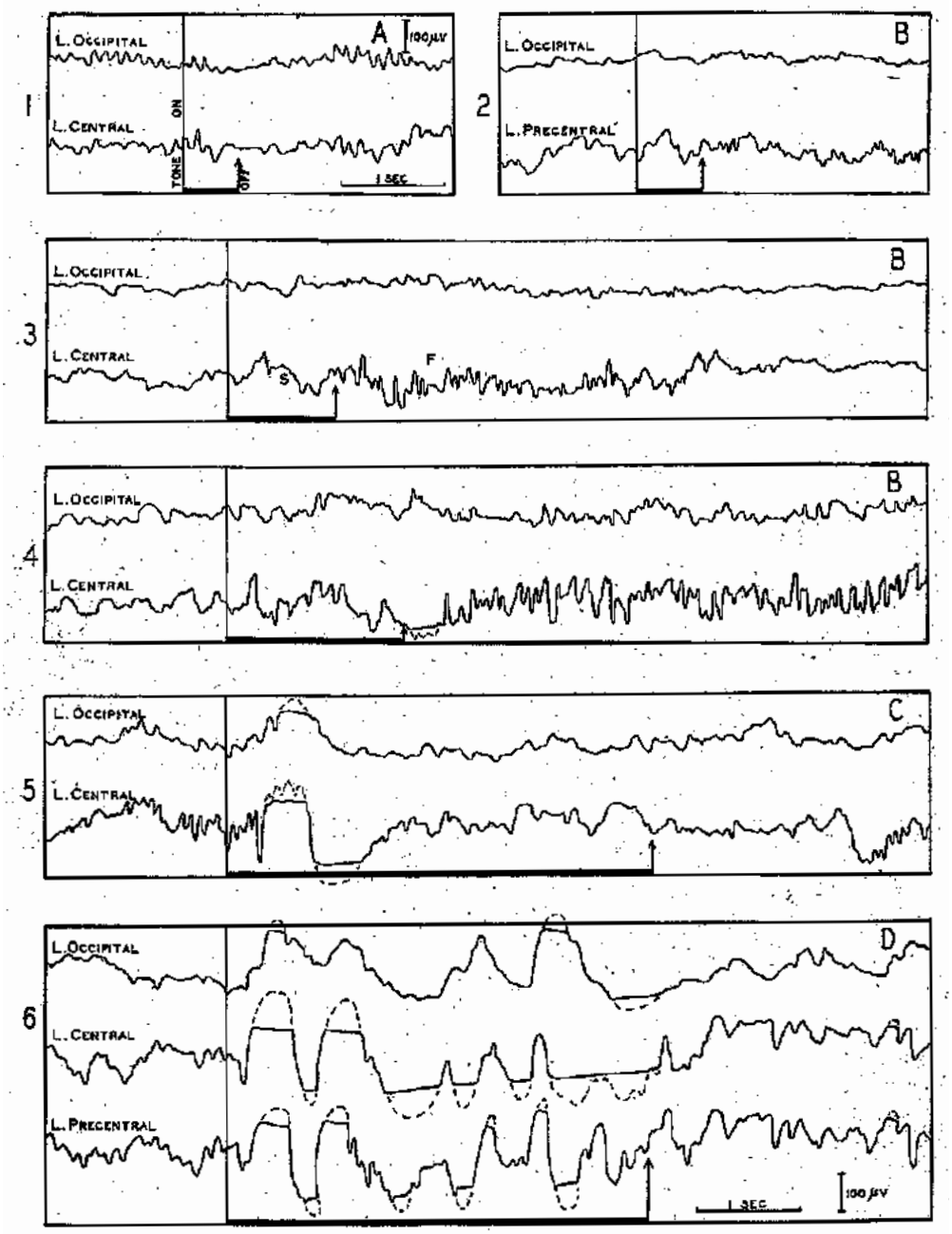

FIG. 3. Responses to tone of 500 cycles during the drowsy state and in sleep. Intensity of tone 70 db in 1, reduced to 55 for 2, 3, 4, 5, and 6. Noise-level about 25 db. Subject is a 14-yr.-old boy, who went to sleep for an afternoon nap. The stages of sleep are indicated by the lines in the upper right-hand corners. (See text for details.) Reference electrode on right mastoid region. Dotted lines indicate the probable approximate course of the potential-changes which are obscured by the current-limiting tube in the output stage.

record shows a strong alpha rhythm, which is almost continuously active (Fig. 3_1), and the alpha waves are unusually responsive to auditory signals. Perhaps the responsiveness is dependent upon the psychological conditions of the experiment, but this subject invariably showed a transient checking of his alpha rhythm whenever the tone was turned on, irrespective of whether he was instructed to turn it off or to pay no attention to it. As the subject became drowsy in this experiment his alpha rhythm became intermittent and returned abruptly when the subject turned off the tone. This reaction corresponds closely to the return from a "float" described in a previous paper (Davis, Davis, Loomis, Harvey, and Hobart, 1938).

The subject then passed into the low-voltage *B* stage of sleep. In this stage (Fig. 3_2) he continued to turn off the tone, although less promptly, but without any return of his alpha waves. The next modification (Fig. 3_3) was the appearance, following the tone, of fast waves at the central region. It should be clear from the central distribution and varied frequencies of these waves that they are not the usual alpha waves. They clearly represent the fast component of the typical *K*-complex. Fig. 3_3 also shows the first beginnings of the slow component, "*S*," during the stimulation. It is remarkable that the subject's EEG is now definitely in the "sleep" category, yet he continued to turn off the tone. From the beginning of the experiment the tone had been turned on automatically every half minute, and up to this point the subject had not once failed to turn it off. In Fig. 3_4 the record before stimulation is even more clearly a sleep record, with quite well-developed delta waves, and the *K*-complex following the stimulus is still better developed, but the subject still squeezed the bulb. The subject's reaction-time became progressively longer, as illustrated in Fig. $3_{1,2,3,4}$. The prolongation correlated well with the changes in electrical pattern, but only when the subject reached the *C* stage (Fig. 3_5), identified by the spontaneous train of 14-per-sec. waves appearing at the central region, did the subject fail to squeeze the bulb. The *K*-complex was then fully developed.

Fig. 3_6 shows the further development of the *K*-complex in the *D* stage of sleep. The fast-wave component has become less conspicuous. Its waves are slower and rounded and can scarcely be identified because of the high-voltage waves of the slow component, on which the fast waves are superimposed. In this *D* stage the slow (delta) activity becomes so rhythmic and so nearly continuous between stimuli that it is often difficult to determine whether there is or is not a response following a stimulus.

In the *E* stage, which was not reached in this experiment, there is no indication of any modification of the electrical record following even a very strong stimulus. It will be recalled that in the *E* stage the spontaneous delta activity is continuous at high voltage and at frequencies of 1 per sec. or less (cf. Fig. 6) and that in the *E* stage the trains of 14-per-sec. waves are absent.

The particular experiment illustrated in Fig. 3 is somewhat unusual in

the persistence of the motor reaction, apparently well into sleep. The progressive development of the *K*-complex is fairly typical, however, if we make allowance for individual characteristics of the *K*-complexes of various subjects. (For example, the prominent 6- to 8-per-sec. waves in Fig. 2 are characteristic of one particular subject and are quite well developed in two others.) A general rule seems to be perfectly clear. *The slow and the fast components of the K-complexes both resemble closely the delta waves and the fast waves which are characteristic of the spontaneous activity of the particular stage of sleep.* In fact, it now seems clear that most of the characteristics originally selected for the identification of the stages of sleep actually are the characteristics of the spontaneous *K*-waves, although the fast component of an evoked *K*-complex corresponds to the stage to which the subject is aroused rather than to the stage in which he was before being stimulated. The low-voltage *B* stage shows little delta activity, and the slow component of the *K*-complex is relatively small and fast (Fig. 3_3, 3_4, and Fig. 5). The fast-wave component is also relatively fast or may be represented by a more or less complete return of the waking pattern. The *C* stage of sleep has well-defined delta activity and prominent trains of 14-per-sec. waves. These trains obviously correspond closely to the fast component of the *K*-complex. The *D* stage is characterized by rhythmic delta waves which obviously resemble the rhythmic slow component of the *K*-complex.

Analysis of the K-complex

We have spoken throughout of the *K* "complex." We may obviously identify two main components—the slow-wave (delta) component ("*S*" in Fig. 2, 3, and 5) and the fast-wave component. Either the fast or the slow component may appear alone, or one may be well developed while the other is rudimentary. The two components may be separated experimentally by stimulation at brief intervals (Fig. 4). A second stimulus delivered within 4 or 5 sec. after a previous stimulus rarely evokes the slow component. If the slow component does appear, it is almost always reduced in size, faster in frequency, and often shows an unusually long latency. The fast-wave component, on the other hand, regularly appears following the second stimulus and merges with the fast-wave sequence of the first *K*-complex, as in Fig. 4.

If a tone is timed to fall 2 or 3 sec. after the major positive swing of a "spontaneous" *K*-complex, it usually fails to evoke a second slow component. The situation is the same whether the first *K*-complex is evoked by a known stimulus or is "spontaneous." It appears as if some part of the mechanism necessary for the generation of the slow component were refractory for several seconds after a previous response. The situation in regard to the fast component is quite different. Not only is its appearance not hindered by a previous *K*-complex, but it is often actually enhanced by it. Also a stimulus may fall in any relation to a "spontaneous" train of 14-per-sec. waves without hindering the appearance of either the slow or fast com-

ponent of the ensuing *K*-complex. The fast component alone does not leave the mechanism refractory for either the fast or the slow component. If there is a refractory period involved, it is so short as to be of quite another order of magnitude than that following the slow component.

If repeated stimuli are given at intervals of 3 or 4 sec. or less, the fast-wave activity tends to become faster and less regular, the waves sharper in contour but lower in voltage. The subject often stirs or awakens. Only if the subject is so deeply asleep that the fast waves of his *K*-response are

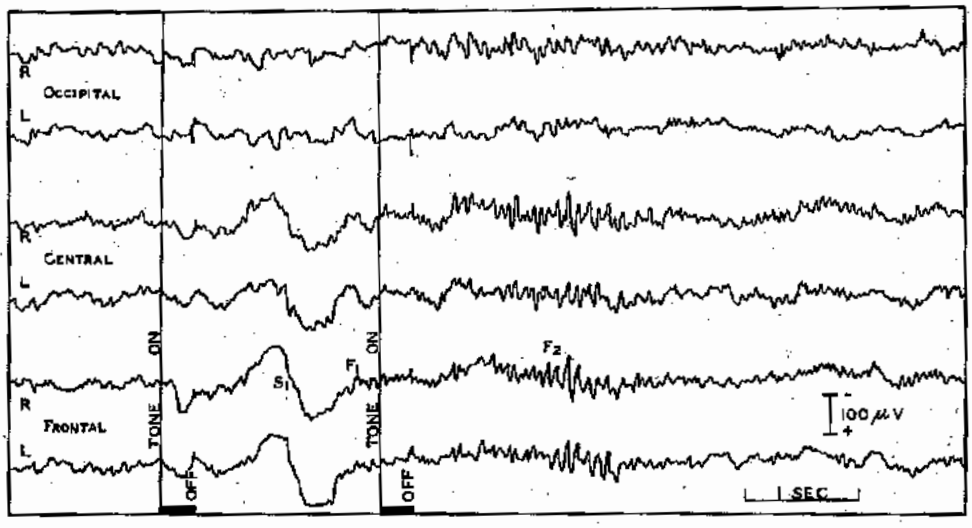

FIG. 4. Response to two brief tones at 2000 cycles at 45 db above threshold during *B-C* stage of sleep. Noise-level 35 to 40 db. Subject is a 41-year-old woman. The slow component, S_1, is of the frontal type. Note almost complete absence of slow components following the second tone, but the greatly increased fast component, F_2. Reference electrodes on right ear lobe for lines 1, 3, and 5; left ear lobe for 2, 4, and 6.

inconspicuous or are slower than 14 per sec. does such repetition of the stimulus fail to shift him to a lighter stage of sleep.

Varities of the slow-wave components

The *K*-complexes of many individuals in light sleep are both characteristic and reproducible. In Fig. 5 the fast-wave component is present, although poorly developed, and the slow rhythm is typical. The sequence begins with a small negative wave whose foot begins about 100 msec. after the stimulus. Successive waves are higher in voltage and longer in duration, so that no definite frequency can be assigned to them. The diagram in Fig. 5 is drawn from the average measurements of voltages and times of 13 *K*-complexes from the same individual. The 13 complexes were selected from 25 responses in approximately the same stage of sleep, because it was evident from actual superposition of the original records that they all resembled

one another quite closely. In a few cases, one or both of the first two small waves were absent, and in several the fourth and fifth waves were poorly developed, but all 13 clearly conformed to the same general pattern. The remaining 12 responses showed one, and usually more, of the diagrammatic waves at their appropriate intervals, but they were superimposed on and partially replaced by a somewhat slower sequence of rounder waves of approximately the same voltage (cf. Fig. 4, central and frontal, and Fig. 3_5). The pattern illustrated in Fig. 5 was always most prominent, *i.e.*, highest voltage, at the central region, while the slower, rounder waves of Fig. 4 were best developed in the frontal region. We therefore tentatively designate these two types of slow wave appearing in the *K*-complex as "central" and

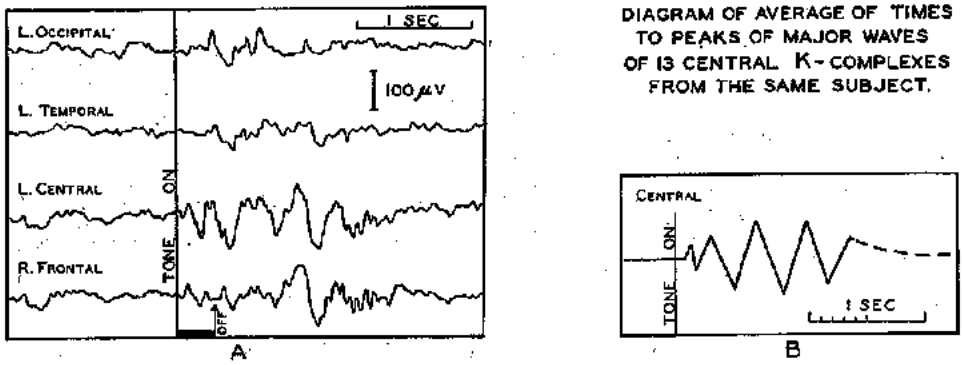

FIG. 5. *A*. Typical *K*-complex in response to a brief tone of 1000 cycles of 70 db above threshold from a 35-yr.-old man in the *B* stage of sleep. This response was selected as most typical of the "central" type of slow component. Reference electrodes on left mastoid region for three upper lines, on right mastoid for lowest.

B. A diagram of the composite of 13 "central" *K*-complexes from this subject.

"frontal," respectively. Some subjects gave a large proportion of pure "central" responses. Others tended to give more of the frontal variety, but more often the responses were mixed in character. In the "mixed" variety, both "central" and "frontal" waves appear both in the central and frontal areas, but the fast are more conspicuous in the record from the central region, and the slower, rounded waves are more prominent in the frontal area.

Intermittent auditory stimuli

The rather prominent 6- to 8-per-sec. "central" rhythm which appeared in some subjects (cf. esp. Fig. 2) and the apparent absence of refractory period for the fast-wave component led us to wonder whether the 6-per-sec. rhythm could be enhanced by stimulating with intermittent sounds (clicks or knocks) at a frequency of 6 per sec. It seemed possible that we might be able to "drive" the waves at frequencies determined by the frequency of stimulation, as Adrian and others have done with the occipital waves in the waking state (Adrian and Matthews, 1934; Loomis, Harvey, and Hobart,

1936). We were unable to produce a corresponding effect in sleep by auditory "flicker." Even rather loud knocks at frequencies near 6 per sec. produced no different response from what we regularly observed with steady tones. Knocking had, however, a much stronger tendency to awaken the sleeper, perhaps because of its intermittent character or because of its psychological associations.

Possible direct-current components of the K-complex

The time-course of the slowest waves and rhythms which appeared in the frontal region raised the question whether our amplifiers, with a time-constant of approximately 0.5 sec., were adequate to record all of the

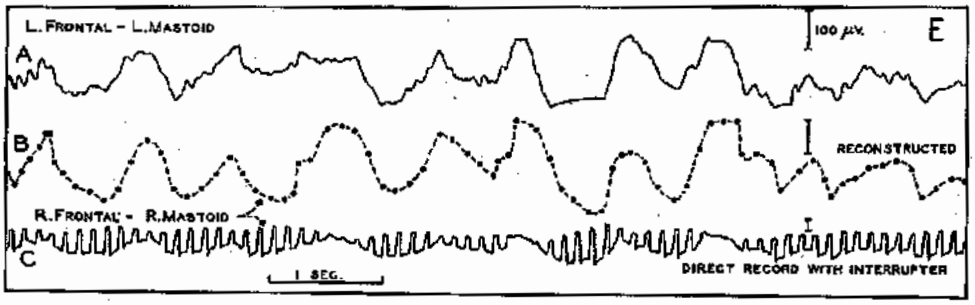

FIG. 6. Comparison of D.C. record of potential changes (line *B*) with a simultaneous record from the opposite side taken by the usual condenser-coupled amplifier. Large delta waves, *E* stage of sleep. *A* and *C* were recorded simultaneously. The input leads of line *C* were short-circuited automatically 8.5 times per sec. (see Davis, Davis, Loomis, Harvey, and Hobart, 1939). Line *B* is subsequent reconstruction from *C*. Distance of dots in *B* from a reference line (not shown) is proportional to the excursions in *C* on opening and closing of the short-circuit.

electrical response. It seemed possible that there might be a slow component,—a shift of the base-line,—as part of the *K*-complex which was not being revealed by our condenser-coupled amplifiers. We therefore employed the method of interrupting the input to one of our amplifiers (Davis, Davis, Loomis, Harvey, and Hobart, 1939) to determine whether such slow changes existed or not. Figure 6 shows how the potential appearing between the input electrodes when the short-circuiting switch is opened is revealed by the height of the square-topped "waves." The course of the potential-change is reconstructed in line *B* on a scale of sensitivity comparable with that of the usual record. Comparison between *A*, taken from the left side of the head, and line *B*, reconstructed from the record taken from the right side, shows that the usual method records with considerable fidelity the slow changes of voltage of the *E* stage of sleep.

Interrupted records taken during stimulation by tones could not follow the details of the *K*-complex, but showed conclusively that there was no slow shift of as much as 50 μV. in the electrical base-line associated with the *K*-complex.

Discussion

In the light of the foregoing experimental facts, the *K*-complex, or "disturbance pattern," of sleep appears as a multiple, diffuse, non-specific, delayed electric response of the brain to external sensory stimulation. It is clearly related to the on-effects seen in the waking state and also to the background of electrical activity characteristic of the stage of sleep in which it occurs. Auditory stimuli have so far proved most effective in evoking it. The effectiveness of auditory stimuli during sleep may be no accident if we consider the general biological function of hearing in the rôle of watchman constantly on guard to signal danger. In sleep the eyes are covered by the eyelids, and vision is in abeyance, but hearing remains active, ready to rouse the sleeper. The electric response is not confined to the auditory projection-area of the temporal region. On the contrary, it appears to be relatively weak over the temporal lobe, and best developed over sensorimotor and frontal areas. Its latency may be considerable, from 0.1 to a full second or even more.

The *K*-complex consists of at least two components,—the fast and the slow. In deep sleep the "fast" waves may be as slow as 10 or even 8 per sec. and resemble a smooth alpha rhythm. As the sleeper becomes more and more aroused, the "fast" waves become faster and less regular, with no clear 10-per-sec. rhythm. They appear to be more closely related to quick or beta waves than to the waking alpha waves (cf. Davis, Davis, Loomis, Harvey, and Hobart, 1938, p. 34). It seems reasonable to interpret the appearance of the fast component as an indication, and possibly even a measure, of the degree to which the subject has been aroused toward the waking state by the stimulus. Repeated stimuli at short intervals cause an increased (summated) fast component, and the subject is quite likely to awake. In deep sleep (stages *D* and *E*), the subject cannot easily be aroused, and the fast component of the *K*-complex is not at all prominent.

The slow component appears to be a definite response, often reproducible in considerable detail, clearly related to the waking on-effect. Its first waves correspond in latency, polarity, and duration to the waking on-effect. It seems reasonable to interpret the slow component as the waking on-effect modified and prolonged by sleep. Even before the subject goes to sleep, the on-effect becomes more prominent as the subject becomes drowsy. This increase in amplitude is broadly similar to the appearance in the animal brain of a delayed secondary discharge in stimulation of the sciatic nerve under deepening barbiturate anesthesia (Derbyshire, Rempel, Forbes, and Lambert, 1936; Forbes and Morison, 1939).

The slow component of the *K*-complex is rhythmic. If the same cells respond in the successive waves, we may be sure that their refractory period is shorter than 1 cycle of the rhythm. The slow-rhythm component as a whole, however, shows a refractory period to a second auditory stimulus, although the second stimulus may fall as much as 3 or 4 sec. after the original stimulus. This refractory period is much longer than 1 cycle of the rhythm. We

may infer that it is the avenue of approach to the cortex which is refractory, and not the responding elements themselves (cf. Forbes and Morison, 1939, for a theoretical discussion of the problem of the refractory state in a closely analogous situation). The refractory state may represent a true refractory period, like the long refractory period under dial anesthesia of the pathways of cutaneous sensitivity (Marshall, 1938), or possibly it is a secondary result of partial rousing of the subject, a shift in the general level of activity of the brain, which renders the brain less prone to this particular form of rhythmic activity. The effect might then be compared to the checking of the alpha rhythm by visual stimulation, attention, or an emotional state.

The slow component of the *K*-complex shows many similarities to the secondary discharge described by Forbes and Morison (1939) in the brain of the cat under barbiturate anesthesia. The resemblance is so close that it seems reasonable to attribute both phenomena to the same type of mechanism and to explain the quantitative differences as due to differences between the brains of the human being and of the cat, between sleep and barbiturate narcosis, and between sound and electrical stimulation of a peripheral nerve. Both phenomena are delayed cortical responses to sensory stimulation. Neither of them appears clearly in the waking state but they become prominent under conditions of depressed cortical activity (sleep and anesthesia) and both increase in size as the depression deepens. Both are generalized responses of the cortex. The latency is considerable in each case. Derbyshire, Rempel, Forbes, and Lambert (1936) state that the usual latency of their secondary discharge is 40 to 80 msec. We have not attempted to measure precisely the latency of the *K*-complex, because the first wave is often small and indefinite, but it is of the order of 100 msec. If ether anesthesia is given to an animal already deeply anesthetized by pentobarbital sodium (nembutal), the latency of the secondary discharge may be as great as 150 msec. (Forbes and Morison, 1939). The secondary discharge and the slow component of the *K*-complex both show a long refractory period in the sense that a response appears only after the first of a series of stimuli repeated at a rate of 4 per sec. The secondary discharge is reduced in amplitude unless the interval between stimuli is considerably more than 1 sec. The corresponding refractory period of the *K*-complex may last for as long as 4 or 5 sec. "Spontaneous" *K*-complexes, or secondary discharges, render the brain incapable of a second response just as effectively as do responses evoked by sensory stimulation. Forbes and Morison (1939) arrived at a similar conclusion concerning their secondary discharge. Bremer (1937) has emphasized the similarity of the electrical activity of the cat's brain in sleep to that under barbiturate anesthesia, in contrast to its activity under ether anesthesia. If our identification of our slow *K*-component with Forbes's secondary discharge is correct, it represents an important unification of observations on normal man with data from animal experimentation.

Forbes and Morison suggest that their secondary discharge may be analogous to the third (slowest and latest) component of the complex re-

sponse to stimulation described by Bishop and his collaborators (Bartley, O'Leary, and Bishop, 1937; Bishop and O'Leary, 1938). On the basis of the time relationships of the waves which he observed, Bishop suggested that his slowest waves represent activation of the mechanism which generates alpha waves in the waking state. Our evidence shows that the slow component of the *K*-complex is probably identical with Forbes's secondary discharge and also with the human waking "on-effect," but that it is clearly distinct from the human alpha waves. It appears therefore that one or another of the various comparisons is at fault. The situation is not disturbing, however, since some of the comparisons rest almost entirely upon similarity in time-relations and it is by no means a necessary conclusion that all electrical waves of similar frequencies represent activity of the same neural mechanism. For example, the "alpha" rhythm at 10 to 12 waves per sec. recorded by Grinker and Serota (1938) from the brains of cats under nembutal anesthesia is probably analogous to the human 14-per-sec. rhythm of sleep and to the "fast" component of the *K*-complex and not to the waking occipital 10-per-sec. alpha rhythm. Incidentally, Grinker and Serota report (*loc. cit.*, p. 575) a combination of slow and faster waves from the hypothalamus of the narcotized cat which corresponds closely to our cortical *K*-complex of sleep.

The appearance of *K*-complexes with two recognizable types of slow component, the "central" and the "frontal," suggest that two more or less distinct, but similar, neural systems may be set into action by the sensory stimulus. One system apparently tends to activate primarily the central, the other the frontal cortex, but sometimes the two systems seem to share the control of a given region, and we see the "mixed" type of response. The spread of "central" waves into the frontal region, and *vice versa*, is not a mere electrical artefact. Successive responses which are nearly identical in the precentral region often vary widely in their degree of spread into other regions. The cortical systems which generate the two types of waves apparently interdigitate to a considerable degree, and the extent of the response of each system varies from one test to another. Our experiments offer no indication whether a given neuron always participates in one, and only one, system or whether it may respond now in one and now in another pattern. The problem is exactly similar to the one raised by the alpha waves in the waking state in the precentral region. Sometimes they are 10-per-sec. waves in phase with similar waves at the occiput. At other times there are larger 8- or 9-per-sec. waves which are small or absent at the occiput (cf. Jasper and Andrews, 1938). Sometimes the 8-per-sec. precentral waves are coincident with low-voltage 10-per-sec. occipital waves, and the combination gives a confused record in which neither rhythm appears clearly, but in which both may be identified by careful inspection. Both in the waking and in the sleeping state we encounter a tendency of different regions of the cortex to react in rather similar ways, sometimes closely coördinated, yet at other times independently. When the reactions are independent, the indi-

vidual features characteristic of different regions may be recognized. The idea of independently reacting neural systems occupying the same cortical areas is not new. On-effects and secondary reactions have long been recognized (see Davis, 1939, for references), and in particular Bartley, O'Leary, and Bishop (1937) and Bishop and O'Leary (1938) have clearly distinguished two neural systems in the optic and also in the sensorimotor cortex of the cat (cf. also Adrian, 1936). The present evidence merely emphasizes once more the complexity of the organization and activity of the brain.

Summary

The electric response of the human brain to auditory stimuli during sleep, previously described and designated as the "*K*-complex," has been investigated in more detail. It is a multiple, diffuse, delayed, non-specific response to external sensory stimulation. Usually a fast component, consisting of a series of more or less regular waves at frequencies of 8 to 16 per sec., is superimposed on a series of slow (delta) waves (Figs. 2, 3, and 5), but either component may appear independently of the other. No shift of electrical base-line ("D.C. component") is associated with the *K*-complex (p. 501).

Light and electric shocks may elicit *K*-complexes, but less effectively than do sounds (p. 503). Typical *K*-complexes may appear "spontaneously" without assignable external cause.

The latency of the *K*-complex is usually of the order of 100 msec. and may be half a second or more. Both fast and slow components are more prominent in the central and frontal than in the occipital and temporal regions (Figs. 2 and 5). The patterns are simultaneous and broadly similar over all these regions, but characteristic differences between central and frontal types of the slow component are described (p. 507).

The fast component is often identical with the trains ("spindles") of 14-per-sec. waves which are characteristic of the *C* and *D* stages of sleep. The appearance of the fast component seems to represent a partial arousal of the sleeper. The slow component develops progressively from the waking "on-effect" (Fig. 1) and increases in amplitude and duration as the subject becomes drowsy and goes to sleep. Both components vary systematically with the stage of sleep (Fig. 3). The waves become slower as sleep deepens, and do not appear in the *E* stage of sleep. The characteristics of the spontaneous *K*-complexes are the chief criteria by which the *B*, *C*, and *D* stages were originally identified.

A sound within 3 or 4 sec. after a previous stimulus usually fails to evoke a second slow component. If it succeeds, the second response is delayed and reduced in amplitude. The fast component, on the contrary, appears full sized at all intervals of stimulation and merges with the fast component of the previous complex (Fig. 4).

Forbes and his collaborators have described a "secondary discharge" which appears in the cerebral cortex of the cat under barbiturate anesthesia

following electrical stimulation of the sciatic nerve. The slow component of the *K*-complex shows the same characteristics as, and is probably strictly analogous to, this secondary discharge (p. 512).

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HYPOTHALAMIC REGULATION OF SLEEP IN RATS. AN EXPERIMENTAL STUDY

W. J. H. NAUTA
Department of Anatomy, University of Utrecht, Holland

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INTRODUCTION

THE ESSENTIAL role of the nervous system in the regulation of the sleep-waking rhythm of higher animals is now widely recognized. No less a person than von Economo, however, drew attention to the fact that the phenomenon of sleep cannot be accounted for by a mere functional change of the central nervous system from its condition during the waking state. It is indeed an important fact that the function of sleep, instead of being characteristic of higher animals, is also observed in organisms which do not possess a central nervous system, and even in several vegetable species. It is therefore impossible to attribute this mysterious function to any special organ. Since all experimental work on sleep has hitherto been confined to mammals, chiefly to cats and monkeys, practically no data concerning the comparative physiology of this phenomenon are available. Nevertheless, it seems probable that during the phylogenetic development the function of sleep, together with many other mechanisms, was progressively centralized into the nervous system from which organ all changes, characteristic of sleep, were ultimately effected. This centralization proceeded so far that the alternation of wake and sleep seems to be governed in mammals by a circumscribed area of the central nervous system, capable of determining physical and psychical activities. The existence of this "centre" for the regulation of sleep is generally accepted by students of this subject. It has, however, given rise to a number of problems, concerned in the first place with the make-up of the centre, and secondly with its mode of action. Is there one single centre for the regulation of the sleep-and-waking rhythm, or must it be thought of as composed of two antagonistic parts, *viz.*, a sleep and a waking centre? And next, on what structures and along what paths does it primarily exert its influence? These questions have been so divergently answered by various investigators that a brief review of the current opinions seems essential.

The first to recognize a central representation of sleep was the Viennese ophthalmologist Mauthner (32), who from his observations of many cases of Wernicke's disease and of "nona" (which was probably identical with von Economo's lethargic encephalitis) concluded that the area surrounding the oculomotor nucleus was of special importance for the regulation of sleep. In later years evidence in favour of a central regulation of sleep was put forward by many clinicians, of whom von Economo in particular disguished himself by his classical study of the Vienna epidemic of encephalitic lethargica (11). The localisation given by Mauthner has been little changed.

Thus von Economo considered a rather extensive area in the posterior and lateral walls of the third ventricle as the site of the regulating mechanism. A number of observations of cases in which this area was destroyed by tumour seemed to confirm the importance for sleep and waking, ascribed by von Economo to the walls of the third ventricle.

This view could be gained only by careful comparison of many clinical cases in which often very extensive lesions of the central nervous system existed. It is, therefore, not surprising that many investigators were, by less critical observation, led to other conclusions. Trömner (46) concluded from a case of narcolepsy, in which autopsy revealed an extensive abscess of the left thalamus, that the regulation of sleep was a function of the thalamus. In later years Spiegel and Inaba (43) adopted the same view on the basis of their experimental work on rabbits and dogs. The experiments of Ranson on monkeys (36), however, clearly indicate that the thalamus is of no special importance for the alternation of wake and sleep, as even extensive destruction of both thalami did not result in any abnormality of this function. On the other hand, bilateral lesions in the area of the mammillary bodies caused the same marked somnolence which is such an outstanding feature of epidemic encephalitis. These results are in accordance with the clinical view that the vicinity of the third ventricle plays a specific role in the regulation of sleep.

How does the central area (whatever its localisation) so strongly affect the state of our physical and psychical activities? This question has been very differently answered. According to Mauthner (32), the first to accept a central regulation of sleep, an inflammatory edema around the oculomotor nucleus would exert a pressure on the important sensory pathways passing through the midbrain, thereby interrupting the corticopetal flow of impulses and thus causing sleep. From this conception it is evident that the special importance ascribed by Mauthner to the environment of the oculomotor nucleus, was attributed by him only to the topographical relations of this area to the main sensory systems. Moreover, sleep, according to Mauthner, would result from an isolation of the cortex from the outer world, and this opinion has received support from various authorities including Spiegel and Inaba (43), who based their concept on cases of somnolence which they obtained by inflicting lesions to the thalamus. The same stand is taken by Kleitman and Camille (30), who, for instance, claim that imperfect relaxation of the skeletal musculature may cause insomnia by keeping up a continuous stream of proprioceptive impulses to the cortex. An essentially similar opinion was expressed by Trömner in 1912. Whereas Mauthner and others apparently considered various unspecific factors (edema, exhaustion, etc.) the cause of the sensory interruption, Trömner accepted the concept of a nervous centre capable of blocking the sensory relaying centres of the thalamus.

The idea of a nervous centre exerting an active influence on the sleep-and-waking rhythm, thereby formulated for the first time, has since received considerable support, although the details of Tromner's concept of this centre, *viz.*, its localisation in the thalamus and its action via sensibility, have been effectively criticized by all the most competent investigators.

In 1918 von Economo published his report on encephalitis lethargica. In those cases of this disease in which somnolence and ophthalmoplegy were the main symptoms, inflammatory lesions were regularly found in the posterior wall of the third ventricle, extending backward to the level of the oculomotor nucleus. In other cases insomnia was observed, together with chorea. These symptoms von Economo ascribed to inflammation of a more rostrally situated part of the hypothalamus, the tuberal region, and of the adjacent portion of the striate body. The objection that these disorders of sleep might be the result of some toxic influence of the inflammation was rejected by von Economo as the encephalitic sleep was promptly reversible and its interruption did not leave any signs of defective mental lucidity, as would have been the case with intoxication. Therefore von Economo is convinced that the affected areas constitute a specific centre as postulated by Trömner. From the contrasts between the somnolent and the sleepless form of epidemic encephalitis, he concluded that the "Schlafsteuerungszentrum" consists of at least two parts (Fig. 1). The conception lay near at hand that the caudal part (inflammation of which caused somnolence) is essentially a waking centre, while the rostral part must for an analogous reason be supposed to act as a sleep centre.

Sleep, according to von Economo, would result from inhibition of thalamus and cor-

tex by the "Schlafsteuerungszentrum." However, von Economo does not agree with previous workers that sleep is brought about by neutralization of sensory stimuli, because his patients suffering from encephalitis lethargica did not show any decrease of sensibility. The most important element of von Economo's opinion, shared with Trömner, is his belief that sleep is caused by active nervous inhibition of different parts of the central nervous system. This view, however, is contradicted by Ranson and his collaborators.

In the course of Ranson, Barris and Ingram's experiments on cats (27, 37) and Ranson's on monkeys (36), in which they inflicted lesions of great diversity to the hypothalamus, they observed many cases of somnolence following lesions of a well-defined hypothalamic area (which has been referred to on p. 304), but never were able to produce sleeplessness. In their 1939 review of the hypothalamus Ranson and Magoun make the following statement, which illustrates their point of view: "There is no good reason to believe that there is a subcortical centre, which, when active, inhibits the cerebral cortex and causes sleep; but there is abundant evidence that some structure or structures in the region of the third ventricle or aqueduct play an important part in maintaining the waking state, because lesions in this region cause somnolence." By theoretical deductions Salmon (42) arrived at the same opinion.

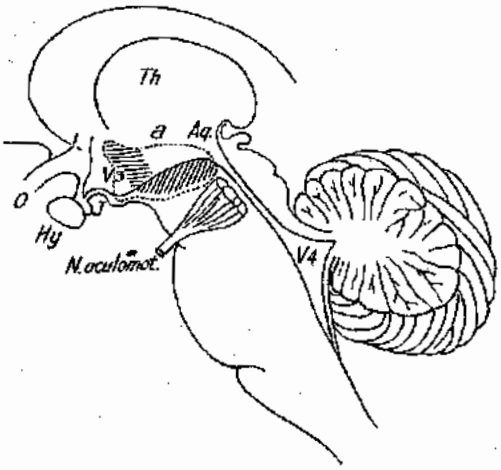

FIG. 1. Von Economo's conception (11) of the localisation of the "Schlafsteuerungszentrum" and its composition in two parts, *viz.*, one (vertically striped) in which inflammatory lesions cause somnolence, and one (horizontally striped) in which similar lesions cause sleeplessness.

The experiments of Hess (23) have often been brought forward in favour of the existence of a sleep centre. By means of a special technique this observer was able to induce sleep in cats by stimulation of points in fore-, tween- and midbrain. These points lay widely scattered over so large an area that it is scarcely believable that Hess invariably stimulated one single centre. Nevertheless, the fact that sleep was obtained by stimulation, *i.e.*, by activation of central nervous tissue, is deserving of our interest. Hess' method of stimulation, however, met with serious criticism from Harrison (21), who claims that it gives rise to electrolytic lesions of the stimulated points. When he altered it so as to avoid destruction of nervous tissue, he never was able to induce sleep. He therefore concludes that sleep in Hess' experiments produced not by stimulation but by lesion. This opinion, however, does not harmonize with the relatively short duration of sleep in Hess' experiments. Whereas the lethargy exhibited by the experimental animals of Ranson and his collaborators persisted for days and weeks, Hess' cats only

slept for a few hours. Probably this discrepancy should not be attributed to differences in the amount of nervous tissue destroyed, as even enormous lesions of fore- and tweenbrain fail to interfere with the regulation of sleep if only a circumscribed area of the hypothalamus is left intact. Nevertheless, Harrison's criticism warns us to be reserved in our appreciation of Hess' early findings. Another reason is that in later years Hess seems to have changed his initial opinion. In 1936, for instance, he stated that sleep could never be brought about by stimulation of the hypothalamus, but constantly appeared when the zone of transition between thalamus and subthalamus was stimulated. In 1944 he published some cases of "adynamia" in cats after hypothalamic stimulation, a condition which he distinguished from the sleep referred to in his previous papers by a concomitant plasticity of the animals. Hess' views on the diencephalic regulation of activity have been expressed in a recent review of his results (26), but his conception that sleep may result from activity from some central area still needs confirmation.

We shall not go into the experiments in which disorders of sleep were caused by the introduction of various chemical substances into the brainstem, as their interpretation is too ambiguous to bring us any nearer to a satisfactory concept of sleep.

Looking back on the various opinions about the central regulation of sleep, a considerable amount of agreement now seems to have been reached as to the localisation of the centre of regulation. About its mode of action, however, some fundamental differences of opinion exist. Whereas von Economo agrees with Trömner's original view that sleep results from activity of the regulating centre, which can therefore be thought of as a sleeping centre, Ranson and his school are by their experiments led to the view that the regulating apparatus essentially serves for the maintenance of the waking state, and that sleep appears when it is reduced to inactivity. In an experimental study described below, we hope to reach some conclusions which may contribute to the solution of the problems mentioned in the previous account.

MATERIAL AND METHODS

Only adult albino rats were used in this study. In these animals the effects of experimental lesions of the hypothalamus and adjacent parts of the brain on the regulation of sleep were observed. The choice of the rat as an experimental animal was forced upon us by war conditions and more especially by the impossibility of feeding larger animals during a sufficiently long period. Because of its small size, it was certainly not the most suitable animal for our purpose.

The various functions of the hypothalamus have hitherto chiefly been investigated either by the method of electrical stimulation or by causing extensive destruction of this part of the brain. Much of our knowledge concerning the lower parts of the brainstem has been obtained by a different method, *viz., the infliction of sharply incised wounds*, and it is a striking fact that this procedure has scarcely ever been used in the study of hypothalamic functions. It has been followed only in the research of descending hypothalamic connections by Beattie, Brow and Long (3), and, more recently, by Magoun, Ranson and Hetherington (31). The method was considered a desirable addition to those procedures by which gross lesions of nervous tissues are brought about. It is probably the most suitable method for the tracing of pathways involved in the function under consideration, the damage to the brain being chiefly confined to interruption of fibre connections.

Unfortunately, however, it is still an open question whether the results of any destruction of brain tissue should be attributed to the exclusion of the destroyed or isolated area or to irritation of adjacent parts. Both conceptions can be and have been defended. The fact that many results of lesions of the central nervous system tend to subside in the course of time is often advanced in favour of irritation. It should be stressed, however, that the remarkable recuperative power which is exhibited by autonomic functions after lesion of the brainstem or spinal cord should in all probability be ascribed either to compensatory activity of those centres which subserve the same functions on a lower level ("automatisme étagé") or to the formation of new centres in adjacent regions. As far as the hypothalamus is concerned, there is another reason to doubt the irritative nature of incised wounds. Whereas unilateral electrical stimulation of this part of the brain is sufficient to cause widespread effects, which are eventually markedly bilateral (*e.g.*, pupillary dilatation), incisions in the hypothalmus proved to be effective in our experiments only when bilateral. The sole stimulatory effect observed was a bilateral pupillary dilatation which occurred regularly during the unilateral introduction of the cutting instrument in the posterior part of the hypothalamus, and persisted for a few minutes after it had been withdrawn. Since the pupillary dilatation would, from various observations (38), seem to be a very constant reaction to hypothalamic stimulation, we could not escape the impression that the irritative action of an incision in the hypothalamus, if it exists, is of short duration. All postoperative effects were therefore interpreted as the results of exclusion of certain parts of the brain and not to irritation of the area surrounding the lesion.

For operative purposes the hypothalamus can be reached in several ways, the most usual of which are the subtemporal and the parapharyngeal approaches. Because of the bilaterality of the lesions which are required to obtain disturbances in the regulation of sleep, the subtemporal approach was unsuitable for our purpose. The parapharyngeal method, by which the hypothalamus is reached through the base of the skull, was greatly interfered with by the flat, expanded hypophysis and its encircling blood vessels. In the experiments described in the following paragraphs, transverse lesions of the hypothalamus were inflicted via perforation of the convexity of the brain. Naturally this primitive method, apart from the important advantage of a better general postoperative condition, has a number of disadvantages, the most important of which is the fact that it gives rise to considerable damage to structures which are situated dorsal to the hypothalamus. In fact, this damage is such that the incisions, instead of being restricted to the hypothalamus, extend throughout the dorsoventral diameter of the brain, so that many sagittal fibre connections in neocortex, archicortex and thalamus are interrupted as well as the longitudinal systems of fibres within the hypothalamus. The objection that many postoperative symptoms might be the result of this additional damage is therefore not unreasonable. Consequently, a number of controls was needed to decide whether or not the structures overlying the hypothalamus are involved in the regulation of sleep. These experiments will now be described briefly.

Results

In a number of animals an incision was made in one of various frontal planes between the anterior and posterior commissures, measuring from 2½ mm. on the right to 2½ mm. on the left side of the median plane, and not extending beyond the ventral border of the thalamus. These wounds corresponded with the most serious accidental lesions encountered (Fig. 2). Animals treated in this way did not develop any disturbances of the sleep-waking rhythm; they rapidly recovered from the operation. It is proved by this observation *that a normal alteration of wake and sleep is kept up so long as the transverse incisions leave the hypothalamus intact.* It does not, however, exclude the possibility that the relevant dorsal structures play some part in the regulation of sleep.

In another group of animals identical lesions were made, but on one side the incision was prolonged to the base of the brain. Consequently only the opposite hypothalamus was left intact (Fig. 3). Although the postoperative

mortality among these animals exceeded that of the first group, most of the rats made a rapid recovery. None of them displayed any disorder of sleep. Obviously one intact hypothalamus is sufficient for maintenance of normal sleep rhythm. The reverse experiment was carried out on a third group of rats. In these animals a combination of bilateral section of the hypothalamus and unilateral section of the dorsal structures was obtained by the introduc-

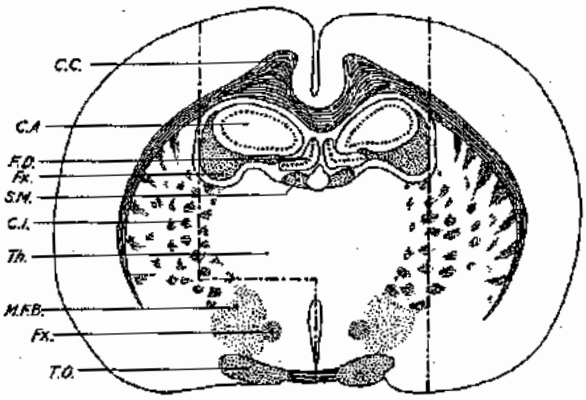

FIG. 2. Bilateral transection (indicated by interrupted lines) of the structures overlying the hypothalamus. C.A., cornu ammonis; C.C., corpus callosum; C.I., internal capsule; F.D., fascia dentata; Fx., fornix; M.F.B., medial forebrain bundle; Th., thalamus; T.O., optic tract.

tion with a "tour de maître" of a small hook-shaped knife, into the hypothalamus depicted in Figure 4. All animals treated in this way developed marked disturbances of the sleep-waking rhythm, which were identical

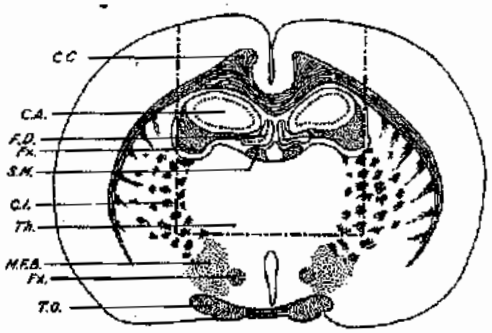

FIG. 3. Bilateral transection of dorsal structures and unilateral transection of hypothalamus. The lesion is indicated by interrupted lines. Abbreviations: see Fig. 2.

with those observed in cases in which bilateral lesions of the structures overlying the hypothalamus were inflicted.

From these observations it is evident *that the dorsal structures (neocortex, archicortex and thalamus) of one side are unable to keep up the normal regulation of sleep*. The disorders of sleep observed after transverse hypothalamic incisions from above may therefore safely be attributed to the lesions of the hypothalamus and not to the damage to more dorsally situated structures.

As to the operative technique, the operations were all carried out under ether anaesthesia and with aseptic precautions. After median incisions of the skin and periosteum,

the latter was pushed aside, and a uni- or bilateral trephine hole of about 4 mm. diameter was made just lateral to the median line, in order to avoid the superior longitudinal sinus. The dura mater was left in situ. In those cases in which the incision was intended to extend to one single lesion through both hypothalami, the small knife, depicted in Figure 4, was used so as to restrict the additional damage to one side. In cases in which it was essenital to leave a medial hypothalamic zone intact—in other words, to restrict the lesions to both lateral hypothalamic areas—two separate incisions were required, and consequently the additional damage to the dorsal structures was inflicted on both sides. In the foregoing

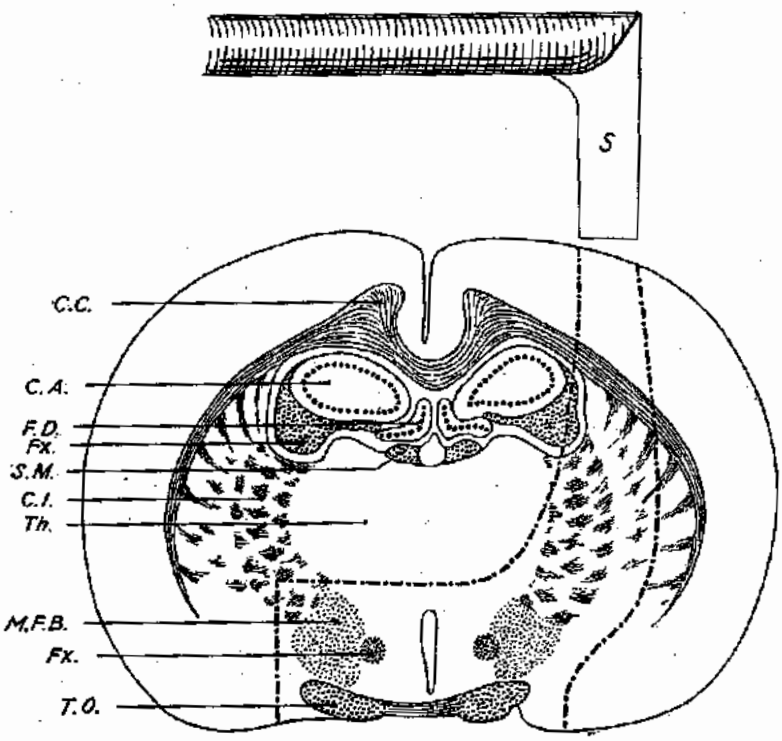

FIG. 4. Unilateral lesion to dorsal structures and bilateral transection of the hypothalamus (interrupted lines). The instrument with which the lesion was inflicted has been indicated with S. For abbreviations see Fig. 2.

account it has already been pointed out that these uni- or bilateral lesions to the structures overlying the hypothalamus had no apparent influence on the regulation of sleep.

After the lesions had been placed and the usual slight hemorrhage had stopped, the periosteum was stitched over the trephine holes and the skin was carefully closed. No dressing was applied. Throughout the operation 3 per cent hydrogen peroxide was used as an antiseptic. The anatomical investigation of the lesions was usually carried out after the animals had died from the results of the operation. When recovery took place the animal was sacrificed some time after the condition had become stationary. After their removal the brains were, as a rule, fixed in 96 per cent alcohol for three days and prepared according to one of Cajal's methods. Sagittal sections were found to be most suitable for the tracing of the transverse incisions. In the following account the disorders of sleep are grouped under two headings, *viz.*, disturbances of the waking capacity and those of the function of sleeping.

Disorders of waking

Certain bilateral lesions of the hypothalamus were found to cause a decrease in the waking capacity. The extent of this decrease varied in different cases.

(i) *Eight animals slept uninterruptedly so long as they were not roused by external stimuli.* They lay curled up on one side, breathing regularly, and could promptly be awakened by sufficiently strong stimuli, *i.e.*, by pinching the tail or handling. When they were left alone afterwards, they would *yawn and stretch* and settle down in a comfortable position to go to sleep again. To strong stimuli the animals reacted vigorously, exhibiting all signs of intense emotion. There were no motor disturbances. Apart from the apparent inability to maintain the waking state, the animals displayed other autonomic disorders, which is not surprising in view of the many regulatory functions of the hypothalamus. All sleeping animals developed a marked hypothermia, which often was such that a rectal temperature of 25°C. was found after a stay of 24 hours in an environmental temperature of 18°C. The condition of sleep evidently did not depend on this hypothermia, as it was not less conspicuous in animals which were kept in an incubator of about 30°C. and consequently had rectal temperatures ranging between 35° and 40°C. Details of the temperature regulation cannot be given as a continuous registration of the temperature was not carried out.

The general condition of all hypothermic animals rapidly deteriorated; they constantly contracted a purulent conjunctivitis and rhinitis. To avoid these undesirable complications it was necessary to nurse the animals in a hot box. Moreover, extra attention had to be paid to their feeding. As many of the operated rats, especially the sleeping animals, did not take any food or drink of their own accord, it was essential to feed them artificially. For this purpose about 5 cc. of lukewarm, diluted skimmed milk was administered by tube (a soft catheter with a diameter of two to three millimetres) three times a day. In spite of all these precautions the animals never survived the operation for a long period. Only once was it possible to keep a rat (no. 55) alive during eleven postoperative days, the other animals dying after four to eight days. In rat 55 after the eighth day there were short periods during which the animal no longer lay curled up in its characteristic sleeping attitude, but sat huddled up with half-opened eyes, without, however, showing any spontaneous activity. It is an open question whether or not the capacity of waking is capable of a complete recovery in these sleeping rats. The animals could not be kept alive long enough and even the period of eleven days was too short to allow of an answer. From the results of the experiments of Ingram, Barris and Ranson (27) on cats and those of Ranson (36) on monkeys, it would seem that the capacity of maintaining the waking state does not completely return in these animals after optimal lesions of the hypothalamus. It is, however, improbable that the lesions in these animals were equivalent to those in ours. Future work on animals, better suited to this purpose than the rat, will have to solve the problem whether the total

loss of the hypothalamic regulation of sleep can be as satisfactorily compensated as, for instance, the thermoregulation after exclusion of the hypothalamus.

(ii) Another group of animals, instead of developing a complete condition of sleep, exhibited various degrees of drowsiness. They were inactive, and during the first days sat huddled up all the time, with eyes shut to slits. Like the other animals these rats could be roused promptly. After a period which lasted from one to three days, the somnolence tended to decline gradually, but in these animals also the general condition rapidly deteriorated and death resulted within a week so that the waking capacity was never observed to restore itself completely. Only occasional periods were observed in which the animals were in a somewhat more active condition, the eyes, for instance, being opened wider. It is of interest that these drowsy rats were never found to be in a typical sleeping state. Their condition was intermediate between waking and sleeping whenever they were observed. Like the sleeping rats they often developed a hypothermia and purulent infections of the mucous membranes and did not show any tendency to take food or drink of their own accord so that they too had to be nursed with tube feeding and hot box.

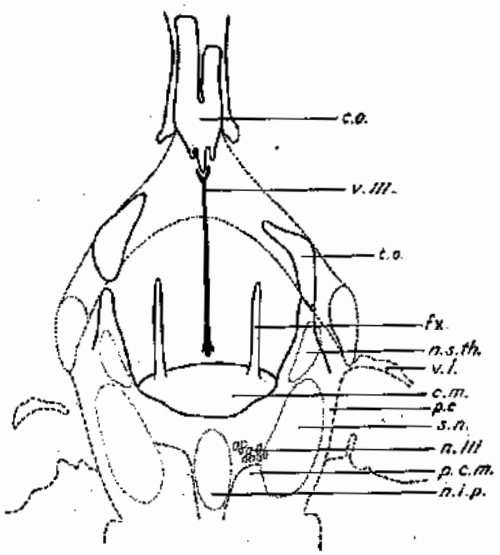

FIG. 5. Key figure to Tables 1–5. The diagram has been composed of two horizontal sections, of which one (solid lines) passes through the dorsal hump of the optic chiasma and through the mammillary bodies. The course of the optic tracts has been indicated by broken lines. The second section (outlines given in broken lines) lies on a more dorsal level and passes through the cerebral and mammillary peduncles (broken lines) and through the substantia nigra, the interpeduncular nucleus and the subthalamic nucleus, outlines of which are stippled. For Tables 1–5 only the basal section has been used. C.M., mammillary body; C.O., chiasma opticum; fx., fornix column; N.I.P., interpeduncular nucleus; N.S.Th., subthalamic nucleus (Luys); N.III, oculomotor nucleus; P.E., cerebral peduncle; P.C.M., mammillary peduncle; S.N., substantia nigra; T.O., optic tract; V.L., lateral ventricle; V.III, third ventricle.

(iii) In a third group of rats the operation failed to produce any disorder of the waking capacity; neither did most of these animals develop any other serious disturbances of the general condition. In order to facilitate a survey of our material we abstained from verbal description of each case. Instead the lesions which were found in every single case were recorded into a diagrammatic horizontal section of the hypothalamus (Fig. 5).

The diagrams obtained in this way have been collected in three tables,

viz., Table 1, on which the findings in the completely sleeping rats are depicted; Table 2, showing the cases of drowsiness in as much of a descending order of intensity as was practically possible; and Table 3, which contains those cases in which the operation did not affect the waking capacity. The following points concerning the figures are of special interest.

(a) In all cases of characteristic sleep (Table 1) bilateral lesions were found which ex-

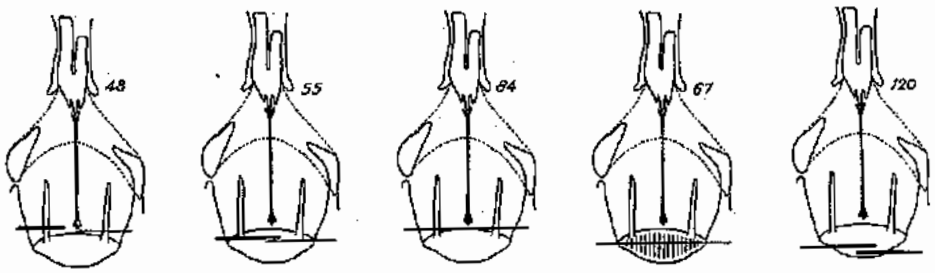

Table 1. Anatomical findings in five rats exhibiting a typical condition of sleep. For an explanation of the diagram, see Fig. 5.

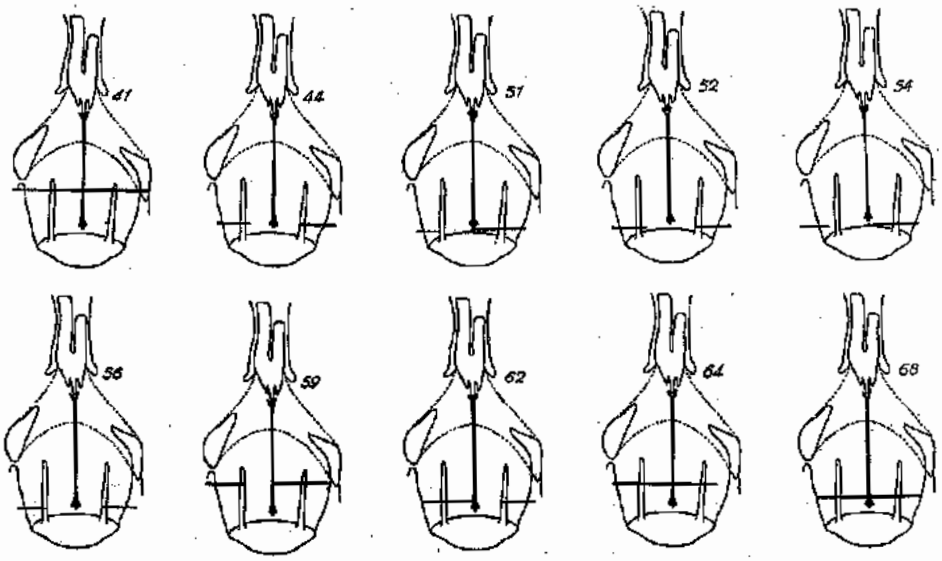

Table 2. Anatomical findings in ten cases of somnolence. See Fig. 5.

tended through the entire—or almost the entire (rat 48)—transverse diameter of both hypothalami. All these lesions were situated in the immediate vicinity of the mammillary bodies. In two of the animals the mammillary bodies themselves were involved in the lesions, in rat 67 these nuclear groups were largely destroyed by hemorrhage. In rats 48 and 84 the lesions were situated on the rostral border of the mammillary bodies; in three other cases, of which only rat 120 is shown, they were found slightly caudal to these cell-groups.

(b) Lesions of the mammillary region were also met with in some of the drowsy animals, collected in Table 2. These transections, however, differed from those found in the

first group in being *incomplete*. The region medial to the fornix column—comprising the periventricular and the medial hypothalamic areas according to Crosby and Woodburne (cited from 6)—had been left intact on both sides in rats 52 and 56, and on the left side in rat 51. In rat 54 the hypothalamic lesion on the left was confined to the lateral half of the lateral hypothalamic area, leaving the remainder of this area and both inner areas undamaged.

Yet this second group also contains a few cases in which a complete transection of both hypothalami was found. In these cases (rats 68 and 41), however, the lesion was situated farther rostrally than in the animals belonging to the first group. In rat 68, for instance, which was very drowsy, a complete transection of both hypothalami was found

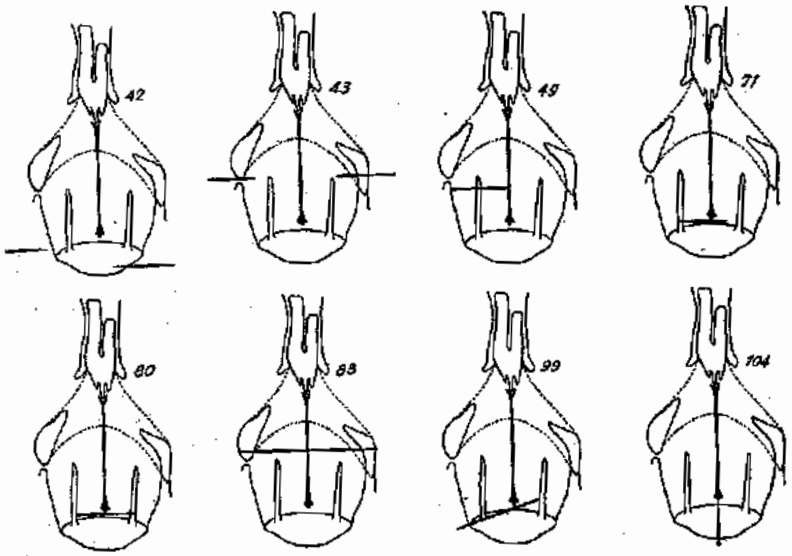

Table 3. Eight cases in which the operation failed to produce a decrease of the waking capacity. See Fig. 5.

about 1 mm. anterior to the mammillary bodies. Only a slight somnolence was displayed by rat 41; in this animal a complete bilateral lesion existed about 2 mm. in front of the mammillary bodies. As an identical lesion was found only 0.2 mm. farther ahead in rat 83 (Table 3) which showed no signs of somnolence, it would seem that the area in which hypothalamic lesions must be situated to cause a decrease in the capacity of waking has its rostral limit in a transverse plane about 2 mm. anterior to the mammillary bodies.

It has not been possible to ascertain the caudal limit of the area under consideration. The most posterior lesion which was found to disturb the waking capacity was situated slightly caudal to the mammillary bodies, *i.e.*, in the tegmental region. More caudal lesions resulted in a loss of consciousness which was too little reversible to enable us to make any statements concerning the regulation of sleep in these animals.

(c) The third group (Table 3), containing a number of animals without any apparent disturbance of the waking capacity, is distinguished from the previous groups in various respects. In some of the animals (rats 42 and 49) unilateral lesions of the hypothalamus were found to exist. It has already been pointed out that unilateral hypothalamic lesions, irrespective of their location, are unable to affect the regulation of sleep. Apparently the same holds good for bilateral lesions which are confined to the medial part of the hypothalamus, *viz.*, the zone medial to the fornic column. This is shown by rats 71 and 80, in which only the inner hypothalamic areas (the medial and the periventricular area) were damaged. It would seem to indicate that the medial part of the hypothalamus is of no special importance for the maintenance of the waking state. In the discussion of the second group it was mentioned, however, that the decrease of the waking capacity was less in

animals in which the lesions were limited to the lateral area of both hypothalami than in those in which, on the same level, the whole hypothalamus was bilaterally sectioned. This indicates that the inner hypothalamic areas do play a certain role in the maintenance of the waking state. We shall revert to this fact in one of the following sections.

The preponderance of the lateral area in the function of waking, already observed by Ranson (36) in monkeys, is clearly demonstrated by rat 99. No drowsiness was observed in this animal in spite of a transverse lesion in the mammillary region which was complete on the left and had been confined to the inner hypothalamic areas on the right. The lateral area of the right side was the only part of the hypothalamus intact, and it proved capable of maintaining the waking capacity. Evidently one lateral area of the hypothalamus is sufficient for maintaining this function. A lesion of exceptional location was encountered in rat 104. In this animal a median incision was found to exist, which reached the base of the brain between left and right mammillary body. Naturally it had severed the supramammillary commissure, which contains the crossing fibres of the hypothalamo-tegmental division of the medial forebrain bundle, in addition to crossing tegmental connections of the fornix column. The animal exhibited a slight drowsiness which entirely disappeared in the course of the first postoperative day. Incidentally, rat 83 was mentioned in the discussion of the second group. The complete bilateral transection of the hypothalamus, found in this case, was apparently situated too far rostrally to interfere with the waking capacity. It will again be reverted to in one of the next sections. A number of supplementary experiments have not been inserted in Table 3. In four rats extensive destructions of both thalami were brought about without causing the animals to show any decrease of the waking capacity. This does not harmonize with the findings of Spiegel and Inaba (43), mentioned in the introduction, and it offers confirmation of Ranson's observations (36).

In addition it should be stressed that bilateral transverse incisions on a level with the mammillary bodies only caused disorders of the function of waking if they involved the basal part of the brainstem, as, for instance, was the case in rat 120 (Table 1). If not extending ventrally beyond the central grey substance around the Sylvian aqueduct, these lesions, intermediate between diencephalon and mesencephalon, fail to interfere with the waking capacity. On this point our findings are in line with the results of Ingram, Barris and Ranson (27). From their experiments, in which somnolence was produced in cats by small bilateral lesions in the basal part of the tegmental area adjacent to the mammillary bodies, we may conclude that the function of waking, as far as it is performed by the midbrain, is localised in the basal part of this structure, *i.e.*, the tegmentum. The conclusions arrived at in the previous account indicate a specific importance of a certain area of the brainstem for the maintenance of the waking state. Certain lesions of this area cause a total loss of this function. In view of the arguments, advanced in the discussion of the operative method pursued in this study, we are inclined to consider this disorder to be a result of the exclusion of a certain centre, which therefore may be termed a waking centre.

Connections of the region of the waking centre

It was pointed out in the preceding section that the region formed by the posterior part of the hypothalamus and a hitherto undefined portion of the adjoining tegmentum mesencephali is likely to contain a waking centre. It is an important fact that the same region of the brainstem, according to the results of Beattie (2), Ranson, Kabat and Magoun (38) and others, is the site of the highest orthosympathetic centre. Its stimulation is followed

by a rise of blood pressure, an increase in rate and depth of respiration, pupillary dilatation, pilo-erection, etc., which give an appearance of intense emotional activity.

It has long been recognized that the autonomic balance lies relatively on the orthosympathetic side during the waking state and shifts to the parasympathetic side during sleep. If one combines this fact with the aforementioned results of stimulation, it does not seem impossible that there exists at least a partial identity between the waking centre and the orthosympathetic centre in the hypothalamus, and that the waking state is merely one of the manifestations of orthosympathetic activity. All orthosympathetic phenomena which result from stimulation of the hypothalamus can be brought about only by a descent of hypothalamic impulses to lower levels of the central orthosympathetic system, from where they are conducted along the peripheral orthosympathetic pathways to the various end-organs concerned.

Those somatic phenomena which indicate the shift to the orthosympathetic side during the waking state are certainly effected along this way. The most striking difference between wake and sleep, however, lies in the degree of consciousness. The question lies near at hand—if perhaps the increase of consciousness caused by the activity of the waking centre is brought about by a conduction of impulses via the same lower centres and the same peripheral pathways to the cerebral cortex. Moreover, there is still another possibility for the hypothalamus to stimulate the cerebral cortex, as stimulation of the hypothalamus brings about a production of adrenalin by the suprarenal gland, which tends to raise the level of consciousness.

Experimental evidence, however, seems to indicate that the peripheral autonomic system is not involved in the maintenance of the waking state. The observations of Cannon and his associates on cats in which practically the entire peripheral sympathetic system, including the medulla of both suprarenals, had been removed (8), have proved that under these circumstances a fairly normal condition can be kept up, so long as the exigencies of the outer world are held within certain limits. They apparently did not observe any change of the sleep-waking rhythm in sympathectomized animals. These facts render it highly probable that the waking centre does not affect the cerebral cortex along peripheral pathways but influences cerebral functions along central corticopetal connections.

At this point the question arises as to what ascending connections may account for the action of the waking centre on the cerebral cortex. As no data concerning this problem could be found in literature, we decided to study the fibre degeneration following lesion of the area in which the waking centre is probably located. For this purpose the mammillary area of the right side was sharply cut across in rat 66. The operation was carried out in the usual way, the wound extending from the dorsal surface to the base of the brain, and consequently the structures overlying the hypothalamus were also damaged.

As could be expected in view of the unilaterality of the lesion, the animal did not develop any disorder of the sleeping rhythm. It made a rapid recovery, and was killed ten days after the operation. Its brain was treated according to the prescription given for the Marchi technique by Romeis (40), and was embedded in paraffin via the graded alcohols and cedar oil, after which it was serially sectioned in the sagittal plane.

On miscroscopic investigation the location of the lesion was found to be as follows. The dorsal surface of the brainstem was reached at the habenula; after traversing this ganglion the instrument had apparently followed the rostral side of the habenulo-peduncular tract for some distance, but on a more ventral level the wound diverged from this bundle in a rostral direction so that it reached the base of the brain through the caudal one-third of the mammillary body (Fig. 6). In a transverse direction it extended from about 0.2 mm. to so far outside the median plane that it had severed the most medial fibres of the cerebral peduncle as its lateral end. Consequently, the whole transverse diameter of the hypothalamus had been cut, with the exception of a narrow medial zone of about 200μ in width. As a result of this lesion a large part of the fibre connections between the hypothalamus and lower parts of the nervous system had been interrupted. Only those fibres running in the undamaged paramedian zone and including the medial part of the periventricular fibre system of Schütz had been left intact.

As could be anticipated in view of the damage to the mammillary body, degeneration was found in some of the fibre systems connected with this cell group. Vicq d'Azyr's

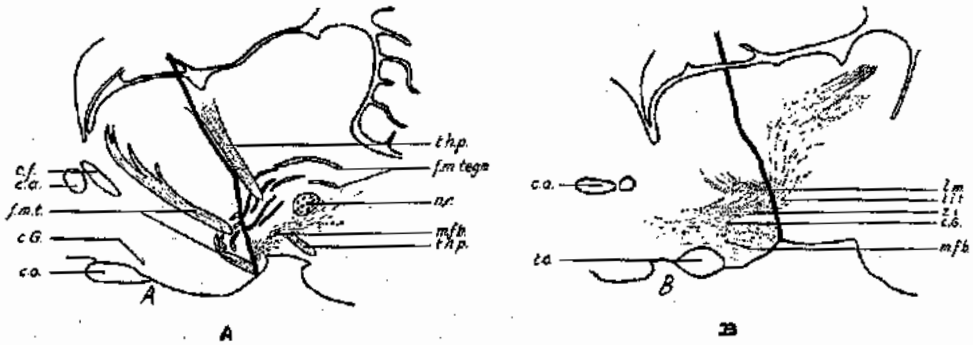

FIG. 6. Sagittal sections through the brain stem of rat 66, Marchi method, ten days after operation. Section A is situated 0.6 mm., section B 1.5 mm., lateral to the median plane. The lesion is indicated with a thick line. Descending (A) and ascending (B) degeneration of the medial forebrain bundle. c.a., anterior commissure; c.f., fornix column; c.G., Ganser's commissure; c.o., optic chiasma; f.m.t., bundle of Vicq d'Azyr; f.m.tegm., mammillo-tegmental fascicle; l.m., lemniscus medialis; m.f.b., medial forebrain bundle; n.r., red nucleus; t.h.p., habenulo-peduncular tract; t.i.t., incerto-tegmental fibres; z.i., zona incerta.

mammillo-tegmental tract was heavily degenerated. Some degeneration was also found in the mammillary peduncle, indicating the occurrence of mammillo-fugal fibres in this bundle, which conflicts with Papez' conception that the system is entirely mammillopetal in nature (34).

Dorsolateral to the mammillary body, in the space between this cell group and the substantia nigra, the lateral hypothalamic area continues into the midbrain tegmentum. Many fibres belonging to this hypothalamic area, chiefly constituents of the so-called medial forebrain bundle, run through this space and connect with tegmental centres. Presumably these fibres, originating in di- and telencephalon, form the first link of a much interrupted pathway to bulbar and spinal autonomic centres. Magoun, Ranson and Hetherington (31) have offered proof that these connections are not arranged into circumscribed bundles in the midbrain but are distributed over almost the entire cross section of its tegmentum. Previously Beattie, Brow and Long (3), working with the Marchi technique, had claimed that the chief descending connections of the hypothalamus course in or near the central grey substance surrounding the Sylvian aqueduct, a position which conforms to that of the periventricular system of Schütz. Probably Beattie *et al.* observed degeneration of this system which connects with the inner part of the hypothalamus, *viz.*, with the periventricular and medial areas. This is in line with the fact that the transverse cut which they inflicted to the hypothalamus was confined to these areas and did not in-

volve the lateral area. They consequently did not observe degeneration of the fibres descending from the lateral hypothalamic area, which are more numerous than those of Schütz's system and, from the results of Magoun, Ranson and Hetherington, would seem to be the chief transmitters of orthosympathetic impulses from the hypothalamus. In our experiment these fibres had been interrupted. By virtue of their degeneration a large number of them could be traced in a caudal direction. Figure 6A shows a rather condensed group of these degenerated fibres, running underneath the red nucleus and radiating in a dorsocaudal direction into the tegmentum. A considerable number, not shown in Figure 6, spreads over more ventral levels of the tegmentum. None of these fibres could be traced into parts lower than the midbrain. A fair number of degenerated fibres ran from the hypothalamus through the supramammillary decussation into the opposite side of the midbrain.

In accordance with the observation of Beattie, Brow and Long (3), a number of osmophilic granules was found in the dorsal longitudinal bundle, *i.e.*, the caudal continuation of the periventricular hypothalamic system of Schütz. As only the lateral part of this system had been damaged, it also contained many normal fibres. Apart from this descending degeneration, a number of degenerated periventricular fibres could be traced in a rostral direction. This proves the occurrence of hypothalamopetal fibres in the system of Schütz, which therefore should not be regarded as completely efferent with regard to the hypothalamus. Identical findings were reported in the opossum by Bodian (7).

A much more extensive ascending degeneration was found in the lateral hypothalamic area. From the lesion a great number of degenerated fibres could be traced rostralward, chiefly occupying the lateral part of the lateral area and obviously belonging to the medial forebrain bundle. On passing forward through the lateral hypothalamic area their number continuously decreased, which suggests a distribution of this ascending system in the hypothalamus. Only a few of the fibres were found to extend farther rostralward, into the septal region, and none could be traced to still higher levels. This ascending system in the medial forebrain bundle conceivably originates in the mammillary region, and farther caudally, in the midbrain tegmentum.[1]

By way of summary we are able to state that our Marchi experiment seems to prove the existence of ascending fibres in several bundles connected with the mammillary body and its adjoining structures, *viz.*, in the mammillo-thalamic bundle of Vicq d'Azyr and in the medial forebrain bundle. The degeneration found in the fornix column cannot give any information concerning the direction in which the fibres of this bundle lead, because both of its terminations—the hippocampal formation and the mammillary body—had been damaged.

In his careful study of the diencephalon of the opossum Bodian (7) did not observe any mammillopetal degeneration in Vicq d'Azyr's fascicle after lesion of this bundle. In contrast to Le Gros Clark and Boggon (9), he concluded that this system is entirely efferent with regard to the mammillary body, a conclusion which seems to be substantiated by Droogleever Fortuyn (15), who in a developmental study of the thalamus observed an outgrowth of fibres only from the mammillary body towards the thalamus and not in the opposite direction. The occurrence of hypothalamo- and septopetal fibres in the medial forebrain bundle has so far not been described.

[1] Although it has no apparent bearing on our problem, it is interesting to note that degeneration was found in Ganser's commissure. Fibres of this heavily myelinated system were found to pass rostralwards through Forel's field, whence they curved downwards to cross underneath the third ventricle to the left lentiform nucleus. This finding is in accordance with the recent observation of Glees (19) that Ganser's commissure contains fibres connecting the medial fillet with the opposite globus pallidus.

In conclusion it seems probable that the region in which lesions must be situated to cause a maximal loss of the waking capacity has efferent connections with the anterior nuclei of the thalamus, the lateral hypothalamic area and the septal region.

The next step to take is to decide which of these connections may transmit the impulses from the waking centre to the cortex. None of the aforenamed ascending connections can be traced to the cortex itself. If a corticopetal system originates in the waking centre, it must be supposed to relay in the thalamus, hypothalamus or septum—perhaps in two or all of these structures. It has been pointed out that destruction of the thalamus, despite the conceptions of Trömner and of Spiegel and Inaba and others, is not followed by any decrease of the waking capacity. Bilateral lesions of the septum also fail to bring about alterations of the sleep-waking rhythm, as is shown by rat 114 (Table 5). Moreover, in one rat, which did not show any tendency to somnolence, autopsy revealed a large abscess, which had destroyed the septal region and the anterior half of the thalamus on both sides. Naturally these observations do not exclude the possibility that the septum and the thalamus do play a certain role in the corticopetal transmission of stimuli from the waking centre. At most it proves that these structures are not the only relaying centres involved in this function.

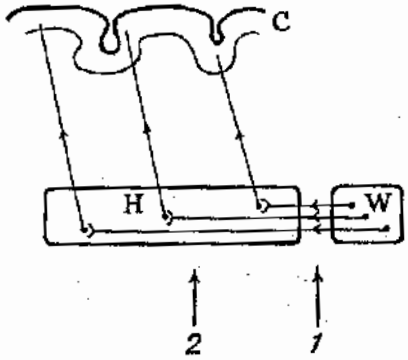

FIG. 7. Diagrammatic representation of the influence of the waking centre on the cortex, as suggested in the text. C., cerebral cortex; H., lateral hypothalamic area; W., waking centre.

It seems reasonable to accept an intensive relay of impulses from the waking centre in the lateral hypothalamic area. The majority of the ascending fibres in the medial forebrain bundle ends here, and it is striking that the degree of somnolence is more or less proportional to the extent to which these ascending fibres have been interrupted, the most effective lesions being situated in the caudalmost part of the hypothalamus and involving its lateral area in which the fibres are contained. If the lateral area of one or both sides partly or completely escapes injury, somnolence is either slight or lacking (cases 64, Table 2; and 43, 80, 99, Table 3). Moreover, the number of ascending fibres severed naturally becomes smaller with more forward localisation of the lesions, and as was pointed out in one of the foregoing sections, the effect of the lesions decreases accordingly. (Cf. Table 1 with cases 68 and 41; Table 2.)

From the fact that a maximal loss of the waking capacity is as well brought about by lesions just in front of the mammillary body as by those closely behind it, it seems probable that the waking centre itself lies in the region caudal to the mammillary body, *viz.*, in the midbrain tegmentum.

We are inclined to suppose that it gives origin to a number of fibres which ascend through the narrow space between mammillary body and substantia nigra which should in this part of their course be considered to be the initial common path of the "waking" stimuli. Rostral to the mammillary body the termination of this system in the hypothalamus—chiefly in the lateral area of this structure—begins, and some fibres even extend farther forward into the septal region, as is demonstrated by our Marchi experiment. Our results seem to indicate that the fibres under consideration synapse in the hypothalamus, whence their stimuli are led off by secondary neurons sideways towards the cerebral cortex. It should, however, be stressed that hypothalamocortical connections, as suggested here, have never been morphologically demonstrated, and that consequently no statements concerning the course of this hypothetic system can at present be made.

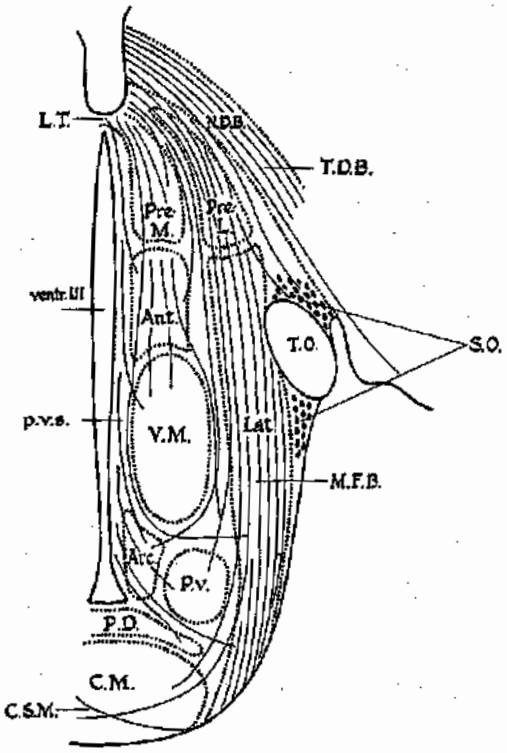

FIG. 8. A diagram of the longitudinal fibre systems in the hypothalamus, as seen in a horizontal section. Note the exchange of fibres between the lateral and the periventricular areas in the premammillary region. Ant., nucleus anterior; Arc., nucleus arcuatus; C.M., corpus mammillare; C.S.M., commissura supramammillaris; Lat., nucleus lateralis; L.T., lamina terminalis; M.F.B., medial forebrain bundle; N.D.B., nucleus of diagonal band; P.D., nucleus praemammillaris dorsalis; Pre.M., nucleus praeopticus medialis; Pre.L., nucleus praeopticus lateralis; P.v., nucleus praemammillaris ventralis; p.v.s., periventricular fibres; S.O., nucleus supraopticus; T.O., tractus opticus; T.D.B., diagonal band of Broca; ventr.III, third ventricle; V.M., nucleus ventromedialis.

Our concept is illustrated by Figure 7, which offers an explanation of the fact that a transection on a level with the mammillary bodies (arrow 1), interrupting the "initial common path," results in greater loss of waking capacity than a similar lesion in a more rostral plane (arrow 2). With more forward location of the lesion a larger number of fibres from the waking centre escapes injury. Finally, at about 2 mm. rostral to the mammillary bodies, their number already ended is sufficient to maintain a normal waking capacity, as is suggested by the absence of somnolence after transections on more rostral levels.

It has already been mentioned in the preceding section that the inner

part of the hypothalamus, although certainly of much less importance for the waking capacity than the lateral area, does seem to play a certain role in this function. Presumably a small number of fibres from the waking centre course in this part, which is formed by the periventricular and medial areas. It is true that no degeneration was found in these areas in rat 66, but it is possible that the fibres under consideration are unmyelinated. There certainly exists an extensive exchange of fibres between the lateral and the two inner areas, especially (Fig. 8) in the region just in front of the mammillary body, and it is possible that a number of ascending fibres deviate from the lateral area to continue their course in more medial parts of the hypothalamus. Possibly these fibres account for what remains of the waking capacity after lesions restricted to the lateral area.

Sleeplessness

In comparison to the vast clinical and experimental literature concerning somnolence, astonishingly little is known about the opposite phenomenon: sleeplessness. It seems that only von Economo (11) has dealt with this subject in extenso. According to his observations inflammation of a rostral part of the hypothalamus, adjacent to the striate body, may result in insomnia. It would thus seem that the exclusion of the relevant hypothalamic area interferes with the function of sleep.

As far as we know, the only experimentally founded conception of insomnia is that of Ranson and Magoun (39) who in the course of many experiments on cats and monkeys never observed any influence of hypothalamic lesions on the capacity of sleeping. Their opinion about the regulating mechanism is sufficiently illustrated by the statement quoted in our introduction, from which it is evident that they deny the existence of a centre subserving the function of sleep in a restricted sense.

In the course of our own experiments we arrived at a different opinion.

(a) In a number of rats the lesion of the hypothalamus was followed by a condition of sleeplessness. After regaining consciousness some of these animals were restless and irritable, reacting vigorously to minor stimuli. Their condition closely resembled the sham rage observed by Fulton and Ingraham (16) in cats after prechiasmatic lesions, and described by Bard (1) as a result of decerebrations through the rostral part of the diencephalon. In a number of operated rats no such change of character was observed, the animals remaining as quiet as before the operation.

In both groups the normal alternation of wake and sleep had completely vanished. Naturally this fact could only be ascertained by means of a continuous observation of the animals. The normal difference in activity between day and night—established for the rat by Szymanski (44) who in a space of 24 hours registered an average of 14 hours of sleep, distributed over 10 periods, which were longer and more frequent during the day than during the night—was in this way found to have disappeared completely, the rats being awake whenever they were observed. The animals showed a normal interest in their environment. Their general condition was excellent at first and they spontaneously took food and drink. Soon, however, their state deteriorated, which is not surprising considering the large amount of sleep to which the rat is accustomed. After a period of 24 hours the sleepless rats usually began to show symptoms of fatigue. They did not eat or drink of their own accord and their interest in the surroundings decreased. Symptoms of sham rage, if present, persisted. In spite of the fatigue and even of the succeeding exhaustion, during which the gait became unsteady, sleep was not forthcoming, the opened eyes and the spontaneous

activity proving that the animals were awake. After a period averaging three days the exhausted animals fell into a state of coma which soon ended in death. A return of the sleeping capacity was never observed in any of the animals.

We did not observe hypothermia in sleepless rats, nor did these animals develop purulent infections of mucous membranes. In a previous section we incidentally mentioned the disappearance of characteristic periods of sleep in drowsy animals. In these cases both the waking and the sleeping capacity seemed to have been disturbed by lesions, situated in the hypothalamic region between the mammillary bodies and a transverse plane about two

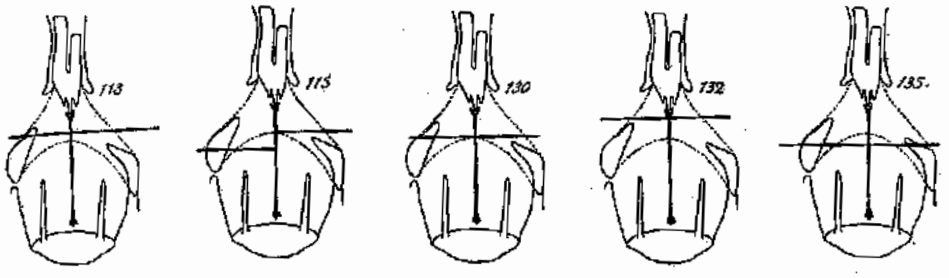

Table 4. Anatomical findings in five rats exhibiting sleeplessness. See Fig. 5.

millimetres in front of these cell groups. The animals referred to in this section, however, showed a loss of the sleeping capacity which was not complicated by any apparent disturbance of the function of waking. In all these cases of uncomplicated asomnia the lesions were found to be situated in the rostral half of the hypothalamus, in contrast to the cases

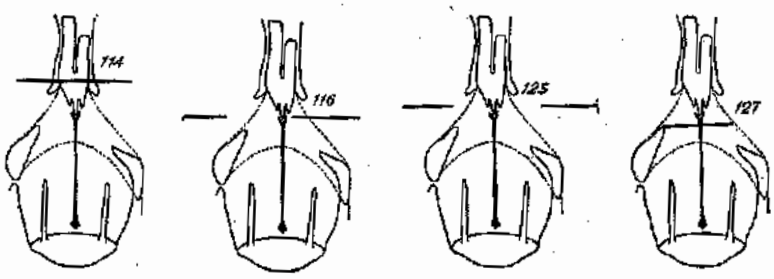

Table 5. Anatomical findings in four rats which did not develop sleeplessness. See Fig. 5.

of sleep or somnolence in which the lesions regularly occupied the caudal half of this part of the brainstem. The border between the two regions lies approximately 2 mm. in front of the mammillary bodies and roughly separates the infundibular and mammillary regions from the more rostrally situated suprachiasmatic and preoptic regions.

Here, also, a long series of verbal descriptions has been omitted. Instead a table is given (Table 4), in which the lesions found in each case are marked in a simple diagram. It will be noticed that in all cases complete bilateral transections were found on various levels in the rostral half of the hypothalamus.

(b) In a second group of animals lesions were found in approximately the same region of the brain. These rats, however, did not develop any apparent disturbance of the sleep-waking rhythm. Four cases of this group are given in Table 5. In one of the animals (rat 114) a transverse section was found in the septal region, slightly rostral to the lamina terminalis. In another rat (no. 125) the paramedian region of the brain, including both hypothalami, had been left intact, while in rat 116 only one of both hypothalami had been

cut across. The latter case indicates that the function of sleeping, like that of waking, can be sustained by one hypothalamus.

(c) We observed only one rat in which the operation resulted in a partial loss of the sleeping capacity. This animal (rat 149, Fig. 9) was sleepless during the first postoperative day, but after that time short periods of sleep occurred with highly irregular intervals. The animal's condition failed only slowly; it could be kept alive for nine days.

The lesions found in this rat are in a sense the reverse of those encountered in rat 127 (Table 5), in which the sleep-waking rhythm was not affected by the operation. Whereas in the latter animal only the medial part of the hypothalamus has been transected, the lesions had been confined to the lateral hypothalamic area in rat 149. Comparison of both cases indicates that the importance of the lateral area of the hypothalamus for the sleeping capacity exceeds that of the inner areas, the latter not being without any significance for this function. It will be noticed that a similar conclusion was reached with relation to the waking capacity. Evidently the rostral half of the hypothalamus, roughly conforming to the suprachiasmatic and preoptic areas, is the site of a nervous structure which is of specific importance for the capacity of sleeping. In the following sections this structure will be referred to as "sleep centre."

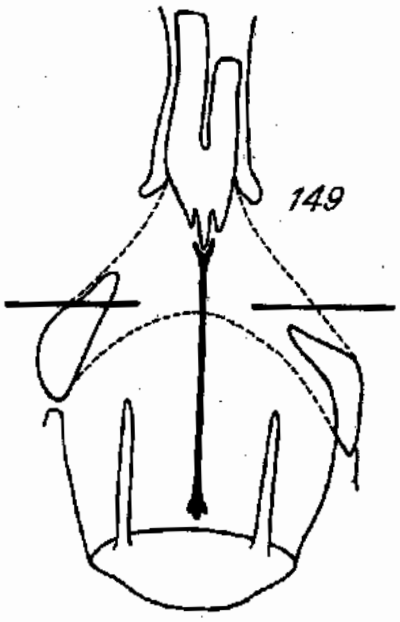

FIG. 9. Lesions in rat 149. Only the lateral area of the suprachiasmatic part of the hypothalamus has been interrupted on both sides.

This conclusion is in agreement with the conception of von Economo (11) who likewise postulated a rostral hypothalamic centre, to be regarded as the effector of sleep, as proved by the appearance of sleeplessness after its exclusion. In the contradictory opinion of Ranson and Magoun (39), this sleeplessness would not result from destruction of any part of the hypothalamus but from an irritating influence exerted by the inflammation on the adjacent waking centre. Our results, however, do not produce much evidence in support of the latter view. If the sharp transections which we inflicted to the hypothalamus really caused insomnia only by way of irritation of the waking centre, a unilateral lesion of the rostral part of the hypothalamus would already be sufficient to evoke this phenomenon because one hypothalamus is able to produce diffuse and eventually bilateral reactions on stimulation. As, on the contrary, unilateral lesions fail to cause any appreciable change in the alternation of wake and sleep, we are inclined to ascribe the insomnia to the exclusion of a certain function rather than to irritation of the waking centre.

Action of the sleep centre

The question which was discussed in a previous section with regard to the action of the waking centre also applies to the sleep centre: in what way does it act? For the time being we shall confine this problem to the cerebral manifestations of sleep.

The occurrence of somnolence after exclusion of the waking centre is open to two different interpretations. In the first place, it would seem possible that it results from an unopposed direct action of the sleep centre—the only part of the regulating apparatus left intact—on the cortex. As pointed out in the introduction, this theory was advanced by von Economo. Another possibility is an inhibitory action of the sleep centre on the waking centre, and in this case sleep would result from inactivity of the latter, a concept which fits into the theory of Ranson and his co-workers. If sleep is really brought about by an inhibitory action of the sleep centre on the cortex, the exclusion of this centre would tend to abolish or decrease the somnolence which follows on exclusion of the waking centre. If, on the other hand, this somnolence is essentially the result of the abolition of a certain stimulatory action exerted on the cortex by the waking centre, it would not be affected by exclusion of the sleep centre.

In the preceding sections evidence was presented that exclusion of the waking centre can be obtained by transection of the mammillary part of the hypothalamus, whereas the sleep centre seems to be put out of action by a similar lesion in the suprachiasmatic region. The above-mentioned problem can thus be put in a more practical way as follows: is the somnolence which follows on transection of the mammillary region affected by similar lesion in the suprachiasmatic region?

The experiment which can answer this question would seem to be a simple one. Unfortunately, however, all operations in which a suprachiasmatic lesion was inflicted to a rat previously made somnolent by operation ended in the animal's death during or shortly after the operation. It will be remembered that transections of the mammillary region are not, as a rule, survived for more than 4–8 days, and consequently the lapse of time between the two operations is of necessity too short to allow of sufficient recovery, which explains the unfavourable outcome of this experiment. We were therefore compelled to simplify our method, which could only be attained by performing both operations in one session. With this procedure transverse lesions were inflicted to the mammillary and to the suprachiasmatic region simultaneously. It is clear that the outcome of this experiment depended on the degree in which the somnolence resulted from active inhibition of the cortex by the sleep centre. If the additional suprachiasmatic lesion would fail to produce any differences between these rats and those in which only mammillary lesions were present, it would be plausible to exclude any direct action of the sleep centre on the cortex and other major parts of the nervous system. In this case the sleep centre might be supposed to exert its

depressing action on the cortex only via inhibition of the waking centre.

The results of some of our experiments will now be described. In rat 138 the operation resulted in a typical condition of sleep. After waking the animal, which was easily done by pinching its tail, it yawned and made stretching movements, and was soon asleep again. In all respects its behaviour resembled that of the animals shown in Table 1. This condition remained unaltered for seven days, after which the animal unexpectedly died. Autopsy revealed a complete transection of the hypothalamus on a level with the middle of the optic chiasma, and a similar lesion at the rostral border of the mammillary body (Fig. 10). It would appear from this experiment that a transection of the suprachiasmatic region, which in itself is able to cause sleeplessness, fails to interfere with the somnolence resulting from lesion of the mammillary region. Similar observations were made in rat 151, in which identical lesions were found.

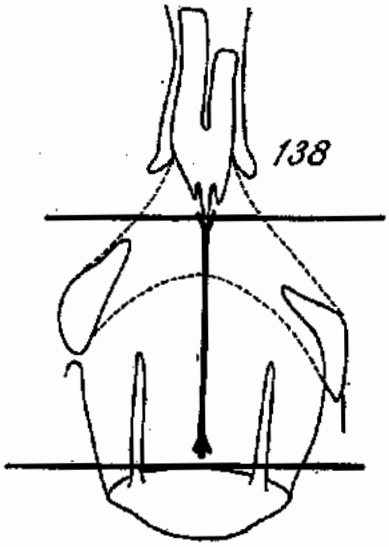

FIG. 10. Hypothalamic lesions in rat 138.

Rat 136. This animal did not develop a complete condition of sleep. Instead it exhibited a constant drowsiness, from which it could easily be roused and which persisted up to its death four days later. In this rat also transverse lesions were found, one in the suprachiasmatic and one in the mammillary region (Fig. 11). The latter lesion, however, was incomplete, leaving a small part of the right lateral hypothalamic area intact, and, as was mentioned in the discussion of the somnolent animals, incomplete transections of the mammillary region may cause drowsiness. The suprachiasmatic lesion had apparently failed to prevent this decrease of the waking capacity.

Rat 140. During the first two postoperative (days this animal displayed a heavy somnolence which in the following period of ten days gradually declined. On the thirteenth day after the operation the animal was completely awake. There were, however, no normal periods of sleep, so that a condition of sleeplessness developed which was comparable to that of the animals of Table 4, and which resulted in death two days later. Two complete transverse lesions of the hypothalamus were found on autopsy. One was situated in the suprachiasmatic region, the other lay about 1 mm. in front of the mammillary bodies (Fig. 12). This case is instructive in various respects. It has already been mentioned that a partial return of the capacity of waking was observed in most of the lethargic animals, but that this return was invariably interrupted by the animal's death. In rat 140, however, the period of survival was longer than usual and, for the first time in this experimental series, permitted us to observe a complete return of the capacity of maintaining the waking state. This observation seems to indicate that the function of waking may completely recover from the disorders which follow on lesions of the infundibular region. We do not see any essential difference between this case and those of the previously described group of somnolent rats, and we are disinclined to ascribe the complete return of its capacity of waking to factors other than its longer survival. In our opinion this case offers a confirmation of the conclusion suggested by our findings in rats 138, 151 and 136, *viz.*, that suprachiasmatic lesions are unable to prevent the results of lesions in the mammillary region. It seems that the results of exclusion of the sleep centre depend on the

condition of the waking centre, and that it causes sleeplessness only if the latter is intact. If the waking centre is simultaneously put out of action, no sleeplessness results; instead a condition of sleep develops. These facts seem to exclude any direct action of the sleep centre on the cortex and other major nervous structures. It is therefore highly probable that the sleep centre may cause sleep only by inhibition of the waking centre.

It is striking that the survival period of animals in which both transections had been made was longer than that of rats in which only a suprachiasmatic lesion was present. In the first case sleeplessness either does not develop at all, or (rat 140) does not immediately develop; in the second group it does. Apparently the vital importance of sleeping is such that even

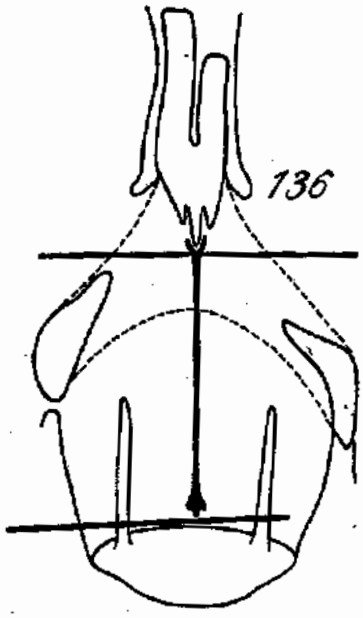

FIG. 11. Hypothalamic lesions in rat 136.

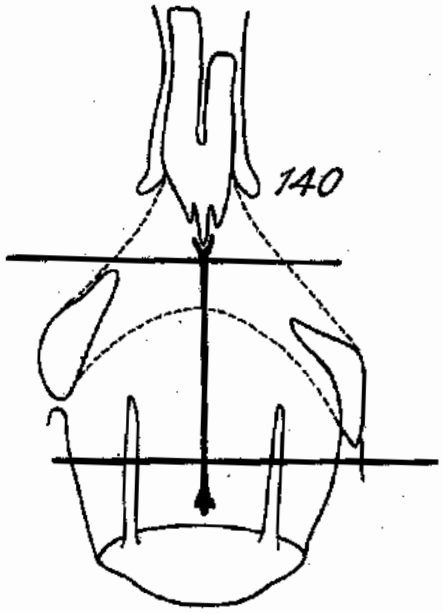

FIG. 12. Hypothalamic lesions in rat 140.

the gross suppression of sleeplessness by means of a second transection of the hypothalamus is able to prolong life.

A large number of fibres which are known to connect the suprachiasmatic with the mammillary region might account for the transmission of impulses from the sleep centre to the waking centre. It would seem from our experiments that these impulses are chiefly conducted through the lateral hypothalamic area, *i.e.*, through the medial forebrain bundle. In one of the preceding sections the possibility was discussed that the impulses from the waking centre are carried in the opposite direction by the same bundle. It thus seems possible that the medial forebrain bundle is serving a double purpose in the regulation of sleep. Our concept is illustrated by Figure 13 which takes into consideration the facts that (i) a transverse lesion on the

level of arrow 3 (the suprachiasmatic region) causes sleeplessness; (ii) that a similar lesion in the infundibular region (arrow 2) results in drowsiness combined with fewer periods of normal sleep; while (iii) a transection of the mammillary region (arrow 1) is followed by a complete loss of the capacity of maintaining the waking state, which masks the simultaneous exclusion of the sleep centre.

If Hess was right when claiming that a stimulation of the diencephalon with weak galvanic currents may cause sleep, it is possible that he observed the result of direct or indirect activation of the sleep centre. It should, however, again be stressed that it is not yet clear how Hess' findings should be interpreted.

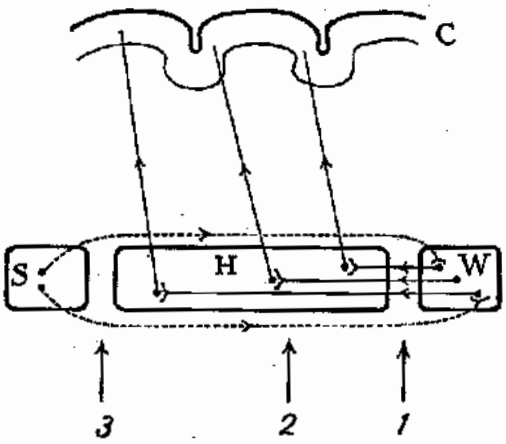

FIG. 13. Diagrammatic representation of the functional relationship between sleep centre and waking centre. Compare with Fig. 7. Fibres carrying "sleep stimuli" have been indicated by interrupted lines. C., cortex cerebri; H., lateral hypothalamic area; S., sleep centre; W., waking centre.

Lastly, von Economo's observation that an initial sleeplessness of patients suffering from epidemic encephalitis usually tends to decline and is gradually replaced by somnolence can be explained on the lines of our concept. Probably the sleeplessness results from inflammation of the sleep centre, and the transition to somnolence seems to indicate a spreading of the process to more caudal hypothalamic parts, finally involving the area of the waking centre. Here, as well as in our experiments, simultaneous exclusion of both centres would result in somnolence. As far as we know, a reverse development of the disease has never been recorded, and this seems to offer a support for our conception that it is the condition of the waking centre which, as far as the regulation of sleep is concerned, determines the manifestations of inflammatory processes of the hypothalamus.

Our point of view with regard to the difference in opinion between the schools of von Economo and Ranson may be summarized as follows. We agree with von Economo that a certain structure in the rostral part of the hypothalamus can be supposed to be of specific importance for the capacity of sleeping. We do not, however, as von Economo did, believe that this structure may cause sleep by active inhibition of the cortex and other parts of the brain. In this respect we fully agree with the American school that sleep results from functional exclusion of the waking centre. Whereas Ranson and his collaborators hold that periods of sleep are caused by more or less intrinsic periodic decreases in activity of the waking centre, we are in-

clined to attribute these decreases to the inhibitory influence of a sleep centre.

Hypothalamic localisation of ortho- and parasympathetic centres and their relation to sleep regulation

The localisation of the centres involved in the regulation of sleep suggests a certain antagonism between rostral and caudal part of the hypothalamus. It is interesting to note that certain analogies with the hypothalamic representation of other functions seem to exist. For this purpose we shall turn our attention to the part which is played by the hypothalamus in the regulation of the autonomic balance.

Nearly all investigations of this problem date from the last forty years. After Winkler's observation (47) that stimulation of the hypothalamus of cats gives rise to a production of sweat on the animal's footpads, Karplus and Kreidl (29) started an extensive investigation of the relation between "Gehirn und Sympathicus," which led them to the assumption of an orthosympathetic centre in the lateral hypothalamic area, close to the medial side of the subthalamic nucleus of Luys. In later years this conception received support from a number of investigators of whom Beattie *et al.* (2), Ectors (13), Crouch and Elliott (10), Morison and Rioch (33) and Ranson, Kabat and Magoun (39) should be mentioned. From the studies of Ranson and his co-workers it would appear that the orthosympathetic area is chiefly confined to the infundibular and mammillary regions. Stimulation of these areas generally results in a rise of blood pressure, an increase in rate and depth of respiration, and pupillary dilatation. The same symptoms appear on stimulation of points in the midbrain tegmentum, which suggests an extension of the sympathetic area into the mesencephalon.

Concerning the existence of a parasympathetic hypothalamic centre divergent opinions exist. Positive findings have been recorded by Beattie (2) and Beattie and Sheehan (4), who observed a number of parasympathetic phenomena on stimulation of the rostral part of the hypothalamus, *viz.*, augmentation of intestinal peristalsis, gastric secretion, decrease of heart rate and of blood pressure, and pupillary constriction. Like Ranson *et al.*, they were able to produce sympathetic symptoms by stimulating the caudal part of the hypothalamus. On the basis of these findings they divide the hypothalamus into a rostral parasympathetic and a caudal sympathetic part.

Later studies offered little confirmation of their concept. Ectors, Brookens and Gerard (14), and also Crouch and Elliott (10), were unable to evoke other than sympathetic phenomena from both parts of the hypothalamus. Morison and Rioch (33) observed a few parasympathetic phenomena only on stimulation of the rostral pole of the amygdaloid nucleus, the basal part of the septum and the lamina terminalis, *viz.*, a relaxation of the nictitating membrane and a decrease of blood pressure. They were led to the conclusion that these parts of the brain contain a mechanism for inhibition of sympathetic activity. In their admirable investigation of the problem, Ranson, Kabat and Magoun (38) observed some parasympathetic phenomena on stimulation of an area which, although it belongs to the surroundings of the third ventricle, is not regarded as a part of the hypothalamus

by Ranson, *i.e.*, the preoptic region. Stimulation of this area resulted in contraction of the bladder and in decrease of blood pressure and of rate and depth of respiration, but was never followed by miosis and intestinal peristalsis, as claimed by Beattie. The depressor reactions could also be elicited by stimulation of several parts of the medial hemispheric wall such as the septum and the genual gyrus. By their results Ranson *et al.* are led to the conclusion that the caudal hypothalamic region contains a complete sympathetic centre, but although some parasympathetic functions seem to be localised in the preoptic region and in adjacent parts of the medial wall of the hemisphere, they are disinclined to regard this area as a complete parasympathetic centre. They further accept the existence of a separate centre in the septal region for contraction of the bladder.

The appearance of parasympathetic phenomena on stimulation of the relevant hypothalamic area is open to two different interpretations. In the first place, one could imagine a conduction of its stimuli to lower parasympathetic centres and from there to the end-organs concerned. Although this mechanism may be involved, it is doubtful whether it offers sufficient explanation for the results of anterior hypothalamic stimulation. There would be little doubt if the parasympathetic picture were more or less complete, but, as pointed out above, intestinal peristalsis, for instance, is lacking. Apart from the contraction of the bladder which seems to have a separate representation in the endbrain, the main results of stimulation of the parasympathetic hypothalamic area are depressor in nature, and this suggests an inhibitory action on the sympathetic centre in the caudal hypothalamic region. It does not seem improbable that the parasympathetic area of the forebrain is essentially a regulator of sympathetic activity. It will be remembered that a similar view is held by Morison and Rioch.

When comparing this concept with that displayed in previous sections, a conspicuous analogy between the regulations of sleep and of autonomic balance is met with. In both functions the rostral part of the hypothalamus seems to exert a depressing action on the caudal part. By this striking congruity in hypothalamic representation one is led to ask what relation exists between the cyclic changes of activity and the autonomic balance. It has already been mentioned that the waking centre and the sympathetic hypothalamic centre are topographically related and perhaps even identical. Moreover, it has long been recognized that the transition from the waking to the sleeping state corresponds to a shift of the autonomic balance from the sympathetic to the parasympathetic side, while the process of awakening is accompanied by a counterchange of autonomic activity. Hess (22) even claims that sleep results from a preponderance of the parasympathetic system, and that the waking state is established by an increase of sympathetic activity. The enhancing influence of adrenalin and related drugs (benzedrine, etc.) on consciousness is in tune with his conception that the waking state is dominated by the sympathetic system, but although it is certain that the autonomic balance lies on the parasympathetic side during sleep, there is little reason to regard sleep as a result of parasympathetic preponderance, because those drugs which are able to imitate parasympathetic activity (acetylcholine and its relatives) fail to produce sleep. Ranson and Magoun (39) are therefore inclined to regard the preponderance of the parasympathetic system during sleep as a result of a decrease of sympathetic activity. This conception is in accordance with our observation that sleep results from inhibition of the caudal hypothalamic area, which contains the highest sympathetic centre.

By way of summary it seems possible to accept a certain topographical and functional congruity between the centres involved in the regulation of sleep and those subserving the regulation of the autonomic balance. Probably both functions are manifestations of one diencephalic mechanism. So far we have dealt only with cerebral symptoms of the cyclic changes of activity. All phenomena belonging to the somatic sphere have been omitted in order to avoid a premature complication of our display, all efforts to explain the somatic manifestations of sleep meeting with considerable difficulties.

It is highly probable that many functions of lower parts of the central nervous system are actively inhibited during sleep. According to Magnus

(17, 18), for instance, the maintenance of the recumbent position during sleep can be explained only by accepting an inhibition of the red nucleus. An important indication of active inhibition of lower centres was recorded by Tarchanow (cited from 35), who demonstrated that the normal inhibition of spinal reflexes during sleep was missing in the distal part of the spinal cord after complete transection in the thoracic region. Apparently the normal suppression of the spinal cord during sleep had been abolished for the segments below the level of the lesion. One is led to ask in which part of the central nervous system this inhibiting mechanism is localised.

According to Gamper (17, 18), no intrinsic changes in intensity are discernible in the decerebrate rigidity which appears after transection below the red nucleus. This would mean that the cyclic changes in muscle tone, which are characteristic of the sleep-waking rhythm, are abolished by decerebration. Gamper arrives at the following conclusion: "Wir können also in den Abschnitten des Zentralorgans, die distal vom Gebiete des roten Kerns liegen, keine den phasischen Ablauf der Lebensvorgänge regulierende Zentralstelle vermuten."

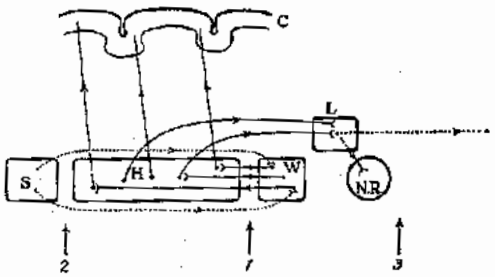

FIG. 14. Diagrammatic illustration of the mechanism of sleep, as proposed in text. C., cortex cerebri; H., lateral hypothalamic area; L., "centre for body sleep"; N.R., nucleus ruber; S., sleep centre; W., waking centre. Fibres conducting "waking" stimuli are indicated by solid lines; broken lines represent fibres involved in the production of sleep.

In a child in which the endbrain had not been developed, Gamper observed irregular periods of sleep. On autopsy the hypothalamus turned out to be poorly developed, but the transitional zone between fore- and mid-brain and the whole neural tube caudal to this region were fairly normal. From these facts Gamper concludes that the nervous apparatus for the regulation of sleep must be localised in the rostral part of the midbrain or in the hypothalamus.

It would seem reasonable to suppose that the inhibition of the lower parts of the brain during sleep is a function of the sleep centre in the rostral part of the hypothalamus. Many difficulties, however, arise on trying to answer the question as to along what ways its impulses descend. There is reason to believe that the influence of the sleep centre is not mediated to lower centres by one uninterrupted pathway, because certain lesions in a lower part of the brainstem, *viz.*, the mammillary region, instead of preventing all somatic manifestations of sleep, result in a typical condition of sleep. Clinical observations indicate that the regulating mechanisms of somatic and cerebral sleep are to a certain extent separate. It is, for instance, a well known fact that soldiers on a long march may finally show unmistakable symptoms of cerebral sleep while walking perfectly, which suggests a certain mutual independence of the centres for somatic and cerebral sleep. Cataplexy is per-

haps an opposite condition. Normally, however, both manifestations of sleep make a simultaneous appearance, which indicates the existence of a superior correlative mechanism. So long as exact data are lacking, no statements can be made concerning the pattern on which the complete phenomenon of sleep is effected. A mechanism which at present seems conceivable is diagrammatically illustrated by Figure 14. We have accepted the existence of a separate centre for somatic sleep (L), situated caudal to the waking centre and inhibited by it via the lateral hypothalamic area during the waking condition. Under normal conditions it would be able to exert its depressing influence only on lower centres (exemplified in our diagram by the red nucleus) after being freed from the action of the waking centre. As discussed in a previous section, this liberation may result from activity of the sleep centre S.

Our diagram offers an explanation of the facts: (i) that a transection slightly caudal to the sleep centre (arrow 2) causes sleeplessness; (ii) that a similar lesion on the level of arrow 1 (the mammillary region) gives rise to a complete condition of sleep; (iii) that transections below the level of the red nucleus (decerebration arrow 3) are followed by a condition in which all somatic symptoms of sleep are lacking.

No experimental data on dissociation of cerebral and somatic sleep can be found in literature. If our conception of a spatial separation of the sleep centre L from other parts of the regulating apparatus is correct, it would not seem impossible that certain lesions are able to produce isolated disturbances in the regulation of either cerebral or somatic sleep.

Discussion

In the foregoing account the expressions "waking centre" and "sleep centre" have been repeatedly used. In order to avoid misunderstanding it should be emphasized that the existence is uncertain of smaller or larger groups of specific cells subserving the regulation of sleep only. The function of each of the separate hypothalamic cell groups—with the exception of the supraoptic nucleus, of which the essential role in the regulation of the salt and water balance has been demonstrated by Fisher *et al.* and others—is still unknown. So long as more exact data are lacking, we are able to state only that some structure in the caudal half of the hypothalamus and in the adjacent part of the tegmentum mesencephali is of specific importance for the maintenance of the waking state, while the preoptic region is likely to contain a structure subserving the function of sleeping. For the sake of brevity these structures may be referred to as "waking centre" and "sleep centre" respectively, but these terms should not give the impression that anything more than what has been stated above can be said concerning them. For instance, the possibility that the regulation of sleep is only one of multiple functions of one single nervous apparatus cannot be excluded since there seems to exist a topographical identity between the hypothalamic regions involved in the regulation of sleep and those regulating the autonomic

balance. The current conception of "centres" has been criticised by Bethe (5), who, by the extreme plasticity of the nervous system of invertebrates and of the more centralized nervous system of higher animals, was led to reject the thought that nervous functions are carried out by specific centres. Nevertheless, one is forced to the conclusion that the nervous structures normally involved in the regulation of sleep occupy a small area, only lesions of a circumscript location being able to interfere with this regulation. Therefore, if the above restrictions are taken into consideration, the term "centre" would not seem to be inappropriate for indicating these structures.

In the experiments of Ranson *et al.*, as well as in ours, "plasticity" was observed in the function of maintaining the waking state. It is still uncertain whether such recoveries from injuries of nervous tissue must be ascribed to compensatory activity of secondary centres already involved in the function under consideration—a conception which is well illustrated by Ch. Foix's term "automatisme étagé" (45)— or to the formation of a new regulating apparatus in a part of the brain which has afferent and efferent connections similar to those of the destroyed area but is situated outside the shortest route in normal animals, or to some other compensating mechanism. It is a striking fact that no return of the capacity of sleeping could be observed in any of our sleepless rats, not even in rat 140 who survived for 13 days.

Cyclic changes in activity were observed in decorticated dogs by Goltz (20) and Rothmann (41), and by Gamper (17, 18) in an acerebral child. Although it is well known that cortical processes have an important influence on the sleep-waking rhythm, we are justified in denying the existence of a dominating autonomic cortical mechanism for the regulation of sleep. It should be stressed that in animals in which a maximal decrease of the waking capacity had been obtained a normal waking condition could still be evoked by sufficiently strong external stimuli. Only the capacity of *maintaining* this condition had apparently been lost. The concepts of sleep being caused by abolition of sensory stimuli seem to apply to these cases only. It is probable that the waking centre endows the cerebral cortex with a power of maintaining a certain functional "tone" in the absence of external stimuli, and that only sensory stimulation of sufficient strength is able to prevent the onset of sleep when the waking centre is reduced to inactivity.

It scarcely needs to be emphasized that our knowledge concerning the course of the impulses from the waking centre to the cerebral cortex is incomplete. If our concept of an ascending flow of these impulses through the medial forebrain bundle is correct, what connections may account for their further transmission is still obscure. It seems improbable that the thalamus is involved in this transmission to any important extent, which, in conjunction with von Economo's observations on the sensibility of his encephalitic patients, renders it highly probable that the waking centre does not essentially act via sensibility. Of what its influence consists is a question open to further investigation.

Our conception concerning the existence of a sleep centre is based solely

on the observation that no periods of sleep could be observed after complete transections in the suprachiasmatic region of the hypothalamus. Kabat, Anson, Magoun and Ranson (28), however, do not mention sleep among the results of stimulation of this region in waking cats, and Ranson *et al.* did not observe sleeplessness after its partial destruction (39). The disagreement between our findings and those of Ranson *et al.* may lie in the difference in techniques. It seems necessary to repeat our experiments in other animals in order to ascertain whether sleeplessness is a general result of anterior hypothalamic transection.

Summary

1. In the rat complete bilateral transection of the hypothalamus, irrespective of location, interferes with the normal regulation of sleep.

2. The location of lesions which cause disturbances of the function of waking indicates the existence of a structure in the caudal hypothalamic region and in the adjacent part of the midbrain tegmentum, which is of specific importance for the capacity of maintaining the waking state during the absence of external stimuli ("waking centre").

3. There is reason to accept a structure in the preoptic region, which is of specific importance for the capacity of sleeping ("sleep centre").

4. Evidence is offered that sleep is caused by an inhibitory action of the sleep centre on the waking centre.

5. The lateral hypothalamic area seems to be of more importance for the regulation of sleep and waking than the inner areas. It seems probable that the medial forebrain bundle, which occupies this area, is implicated in the transmission of impulses determining the sleep-waking rhythm.

6. The hypothalamic centres involved in the regulation of sleep are topographically identical with those determining the autonomic balance.

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BRAIN METABOLISM IN EMOTIONAL EXCITEMENT AND IN SLEEP

D. RICHTER AND R. M. C. DAWSON

From the Neuropsychiatric Research Centre, Whitchurch Hospital

CARDIFF, SOUTH WALES

EVIDENCE has been obtained that the metabolic activity of the brain is increased in convulsions, trauma, anoxia and shock. This is indicated by the rise in lactic acid and decrease in high-energy phosphorus compounds found in the brains of animals killed under these conditions. Conversely, there is a fall in the lactic acid in the brain and an increase in labile phosphate in animals killed under anesthesia (1–3). The present investigation was carried out to test if evidence could be found of similar biochemical changes in the brain in sleep and in emotional excitement under normal physiological conditions.

METHODS

Lactic acid estimations were carried out on the whole brains of young Wistar albino rats of 30 to 40 gm. The animals were killed by immersion in liquid air, which produced a rapid fixation of any biochemical changes in the tissues and limited the formation of lactic acid in the brain by post-mortem glycolysis.

Method of fixing with liquid air. Stone (1) found it took 2 to 3 seconds to freeze the brain of a mouse, but Le Page (3) found it took about 40 seconds to freeze completely with liquid air the abdominal organs of a 300-gm. rat. In view of the rapidity of post-mortem changes in the brain, the rate of freezing was reinvestigated with rats of the size used in the present work. Experiments with a calibrated thermocouple inserted into the cranial cavity of 35-gm. rats showed that the surface of the cortex fell to 0°C. in 4 to 5 seconds on immersion of the whole animal in liquid air. With the thermocouple in the deeper parts of the brain the temperature remained practically stationary at 37°C. until a sudden drop in temperature occurred, bringing it below 0°C. in 9, 20, 9 and 16 seconds in four consecutive experiments. While it clearly took several seconds for the wave of freezing to spread from the surface to the interior of the brain, it is unlikely that the circulation of the central parts of the brain stopped immediately or that true post-mortem changes occurred in the interior of the brain throughout the whole of this period. This view is supported by the work of Kerr (4), who found that satisfactory phosphagen figures can be obtained by applying liquid air to the skulls of young cats, in which the process of freezing the brain must take much longer. The observed lowering of the brain lactic acid in sleep, which was found in the present investigation, gave further evidence that post-mortem changes during the process of freezing were probably not extensive with the technique employed.

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In obtaining normal values the rats were transferred rapidly from their cages into the liquid air, as any delay in this procedure tended to frighten them and caused the brain lactic acid level to be raised. Killing by decapitation and subsequent freezing of the heads was found to be less satisfactory as it gave much higher lactic acid figures for normal animals: in three experiments the brain lactic acid figures obtained by this method were 43, 37 and 47 mg. per cent when the heads were transferred to liquid air in 2, 3, and 15 seconds respectively after decapitation. Kerr also found autolytic changes more marked after decapitation than when the brain was frozen in the whole animal. The reason may be that with the circulation cut off the brain rapidly becomes anoxic and glycolysis proceeds in the interior during the period of freezing through from the surface.

Lactic acid estimation. After careful dissection the frozen brains were powdered in a previously cooled crusher and the powder was transferred to weighed centrifuge tubes containing 4 ml. zinc sulphate solution at 0°C. as described by Blatherwick, *et al.* (5). The method of estimation was that of Friedemann, Cotonio and Shaffer (6), with the modifications and improvements introduced by Friedemann and Graeser (7), Edwards (8) and Stone (1). Although more laborious, this method was found to give more accurate and more reliable figures than the colorimetric methods of Miller and Muntz (9) and Barker and Summerson (10). The distillation apparatus was similar to that used by Stone (1), but made all in one piece and therefore containing no joints, tap-grease or rubber connections. Talc powder was found more satisfactory than glass beads to prevent bumping. The use of the copper hydroxide precipitation made the method very specific for lactic acid and recovery tests with a standard solution of recrystallized lithium lactate, which were repeated with each experimental series, gave recoveries within 3 per cent of the theoretical with quantities down to 0.1 mg. lactic acid.

RESULTS

Normal series. In a preliminary series of 10 normal rats taken in the resting state the brain lactic acid level ranged from 13.4 to 24.4 mg. per cent with a mean of 18.8 (table 1). This figure agreed with the mean of 18.9 mg. per cent for mouse brain found by Stone (1), who also found a wide range of individual values ranging from 1 to 23 mg. per cent.

Brain lactic acid in sleep. The animals comprising the normal series were mainly littermates of almost identical size and weight and in looking for an explanation for the wide individual variation in the brain lactic acid level, it was noted that lower values were generally given by animals which were dozing at the time when they were transferred to the liquid air, while higher values were obtained with animals which were wide awake. The investigation of the brain lactic acid in sleeping animals met with considerable difficulty until it was found that deep sleep could be induced by leaving the rats for a time in strong sunlight. Artificial sunlight was equally effective. Dozing animals opened their eyes at once when touched, but animals in deep natural sleep did not open their eyes or appear to wake up in the brief period of less than a second required to transfer them from their cages into liquid air. This was therefore taken as the criterion of sleep. A series of 6 rats taken in the sleeping state show-

less individual variation in the brain lactic acid and a mean level of 12.2 mg. per cent, which was considerably lower than that of the normal series. The difference was statistically significant ($P < 0.01$) when tested by Fisher's 't' test (table 2). The mean for sleeping animals approached the mean of 9.8 mg. per cent lactic acid found for a group of rats lightly anesthetized for a period of 8 to 30 minutes with nembutal.

TABLE 1. LACTIC ACID CONTENT OF BRAIN IN NORMAL RATS

RAT NO.	WT. OF RAT	LACTIC ACID	REMARKS
	gm.	*mg. %*	
1	36	16.2	Dozing
2	38	16.7	Dozing
3	40	20.1	Awake; resisted handling
4	48	17.9	Resting; slight movement
5	43	24.4	Quiet
6	31	22.6	Moving
7	31	22.3	Awake; resisted handling
8	25	15.5	Dozing
9	23	13.4	Quiet
10	40	19.1	Quiet; resisted handling
MEAN.....		18.8	

Recovery of lithium lactate standard 98%.

TABLE 2. LACTIC ACID CONTENT OF RAT BRAIN IN SLEEP AND IN ANESTHESIA

A. SLEEP		B. ANESTHESIA		
Rat no.	Lactic acid	Rat no.	Period of anesthesia	Lactic acid
	mg. %		*min.*	*mg. %*
1	12.3	7	8	13.2
2	10.3	8	8	7.7
3	11.9	9	15	8.0
4	10.8	10	15	4.8
5	13.9	11	30	15.4
6	14.1			
Mean.....	12.2			9.8

Recovery of lithium lactate standard 98%. Brain lactic acid in normal rat included in this series 17.5 mg. %. Period of sleep about 30 min. Anesthesia obtained by intraperitoneal injection of nembutal 50 mg/kg.

Effect of emotional excitement. Of the various methods of producing emotional excitement which were tried, the simplest was that of repeatedly removing their support by allowing them to drop from side to side in a glass beaker. There was a good deal of individual variation in their response to this treatment and some animals were less disturbed by it than others. Often there was a latent period of up to half a minute in which they showed little reaction, but finally they all gave objective evidence of fear, as by urinating, defecating and looking frightened. A few of them

made vigorous muscular movements and tried to jump out of the vessel, but more often they remained perfectly still and gave up trying to right themselves, so that little muscular exercise was involved. There was probably an element of anger as well as fear in their emotional state, for some of the rats were ready to bite when in this condition; but it may be doubted whether the emotional reactions of the rat can be accurately described in terms which are mainly applicable to man.

Estimations of the lactic acid content of the brains of rats taken after being frightened for 1½ to 4 minutes by the method described gave consistently higher values than those of normal littermate controls which were examined at the same time. In

TABLE 3. EFFECT OF EMOTIONAL EXCITEMENT AND EXERCISE ON THE LACTIC ACID CONTENT OF THE RAT BRAIN

A. FRIGHTENED		B. FRIGHTENED AFTER TUBOCURARINE		C. MUSCULAR EXERCISE	
Rat no.	Lactic acid	Rat no.	Lactic acid	Rat no.	Lactic acid
	mg. %		mg. %		mg. %
1	47.2	12	34.5	17	13.9
2	24.2	13	36.5	18	15.2
3	45.7	14	29.4	19	13.9
4	36.7	15	37.4	20	15.0
5	40.2	16	40.7	21	15.4
6	34.8			22	13.0
7	34.0				
8	23.7				
9	32.2				
10	50.3				
11	43.5				
Mean.....	37.5		35.5		14.4

a) Period of frightening 1½ to 4 min. *b*) Rats given tubocurarine and after about 5 min., when the muscles were relaxed, frightened for 2 to 3 min. The blood lactic acid in 3 rats decapitated after treating them in the same manner was 17.8, 22.8 and 18.8 mg.%. All blood samples were taken from the carotid artery after decapitation. *c*) Exercise was vigorous running for 4 min. Recovery of lithium lactate standard 99%.

the frightened animals the lactic acid content ranged from 24.2 to 50.3 mg. per cent with a mean level of 37.5 for a series of 11 animals. The difference was statistically significant ($P < 0.01$), (table 3).

Experiments in which the period of emotional excitement was varied showed that the rise in brain lactic acid in emotional excitement was a rapid process (fig. 1), which must correspond to a relatively high rate of metabolic activity in the brain. When the excitation was discontinued, the brain lactic acid soon came back to normal again and normal values were generally obtained within five minutes after discontinuing the stimulus. The rise in the brain lactic acid appeared to be a transient effect and there was a good deal of individual variation in the rate of rise and fall, as some animals were more easily frightened and remained frightened longer than others.

Effect of muscular exercise. As far as could be judged from simple observation the rise in brain lactic acid in the previous experiments corresponded closely with the

degree of emotional excitement and showed no relation to the muscular activity observed in a number of the animals; but since it is known that muscular exercise can cause a rise in the blood lactic acid level, the effect of muscular exercise on the brain lactic acid required careful investigation. The blood lactic acid level is 12 to 18 mg. per cent in the normal rat. In 3 rats taken after four minutes of emotional excitement the blood lactic acid was found to have risen to 52, 47 and 67 mg. per cent; but, assuming the blood content of the brain to be approximately 5 per cent, the blood

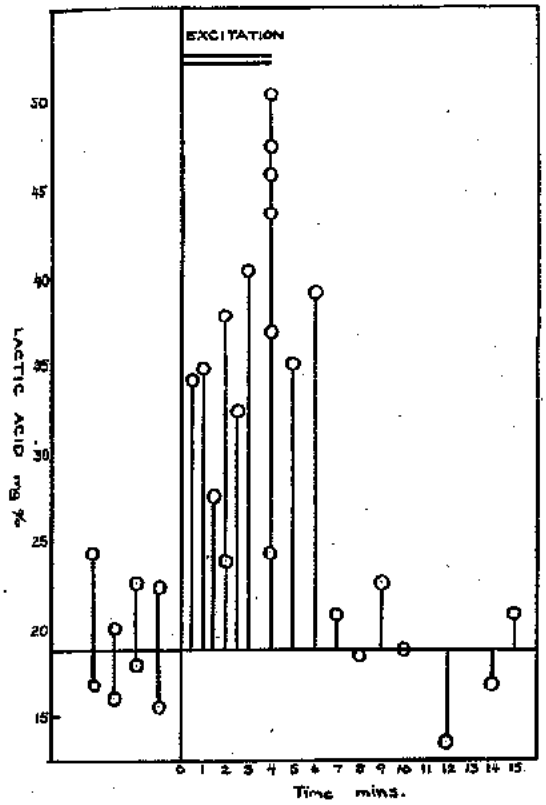

Fig. 1. Showing effect of emotional excitement on the brain lactic acid. The points on the left of the diagram are normal values, the horizontal line at 18.8 mg. % giving the normal mean. The points on the right of the diagram give lactic acid values for rats sacrificed at the times given on the time scale. The method of frightening was continued for 4 min., except for animals killed after a shorter period of frightening.

lactic acid could not nearly account for the mean level of 37.5 mg. per cent found in the brain. It was unlikely in any case that the brain lactic acid could have come from the blood, since the blood-brain barrier is relatively impervious to anions and it has been shown by Dameshek and Myerson (11) and by Stone (1) that lactic acid injected into the blood stream is not taken up significantly by the brain. This has recently been confirmed by Klein and Olsen (12), who showed in addition that the brain lactic acid is not increased by intravenous glucose, so that it was unlikely that emotional hyperglycemia had played any part. It was concluded that the brain lactic acid was formed in the brain and had not come from the blood.

The view that the rise in lactic acid in the brain in emotional excitement was not attributable to muscular activity was confirmed in a series of experiments in which

rats were excited after administering tubocurarine, so that muscular activity was practically abolished. The effective dose for this purpose was 0.1 ml. of a solution of 0.1 mg/ml. d-tubocurarine chloride per 40-gm. rat, given intraperitoneally. With this dose the respiration was not unduly embarrassed and the animals were not cyanosed, but muscular activity was greatly diminished. Emotional excitement produced the same rise in brain lactic acid in these animals, the figures ranging from 29.4 to 40.7 with a mean of 35.5 mg. per cent, although the blood lactic acid remained almost in the normal range (table 3). It therefore appeared that the rise in lactic acid in the brain in emotional excitement could not be attributed to the accompanying muscular activity.

In a series of further experiments designed to test directly the effect of muscular exercise alone on the brain lactic acid it was necessary to take special precautions to avoid emotional excitement, for it is hardly possible to induce untrained animals to take vigorous muscular exercise without exciting them. With this object in view a series of young rats weighing about 15 gm. were slowly conditioned to running for periods up to four minutes twice daily on an exercising wheel. After training in this way for eight days, by which time they weighed about 35 gm. they took their exercise without showing any signs of anxiety and indeed they appeared to enjoy it. Brain lactic acid estimations on a series of 6 trained rats after a period of four minutes vigorous running gave figures ranging from 13.0 to 15.2 with a mean of 14.4 mg. per cent. There was thus no evidence of any rise in the brain lactic acid in muscular exercise: the mean level after exercise was even somewhat below that of the norma series. This may be due to the effect of frequent handling in reducing their anxiety when handled.

DISCUSSION

It has been shown that the lactic acid content of the rat brain, analyzed after rapid fixation by freezing in liquid air, depends on the physiological state of the animal at the time. Rats taken in the sleeping state gave a significantly lower brain lactic acid content than controls in the normal waking state. Rats taken during emotional excitement gave a brain lactic acid level considerably higher than the normal and 300 per cent above the mean level for sleeping animals. Unless it is believed that these changes occurred in the brief period of freezing with liquid air, it must be concluded that they represent biochemical changes occurring in the brain *in vivo* under normal physiological conditions.

Muscular exercise appeared to play no part in the rise in lactic acid in the brain in emotion since *a*) the effect was still observed in animals immobilized by tubocurarine and *b*) no rise in the brain lactic acid occurred in muscular exercise alone without emotional excitement. The lactic acid content of the brain is not increased by adrenaline injection (1, 12) and the rise in lactic acid in the brain in emotion was observed in the absence of any significant rise of lactic acid in the blood. The simplest explanation of these observations is that in emotional excitement the increased functional activity of the brain is associated with increased glycolytic activity, involving a breakdown of high energy phosphorus compounds and the liberation of lactic acid. The changes in the brain would thus parallel those which occur in func-

tional activity in muscle. This view is supported by the work of Stone (1) and Le Page (3) on the changes in the brain produced by anesthetic and convulsant drugs. That biochemical changes occur in the brain in emotion is indicated by the changes in the electroencephalogram, as also by the chromatolysis in the nerve-cells in prolonged emotional excitement.

The results of the present investigation are in general agreement with the observations of Stone and of Le Page, but they suggest that the rise in brain lactic acid in exercise observed by Stone should be attributed rather to the emotional excitement, which is hardly avoidable when untrained animals are made to take strenuous exercise. Emotional excitement may contribute to the biochemical changes in the brain produced in some cases by drugs and in experiments such as those of Le Page on experimental shock. Gibbs *et al.* (14) reported that the brain normally liberates a small but significant amount of lactic acid into the blood, as shown by arterio-venous differences in experiments on man. This gives evidence of the formation of lactic acid in the brain under normal physiological conditions. The present work suggests that the rate of formation of lactic acid varies with the functional activity of the brain, being lowered in sleep and increased in emotional excitement.

SUMMARY

The lactic acid content of the rat brain is reduced in sleep and increased in emotional excitement. The rise in lactic acid in the brain in emotion is not due to concomitant muscular activity, since the effect was still observed in animals immobilized by tubocurarine. The brain lactic acid was not raised by muscular exercise in trained animals. The rise in lactic acid in the brain in emotion is a transient effect, followed by a rapid return to normal when the stimulus is discontinued.

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THE ELECTRICAL FIELDS AT THE SURFACE OF THE HEAD DURING SLEEP [1]

Mary A. B. Brazier, Ph. D.

Department of Anæsthesia, Massachusetts General Hospital and Harvard Medical School, and the Department of Psychiatry and the Electroencephalographic Laboratory, Massachusetts General Hospital, Boston

These studies were undertaken as part of an investigation of the action of sedatives. Since one of the effects of sedatives is to induce sleep, some objective test was sought to determine whether or not a person was asleep. A second objective was to search for information as to the neuronal pathways carrying the electrical activity of the brain to the surface during sleep. With these aims a study has been made of the electroencephalogram during the night throughout periods when the subject was awake, drowsing and sleeping.

That slow potentials appear in the record when the subject is asleep was one of the first observations to be established in electroencephalography: and since Berger's (1932, 1933, 1935) original demonstration of this change, it has been plentifully confirmed by subsequent workers. In general these workers have not studied the locus at which these slow waves appear on the skull but have concerned themselves mostly with the frequency changes. By inference, the slow potentials have been regarded by some as a slowing of the synchronized beat of the same neuronal systems which are responsible for the waking alpha rhythm. The waking alpha rhythm is well-known to be principally localized to the parieto-occipital region in man but there is good evidence that there may be more than one source of these potentials in some individuals since we have confirmed Jasper and Andrews' (1938) observation of independant foci of alpha waves in other regions of the head. Only Bakuradze and Narikashvili (1945) and Liberson (1944) (1945) have made at all detailed studies in man of the locus of the slow waves seen in sleep. Liberson found several foci of slow waves and showed that the region of the vertex was among the first to show localized 'paroxysmal' 3 - 6 per sec. waves at the beginning of sleep but believed that this selective localization did not persist during deep sleep; that in deep sleep even slower waves (½ to 3 cycles per sec.) appeared and that these waves originated, not at the vertex but from the frontal and temporal regions. Further mention of Liberson's careful studies will be made later in this paper when our data have been reported. Bakuradze and Narikashvili (1945) found foci in the central and frontal regions, but not in the temporal lobes. Gibbs (1935) in an early paper commented on the change in frequency but used an electrode placement which was not designed to give information as to localization.

The earlier studies of Blake and Gerard (1937 a and b) were made with one amplifier and were not concerned with localization. From their later work (1939) they reported maximal amplitude of the slow activity at the vertex, but they concluded that "similar patterns of delta waves are clearly simultaneous at the parietal, occipital, frontal, and temporal regions". They did not relate this finding to a spread of activity from a single focus.

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Davis, Loomis and their co-workers (1935, 1937, 1938) at first used not more than 3 or 4 electrodes which gave them inconclusive data as to the origin of the slow waves. In a later work (1938b) they used more electrodes and 6 amplifiers. Their published records show slow potentials centering at the frontal electrodes. Although they commented on the fact that the slow activity was most prominent on the 'top' of the head and could be recorded elsewhere, they did not relate this to electrical spread but emphasized their opinion that the cortex acted as a whole. Adrian and Yamagiwa, (1935) surprisingly, did not find the focus of slow activity in their studies using 5 midline electrodes from front to back of the head.

TECHNIQUE

In the present work multichannel Grass inkwriting oscillographs were used for permanent recording, with simultaneous monitoring by a double-beam cathode ray oscilloscope. Photographic records of the cathode ray traces were used to prove the identity of electrical signals appearing in more than one pair of leads, since by this method the waveform could be studied on a much broader time scale and with greater accuracy. For the same reason many of the inkwriter records were run at a speed of 6 cms. per second and at a higher amplification than is standard for clinical electroencephalography. In some stages of sleep it was, of course, found necessary to reduce the amplification to avoid blocking of the amplifiers by waves of high voltage. Electrodes were applied *ad hoc* in order to surround and confirm the foci when found. In some subjects a nasopharyngeal electrode was also used.

All recordings were made with amplifiers incorporating 'push-pull' operation and connected in the standard manner so that an electrically negative signal on the input of grid 1 of each amplifying system gave an upward deflection of the recording pen, whereas a negative signal on grid 2 gave a downward deflection.

RESULTS

In all of the 32 experiments on the 16 subjects so far studied there has been alpha activity localizable to the parieto-occipital regions when they were awake.

In figure 1 two samples of the EEG of an individual are shown: that on the left taken while he was awake, and that on the right while he was asleep. In this particular case electrode 5 was 2 cms. below the inion, and the distance between each pair of electrodes was 6 cms. This brought electrode 2 to a position just anterior to the vertex on this head. In the sample shown the spatial phase-reversals indicate that the alpha activity is originating in an area in the occiput nearest

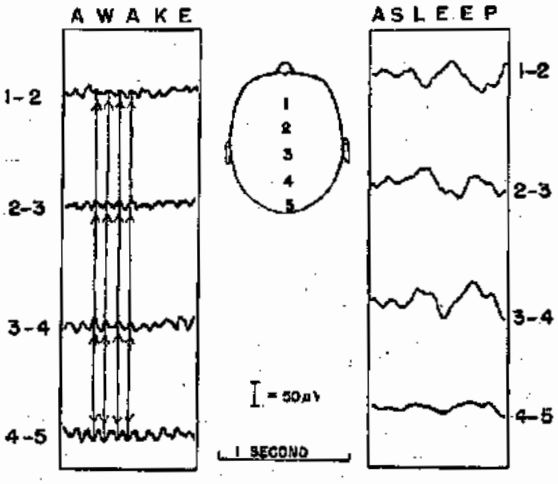


Fig. 1

EEG of the same individual awake and asleep showing the shift of focus from the occiput to the frontal regions.

electrode 4. From this position forward all the alpha waves are synchronous and in phase and show a falling gradient of voltage, indicating that they have a common origin at the occiput and that the tracings recorded from the electrodes anterior to the occiput are of the electrical spread of this activity. This is the classical distribution originally described by Adrian (1934) (1935). A single line of electrodes thus placed along the midline gives a localization only in the anterior-posterior direction and

does not of course give any information as to the transverse plane or as to whether there are separate foci in each hemisphere. The work of Adrian (1934) (1935), Jasper (1938) and of Cohn (1948) and others has firmly established the existence of separate foci in the two hemispheres so that, since our results are in general confirmation of their findings, the evidence will not be restated here.

prominent of these slow potentials of deep sleep are in the frontal region. The usual focus is somewhat anterior to the vertex on the part of the skull which, as far as one can tell, probably lies over area 6. This point will be taken up again later.

With the same electrode placement and linkages as were used for the waking record depicted on the left of figure I, the focus of the slow activity in sleep, shown in the re-

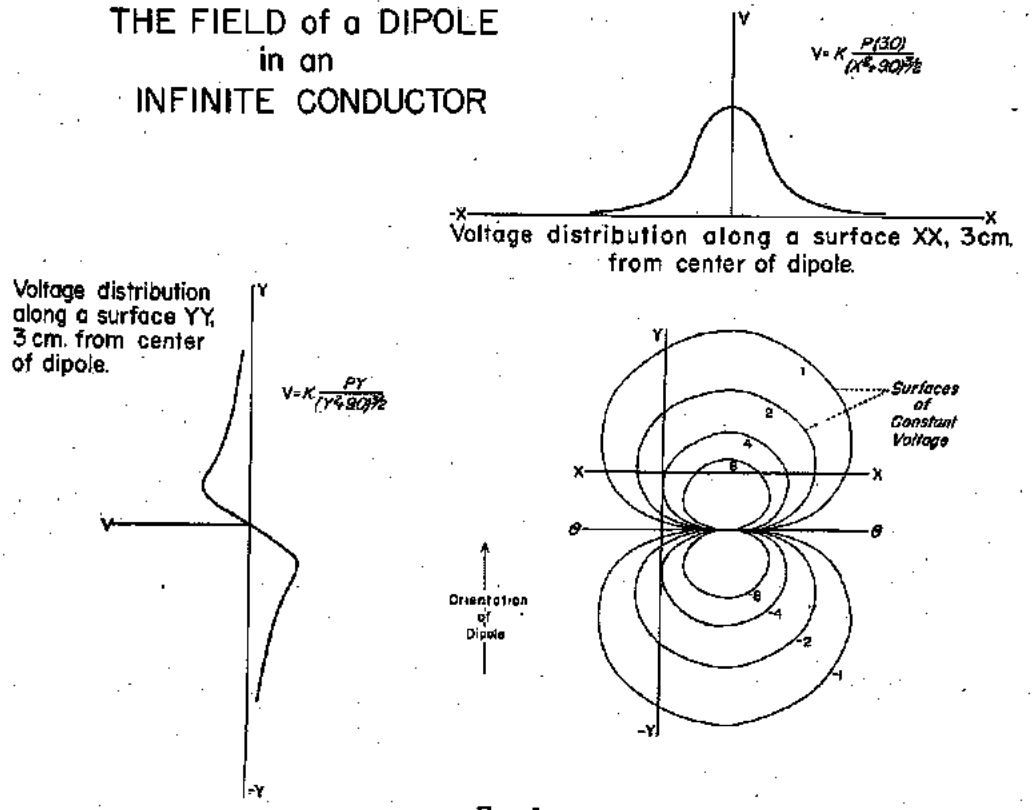


Fig. 2

Fields around a dipole in an infinite medium. Voltage gradients on an axis parallel to the dipole (YY), and on an axis normal to the dipole (XX).

The well-known slow activity of high voltage seen during normal sleep has quite clearly defined foci, not in the occiput, but in other parts of the head. Contrary to the suggestion of some workers, these slow potentials are not equally represented all over the head. In the present work it has been found that the principal foci of the most

cord on the right of the same figure, is found by spatial phase-reversal to be at the electrode common to the top two tracings. This sleep record is from the same subject whose EEG when awake is also seen in figure I. This is evidence for the origin of these waves being in the anterior part of the head but it gives no information as to

whether there is a single focus at the midline or two synchronously fired foci, one in each hemisphere.

We have found that the electrical fields on the surface of the head resemble those of a dipole-like field such as, for example, the great average of a double-layer with its axis oriented perpendicularly to the skull. In theoretical physics a double-layer can be represented as a plane consisting of many dipoles of infinitely small length, perpendicular to that plane. Figure 2 shows a standard diagram of the fields of voltage distribution around a dipole with the voltage on the axis parallel to the dipole (YY), and on an axis normal to the dipole (XX). Our data show that it is to a field on the latter axis that the EEG voltage gradients conform in sleep.

When electrodes are placed across the head in a line through the point where the A-P focus is found, the type of record obtained is generally similar to that shown in figure 3. In this illustration a schematic diagram has been made of the electrical voltage field which would fit the data at the moment in time marked by the arrow on the sleep record. Such a sketch can be only approximate for many reasons, among which are that the curvature of the head is foreshortened in the drawing and that the number of phase relationships and measurements of voltage gradients that can be made for any one moment is limited by the number of channels of the electroencephalograph in use. Also the fact that in the head the volume conductor is a finite one, producing distortion of the field at the surface. The effect of the

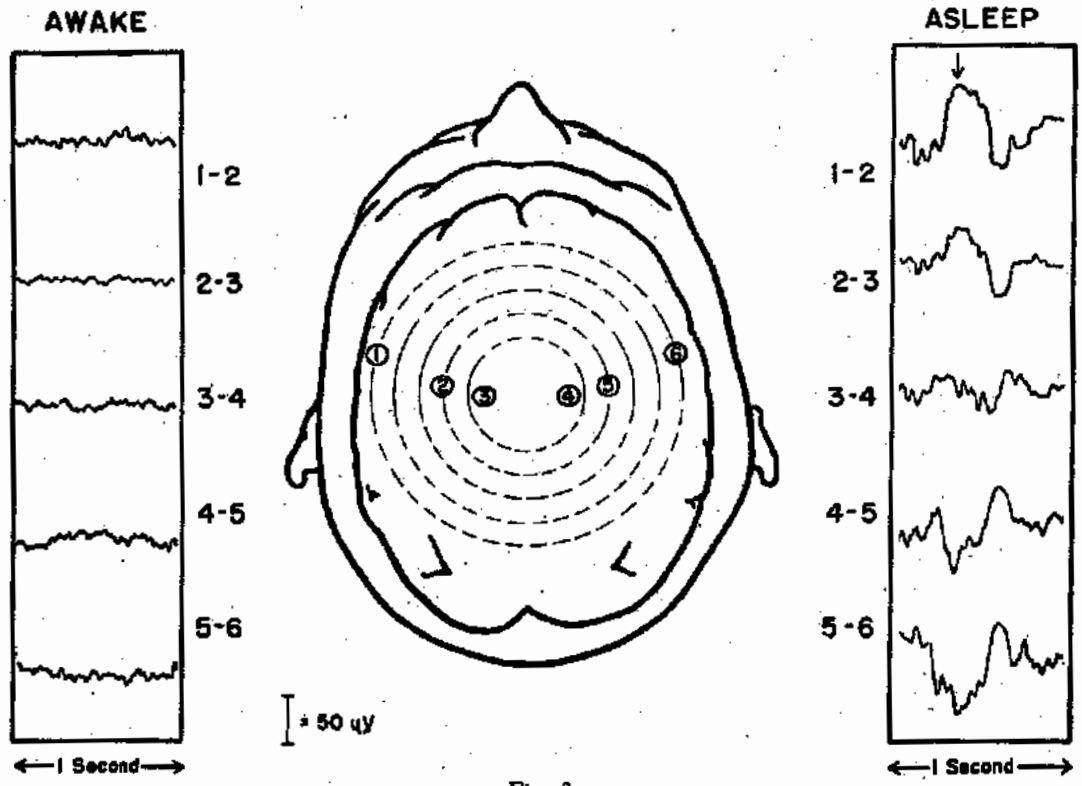


Fig. 3

Schematic diagram of the fields suggested by the data in the EEG illustrated on the right. Precentral focus of slow activity (3 c/s and 6 c/s waves).

boundary on the field is to give a greater voltage on the surface in the vicinity of the dipole than would occur in an infinite medium at a similar distance from the source. A more complete mathematical study of the fields of these potentials is the subject of another communication.

In figure 3 the field has been plotted to fulfil the following voltage relationships for the slow transient marked by the arrow, namely: electrode 1 strongly negative to electrode 2; 2 rather less negative to 3; 3 and 4 approximately isopotential; 4 positive to 5; and 5 strongly positive to 6. The voltage lines of the field have been spaced in proportion to the height of the deflection at the point marked by the arrow in each channel. The data from the small sample shown justify only those parts of the field drawn in solid lines. The broken lines are inserted from inference and by deduction from other parts of the same EEG record in which other electrode linkages were used. The fields would in fact be circles only in the theoretically ideal situation of complete symmetry in an infinite conductor. This of course is never the case on the human head so that the sketch must be regarded as highly schematic.

For using this method of representing fields it is clearly of the utmost importance to have the pens in exact alignment and the channels equally calibrated. It is, of course, also important that the amplifiers should not be allowed to block since this would mask the waveform and hinder the identification in different channels of an individual signal. Phase distortion by the amplifiers is another hazard.

Such a focus of slow wave activity as is shown in figure 3 might suggest a single midline focus were it not for the fact that any localization found by scalp electrodes is the recording at a distance (at least the distance of the skull and scalp) from the electrical event presenting at the cortex; the fields surrounding a generator fall away very steeply in voltage when recording electrodes are close to the source and then more gradually as the distance is increased (see figure 2). In the EEG recorder from the scalp the sharp fall of potential is always lost since the electrodes never come close enough to the source. Usually the curve is already flattening before the closest positioning of electrodes can register a potential difference. Thus one is always recording on the far outer surfaces of potential fields.

It follows that if two bilaterally homologous areas of the cortex are being triggered to discharge synchronously, and if these lie very closely together, the scalp leads will usually be unable to record these two foci as anything but a plateau, an area of isopotential value. Physiologically, since man develops bilaterally it seems likely that this is the explanation of the plateau found at the midline in sleep, and in fact we have in a few of our subjects, been able to obtain records of two discrete foci, one in each hemisphere lying very close to the longitudinal fissure (see figure 4).

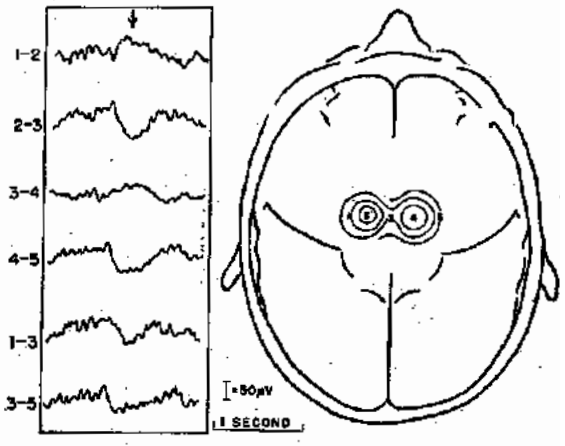


Fig. 4

Schematic diagram of the fields suggested by the EEG record on the left. Synchronous foci of slow waves in the precentral regions of the two hemispheres during sleep.

In the case of the two simultaneous foci illustrated in figure 4, the data are consistent with two generators each presenting its field at the surface. At the moment in time marked by the arrow, electrode I is nega-

tive to electrode 2, 2 is positive to 3, 3 is negative to 4, 4 positive to 5 (and the midline electrode 3 is also, but less positive to 5 and is slightly negative to 1). Thus two reversals are clearly seen, one in each hemisphere. These data would suggest a common triggering of activity reaching the cortex of each hemisphere in approximately area 6 (Brodmann).

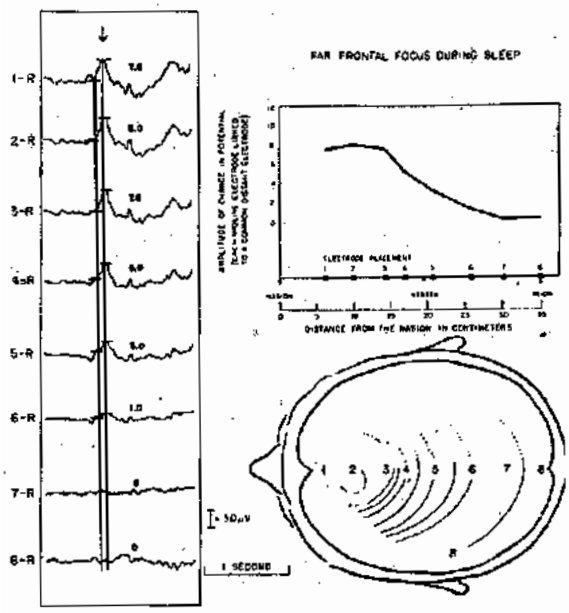


Fig. 5

Far-frontal focus of slow transients during sleep. For explanation see text.

This is not the only focus of slow activity we find in sleep. Another focus is often found farther forward on that part of the skull which woud appear to be over area 9, although to make a definite localization to this area through the skull would seem unjustified. An example of this far-frontal focus is shown in figure 5. In this record 8 electrodes were placed in a line from front to back of the head at the midline and each in turn was connected to a distant electrode, R (shown in the diagram). The amplitude of the change in potential in the time between the two vertical lines was measured in millimeters for each midline electrode referred to the distant electrode. This represents the negative slope of the slow transient marked by the arrow. These measurements are entered on the EEG record and are also plotted on the ordinate of the graph. On the abscissa is plotted the length in centimeters of a line from the nasion to the inion and the placement along this line of the electrodes. These measurements were made on the arc of the head and their projection onto the plane of the paper carries the error familiar to map-makers. The peak of the amplitude difference is seen to be near electrode 2, which was 10 cms. from the nasion and 9 cms. forward of the vertex in this individual.

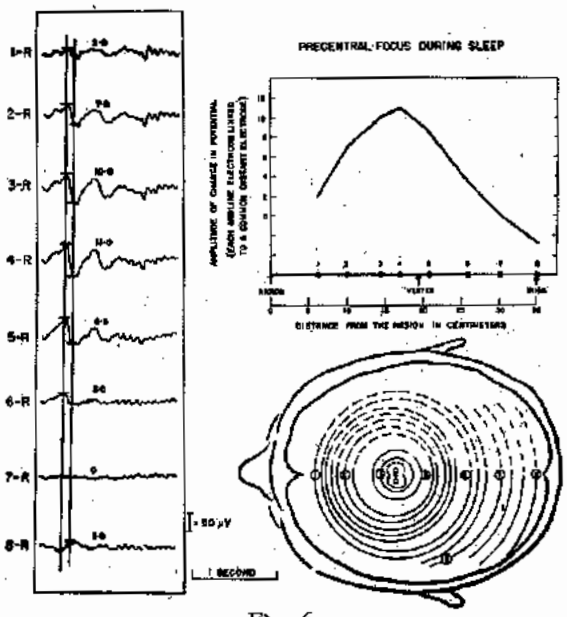
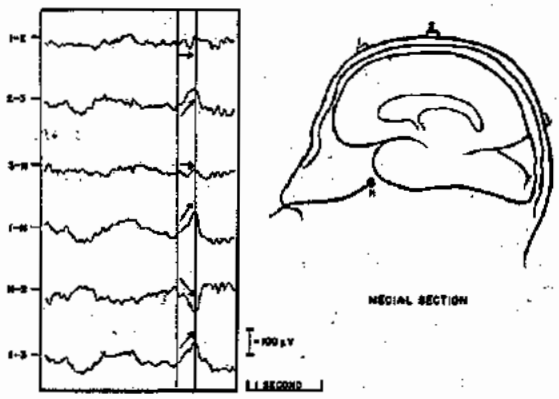


Fig. 6

Precentral focus of slow waves during sleep. For explanation see text.

In the schematic drawing of the head in figure 5, the simplest fields which would fit these data are sketched diagrammatically. For demonstration purposes one contour line has been drawn for each millimeter of pen excursion measured on the EEG. This is the same linear relationship as plotted on the ordinate of the chart. The head is also drawn to the scale of the abscissa of the same chart.

For purposes of comparison an EEG is shown in figure 6 which is from the same individual at another moment during the same period of sleep. This sample has been subjected to the same method of measurement, charting and sketching of fields as that in figure 5. The focus is clearly near electrode 4 which was 17 cms. from the nasion and 2.5 cms. forward of the vertex. This lies approximately over area 6, and most likely represents the same activity as was previously illustrated in figures 1, 3 and 4. In our experience the far-frontal focus does not only occur in the later stages of sleep, as suggested by Liberson, but during the same period as the precentral focus. Frequently the two different foci of slow activity are found within a few seconds of each other. They appear to be the same foci as those suggested by Davis (1939a) for the non-specific electrical response of the brain to external sensory stimulation.



RECORDINGS WITH A NASAL LEAD DURING SLEEP

Fig. 7

Medial section through the head to show approximate position of nasopharyngeal electrode. Focus of slow waves in the precentral region.

In our experience these would appear to be the two principal areas giving the most prominent waves during sleep. Superimposed on these slow transients many other types of faster activity can be seen. In a search for foci at the base of the brain we have in two subjects recorded from nasopharyngeal electrodes; these were electrodes designed by Dr. Paul MacLean (1949) and the experiments were carried out with his help. As yet we have been unable to find evidence for a focus at this site during sleep. The result of a typical recording with the nasal electrode is shown in figure 7.

We have been interested also in localizing the 14 cycle spindles which are as characteristic of sleep as are the slow waves. Experiment shows these frequently to have the same field as the slow activity and to vary in frequency through a range of at least 12 to 15 cycles per second in different individuals. Because of the faster frequency, identification of these waves is more difficult than that of the slow waves. The recording

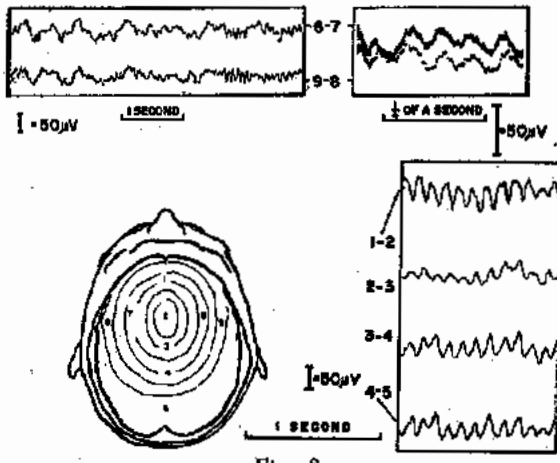


Fig. 8

Localization of 'spindles' during sleep. Left upper sample: to show similarity of activity in the two hemispheres. Right upper sample: Cathode ray oscilloscope record of 5 of these waves to show similarity in the two hemispheres. Right lower sample: anterior-posterior localization of 'spindles'. Head diagram: Fields which would fulfil all the data illustrated.

in figure 8 was made with two of the linkages run simultaneously on the cathode ray oscilloscope to determine whether or not the waves were indeed identical. This example shows a focus similar to that which we have called the precentral focus when describing the slow activity. This appears to be the same location for these spindles as that described by Jasper and Andrews (1938) who

traced the progressive change in frequency of the normal beta activity in the precentral region to a 14 cycle rhythm as the subject fell asleep.

We have also found these spindles in the occiput and have not yet exhausted the possibility that they may also appear elsewhere.

These are not the only rhythms found in sleep. A fast rhythm of approximately 25-28 c/sec. not present in the waking record, has been prominent in some of our subjects and is now being studied.

DISCUSSION

In the records discussed in this paper two foci of slow activity have appeared more prominently than others during sleep. These have been referred to descriptively as a precentral focus and a far frontal focus. As yet we have found no evidence for a major focus in the temporal lobe, such as has been described by Liberson (1944) (1945) in schizophrenic patients. Our evidence is contradictory to the opinions of early workers that the 'cortex acts as a whole'.

We have not specifically studied the so-called 'K' complex, but our data are in agreement with Davis' (1939a) observations as to localization. It may be remarked that these disturbance patterns may be set up by any external sensory stimulus and not solely by an auditory one, and that they are similar in waveform, frequency, and localization to activity occurring during sleep in the absence of any stimulus consciously applied by the observer. This is of interest in view of Davis' (1939a) hypothesis that these non-specific responses to sensory stimuli are analogous to the secondary discharge of Forbes and Morison (1939). This would suggest that the electrical activity of the brain during sleep is not the electrical concomitant of 'resting' cells, or of a quiescent brain, but the signal of activity in certain sub-cortical networks. Our data suggest that the projection areas involved may possibly be areas 6 and 9. To confirm this suggestion experiments are in construction for checking these localizations by animal experimentation, both by surgical methods and with reversible deafferentation by drugs.

Further conjecture is not justifiable from experiments on the intact human head and further identification of the structures involved must await the results of the animal experiments.

We have found the plotting of our data in the form of fields an aid to clear localization of the electrical activity we are studying. All our data from experiments on sleep conform to dipole-like fields oriented perpendicularly to the surface of the head. They are therefore more in keeping with Adrian's (1934) (1935) proposal (made for the waking alpha rhythm) of dipoles with their axes mainly perpendicular to the scalp, than with that of Beevers (1944) who suggested a system of dipoles with their axes parallel to the surface of the cortex. It may however be noted parenthetically that there are some data from this laboratory (as yet unpublished) indicating that a certain type of electroencephalographic activity can be recorded from the brain which creates a field consistent with that of a dipole effect parallel to the scalp. This is the activity to which Kennedy (1948) first drew attention and which he named the kappa rhythm. There is also a hint that some sources of alpha activity may be oriented in this way. In these cases, where more than one source is apparent in the records, the concept of dipole sources and the plotting out of the fields has helped us to sort them one from the other.

SUMMARY

(1) A method of charting the electrical fields at the surface of the head has been described which has proved useful in the localizing of EEG activity during sleep.

(2) A shift of focus of maximum activity from the parieto-occipital region when awake to the frontal lobes when asleep has been described.

(3) More than one focus, both of slow potentials and of spindles, have been demonstrated.

The author wishes to thank Mr. James Casby for technical help and instruction.

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COMMUNICATIONS

BRAIN STEM RETICULAR FORMATION AND ACTIVATION OF THE EEG [1]

G. Moruzzi, M.D. [2] and H. W. Magoun, M.D.
Department of Anatomy, Northwestern University Medical School

Transitions from sleep to wakefulness, or from the less extreme states of relaxation and drowsiness to alertness and attention, are all characterized by an apparent breaking up of the synchronization of discharge of elements of the cerebral cortex, an alteration marked in the EEG by the replacement of high-voltage slow waves with low-voltage fast activity. The magnitude of the electrical change parallels the degree of transition, and that most commonly observed in clinical electroencephalography is a minimal one, consisting of an alpha-wave blockade during attention to visual stimulation. Such activation of the EEG may be produced by any type of afferent stimulus that arouses the subject to alertness, or it may be centrally generated, but the basic processes underlying it, like those involved in waking from sleep, have remained obscure.

Recent experimental findings which may contribute to this subject have stemmed from the observation that EEG changes seemingly identical with those in the physiological arousal reactions can be produced by direct stimulation of the reticular formation of the brain stem. The following account describes such features of the response and its excitable substrate as have been determined, provides an analysis of changes in cortical and thalamic activity associated with it, and explores the relations of this reticular activating system to the arousal reaction to natural stimuli. Alterations produced by acute lesions in this system are presented in a succeeding paper. The effects of chronic lesions within it are under investigation.

[1] Aided by a grant from the National Institute of Mental Health, U. S. Public Health Service.

[2] University of Pisa, Italy. Visiting Professor of Neurology, supported by the Rockefeller Foundation.

METHODS

The experiments were performed in cats under chloralosane anesthesia (35-50 mgm./K, intraperitoneally) or in the "encéphale isolé" of Bremer, prepared under ether, with exposure margins infiltrated with procaine. Ephedrine was administered intravenously immediately after transection of the cord at C 1. At least an hour elapsed after ether was discontinued before work was begun.

Concentric bipolar electrodes, oriented with the Horsley-Clarke technique, were used for stimulation of, or pickup from, the brain stem. Condenser discharges from a Goodwin stimulator were employed routinely. Lesions were made surgically or electrolytically, and their positions, together with those of electrode placements, were verified histologically.

Potentials were recorded with a Grass model III amplifier and inkwriter. Some cortical records were taken directly from the pial surface, but usually as much of the brain case as possible was left intact, and most cortical pickups were between two screw electrodes, 5-10 mm. apart, inserted through burr holes in the calvarium until their tips rested on the dura overlying functional areas. With bipolar leads and by grounding the scalp, stimulus artifacts were negligible. Other technical details are given in the legends.

RESULTS

The response to reticular stimulation consisted of cessation of synchronized discharge in the EEG and its replacement with low-voltage fast activity. The intensity of the alteration varied with the degree of background synchrony present. Conspicuous effects were thus observed against the high-voltage slow waves of chloralosane anesthesia (fig. 1 C, D), while a fully activated EEG was not further affected (fig. 2A). Responses were seen to best advantage when the unanesthetized brain exhibited some relaxation (fig. 2 B and C) or when light chloralosane anesthesia had induced synchronization without greatly impairing neural excitability (fig. 1 A and B). With deeper chloralosane, slow waves were blocked, but low-voltage fast activity was not elicited (fig. 1 C and D).

The response was a generalized one, being observed in the sensory-motor cortex

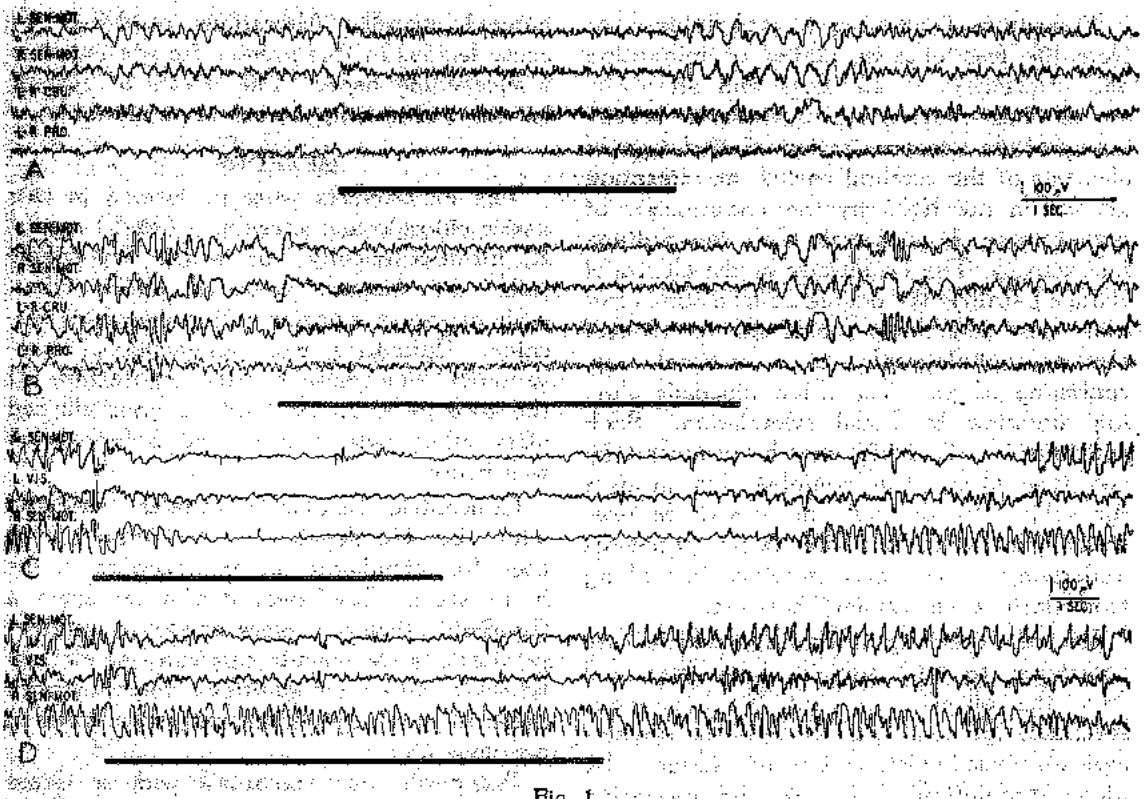

Fig. 1

Effect of stimulation of the brain stem reticular formation upon electro-cortical activity of chloralosane preparations.

A and B. "Encephale isolé" with 7 mgm. chloralosane/K. Replacement of high voltage slow waves, present in A and more pronounced in B, with low voltage fast activity during left bulbo-reticular stimulation (1.5 V., 300/sec.).

C. Intact cat with 50 mg. chloralosane/K. Left bulbo-reticular stimulation (3 V, 300/sec.) blocks chloralosane waves bilaterally, but more rapidly and for a longer time in the ipsilateral cortex. Note that low voltage fast activity does not appear.

D. Like C, but frequency of reticular stimulation reduced to 100/sec. Effect limited to ipsilateral cortex and doesn't outlast stimulus.

In all records, the origin of activity in different channels is given at the left: L. SEN. MOT. signifies left sensory-motor cortex; L.-R. CRU., left to right cruciate gyrus; L.-R. PRO., left to right gyrus proreus; L. VIS., left visual area; L. AUD., left auditory area; L. THAL., left thalamus. The period of bulbar stimulation is marked by a heavy line beneath the record. Calibration and time are stated.

(fig. 1), where it was often most pronounced, and in the visual (fig. 1 C) and auditory (fig. 2 B, C) cortical areas as well. With minimal reticular stimulation, alterations were best obtained in the ipsilateral hemisphere and were sometimes limited to it (fig. 1 D).

The response was readily obtained with low intensities of reticular stimulation; voltages of 1-3 being usually employed. Brief shocks, with a falling phase of 1 msec. were used routinely and were as effective as longer lasting ones. Stimulus frequencies of 50/sec. were the lowest at which definite alterations could be elicited and the response was considerably improved by increasing frequencies up to 300/sec., which were regularly utilized. Thus the EEG response to reticular excitation was best obtained with low voltage, high frequency stimulation.

These responses were not secondary to any peripheral effects of brain stem stimulation. By direct test they were independent of changes in respiration, blood pressure and heart rate. They occurred in the isolated brain after full atropinization and curarization. As will be seen, they were unquestionably mediated by neural connections between the reticular formation and the cerebral hemisphere.

The distribution of the excitable area is projected upon a reconstruction of the midsagittal plane in figure 3, and includes the central core of the brain stem, extending from the bulbar reticular formation forward through the pontile and mesencephalic tegmentum into the caudal diencephalon. At the

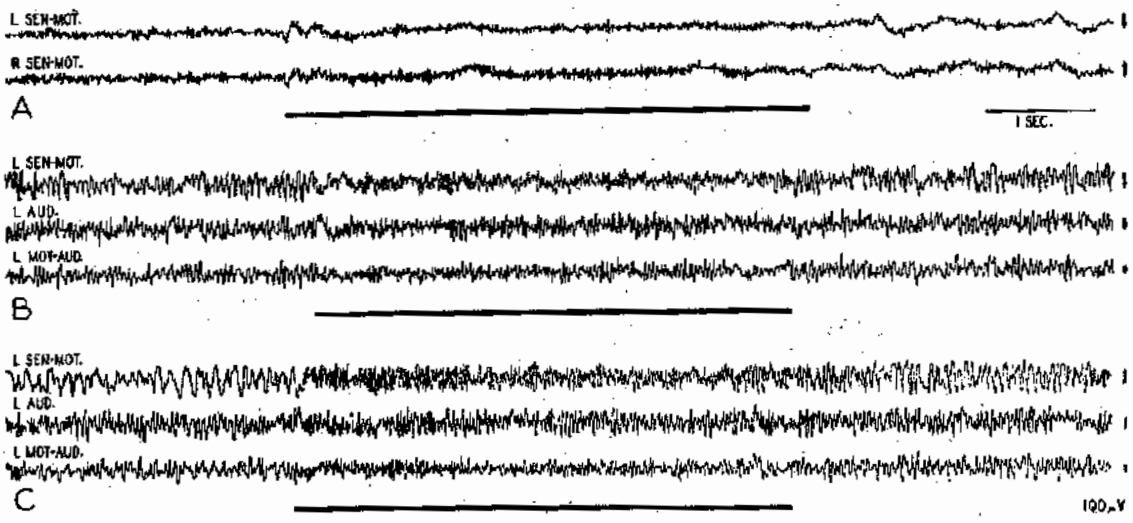

Fig. 2

Effect of reticular stimulation on electro-cortical activity of the unanesthetized "encéphale isolé". A-C. Left bulbo-reticular stimulation (3 V, 300/sec.) is without effect upon the fully activated cortex (A), but evokes characteristic low voltage fast activity when spontaneous synchrony is present (B and C).

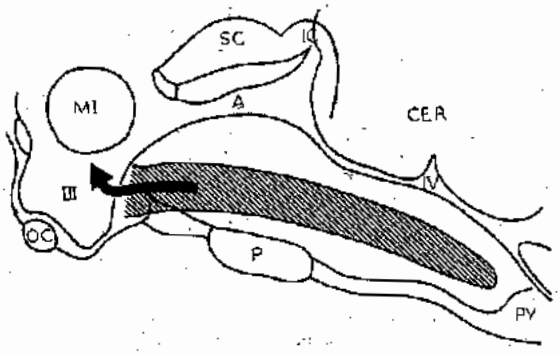

Fig. 3

Reconstruction of midsagittal plane of cat's brain stem upon which is projected, with cross-lining, the distribution of the ascending reticular activating system.

Abbreviations are as follows: A, aqueduct; CER, cerebellum; IC, interior colliculus; MI, massa intermedia; OC, optic chiasma; P, pons; PY, pyramidal crossing; SC, superior colliculus; III, third ventricle; IV, fourth ventricle.

bulbar level, excitable points were distributed in the ventromedial reticular formation and the area of their distribution coincided with that from which suppression of motor activity (Magoun and Rhines, 1946) could be elicited (fig. 4A). Exploration of the overlying cerebellum has revealed excitable points in its fastigial nuclei, the responses possibly being mediated by connections of the roof nuclei with the brain stem reticular formation (Snider, Magoun and McCulloch, 1949). In the midbrain, responses were obtained from the tegmentum bordering the central grey and extending in a paramedian position beneath it (fig. 4B). In the caudal diencephalon, effective points were located near the midline in the dorsal hypothalamus and subthalamus (fig. 4C). From this region, the excitable system is evidently distributed to the overlying thalamus, through which its effects are exerted upon the cortex, and some data bearing on its thalamic mediation will be given later.

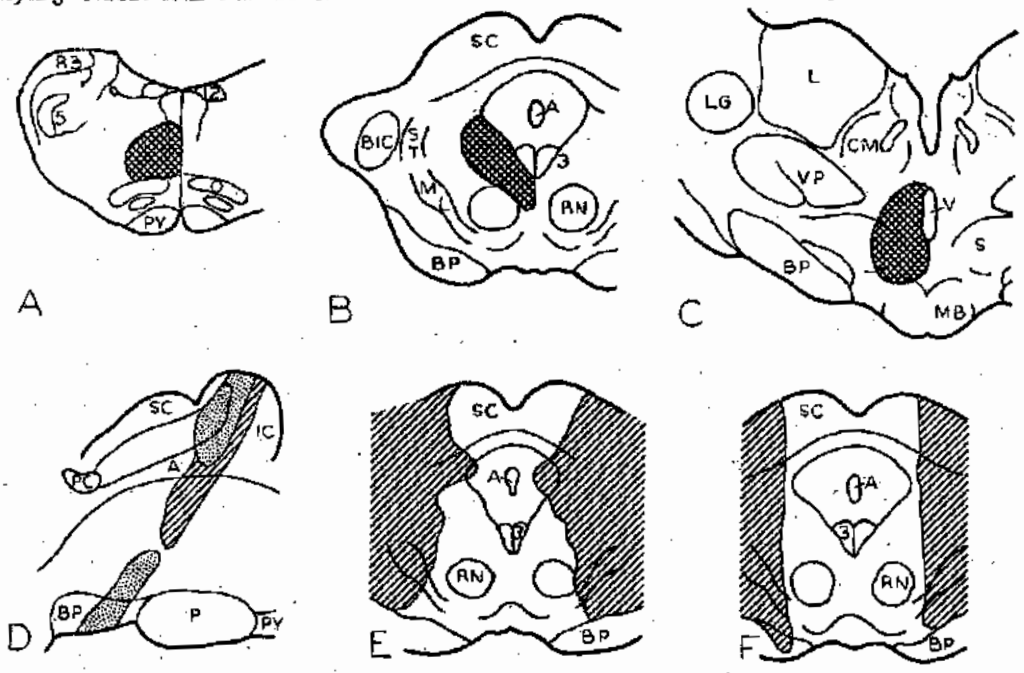

Fig. 4

A-C. Transverse sections through bulbar (A), mesencephalic (B) and caudal diencephalic (C) levels, with cross-lining indicating the area from which reticular responses were elicited with lowest voltage and without complications from exciting other ascending or descending neural connections.

D. Reconstruction of midsagittal plane of the midbrain upon which is projected, with stipple, the position of tectal and peduncular lesions which failed to block the EEG response to bulbo-reticular stimulation. Cross-lining marks the position of a tegmental lesion which abolished this response to bulbar stimulation.

E, F. Transverse sections through the midbrain of two cats, showing the extent of lesions which interrupted the medial and lateral lemnisci and spinothalamic tracts, but which failed to impair the EEG response to bulbo-reticular stimulation.

Abbreviations are as follows: A, aqueduct; BIC, brachium of inferior colliculus; BP, basis pedunculi; CM, centre médian; IC, inferior colliculus; L, lateral thalamic nucleus; LG, lateral geniculate body; MB, mammillary body; ML, medial lemniscus; O, inferior olive; P, pons; PY, pyramid; RB, restiform body; S, subthalamus; SC, superior colliculus; ST, spino-thalamic tract; VP, posterior part of ventral thalamic nucleus; 3, oculomotor nucleus; 5, spinal fifth tract and nucleus; 12, hypoglossal nucleus.

The distribution of this ascending system within the midbrain was studied further by observing the effect of lesions here upon the

EEG response to bulbo-reticular stimulation. Such responses were unimpaired following sections of the cerebral peduncles or tectum, but were blocked by injury to the mesencephalic tegmentum (fig. 4D). Typical cortical responses to bulbo-reticular stimulation were still obtained after bilateral destruction of all laterally placed mesencephalic structures, including the medial and lateral lemnisci and the spinothalamic tracts (fig. 4 E, F), leaving intact only the paramedian region from which responses were obtained on direct stimulation (fig. 4B).

(fig. 4 D). Furthermore, single shock stimuli to effective reticular sites did not evoke antidromic potentials in the sensory-motor cortex (fig. 5 C and E) (fig. 10 A), nor did direct stimulation of the bulbar pyramid reproduce the EEG response to reticular stimulation.

A cortico-bulbo-reticular path from area 4-S is distributed to the excitable reticular area of the lower brain stem (fig. 4 A) (McCulloch, Graf and Magoun, 1946), but it is similarly impossible to attribute the EEG responses to its antidromic stimulation.

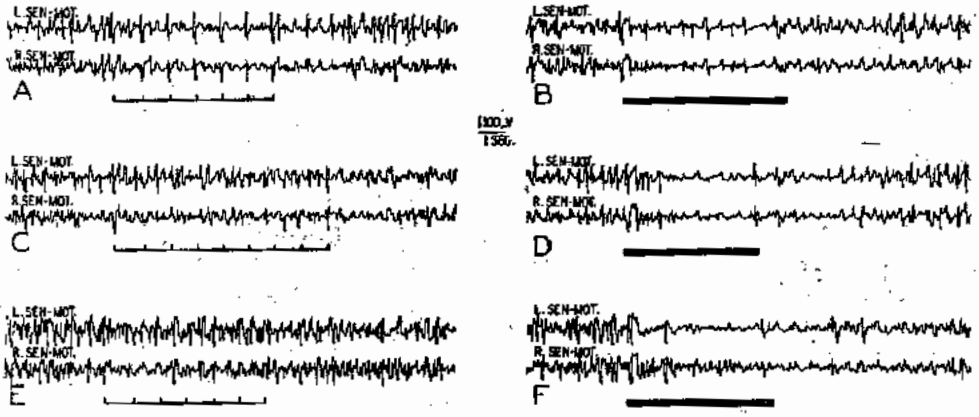

Fig. 5

Comparison of the effects of stimulating the right posterior column (A, B) and the left reticular activating system at bulbar (C, D) and midbrain (E, F) levels, under full chloralosane anesthesia. Stimulus frequency is 1/sec. in left records (A, C, E) and 300/sec. in right records (B, D, F); intensity is 3 V throughout.

Single shock stimuli to the posterior column evoke sensory potentials in the cortex (A), not elicited by similar reticular stimulation (C, E). High frequency stimulation of the posterior column causes some desynchronization of the EEG (B), but more pronounced effects are induced by reticular stimulation (D, F).

A series of ascending reticular relays is presumed to constitute the structural substrate of this brain stem activating system. That responses are not attributable to the antidromic excitation of corticifugal paths, nor to the dromic stimulation of known afferent paths, bordering the reticular area, is indicated by a variety of data.

As regards the pyramidal tract, movements referable to its excitation never accompanied EEG responses to reticular stimulation, and the latter were still obtained from the bulbar level after section of the fibers of this tract in the basis pedunculi

This path accompanies the pyramidal tract in the basis pedunculi (McCulloch, Graf and Magoun, 1946) section of which, as noted, left reticular responses unimpaired. The absence of antidromic potentials in the sensory-motor cortex, on single shock stimuli to the bulbar reticular formation (fig. 5 C; 10 A), might be explained by the small size of the suppressor areas in the cat (Garol, 1942), but a more likely possibility is that the unmyelinated terminals of this extrapyramidal path were never excited with the low intensities of reticular stimulation employed in the present experiments. Reticular

responses elicited from brain stem levels cephalad to the bulb are, moreover, impossible to explain on the basis of antidromic stimulation of this extrapyramidal pathway.

It is equivalently impossible to ascribe reticular responses to the dromic activation of known afferent pathways ascending to the cortex through the brain stem. The medial lemniscus is adjacent to the excitable reticular area through much of its course, and high frequency stimulation of the lemniscal system, like that of the sciatic nerve (Gellhorn, 1947), exerts a desynchronizing influence upon the EEG (fig. 5 B). This influence is not as pronounced as that of the reticular formation and higher voltages of stimulation are required to induce it than those which yield primary and secondary cortical sensory responses.

Three lines of evidence clearly show, however, that the desynchronizing influence of the reticular formation cannot be attributed to activation of the lemniscal system, either through physical spread of stimulating current, or by antidromic excitation of possible lemniscal collaterals to the brain stem reticular formation. First, single shock stimuli to excitable reticular points at bulbar (fig. 5 C) or midbrain (fig. 5 E) levels never evoked potentials in the sensory-motor cortex, as was invariably the case when such shocks were applied to the lemniscal system (fig. 5 A), and this simple control was routinely applied throughout the work. Second, the distribution of the excitable reticular area was distinct from that of the course of the medial lemniscus through the brain stem (fig. 4, A-C). Third and finally, EEG responses to bulbar stimulation were unaffected by mesencephalic lesions which bilaterally interrupted the medial and lateral lemnisci and the spino-thalamic tracts (fig. 4 E, F).

Elimination of these possibilities and the distribution of excitable points through the brain stem both indicate that this response is mediated by a paramedian system of ascending reticular connections. Single shock stimuli to effective bulbar sites do not evoke potentials at effective midbrain or diencephalic sites, however, suggesting that a number of relays are present and that the synapses involved are iterative in nature.

Having now described the desynchronization of the EEG induced by brain stem stimulation and presented evidence that this alteration results from exciting a system of reticular relays ascending to the diencephalon, attention may next be directed to the effect of reticular stimulation upon types of evoked activity in the cortex.

Effect upon evoked sensory potentials. In the chloralosane cat, a single afferent volley, initiated either by natural stimuli or by shocks to the sciatic nerve or posterior column, evokes primary and secondary[1] cortical potentials and sensory "after-discharge" succeeding them. The secondary response and after-discharge occur generally in the cortex and are readily observed in the EEG. During stimulation of the brain stem reticular formation, such secondary responses continued to be evoked by afferent volleys, usually without alteration (fig. 6 A), but sometimes with reduction of amplitude and simplification of potential form, particularly in cortical areas outside the sensori-motor region (fig. 8 B). Following conclusion of reticular stimulation, transient enhancement of the secondary response was occasionally observed (fig. 6 B).

The succeeding high-voltage slow waves, called sensory after-discharge, were invariably abolished during reticular stimulation (fig. 6 A-C). In full anesthesia, the cortical record then became flat between secondary responses (fig. 6 A, B), while, if anesthesia was light, low-voltage fast activity was present in these intervals (fig. 6 C). The abolition of sensory after-discharge might thus be simply another manifestation of the desynchronization of the EEG induced by brain stem stimulation.

[1] These "secondary potentials" resemble those of Forbes and Morison (1939) recorded, in deep barbiturate anesthesia, in and also outside of the somatic receiving area and disappearing when the frequency of afferent stimuli rose above 5/sec. Since under chloralosane anesthesia, they are associated with pyramidal discharge they correspond to the "efferent waves" of Adrian (1941).

Such sensory after-discharge was not impaired, however, during cortical desynchronization induced by high frequency stimulation of the sciatic nerve (fig. 8 D). desynchronization resulting from reticular stimulation (fig. 5 B, D, F) opposed simultaneous discharge of a sufficient number of interneurons connecting the sensory with

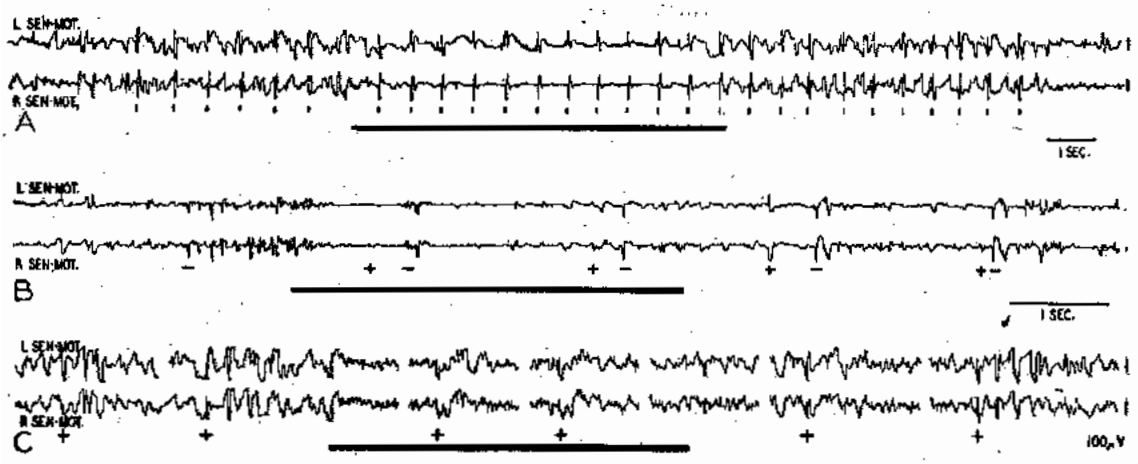

Fig. 6

Effect of reticular stimulation upon cortical sensory responses.
A. Tapping skin of ankle. B. Make and break shocks to the sciatic nerve, under full chloralosane anesthesia as in A. C. Single shocks to the upper end of the posterior column, in "encéphale isolé" with 7 mgm. chloralosane/K. In each instance the evoked sensory spike is unaffected, while consequent after-discharge is abolished. Note low voltage fast activity during reticular stimulation in C, with minimal anesthesia, and its absence in A and B, with full anesthesia.

Effect upon evoked pyramidal discharge. In the chloralosane cat, afferent volleys arriving at the cortex there evoke pyramidal discharges which are responsible for the jerky movements characteristic of this anesthesia (Adrian and Moruzzi, 1939). Although afferent volleys continued to reach the cortex during stimulation of the brain stem reticular formation, such pyramidal discharge, recorded from the basis pedunculi, was reduced or abolished (fig. 7 A) and contraction of leg muscles, induced by it, disappeared (fig. 7 B; 8 F). This disappearance of movement was not attributable to spinal inhibition, for reflexly induced contraction of the same muscles was not affected by such midbrain stimulation (fig. 8 G). The movements induced by this pyramidal discharge were not reduced during desynchronization of cortical electrical activity by high-frequency sciatic stimulation (fig. 8 E), and the facilitation observed might have been due to spinal alterations. Whether the more pronounced cortical

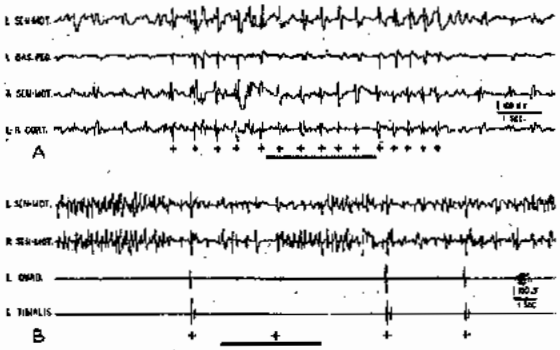

Fig. 7

Effect of reticular stimulation on pyramidal discharges and chloralosane jerks.
A. Break shocks to sciatic nerve cause sensory cortical responses and corresponding pyramidal discharge, recorded from the basis pedunculi (channel 2). The latter and sensory after-discharge are almost abolished by bulbo-reticular stimulation (3 V, 300/sec.), which leaves cortical sensory spikes unaffected. B. Break shocks to sciatic nerve cause chloralosane jerks, recorded in myograms of the quadriceps and tibialis (channels 3 and 4). Movement was abolished during stimulation of the midbrain tegmentum (3 V, 300/sec.), although cortical sensory potentials were still elicited. Such midbrain stimulation had no effect on spinal reflexes.

the motor cortex to prevent threshold activation of the cells of origin of the pyramidal tract, or whether these cells were somehow rendered incapable of being excited by afferent cortical volleys, during brain stem stimulation, remains unsettled.

tion of the diffuse thalamic projection system consists of a series of high-voltage slow waves, one for each shock, which recruit to a maximum during the initial period of stimulation (figs. 10, 11, 12, 13) (Morison and Dempsey, 1942; Dempsey and Morison,

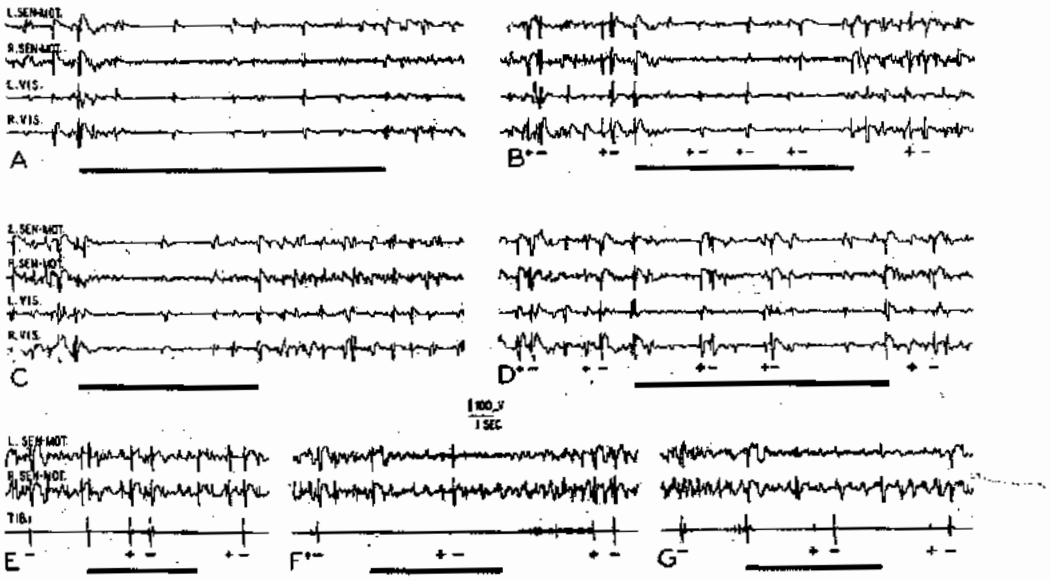

Fig. 8

Comparison of effect of reticular and sensory stimulation upon spontaneous and evoked electro-cortical activity.
A, C. Abolition of chloralosane waves during (A) bulbo-reticular stimulation (2 V, 300/sec.) and (C) sciatic nerve stimulation (3 V, 300/sec.).
B, D. Sensory cortical potentials evoked by make and break shocks to sciatic nerve are reduced by bulbo-reticular stimulation at 2 V, 300/sec. (B), but not by stimulation of the contralateral sciatic nerve at 3 V, 300/sec. (D).
E, F. Chloralosane jerks evoked by break shocks to the sciatic nerve, and recorded in myograms of the tibialis anticus, were augmented (E) by contralateral sciatic nerve stimulation (3 V, 300/sec.) and abolished (F) by stimulation of the midbrain tegmentum (3 V, 300/sec.). Such midbrain stimulation did not influence tibialis contraction in the ipsilateral flexor reflex (G).

Effect upon cortical strychnine spikes. The recurring spikes produced by local strychninization of the sensori-motor cortex were not prevented by exciting the brain stem reticular formation, nor was conduction of this discharge to the opposite cortex interfered with (fig. 9 B). Synchronized convulsive waves in a cortical fit, induced by supramaximal stimulation of the motor cortex, were similarly unaffected by bulbo-reticular stimulation.

Effect upon recruiting response. The cortical response to low frequency stimula-

1942; Jasper and Droogleever-Fortuyn, 1946; Jasper, 1949). These waves may be confined to the ipsilateral hemisphere, but are usually present, though smaller, contralaterally as well. Depending upon the site of thalamic stimulation, they may be distributed anteriorly, posteriorly, or generally in the cortex.

In the unanesthetized "encéphale isolé", such a recruiting response, in both sensori-motor cortices and the ipsilateral auditory area (fig. 10 D), was either abolished or greatly reduced in all regions during intercurrent

bulbo-reticular stimulation and recruited again upon its cessation (fig. 10, E, F). Exciting the rostral end of the reticular system in the subthalamus had a similar effect (fig. 11 E). Another instance is shown in figure 9 A, in which case, strychnine was then applied locally to the cortex. The recruiting response was transiently abolished following strychnine spikes interspersed in its course, suggesting that identical cortical neurons were involved in these two activities

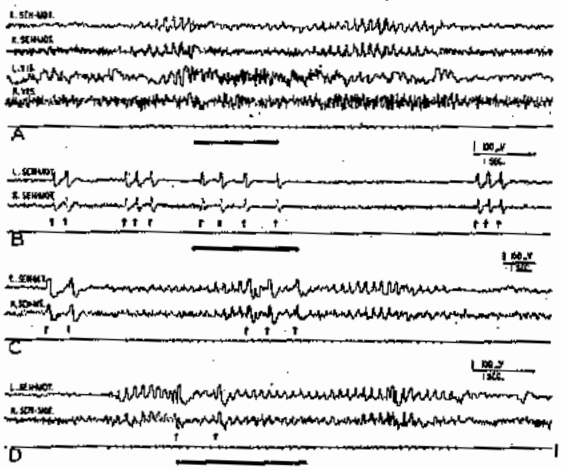

Fig. 9

Effect of reticular stimulation upon recruiting response and cortical strychnine spikes.

A. Recruiting response to left thalamic stimulation (5 V, 7.5/sec.) in "encéphale isolé," abolished by left bulbo-reticular stimulation (2 V, 300/sec.).

B. Strychnine spikes in both sensory-motor areas, induced by local application of strychnine to left motor cortex, were not decreased by left bulbo-reticular stimulation (2 V, 300/sec.).

C. Decrease of recruiting response (evoked as in A), following interspersed strychnine spikes.

D. Recruiting response (evoked as in A) markedly decreased by left bulbo-reticular stimulation (2 V, 300/sec.) which did not affect strychnine spikes.

(fig. 9 C). Subsequent repetition of reticular stimulation again opposed the recruiting response without, as noted above, altering the spikes induced by strychnine (fig. 9 D). It should be noted that low frequency stimulation of the ascending reticular system, even in the subthalamus, did not itself induce a recruiting response (figs. 10 B; 11 D).

Of the different types of evoked cortical activity upon which the effect of reticular stimulation was tested, certain ones, then, secondary sensory responses and strychnine spikes, exhibited little or no alteration, while others, sensory after-discharge and recruiting responses, were abolished. Of the two types of transcortical conduction observed, that from the sensory to the motor cortex, underlying the pyramidal discharge to afferent volleys under chloralosane anesthesia, was blocked, while the other, from a strychninized area of the cortex to the opposite cortex, was unaffected. It is not at present possible to decide whether any common factors underly these similarities and differences.

Thalamic mediation of response. The generalized distribution of the alteration in the EEG induced by reticular stimulation has implications for the manner of its mediation by the thalamus. It seems likely that the reticular formation could exert its influence upon all parts of the cortex either by acting generally upon the thalamus or by influencing its diffuse projection system alone. At present, each possibility appears relevant, for there is indication both that the diffuse projection system is involved and that the reticular influence may not operate exclusively through it.

Evidence for the mediation of the reticular effect by the diffuse thalamic projection system is presented in figure 12. The low-frequency stimulation of a portion of this system, on one side of the midline, induced recruiting responses not only in both cortices but in a corresponding region of the opposite thalamus as well (fig. 12 A). This evoked intra-thalamic activity was then abolished during intercurrent bulbo-reticular stimulation and returned again upon its cessation (fig. 12 B, C), thus demonstrating a reticular influence upon the diffuse projection system at the thalamic level. It is uncertain whether the corresponding cortical changes were secondary to those in the thalamus in these instances, however, for though cortical recruiting responses were greatly reduced, small cortical waves were still present dur-

ing reticular stimulation at a time when all synchronized activity was absent from the record of this thalamic sample (fig. 12 B, D: compare left cortical and thalamic channels). This same preparation was next lightly anesthetized with chloralosane, with the development of characteristic high-voltage slow waves both in the cortex and subcor-

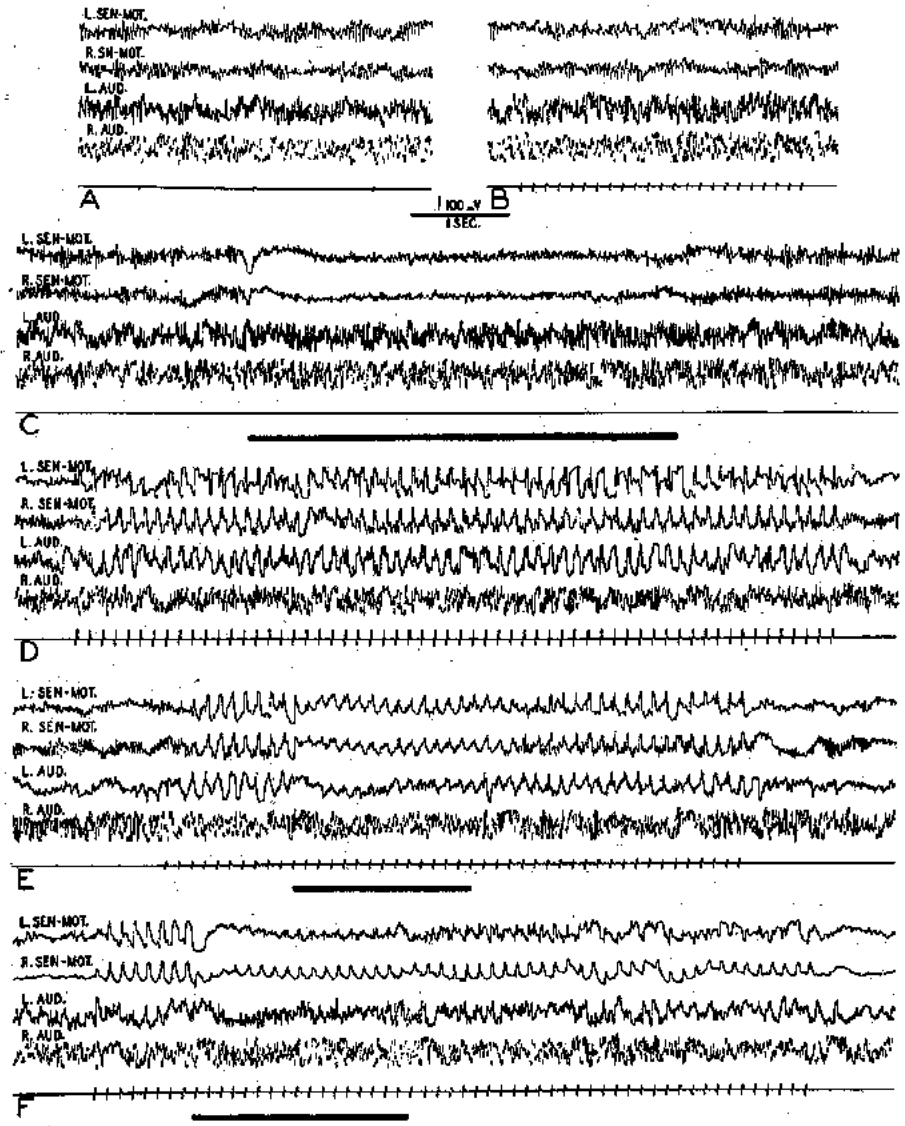

Fig. 10

Effect of reticular stimulation upon recruiting response. Left bulbo-reticular stimulation at 3 V in "encéphale isolé".

A. Single shocks to bulb do not evoke cortical potentials.
B. Bulbar stimulation at 7.5/sec. does not evoke recruiting response.
C. Bulbar stimulation at 300/sec. activates EEG.
D. Recruiting response evoked by left thalamic stimulation (5 V, 7.5/sec.).
E. Recruiting response to left thalamic stimulation reduced or abolished by left bulbar stimulation (3 V, 300/sec.).
F. Recruiting response to right thalamic stimulation reduced or abolished by left bulbar stimulation (3 V, 300/sec.).

tically, within and between components of the diffuse thalamic projection system. Bulboreticular stimulation then desynchronized this activity as effectively in the electrothalamogram as in the EEG (fig. 12 D, E).

Further indication that the reticular influence may be mediated by the diffuse thalamic projection system is provided by

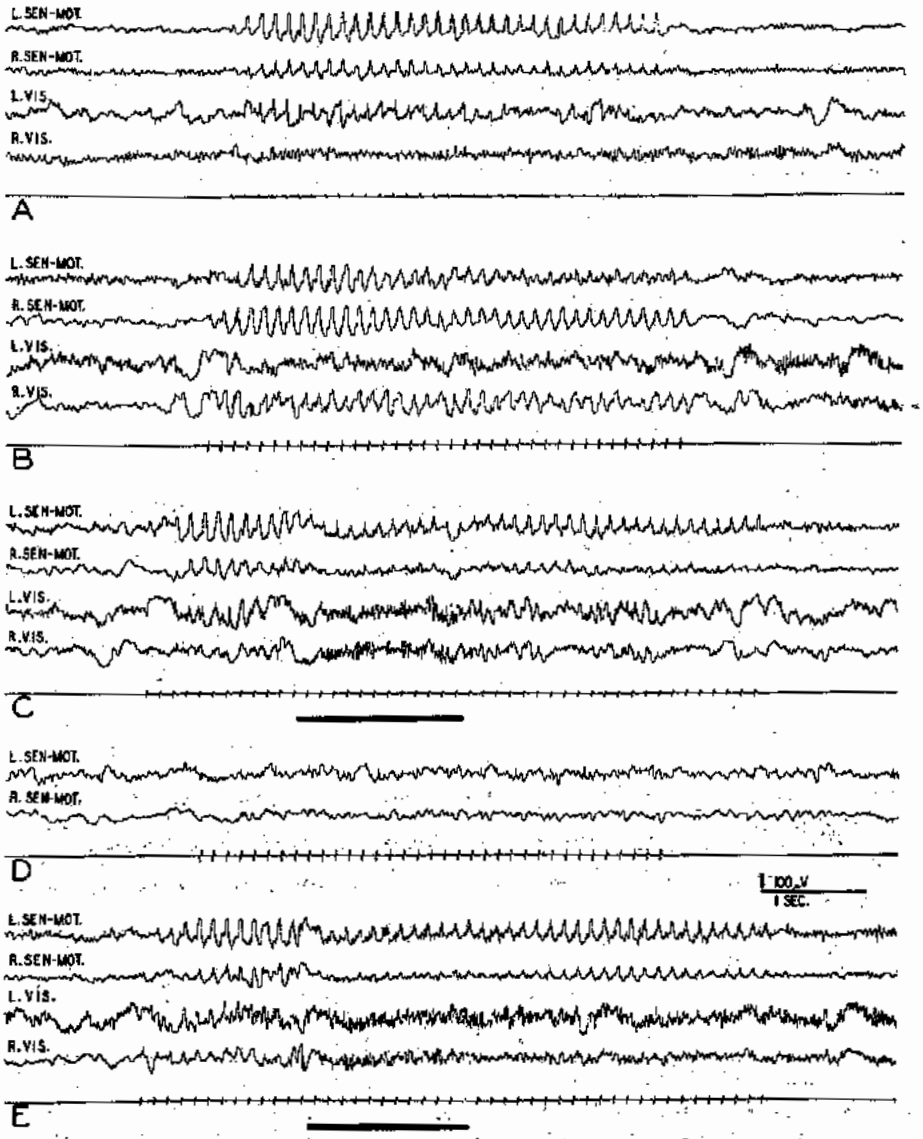

Fig. 11

Reproduction of reticular response by high frequency stimulation of diffuse thalamic projection system.

A and B. Recruiting responses induced by left (A) and right (B) thalamic stimulation (5 V, 7.5/sec.) in "encéphale isolé".

C. Recruiting response to left thalamic stimulation reduced or abolished by stimulating the same right thalamic site as in B, but with 5 V, 300/sec.

D. Right electrode lowered into subthalamus, the stimulation of which with 5 V, 7.5/sec. fails to induce a recruiting response.

E. Subthalamic stimulation, with 5 V, 300/sec., reduces or abolishes the recruiting response to left thalamic stimulation.

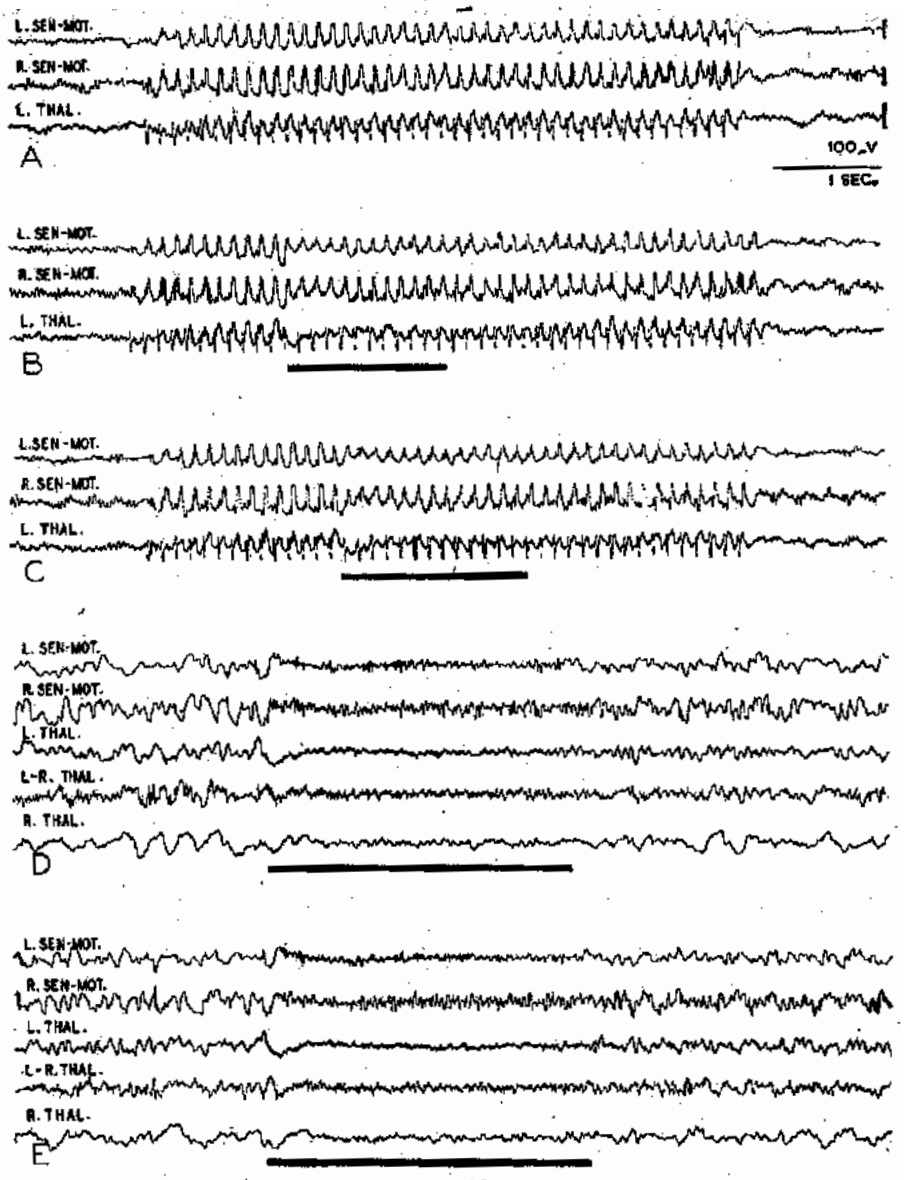

Fig. 12

Effect of reticular stimulation upon electrothalamogram of diffuse projection system. A-C. Unanesthetized "encéphale isolé".

A. Recruiting response to right thalamic stimulation (8 V, 7.5/sec.) is recorded both from cortex and from and between thalamic sites yielding recruiting responses or response on stimulation.

B, C. Recruiting response in cortex and left thalamus, evoked by right thalamic stimulation as in A, is reduced or abolished during left bulbo-reticular stimulation (3 V, 300/sec.).

D, E. Same preparation with 7 mgm. chloralosane/K. Chloralosane waves recorded from cortex and from left thalamic site (channel 3), which itself yielded a recruiting stimulation, are abolished in all areas and replaced by low voltage fast activity during left bulbo-reticular stimulation (2 V, 300/sec.).

comparing its effect upon the EEG with that of direct, intra-thalamic stimulation of this system. Recruiting responses were obtained by successively stimulating portions of the diffuse system in the left (fig. 11 A) and right (fig. 11 B) sides of the thalamus. The stimulation has the same effect upon the electrogram of its thalamic components that it does upon the EEG, and this influence upon the EEG can be reproduced by the direct high-frequency stimulation of this system within the thalamus.

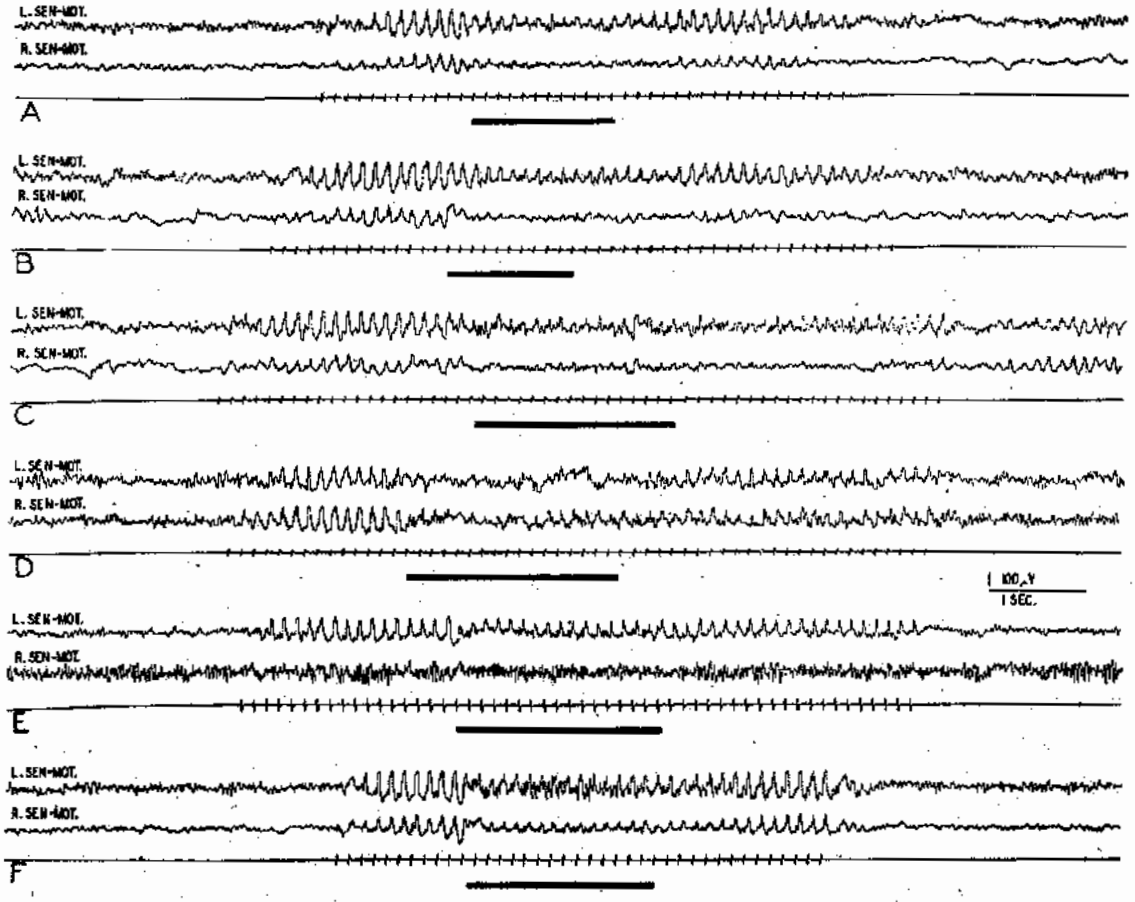

Fig. 13

Abolition of recruiting responses by sensory and reticular stimulation.
Recruiting responses, evoked by left thalamic stimulation (5 V, 300/sec.) in an "encéphale isolé", identically reduced or abolished by loud whistling (A), blowing air on head (B), rubbing nose (C), blowing air on eyes (D), stimulating the right posterior column at 2 V, 300/sec. (E), and stimulating the left bulbar reticular formation at 2 V, 300/sec. (F).

recruiting response to left thalamic stimulation was then repeated and intercurrent stimulation of the same right thalamic site at 300/sec. abolished it as effectively (fig. 11 C) as did subsequent stimulation of the rostral end of the reticular system in the subthalamus (fig. 11 E). As regards the diffuse thalamic projection system, then, reticular

Similar desynchronization, both of spontaneous activity and of the recruiting response has been observed, however, to result from high frequency stimulation of the discretely projecting, posterior part of the ventral thalamic nucleus, and the effect was generalized in the cortex. It remains for further study to determine whether such re-

sponses were mediated by direct cortical projections or, as seems more likely, through other subcortical systems.

After ipsilateral destruction of the intralaminar thalamic region, bulbo-reticular stimulation still desynchronized the EEG bilaterally and as markedly as in initial controls. After extending the lesion until the massa intermedia and intralaminar regions of the thalamus were destroyed bilaterally, bulbar stimulation still seemed to have some effect upon the EEG, but cortical activity was then so reduced that it was difficult to draw conclusions concerning the significance of the results. These findings only serve to introduce the problem of thalamic mediation of the lower brain stem influence upon the EEG, and much added study will be necessary to clarify this subject.

The reticular effect and arousal reactions. In the acute study of arousal reactions, anesthesia cannot be employed, for its major action is to block them, nor is the unanesthetized "encéphale isolé" suitable, for its EEG is typically activated and only rarely exhibits spontaneous synchrony. In the latter preparation, however, recruiting responses sometimes provide a background of cortical activity upon which the arousal effect of natural stimuli can be tested. Figure 13 shows a series of such instances, in which the high-voltage slow waves of the recruiting response were abolished and replaced by low-voltage fast activity, during loud whistling (A), rubbing the nose (B), and blowing air on the head (C) and eyes (D). Indistinguishable from these changes to natural stimuli, except for somewhat faster low-voltage activity, were those produced by electrical stimulation of the posterior column (E) and bulbar reticular formation (F).

Such abolition of recruiting responses by natural or bulbar stimulation was observed only when the frequency and intensity of thalamic stimulation yielding the recruiting response was just above threshold, and in some cases reticular stimulation could still abolish the recruiting response at a time when natural stimuli were ineffective. Because of these and other difficulties in securing stable testing conditions, attempted repetition of arousing natural stimuli after differential interruption of ascending sensory and reticular paths in the anterior brain stem was abandoned in favor of chronic preparations.

DISCUSSION

The evidence given above points to the presence in the brain stem of a system of ascending reticular relays, whose direct stimulation activates or desynchronizes the EEG, replacing high-voltage slow waves with low-voltage fast activity. This effect is exerted generally upon the cortex and is mediated, in part, at least, by the diffuse thalamic projection system. Portions of this activating system, chiefly its representation in the basal diencephalon, have previously been identified.

In the pioneer studies of Morison and his associates, in which the foundation for so much current work upon the EEG was laid, hypothalamic, subthalamic and medial thalamic excitation was found, in 1943, to suppress intermittent Dial bursts without affecting other types of cortical activity, such as responses to sensory stimulation (Morison, Finley and Lothrop, 1943; Dempsey and Morison, 1943). The effect was considered to be inhibitory in nature and was attributed to the excitation of afferent pathways simply passing through this region.

Two years later, Murphy and Gellhorn (1945) found this suppression of Dial bursts, on hypothalamic stimulation, to be accompanied by dispersal of strychnine spikes and by prolonged increase in the frequency and amplitude of low-voltage, background, electro-cortical activity. They pointed out that these latter alterations were excitatory or facilitatory in nature, and attributed the disappearance of bursts to an associated lessened degree of synchrony of firing of cortical neurons, rather than to inhibition. Connections from the hypothalamus to the dorsomedial and intralaminar thalamic region, and thence to cortex, were suggested to provide the channels by way of which these effects were produced and, though the study

was undertaken principally to elucidate hypothalamic facilitation of the motor cortex, the generalized distribution of the EEG changes was emphasized.

More recently still, Jasper and his associates (1948) observed a generalized acceleration of spontaneous electrocortical activity, simulating an arousal or waking reaction, from stimulation of the periaqueductal portion of the midbrain, the posterior hypothalamus and the massa intermedia of the thalamus; and Ward (1949) obtained a prolonged generalized increase in both voltage and frequency of the EEG following stimulation of the bulbar reticular formation.

While interpretation of these findings has been varied, their basic similarity can leave little doubt that each of these investigators has dealt with manifestations of the same system as that described above. The present work thus confirms, extends and interrelates these earlier contributions and, from the mass of observations brought to bear upon it, the existence of this brain stem activating system now seems firmly established.

In discussing the general significance of these findings for electroencephalography, attention should certainly be focussed upon the arousal reaction. The breaking up of synchronous cortical discharge by afferent stimulation, first observed by Berger (1930) as alpha blockade on opening the lids, and since found to be a common response to any type of afferent stimulation, is currently attributed to the desynchronizing action of afferent volleys arriving directly at the receiving areas of the cerebral cortex (Adrian and Matthews, 1931; Adrian, 1947; Bremer, 1938, 1944; Walter and Walter, 1949). A number of relevant observations are difficult to explain on this basis, however.

More than a decade ago, Ectors (1936) and Rheinberger and Jasper (1932) observed that serially repeated stimulation soon failed to induce activation, though afferent volleys presumably continued to reach the cortex, and it was noted that, in order to be effective in this regard such stimuli must arouse the subject to alertness or attention. In addition, when an activation pattern was so induced, it was by no means confined to the receiving area of the afferent system stimulated (see also Bremer, 1943), nor did it appear first in this area and radiate from it. Whether somatic, auditory or, to a lesser extent, visual stimulation was employed, when an arousal reaction was evoked, it appeared simultaneously in all parts of the cortex and often continued for considerable periods in it after afferent stimulation had ceased.

More recently, Monnier's (1949) analysis of the sequence of EEG events induced by visual stimulation in man has shown that alpha blockade is not initiated for a considerable period after the electrocortical changes evoked by the afferent volley are completed, and its prolonged latency might more easily be explained by invoking a subsidiary mechanism than by accounting for it through direct cortical action. Furthermore, the generalized arousal reaction to vestibular stimulation has been shown by Gerebtzoff (1940) to be still elicitable after ablation of the cortical receiving area for this afferent system.

In the present experiments, typical EEG arousal reactions have been reproduced by stimulating the brain stem reticular formation, without exciting classical sensory paths. Crucial evidence that the reticular formation is involved in the arousal reaction to natural stimuli may not yet be obtained but, in addition to being suggested by the data at hand, such a possibility might offer an explanation for the failure of afferent stimuli to evoke arousal from somnolence, lethargy or coma, resulting from injury to the upper brain stem, which left the major sensory paths to the cortex intact (Ingram, Barris and Ranson, 1936; Ranson, 1939; Magoun, 1948). A conception of the arousal reaction in which collaterals from sensory paths first activated the brain stem reticular formation and exerted their influence upon cortical electrical activity indirectly through it, seems a logical postulate from all these observations, and was, in fact, proposed as long ago as 1940 by Gerebtzoff to account

for his observations to which reference was made above.

The proposed participation of the brain stem activating system in the arousal reaction, if established, might represent an aspect of its function concerned with alerting the cortex to abrupt and more or less pronounced alterations in the external environment. It may next be proposed that the presence of a steady background of less intense activity within this cephalically directed brain stem system, contributed to either by liminal inflows from peripheral receptors or preserved intrinsically, may be an important factor contributing to the maintenance of the waking state, and that absence of such activity in it may predispose to sleep.

Bremer's fundamental discovery (1935, 1938) that the EEG of the unanesthetized cerebrum, isolated from the rest of the nervous system by mesencephalic transection, resembled that of an intact brain in natural sleep or under barbiturate anesthesia, led him to the conclusion that sleep is the result of deafferentation of the cerebral cortex. Afferent impulses from olfactory and visual receptors are still accessible to such a "cerveau isolé", and more recent work has indicated that sleep changes in the EEG are best produced by basal diencephalic injury (Lindsley, Bowden and Magoun, 1949). But putting these qualifications aside, it should be pointed out that at the time Bremer's discovery was made, classical sensory paths were the only known connections ascending through the midbrain, to the interruption of which the ensuing sleep changes in the "cerveau isolé" could be attributed. The present identification of a second, parallel system of ascending reticular relays, whose direct stimulation induces EEG changes characteristic of wakefulness, now raises a possible alternative interpretation of Bremer's observations, for the obvious question arises: is the production of sleep in the cerebrum, following mesencephalic transection, to be attributed to deafferentation in the strict sense, or to the elimination of the waking influence of the ascending reticular activating system? Two lines of evidence favor this latter possibility.

As regards barbiturate sleep, Forbes et al (1949) have recently pointed out that the ready conduction of afferent impulses to the cortex under deep barbiturate anesthesia is inconsistent with the view that the sleep-inducing properties of these drugs depend upon functional deafferentiation.[1] Conversely, it has been found in the present study that under barbiturate anesthesia, bulboreticular stimulation is much less effective in activating the EEG than in a chloralosane or unanesthetized preparation. The fact that hypothalamic stimulation is effective under such anesthesia (Morison, Finley and Lothrop, 1943; Murphy and Gellhorn, 1945; Jasper, Hunter and Knighton, 1948) suggests that the blocking of reticular relays within the brain stem may be involved in the production of sleep by barbiturates.

As regards sleep induced by rostral brain stem injury, prolonged somnolence has followed chronic lesions in the basal diencephalon and anterior midbrain which did not involve afferent pathways to the cortex, but which were placed medial and ventral to them in the region of distribution of the ascending reticular activating system (Ingram, Barris and Ranson, 1936; Ranson, 1939), and similar results have followed injury to this region from tumors (Fulton and Bailey, 1929) or encephalitis (von Economo, 1918; Richter and Traut, 1940) in man.

Though somnolence was incontestable, EEG studies were not undertaken in the animals or patients to which reference is made, but more recently Ingram, Knott and Wheatley (1949) have studied alterations in the EEG following chronic, experimental hypothalamic lesions, and the results of acute basal diencephalic and lower brain stem destruction are reported in the succeeding paper (Lindsley, Bowden and Ma-

[1] This argument would appear to apply only to the conduction of a single afferent volley. W. H. Marshall (*J. Neurophysiol.*, **1941**, *4*: 25-43) has observed impairment of conduction of repeated afferent volleys to the cortex under nembutal anesthesia, due to great prolongation of thalamic recovery time.

goun, 1949). In the latter investigation, sleep changes in the EEG, identical with those of barbiturate anesthesia, resulted from basal diencephalic and anterior midbrain lesions which spared sensory pathways to the cortex, but interrupted the rostral distribution of the ascending reticular activating system. Conversely, extensive deafferentiation of the cortex, by section of ascending pathways in the lateral portion of each side of the midbrain, together with bilateral interruption of the optic and olfactory tracts, failed to induce such alterations.

The conception of sleep as a functional deafferentation of the cerebrum is not opposed by this evidence if the term "deafferentation" is broadened to include interruption of the ascending influence of the brain stem reticular activating system, the contribution of which to wakefulness now seems more important than that conducted to the cortex over classical sensory paths.

SUMMARY

1. Stimulation of the reticular formation of the brain stem evokes changes in the EEG, consisting of abolition of synchronized discharge and introduction of low voltage fast activity in its place, which are not mediated by any of the known ascending or descending paths that traverse the brain stem. The alteration is a generalized one but is most pronounced in the ipsilateral hemisphere and, sometimes, in its anterior part.

2. This response can be elicited by stimulating the medial bulbar reticular formation, pontile and midbrain tegmentum, and dorsal hypothalamus and subthalamus. The bulbar effect is due to ascending impulses relayed through these more cephalic structures. The excitable substrate possesses a low threshold and responds best to high frequencies of stimulation.

3. Some background synchrony of electrocortical activity is requisite for manifestation of the response. In the "encephale isolé", reticular stimulation has no additional effect upon the fully activated EEG. With synchrony, in spontaneous drowsiness or light chloralosane anesthesia, the effect of reticular stimulation is strikingly like Berger's alpha wave blockade, or any arousal reaction. In full chloralosane anesthesia, high voltage slow waves are blocked but no increase in lower amplitude, fast activity occurs. With barbiturate anesthesia, the reticular response is difficult to elicit or is abolished.

4. In the chloralosane preparation, the secondary cortical response evoked by a sensory volley is generally unaffected by reticular stimulation. Consequent sensory after-discharge is abolished, however, as is pyramidal tract discharge and jerky movements referable to it. Outside the sensory receiving area, secondary responses themselves may be reduced or prevented.

5. The convulsive spikes produced by local strychnine and those of a fit following supramaximal cortical excitation, are not decreased by stimulating the reticular formation.

6. The cortical recruiting response induced by low frequency stimulation of the diffuse thalamic projection system is reduced or abolished by reticular stimulation.

7. There is some indication that the cortical effect of reticular stimulation may be mediated by this diffuse thalamic projection system, for synchronized activity within it is similarly prevented by reticular excitation, and direct high frequency stimulation of this system, within the thalamus, reproduces the reticular response. It is possible, however, that other mechanisms may be involved in its mediation.

8. The reticular response and the arousal reaction to natural stimuli have been compared in the "encéphale isolé", in which EEG synchrony was present during spontaneous relaxation or was produced by recruiting mechanisms, and the two appear identical.

9. The possibility that the cortical arousal reaction to natural stimuli is mediated by collaterals of afferent pathways to the brain stem reticular formation, and thence through the ascending reticular activating system, rather than by intra-cortical spread follow-

ing the arrival of afferent impulses at the sensory receiving areas of the cortex, is under investigation.

10. The possibility is considered that a background of maintained activity within this ascending brain stem activating system may account for wakefulness, while reduction of its activity either naturally, by barbiturates, or by experimental injury and disease, may respectively precipitate normal sleep, contribute to anesthesia or produce pathological somnolence.

CONCLUSIONS

Experiments on cats have identified a cephalically directed brain stem system, the stimulation of which desynchronizes and activates the EEG, replacing high-voltage slow waves with low-voltage fast activity.

This system is distributed through the central core of the brain stem and appears to comprise a series of reticular relays ascending to the basal diencephalon. Its effects are exerted generally upon the cortex and are mediated, in part, at least, by the diffuse thalamic projection system.

Possible implication of this system in the arousal reaction to afferent stimulation and in the maintenance of wakefulness is discussed.

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Motility, and Concomitant Phenomena, During Sleep[1]

Eugene Aserinsky[2] and Nathaniel Kleitman

Department of Physiology, University of Chicago, Chicago, Illinois

Slow, rolling or pendular eye movements such as have been observed in sleeping children or adults by Pietrusky (*1*), De Toni (*2*), Fuchs and Wu (*3*), and Andreev (*4*), and in sleep and anesthesia by Burford (*5*) have also been noted by us. However, this report deals with a different type of eye movement—rapid, jerky, and binocularly symmetrical—which was briefly described elsewhere (*6*).

The eye movements were recorded quantitatively as electrooculograms by employing one pair of leads on the superior and inferior orbital ridges of one eye to detect changes of the corneo-retinal potential in a vertical plane, and another pair of leads on the internal and external canthi of the same eye to pick up mainly the horizontal component of eye movement. The potentials were led into a Grass Electroencephalograph with the EOG[3] channels set at the longest

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[2] Public Health Service Research Fellow of the National Institute of Mental Health.

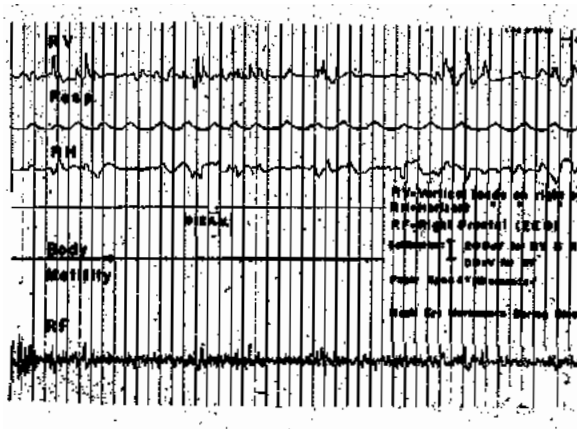

FIG. 1. Sample record exhibiting rapid eye movements i a sleeping subject. RV = vertical leads on right eye; RH horizontal leads on right eye; RF = right frontal (EEG) Calibration: { 200 μv for RV & RH / 50 μv for RF } ; paper speed: 10 se

time constant. Brain waves, lid and jaw muscle ac tivity, and electrode movement introduced superfluou potentials which severely hindered the identificatio of eye movement potentials. To eliminate this diff culty, a monopolar recording was made simultane ously from the frontal area (and occasionally fron the anterior temporal area) to be compared with th bipolarly recorded electrooculogram. In this way, th eye movement potential could be recognized easily a a wave in phase on the monopolar and bipolar re cordings, but with a potential from 2 to 4 time greater on the latter recording. Note that the gain set tings (Fig. 1) for the bipolar recording (RV) an monopolar recording (RF) were adjusted so that a equal excursion of both pens signified that the bipola potential was actually 4 times greater than the mono polar potential. The criterion for identification o eye movement was confirmed by direct observation o several subjects under both weak and gradually inten sified illumination. Under the latter condition, motio pictures were taken of 2 subjects without awakenin them, thereby further confirming the validity of ou recording method and also the synchronicity of ey movements.

Twenty normal adult subjects were employed i several series of experiments although not all the sub jects were involved in each series. To confirm the con jecture that this particular eye activity was asso ciated with dreaming, 10 sleeping individuals in 1 experiments were awakened and interrogated durin the occurrence of this eye motility and also after a period of at least 30 min to 3 hr of ocular quiescence. The period of ocular inactivity was selected on the basis of the EEG pattern to represent, as closely as possible, a depth of sleep comparable to that presen during ocular motility. Of 27 interrogations durin ocular motility, 20 revealed detailed dreams usually involving visual imagery; the replies to the remaining 7 queries included complete failure of recall, or else "the feeling of having dreamed," but with inability to

[3] Electrooculogram.

From Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science*.;118(3062):273-274. Reprinted with permission from AAAS.

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recollect any detail of the dream. Of 23 interrogations during ocular inactivity, 19 disclosed complete failure of recall, while the remaining 4 were evenly divided into the other 2 categories. Recognizing the inadequacies of employing a χ^2 test for the independence of the 2 groups of interrogations, the probability nevertheless on a χ^2 basis is that the ability to recall dreams is significantly associated with the presence of the eye movements noted, with a p value of less than 0.01.

Eleven subjects in one series of 16 experiments were permitted to sleep uninterruptedly throughout the night. The mean duration of sleep was 7 hr. The first appearance of a pattern of rapid, jerky eye movements was from 1 hr 40 min to 4 hr 50 min (3 hr 14 min, mean) after going to bed. This pattern of eye motility was of variable duration and frequently disappeared for a fraction of a minute or for several minutes only to reappear and disappear a number of times. The period from the onset of the first recognizable pattern to the disappearance of the last pattern was from 6 to 53 min with a mean of 20 min. A second period of eye movement patterns appeared from 1 hr 10 min to 3 hr 50 min (2 hr 16 min, mean) after the onset of the first eye motility period. With lengthier sleep there occurred a third and, rarely, a fourth such period. The electrooculogram disclosed vivid potentials with amplitudes as high as 300–400 μv, each potential lasting about 1 sec. This was further striking in comparison with simultaneously recorded monopolar EEG's, from the frontal and occipital areas, which were invariably of low amplitude (5–30 μv) and irregular frequency (15–20/sec and 5–8/sec predominating).

In another series of experiments involving 14 subjects, the respiratory rate was calculated for a minimum of ½ min during eye motility and compared with the rate for a similar duration 15 min before and after an eye motility period. The respiratory rate had a mean of 16.9/min during eye motility in contrast with 13.4/min during ocular quiescence. By using Fisher's t-method, the difference in rates was found to be statistically significant with a probability of less than 0.001. Experiments now in progress suggest that heart rate also is probably higher in the presence of these eye movements. Body motility records were secured in 6 experiments by attaching a sensitive crystal to the bed spring and leading the output through a resistance to a Grass preamplifier. In every case the eye motility periods were associated with peaks of overt bodily activity although the latter were frequently present in the absence of eye movments.

Data obtained from the 2 female subjects used in these experiments were at least qualitatively similar to that obtained from males.

The fact that these eye movements, EEG pattern, and autonomic nervous system activity are significantly related and do not occur randomly suggests that these physiological phenomena, and probably dreaming, are very likely all manifestations of a particular level of cortical activity which is encountered normally during sleep. An eye movement period first appears about 3 hr after going to sleep, recurs 2 hr later, and then emerges at somewhat closer intervals a third or fourth time shortly prior to awakening. This method furnishes the means of determining the incidence and duration of periods of dreaming.

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Sleep Characteristics of Infants[1]

NATHANIEL KLEITMAN AND THEODORE G. ENGELMANN.
From the Department of Physiology, University of Chicago, Chicago, Illinois

ON THE BASIS of older reports in the medical literature, the Children's Bureau (then of the Department of Labor), in its folder on the subject, published in 1937 (1), suggested that at birth an infant required 20–22 hours of sleep per 24 hours, and at 6 months (including daytime naps) 16–18 hours. However, published figures showed that actually few infants had the 'required' amount of sleep. From 624 records of 107 infants, obtained by the parent interview method, Thompson (2) found that the duration of sleep of infants was 19.8 hours in the fourth week of life and gradually decreased to 15.6 hours in the 28th week. That even these figures were probably too high was realized by Thompson herself, as she had no way of determining the fraction of the time that the infants were awake, though lying quietly in their cribs. Precise information was obtained by the laborious method of continuously watching a new-born infant during the first 15 days of life. As summarized by Gesell and Amatruda (3), the figures for the particular infant show that it slept on the average, only about 62.5% of the time, or 15 out of every 24 hours. Furthermore, even at this early age there was a disparity between the incidence of sleep in the daytime (27%) and at night (35.5%). These figures were in line with the earlier observation of Marquis (4), made on four neonates on a self-demand feeding schedule, that the interfeeding intervals were, on the average, 2.86 hours by day and 3.61 hours at night, with the day-night difference for each infant statistically significant. She also noted that periods of quiet exceeding 3 hours predominated at night (23 out of 28), whereas periods of less than 2 hours of inactivity occurred mainly in the daytime (34 out of 48). Still, the widely-circulating *Infant Care,* the eighth edition of which was published by the Children's Bureau (now of the Federal Security Agency) in 1951 (5) maintains that "for the first week or two a baby may be awake only about 2 hours out of the 24", and that at 6 months the total duration of sleep may be 15–17 hours—a decrease of one hour from the 1937 figures.

The data of Marquis and those of Gesell and Amatruda called for a reevaluation not only of the currently accepted figures for total duration of sleep in the young infant, but also of evidence of very early acculturation to the diurnal pattern of community and family living.

METHODS

The use of costly recording equipment limited the number of subjects (10 boys and 9 girls), and we chose those whose parents were either University students or professional people living in the University neighborhood. Observations usually

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started within a few days after the return of the mother and baby from the hospital and thus comprised the span from the 3rd to the 26th week of life. It was decided not to carry the study beyond 6 months because at that age, as shown by their diurnal body temperature curves (6), the infants are well acculturated, and, more important, they no longer 'stay put' when placed in their cribs.

The mothers were supplied with mimeographed daily data forms with two columns of 12 hours each corresponding to the calendar day. There was ample room for reporting events on a quarter-hourly basis, and a simple code letter and line system made notation easy, thus encouraging full reporting. The forms were collected every week or oftener and the contents checked with the mothers while the events were still fresh in their minds.

More objective data were obtained by means of a mechanical recording device attached to each crib on the incidence and magnitude of the babies' movements (except for the time they were out of the cribs). The records (actograms) consisted of continuous tracings on waxed-paper tape driven at a rate of $3\frac{5}{32}$ in/hr. by a synchronous electric motor. One crib had, additionally, an electronic device (detailed description in another paper) having an electric clock running only when the infant moved, and every summated minute of activity run-up on the clock was automatically marked by a signal magnet on the actogram. Data on two infants were obtained by this device.

The mothers were required to enter on the daily data forms, as accurately as possible, *a*) the time the infant spent in and out of the recording crib; *b*) the time asleep and awake; *c*) the time of feedings and their nature (breast, bottle, spoon, etc.) and amounts fed in ounces or teaspoonfuls; and *d*) baths, diaperings, outings, crying spells, play, etc.; also sicknesses and inoculations. They were expected to see that their babies received a monthly pediatric check-up while they were subjects in this study. Finally, they began, not earlier than at the age of 6 weeks, a feeding program, with the pediatrician's consent, calling for: *a*) meat, in a finely divided form, at least once daily for 2 weeks; *b*) no meat for 2 weeks; *c*) meat, at least once daily, on alternate days for 2 weeks. This 6-week feeding schedule was followed until the infants reached the age of 26–28 weeks.

A large sheet of graph paper (K and E Simplex 8 x 8 cross-section, illustrated in fig. 3) was used for a condensed account of each infant's collected entries. A single line was given to each 24-hour period, with divisions for 2 hours, 1 and quarter hours. Blackened stretches of these lines represented periods of sleep. Every eighth horizontal line was left blank, thus breaking up the record into weeks. The week was the smallest time unit used for tabulating the development of the sleep-wakefulness pattern in the individual infants, as well as for composite figures on all the subjects. In the latter case, data for boys were grouped separately from those for girls. A larger time unit, the 4-week interval, of which there were six within the time-span of observation, was utilized for determining the longer range changes in the diurnal distribution of sleep-wakefulness, feedings, and diaperings.

By arrangement with, and at the convenience of, individual mothers, direct notations of the infants' behaviors were made by two observers who concentrated their attention on the different positions assumed and types of movements executed by the infants, prior to, during and immediately following daytime naps, thus obtaining information on sleep characteristics not furnished by the mothers, nor revealed by the actograms.

An attempt was made to determine the amount of activity as well as the type

of movement associated with the onset of 'frank' sleep and with waking from such sleep. 'Frank' sleep was defined as a period of 15 minutes or more, occurring after eye closure, during which no muscle activity was observed.

The subjects were nine of the infants (5 males and 4 females), ranging in age from 1½–6 months. They were observed in their homes during mornings and afternoons, while lying in specially constructed cribs described above. As these observations were made during the summer months, the infants were rarely covered. Thus were they more free to move than if weighed down by several blankets, and their movements were more easily observed.

Notes were made of all motility occurring during each minute of the observation period. Symbols of two kinds (letters and numbers) were used to denote the various types of movements. The letters referred to the part of the body involved as well as to posture and the numbers referred to the type of activity, which also included sounds. To score the amount of activity per minute, three categories were used: low (one recorded movement/min.), medium (2–3 movements), and high (4 or more movements). Later the individual observations on each infant were combined into a single curve giving that baby's activity pattern.

Closure of the eyes is a generally accepted behavior feature associated with the process of going to sleep. In this phase of the study an attempt was made to describe in detail the types of eye movements (both of the eyeballs and of the lids) and their changes in relation to the onset of sleep. Fourteen infants (8 males and 6 females), ranging in age from 1–6 months, were the subjects for direct observations. In all cases the infants were studied while they lay in the specially constructed cribs which recorded general body motility upon a moving tape. The observer inscribed upon this tape symbols denoting the state of the eyes, whether open or closed, and also the movements as they occurred. For recording eye movements, such as blinking, a signal magnet was set up whereby a mark was inscribed by the observer.

Results

Data obtained were treated under several headings: variation in the duration of sleep per 24 hours in each of the 24 weeks of observation, with a similar determination of the number of feedings and diaperings per day; the diurnal distribution of sleep and wakefulness as well as the incidence of feeding, by hours, for six successive 4-week periods; direct observation of infants during afternoon naps and the reinterpretation of the motility records in the light of these observations; lastly, the effect of meat in the diet on the several sleep-wakefulness characteristics investigated.

The total duration of sleep and its variation in individual infants are shown in table 1. The mean values, based in part on the data supplied by mothers, but corrected by the information obtained from the actogram records, are all much lower than had heretofore been accepted for infants in the age range studied. Not only were there no summated durations of sleep of 21–22 hours/day for even the youngest infants, but, as can be seen from table 1, out of 2873 infant-days, on only 73 (slightly over 2.5%) was the total sleep 18 hours or over, and this was more than balanced by the 128 days (4.5%) when the sleep per 24 hours was under 11 hours. Furthermore, the total sleep of individual infants, arranged in an ascending order, ranged from a mean of 49% (11.76 hr.) to 68% (16.32 hr.). The figures for several infants show good normal curve distributions, with the modes ranging from a low of 12–12.99 hours to a high of 16–16.99 hours. The frequency distribution of the total

hours of sleep per 24 hours for the whole group of infants, in the farthest right column of table 1, fall into a much smoother probability curve, whose mode of 14–14.99 hours is exactly midway between the extreme values for individual infants.

The progressive changes in the total duration of sleep for the group as a whole in the course of the period of observation are given in table 2. It can be seen from the latter that the group mean total duration of sleep in the 3rd week was a little under 15 hours, and it remained fairly constant, with minor fluctuations, till the 14th week, inclusive—the first half of the period of observation. During the remaining 12 weeks there was a gradual but consistent decline to a low of 13 hours and 48 minutes for the 26th week. There was thus no change in the total duration of sleep during the first 3 months of the group's postnatal life, and a mean decrease of only 1 hour in the second 3-month period.

More revealing are the variations in the sleep-wakefulness partition for the two 12-hour halves: the night fraction, corresponding (with slight variations for individual infants) to the hours of 8 P.M. to 8 A.M., and the remaining day hours, 8 A.M. to 8 P.M., also shown in table 2. The mean duration of the night sleep for the group was $8\frac{1}{2}$ hours for the 3rd week. This gradually rose to reach and then surpass 10 hours during the 12th week and thereafter remained remarkably constant to the end of the 26th week. An entirely different variation was found in the mean total duration of sleep for the 8 A.M. to 8 P.M. interval which even in the 3rd week was not quite $6\frac{1}{2}$ hours, or 2 hours under the duration of the night sleep. The total length of the day sleep decreased slowly and continuously until it was a little over $3\frac{1}{2}$ hours in the 26th week. For the first half of the period of observation (weeks 3–14) the decrease in the day sleep almost exactly balanced the increase in the night sleep, but thereafter the decreasing values for the day sleep completely accounted for the progressive falling-off in the total duration of sleep per 24 hours.

The constantly increasing influence of acculturation, and the resulting disparity between the day and the night sleep-wakefulness demarcations, are shown in the spot curves of figure 1. The day-night asymmetry already present in the first 4-week period (weeks 3–6) becomes more pronounced in the following five periods. The

TABLE 1. FREQUENCY DISTRIBUTION OF HOURS OF SLEEP/24 HR. OF INDIVIDUAL INFANTS DURING WHOLE PERIOD OF OBSERVATION (WEEKS 3–26)

Duration of sleep *hr.*	Infants																		
	6M	*1M*	*7F*	*8M*	*5F*	*2M*	*4F*	*9M*	*10M*	*6F*	*3F*	*8F*	*4M*	*2F*	*7M*	*3M*	*9F*	*10F*	*5M*	Total
7– 7.99	2																			2
8– 8.99	8		1	2		1			1											13
9– 9.99	11	5	4	4	1					1	1									27
10–10.99	26	17	5	11	6		2	2	3	3	1									76
11–11.99	34	22	9	13	9	12	4	3	8	10	9	1		2		3	2	1		160
12–12.99	57	27	33	40	33	29	21	7	13	18	14	8	6	10	6	6	5	2	1	336
13–13.99	25	27	55	51	55	34	41	19	40	31	23	31	11	19	19	31	12	13	3	528
14–14.99	1	16	29	34	27	47	39	30	27	35	51	45	34	40	39	18	24	23	15	578
15–15.99	4	11	9	8	20	26	37	16	37	33	35	42	44	43	36	34	37	32	44	548
16–16.99		3	7	1	8	14	19	10	14	10	25	14	26	32	37	26	26	25	51	348
17–17.99			1	3	3	4	5	4	8	9	7	5	7	12	20	27	10	19	38	181
18–18.99			2		1	1			2	5	1		1	8	5	15	7	5	5	58
19–19.99									1	2	1			2	1		1	4	2	14
20–20.99																1				1
Mean duration of sleep, %	49	53	55	55	57	59	60	60	60	60	61	62	64	64	65	65	65	65	68	

night portions of the curves (8 P.M. to 8 A.M.) are well established during the third 4-week period. However, in all six periods the incidence of sleep is greatest for the hours of 1–3 A.M., the fractions of time being spent in sleep during these 2 hours, for the six periods, being, successively, 0.795, 0.895, 0.955, 0.970, 0.965, and 0.985. The day halves of the curves show two characteristic features. One is that the lowest incidence of sleep was not in the middle of the day, but toward its end, corresponding to the evening meal hours. For the first three periods the hours with the least sleep

TABLE 2. VARIATION IN MEAN DURATION OF INFANTS' SLEEP FROM 3RD–26TH WEEK OF LIFE, EXPRESSED AS FRACTIONS OF TOTAL TIME AND AS CORRESPONDING HOURS, AND MEAN NUMBERS OF FEEDINGS AND DIAPERINGS/DAY

		Da		Ni		T			
W	Nu	f	h	f	h	f	h	F	Di
3	10	.530	6.36	.708	8.50	.617	14.86	7.3	9.2
4	14	.537	6.44	.694	8.33	.618	14.77	6.9	9.0
5	15	.523	6.28	.703	8.42	.613	14.70	6.7	9.2
6	16	.503	6.04	.702	8.42	.603	14.46	6.6	9.1
7	16	.472	5.66	.724	8.69	.598	14.35	6.2	8.9
8	16	.457	5.48	.753	9.04	.603	14.52	6.0	8.6
9	19	.456	5.47	.769	9.23	.612	14.70	5.9	8.7
10	19	.449	5.39	.797	9.56	.622	14.95	5.4	8.3
11	19	.432	5.18	.803	9.64	.618	14.82	5.2	8.7
12	19	.413	4.96	.841	10.05	.627	15.01	4.9	8.7
13	19	.405	4.86	.840	10.04	.622	14.90	4.7	8.1
14	19	.409	4.91	.835	10.01	.622	14.92	4.8	8.2
15	19	.386	4.64	.835	10.01	.611	14.65	4.7	8.1
16	18	.369	4.43	.854	10.12	.613	14.55	4.9	8.7
17	18	.361	4.33	.856	10.13	.608	14.46	5.1	8.9
18	18	.362	4.34	.845	10.07	.605	14.41	5.0	8.9
19	18	.353	4.24	.828	9.95	.590	14.19	5.0	8.6
20	18	.352	4.22	.836	10.02	.594	14.24	5.0	8.5
21	18	.335	4.02	.837	10.02	.587	14.04	5.2	8.5
22	18	.329	3.95	.838	10.03	.584	13.98	5.0	8.7
23	18	.338	4.06	.839	10.04	.589	14.10	5.0	8.5
24	18	.322	3.86	.841	10.05	.582	13.91	5.0	8.4
25	17	.318	3.82	.843	10.06	.578	13.88	5.0	7.9
26	16	.301	3.61	.848	10.08	.575	13.69	5.1	8.0

W, week of life; *Nu*, number of babies; *Da*, day interval, usually 8 A.M.–8 P.M.; *Ni*, night interval, usually 8 P.M.–8 A.M.; *T*, 24-hr period of day and night; *F*, feedings; *Di*, diapering; *f*, fraction of period; *h*, corresponding hours.

were 6–8 P.M., and for the last three, 5–7 P.M., the corresponding six values of diminishing sleep fractions were 0.460, 0.395, 0.295, 0.245, 0.225, and 0.190. The other feature is the establishment of regular daytime nap-periods of 10 A.M. to noon, and 3–4 P.M. A suggestion of these can be seen in the curves for the third and fourth periods (weeks 11–18), but they are definitely marked-out in the last two periods (weeks 19–26).

The mean number of feedings per day, starting out with about seven, dropped to just under five by the 12th week (table 2) and thereafter, following a further slight decrease during weeks 13–15, rose to about 5, where, like the duration of night sleep,

it became stabilized. That the decrease in the number of feedings was due mainly to the elimination of the night feedings is shown by a breakdown of the incidence of

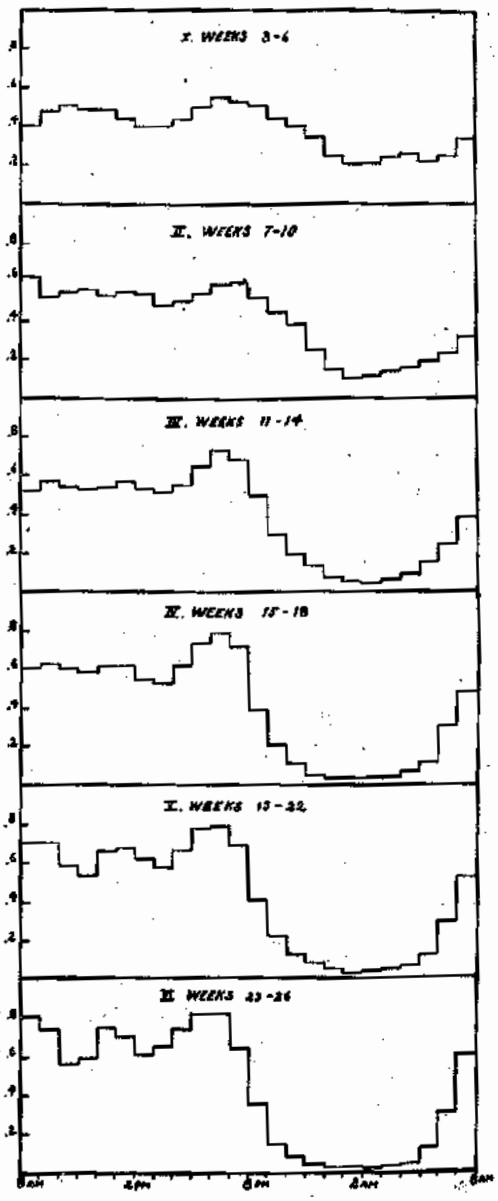

FIG. 1. The sleep-wakefulness partition in each of six successive 4-wk. periods of observation. Twenty-four hourly fractions of the day from 8 A.M. are indicated in the *abscissae* of the lower-most section but apply to all the sections. The height of the column above each hourly division, as indicated in the *ordinates*, represents the mean fraction of the hour that the group was awake. The area below each line of demarcation thus represents the total fraction of the 24 hr. that the infants were awake. Conversely, the areas above the lines of demarcation represent the corresponding sleep fractions. Total mean duration of sleep figures for the successive 6 periods were 14.70, 14.63, 14.91, 14.52, 14.11, and 13.90 hr.

feeding into day and night fractions, the former being quite uniform during all periods and the latter dropping from a little over three to slightly over one by the beginning of the third 4-week period (fig. 2). The 2-hour interval of the highest mean incidence of feeding was 5–7 P.M. (parents' supper time) and showed a gradual rise

(0.67, 0.72, 0.74, 0.81, 0.87, and 0.89 feeding in these 2 hours) through all six 4-week periods. The lowest mean incidence of feeding, occurring between 1 and 3 A.M., showed a sharp drop in the first two 4-week periods (weeks 3–10) and remained constant, and extremely low, from then on (0.37, 0.14, 0.07, 0.07, 0.03, and 0.03 feeding in these 2 hours).

The mean numbers of diaperings per day averaged about $8\frac{1}{2}$ (table 2), and there was little variation in the several 4-week periods, except that they were slightly higher than the mean in the first (weeks 3–6) and a little lower in the last (weeks 23–26). There were, however, considerable variations in the mean number of diaperings per day among the several infants, for some the mean value for the whole period of observation being five or less, whereas for others it exceeded 11. Whether these mean numbers depended upon the needs of the particular baby, or the over-solicitude or negligence of the mother, was not determined.

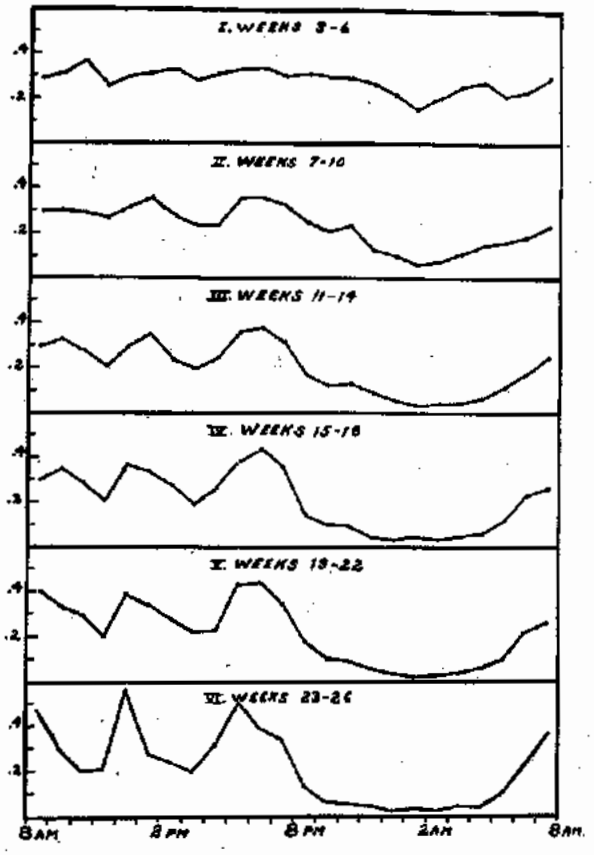

FIG. 2. Development of a diurnal feeding pattern through the six successive 4-wk. periods of observation. *Abscissae* are the same as in fig. 1. *Ordinates* represent the mean incidence of feeding for each of the 24 hr. of the day and night. A value of one in the *ordinate* would indicate that all the infants were fed during that hour on each of the 28 days of the 4-wk. period, and that never occurred.

Although the meat feeding was started in some infants at the age of 35–45 days, the treatment of the duration of sleep figures as related to that factor was confined to the last four 4-week periods (weeks 11–26). During these 16 weeks, it will be recalled, the duration of night sleep was constant and thus could have no bearing on the order in which the three schedules were staggered (2 weeks of daily meat feeding,

2 weeks of cereal substitute for meat, and 2 weeks of alternate meat and cereal feedings). The results obtained revealed no difference individually or collectively between the night hours of sleep on the various feeding schedules, thus demonstrating that meat feeding in no way interfered with the infants' sleep.

In arranging the numerical data, the figures for the boys were always tabulated separately from those of the girls. The mean values for the two sexes were then compared and the statistical significance of the differences, if any, between the two group means, determined. Thus, it was found that as a group the girls slept a little longer than the boys, but the difference, about 15 minutes, was of no statistical significance, and was found to result from some unusually low values for a few boys. A glance at table 1 will reveal that the two lowest mean sleep durations (49% and 53% of the time) were those of boys (*M*), whereas for the two highest ones (65% and 68% of the time) the sexes were mixed. The difference between the mean longest unbroken sleep durations of the two sexes was much more pronounced, the figures being 8.4 hours for the boys and 9.45 hours for the girls, but the intra-group variations were so great that even this large difference was not statistically significant.

It was also found that the boys averaged a fraction of a feeding to a whole feeding more per day than the girls, and that the boys required about one more diapering per day than did the girls, but these differentials were not significant. For other variables, the figures for the two sexes were so close and their courses criss-crossed so many times that there were no differences to evaluate.

One girl infant's adjustment to the community diurnal pattern was so striking as to merit special description. It was a first baby and its parents were sufficiently indulging to permit it to set its own sleep-wakefulness and feeding schedule. The top and bottom of figure 3, in which the progress of this infant is shown, do not differ from any other infant's chart. They show an initial haphazard distribution of sleep and feedings and a terminal adjustment to an uninterrupted 10-hour sleep during the night (8 P.M. to 6 A.M.), short naps and feedings during the intervening hours. But there the similarity ends. This infant began its adjustment by developing a 25-hour periodicity. This is evident from the successive displacement to the right of the clusters of daily feedings, the white spaces of wakefulness and the bands of 'long' sleeps, which all together give the impression of a milky way running diagonally across. From the 4th to the middle of the 7th week a whole 24 hours was thus gained, and the milky way begins its second spiral. (It is best to envisage the chart as the side-surface of a cylinder, with a circumference of 24 hours, slit along the midnight line and laid flat. With a slight distortion, the lines would form a continuous time-line, as the end of one day is the beginning of the next.) The second turn of the milky way is whiter, due to a partial consolidation of the sleep and wakefulness fractions, and also slightly steeper, because of the shortening of the 'diurnal' period from 25 hours to a mean of 24.86 hours during the 4-week interval between the middle of the 7th week and middle of the 11th. The mean total duration of sleep up to this point is slightly over 63% of the time, which is quite in agreement with the corresponding figures for other infants. The third spiral of the milky way has a much greater slope than the first two, requiring 7 weeks (to the middle of the 18th week) to gain 24 hours, the mean 'diurnal' period being down to 24.5 hours. The mean total duration of sleep during the 7 weeks in question is down to 61% of the time. From the middle of the 18th to the end of the 21st week, the consolidated long sleep hours, as well as the much widened light space, appear stationary, indicating that the diurnal periodicity is now down to the astronomically correct 24 hours.

However, community-wise the adjustment is far from perfect, as the long sleep starts at midnight or later. A secondary adjustment, involving a temporary shortening of the diurnal period to 23.86 hours, causing a leftward displacement of the night sleep to the 8 P.M. to 6 A.M. interval, occurred during weeks 22–24, and the last 2

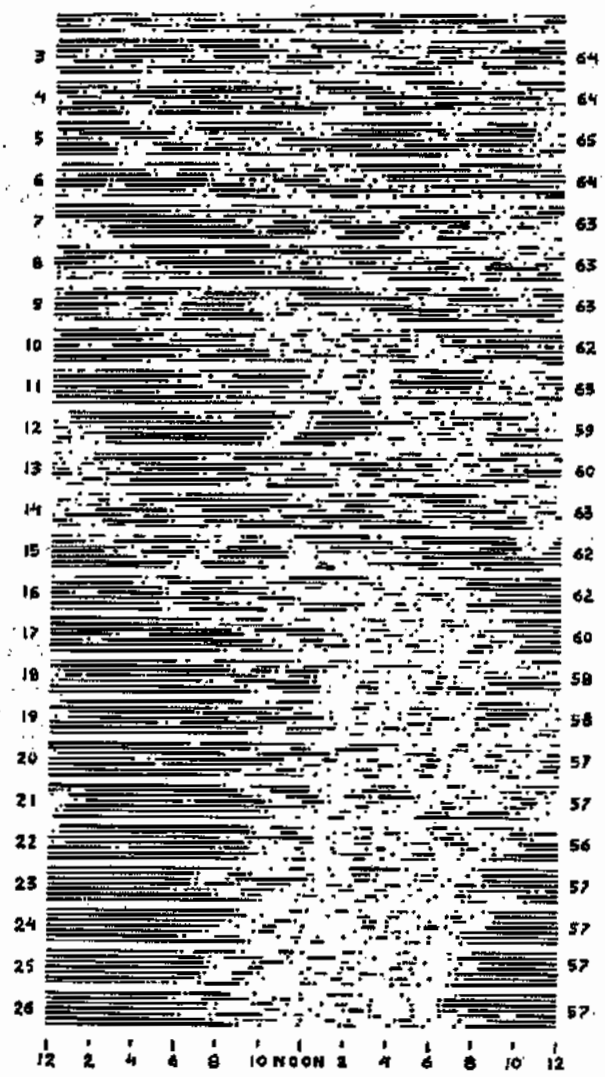

FIG. 3. The incidence of sleep and feeding in Infant *4F*, from the birth to the 182nd day of life. Each line represents a 24-hr. calendar day; the *dark bands* are sleep periods, measured to the nearest 5-min., the *breaks* between the lines—wakefulness, the *dots*—feedings. Each group of 7 lines is separated from the adjacent groups by a double space, the weeks are numbered on the left, the figures on the right being the percentage of time spent in sleep during the successive weeks. Time, in 2-hourly intervals, at the bottom. (Further details in text.)

weeks of observation again show a 24-hour periodicity, with adjustment, both astronomical and social, complete. The mean total duration of sleep from the middle of the 18th week fluctuated about 57% of the time, which is again in accord with the data for other infants. How many other infants would manifest a similar non-24-hour periodicity prior to complete diurnal adjustment, if their parents were as indulgent as those of *infant 4F*, is hard to say, but we noted a suggestion of spirals in the chart of another infant, who enjoyed a complete self-demand schedule of feed-

ings. However, the charts for practically all of the other infants show a rather definite, though not always sharp, consolidation of the night sleep at the conventional hours by the 12th–14th week of life.

Body Positions and Motility. Of the 45 observations made (38 male and 17 female) 40 (31 male and 9 female) were suitable for this treatment. Because of the small number of female observations in relation to male observations, it was felt that no valid comparison could be made between the two sexes.

In general, the amount of activity during the onset of sleep decreased gradually, though with minor fluctuations, from high to zero motility over a period of about 20 minutes. Toward the end of this period, there were usually several minutes of quiescence, interspersed with minutes of low and sometimes medium motility. The pattern of awakening with relation to the amount of activity was the reverse of that during the onset of sleep, in that there was a rise from quiescence to high motility. However, the rise occurred more quickly, and minutes of quiescence between minutes of low or medium motility were found less frequently. No age difference in the pattern of activity was discerned in the group studied.

A somewhat different pattern than the above was observed in one male infant. He showed not only a shorter period preceding 'frank' sleep, but also a sharper falling-off in activity from high to zero, with single minutes of quiescence occurring rarely. His awakening pattern was also more abrupt than that of other infants, usually rising from zero to high in a few minutes.

As to type of movement during the onset of sleep, high motility was characterized by continuous movement which tended to involve the whole body. The movements were often so rapid that they could only be described as general body activity. As activity decreased, individual movements were discernible, and they often involved only a part of the body, as a turn of the head. The movements of the whole body which did occur were of short duration and more reflexive, as a body jerk, than those during high motility. The type of movement observed during awakening was very similar to that during onset of sleep, except that the low motility periods showed differences in frequency of some of the movements. A comparison was made of the last movement at the onset of sleep with the first movement after deep sleep. In both cases body stirrings occurred most frequently: 42% of the time at the onset of sleep and 48% after deep sleep. The second most frequent movements were turning of the head at the onset of sleep and body squirmings after deep sleep, both in 29% of the sleep sessions. While head turnings occurred after deep sleep and body squirmings before, they were rather rare. The third most frequent movement was a body jerk: in 16% of the cases before, and in 9% after deep sleep. An age difference in type of movement was apparent only during high motility, showing itself in the older infants in better coordination and a larger repertoire of movements. During the medium and low periods of motility the same type of movements were observed at all ages in our sample.

Eye Positions and Motility. Of a total of 119 daytime observations, there were obtained only 68 records (51 on 7 males and 17 on 4 females) which were suitable for analysis. In general, the eyes did not close abruptly during the change from wakefulness to sleep. Instead, there was a variable period in which the eyes alternately opened and closed. While the eyes were closed, the eyeballs could be seen moving in all directions. Vertical eye movements were less frequent than horizontal movements. However, the vertical eye movements were rather prominent in the early period and often pushed the lids upwards, so that the sclera or cornea was uncovered. While the

eyelids were closed, the eye movement decreased in frequency, until no overt activity could be discerned by the observer. These movements lasted a variable period up to a half-hour in one instance, but usually continued approximately 5–10 minutes. Body movements appeared to be present whenever eye movements were noticed. However, eye movement often persisted for a few minutes after the cessation of all body movement.

The period of 'absolute' quiescence or 'deep' sleep, in which neither ocular nor body motility was observed, endured for a fairly constant limited range of time. The mean time for the group of infants was about 23 minutes, but the mean for individual infants varied from 16.9–26.8 minutes. Neither an age nor a sex difference was apparent. Eye movements either began abruptly with the first body movements of awakening, or else preceded these body movements by a very short interval, usually less than one minute. Generally, the period of 'absolute' quiescence ended with an abrupt eye squinching followed by eye opening and general body motility. The infant then either became obviously awake (crying, etc.) or else went through another sleep period.

One of the purposes for which direct observations were made of waking and sleeping infants, while they were in the 'recording' cribs, was to enable us better to evaluate the continuous tape records of their motility. It was thus possible to distinguish motility during sleep from that in the waking state and thereby to get a more correct figure for the hours of sleep, usually lower than derived from the mother's protocols. Further, the correlation of direct observations of body and eye motility with the concurrently made autograms permitted the detection of short sleep-wakefulness cycles, which could otherwise not be deduced from the tape records alone. Three hundred and seventy-three such cycles were delineated in records of seven infants (5 boys and 2 girls), covering 104 days, including, of course, the hours between midnight and 6 A.M., when the infants were generally thought to be continuously asleep. The motility patterns on the tapes indicated that periods of 'absolute' quiescence similar to those observed directly in the day time were interrupted by intervals of activity in a fairly regular fashion. The mean duration of a complete sleep-wakefulness (quiescence-motility) cycle was about 1 hour. By comparison, direct observation of one infant at night revealed a mean cycle length of 56.3 minutes, for three cycles, and similar observations of seven infants during the day time yielded a mean value of 59 minutes, for 17 cycles.

Electronic Recorder. By its use, data were obtained on the actual time spent in motility, expressed in minutes per hour, by two boys: *11M*, between the 8th and 16th weeks of life, and *12M*, between the 11th and 26th weeks. The diurnal fluctuations in the time spent in motility closely paralleled the variations in frequency and amplitude of movements, as revealed by the actograms, also obtainable only while the infants were in their cribs, and, when charted, resembled the sleep-wakefulness curves shown in figure 1. The smallest time spent in motility was 2–4 min/hr., between 10 P.M. and 4 A.M., by *11M*, and 1–2 min/hr. between 1 and 7 A.M., by *12M*. As these were nightly sleep hours, infant motility is somewhat higher than that of adults during sleep, the latter averaging about 30 sec/hr. (7). Highest motility, 16–18 min/hr., was registered by *11M* at 8–10 A.M. and 7–8 P.M., and like his sleep motility, was only one half that much for *12M*, occurring for the latter from noon to 2 P.M., and 8–9 P.M. It should be remembered that the figures for the highest motility cited were obtained while the infants were in their cribs, though undoubtedly awake, and did not necessarily represent maximum activity of an infant, playing or

crying, outside of the crib. Therefore the minimal values, as obtained by the electronic recorder at night, while the infants were practically continuously in their cribs, are probably more representative of motility during sleep than the maximal ones, obtained during hours partly spent outside of the crib, are of activity of infants while awake. With this limitation in mind, the total time spent in activity by summating the means for the individual hours comes out as 3.75 hours for *11M*, and 1.5 hours for *12M*, per 24 hours. It is clear that wakefulness in infants is not synonymous with overt skeletal muscular activity.

Discussion

Although the findings of Gesell and Amatruda (3) that a neonate slept only 15 hours out of 24 seriously challenged the older notion concerning almost continuous sleep of young infants, the figures applied to only one individual, who might have been an exceptional case. Furthermore, they were obtained by uninterrupted direct observation for 14 days, and this is not only costly, but is inapplicable to behavior studies under family home conditions. On the other hand, dependence on parents' reports alone is unsatisfactory, and a combination of the latter with actograms is only a little better, if the motility records are not properly evaluated. In our study, concurrent direct observation and automatic recording of the infants' motility enabled us to distinguish between wakefulness and sleep, and thus to determine accurately when and for how long the infants were awake when presumed to be asleep. As seen from table 1, our figures, gathered on 19 infants, not only confirm those of Gesell and Amatruda, but extend them to the end of the first half-year of life. While our subjects as a group had a mode of 14–15 hours of sleep, individual infants had their own ranges of total duration of sleep, with modes as low as 12–13 hours and as high as 16–17 hours.

That there was a decrease of only one hour in the total sleep in the first 6 months of life was also in conflict with accepted notions of a drop from 22 to about 16 hours in that length of time. This small change in total duration of sleep was overshadowed by the dramatic distributional shift of early acculturation. This, too, was seen in the neonate by Gesell and Amatruda, as well as by Simsarian and McLendon (8), who also reported figures on only one infant, from the 3rd to 14th day of life. Less accurately determined, the mean duration of sleep of the latter neonate was 16.5 hours, of which 9 were at night and 7.5 in the day time. The inequality in the distribution of the periods of quiet and the length of the interfeeding periods of four newborn infants reported by Marquis (4) point in the same direction. We were able to extend these pioneer findings, with weeks 3–26 fairly evenly divided into *a*) 12 weeks in which the decrease in day sleep matches an increase in night sleep, the total duration of sleep unchanged, and *b*) 12 weeks in which the decrease in the total duration of sleep is entirely due to a smaller day fraction, the duration of the night sleep remaining the same. From the developmental standpoint, it may be said that the infants showed no increase in the total hours of wakefulness per 24 hours in the first 3 months of life, but were able to add 1 hour of wakefulness during the second 3 months.

The existence of a day-night disparity in incidence and duration of sleep in the newborn, prior to acculturation, is probably related to differences in temperature, noise, and other extraneous periodicities of a diurnal wave length. The detection of a 25-hour sleep-wakefulness cycle in one infant (*4F*) suggests that there may be a 'natural' rhythm which only has to be adjusted to the 24-hour alternation of night and

Under ordinary conditions, community and family routine of living is suffi-ly dominant to prevent periodicity other than the 24-hour one from manifest-itself during acculturation.

With respect to the number of feedings per day, our data are in agreement with e of Marquis (4) and of Sinsarian and McLendon (8). The decrease from seven ings to five per 24 hours is accomplished within the first 3 months of life, con-itantly with the establishment of a continuous 10 hours of sleep at night, and is a part of the acculturation process. Early feeding of finely pureed meats does interfere with this process.

Our data on number and type of body movements confirm, in the main, earlier lts of Irwin (9), from whom we borrowed the system of notation, and of Marquis). Aside from enabling us to interpret the actograms with greater accuracy, the ct observations led to the detection of a fundamental rest-activity cycle of about hour, later modified, distorted, and in part abolished, by the adjustment to the nal routine of living. This cycle has been previously described by several authors, ably Denisova and Figurin (11) who found that the respiration and heart rate sleeping infants underwent regular acceleration and retardation, with a periodic-of about 50 minutes. Further treatment of this fundamental short-term cycle ll appear in another report.

Summary

From protocols kept by their mothers on specially designed forms and continu-s actograms, the incidence and duration of sleep was followed in 19 infants, from e 3rd to the 26th week of life, under family home conditions. Even the earliest cords revealed a diurnal disparity, the mean group duration of night sleep being 4 hours, as against 6.4 hours for day sleep. The adjustment of the sleep-wakefulness attern manifested itself mainly in a progressively more pronounced diurnal periodic-y, culminating in one long unbroken period of night sleep and short morning and fternoon naps.

For the several infants observed, the rate of activity at the onset of sleep de-reased gradually, though not always steadily, to zero. During awakening, activity ncreased more abruptly than it had previously decreased and showed fewer fluctua-ions or a more steady rise. Eye movements gradually subsided during the change from wakefulness to sleep. The complete cessation of ocular movement (as seen directly) lasted for a less variable period, which was approximately 23 minutes for the several infants observed. On the basis of eye movements alone, awakening ap-peared to be more abrupt than the onset of sleep.

The afternoon naps or long night sleep stretches of these infants were not homo-geneous, but appeared as rest-activity cycles which had a duration of considerable range, with a mean value of about 1 hour. The cycles were modified and often dis-torted by feedings, play, noise, etc. At night, the infants generally proceeded from one cycle to the next without any great outburst of activity.

We thank Professor M. Edward Davis of the Department of Obstetrics and Gynecology, and Professor F. Howell Wright of the Department of Pediatrics, of the University of Chicago, for engag-ing the interest of the infants' parents, and the latter for their splendid cooperation in the collection of data which made it possible, for the first time, to carry out a group study under normal family living conditions. For making the direct observations of general body and eye motility, respectively, we are greatly indebted to Mrs. Virginia C. Miller and Mr. Eugene Aserinsky; to the latter also for the analysis of the actograms that led to the detection of the fundamental hourly periodicity; and for assistance in coding and tabulating the data, to Miss Diane Stewart-Alexander.

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Two Types of Ocular Motility Occurring in Sleep

E. ASERINSKY[1] AND N. KLEITMAN. *From the Department of Physiology, University of Chicago, Chicago, Illinois*

ONE IS LED to suspect that the activity of the extra-ocular musculature and the lids might be peculiarly sensitive indicators of CNS changes associated with the sleep-wakefulness cycle. The disproportionately large cortical areas involved in eye movements, the well-defined secondary vestibular pathways to the extra-ocular nuclei, and the low innervation ratio of the eye muscles point to at least a quantitative basis for their reflection of general CNS activity. A more specific relationship of ocular motility to fluctuations in the sleep-wakefulness cycle is suggested by anatomical proximity of the oculomotor nuclei to a pathway involved in maintaining the waking state (1) and by the oddity that the orbicularis oculi contracts during sleep while other skeletal muscles relax. Yet, in the waking state, there is a periodic contraction (blinking) of the orbicularis oculi which is not paralleled by similar contractions of other muscles.

Despite the assertion in some textbooks (2, 3) that the position of the eyeballs during sleep is upwards and outwards, there is abundant evidence that the eyes are not stationary throughout sleep. Some observers (4-6) have concluded that the frequency of eye movements decreased as sleep deepened. On the other hand, Andreev (7), although confirming the existence of slow, pendular swings of the eyeballs in sleep, claimed that those movements were characteristic of the beginning and end of sleep, not necessarily the 'shallowness (sic) of sleep.' Wagner (8) actually employed lid movements (including those resulting from eyeball activity) as a major criterion in classifying the depth of sleep in infants.

In none of the experiments cited above was the activity of the eyeball recorded directly. Thus there remained the question as to whether lifting or touching the lid induced ocular motility. Furthermore, with regard to the studies on adults, no objective means of determining the depth of sleep was mentioned, nor was there any indication that observations were made at regular and close intervals throughout an entire night's sleep. The purpose of the present work was to re-examine the condition of ocular motility during the whole course of undisturbed sleep and to clarify the relationship of the eye movements to other events recorded simultaneously.

MATERIAL AND METHODS

Subjects and Procedures. One 10-year-old boy and 26 adults including two women were the subjects for the several sets of experiments. All were presumably normal and in good health. Except for a series of direct observations and a group of experiments involving interrogation of the subjects, it was unnecessary to enter the subject's room.

Preparations were completed so that each subject could retire at his usual or preferred time. Except for the experiments involving a response to an auditory stimulus, the subjects received no instructions other than to sleep until they awakened spontaneously in the morning. Due to the length of the EEG and electro-oculogram leads, the only restraint upon the subject

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[1] Work performed during the tenure of a U. S. Public Health Service Fellowship. Present address: Department of Physiology, Jefferson Medical College, Philadelphia 7, Pa.

was the inability to make a complete body revolution. However, this restriction did not entail any great discomfort.

Eye movements were recorded as an electro-oculogram (EOG). The latter is a record of the changes of the resting potential of the eye (corneo-retinal potential) with respect to fixed electrodes near the eye.

EOGs were obtained by attaching silver plated disks filled with electrode paste on the supra-orbital and infra-orbital ridges midway between the canthi of the right eye. For the horizontal vector of eye movement, the electrodes were placed close to the inner and external canthi of the same eye. When simultaneous records were taken of both eyes, a set of electrodes was placed similarly around the left eye. Elastic adhesive tape (Elastoplast) secured the electrodes to the skin. The potentials were led into a 4-channel Grass Electroencephalograph and the power amplifiers set at the longest time constant (EKG setting).

EEGs were recorded monopolarly from the right occipital and right frontal areas using similar type electrodes. The occipital electrode was placed approximately 3–4 cm anterior, and 2–3 cm lateral to the occiput, and attached to the scalp by means of a low-melting paraffin. This placement aided in maintaining the position of the electrode despite the considerable head movements during the night. The reference electrode for the occipital recording was on either ear. The frontal lead was attached in the conventional location, and the right ear was used as the reference. The standard EEG time constant was employed and the gain set so that a 7.5 mm deflection was equivalent to 50 microvolts. For specific analysis of low amplitude components, the gain was readjusted so that an 18-mm deflection equalled 50 microvolts.

Body motility could be recognized as an artifact on the EEG; in one set of observations, this type of movement was additionally recorded by means of a sensitive crystal attached to the bed spring and connected through a 1000-ohm resistance directly into a Grass pre-amplifier.

Heart rates were determined from electrocardiograms.

Respiration was recorded through a pneumograph bound to the chest. Pressure tubing led to an ink writer in the recording room. Because the pneumograph proved to be an impediment to restful sleep, no attempt was made to prevent loosening of the band around the chest during the night. Consequently, no calibration was made to ascertain accurately the changes in the depth of respiration.

A rubber bulb taped to the subject's right hand enabled him to activate a pneumatic device which recorded responses to a sound signal.

Evaluation of the Electro-oculogram. When the subject's eyes are open it is relatively simple to recognize eye movements from the EOG (9). Even voluntarily executed movements with the eyes closed are distinctly recognizable (10). However, involuntary movements such as occur during sleep are obscured by numerous artifacts including those produced by movements of the electrodes, brain waves, respiration, skin potentials and muscle potentials as shown in figure 1 *a* and *b*.

Since the EOG is in effect a bipolar recording of a moving dipole (eyeball), a monopolar recording should yield a potential of about half the amplitude. Indeed, it was found empirically that for a given movement of the eye, the potential recorded by the supra-orbital and infra-orbital pair of leads was from 2 to 4 times the magnitude of the simultaneously recorded potential from the right ear and frontal EEG leads. The variations were due mainly to the location of the frontal electrode with respect to the eye and to the probability that the ear reference electrode was affected by the corneo-retinal potential and therefore not completely inactive.

With the actual gains employed in the experiments, a deflection on the vertical EOG record was definitely an eye movement only if it were equal to or greater in amplitude than the corresponding deflection on the frontal EEG record, the polarities being in the same direction. This was confirmed by having the subject move his eyes voluntarily while the lids were shut and then noting the effect on the EOG and frontal EEG as shown in figure 1*c*.

A similar but more complex relationship was found for horizontal eye movements, comparing the horizontal EOG with anterior temporal-ear leads. However, the vertical component of eye movement was found to be sufficient for detecting ocular motility and therefore anterior temporal leads were rarely utilized.

It is to be noted that in the absence of the criterion employed, eye movements could not be recognized with certainty from either the EOG or EEG alone.

A study of extremely slow eye movements would require a direct-coupled amplifier (11). Despite the limitations of the Grass Electroencephalograph, many slow eye movements could nevertheless be detected on the EOG. But the various artifacts mentioned previously, especially those due to respiration, made interpretation of the EOG at times impossible. A method which proved useful in establishing that certain waves on the EOG were definitely *not* eye movements involved comparison of two monopolar records taken simultaneously in the same plane of ocular rotation. For instance, in comparing records from the 'right inner canthus—right ear' pair of leads and the 'right external canthus—left ear' leads during a known eye movement, the deflections are of opposite polarity inasmuch as one active electrode becomes negative at the same time that the other active electrode becomes positive. When deflections on such a pair of EOGs during sleep had the same polarity, they were considered to be artifacts. The limitation of this phase method was that the monopolar recordings were of lower amplitude than the usual bipolar EOGs and consequently necessitated an increased gain which introduced other interference into the records.

Confirmation of the validity of the eye movement criteria was obtained by direct observation. In addition, motion pictures were made simultaneously with EOGs on two adult subjects, showing typical eye movements during sleep. For the photography, the lids were blackened with grease paint, and the illumination of the room elevated gradually over a period of 2 hours until the lighting was adequate.

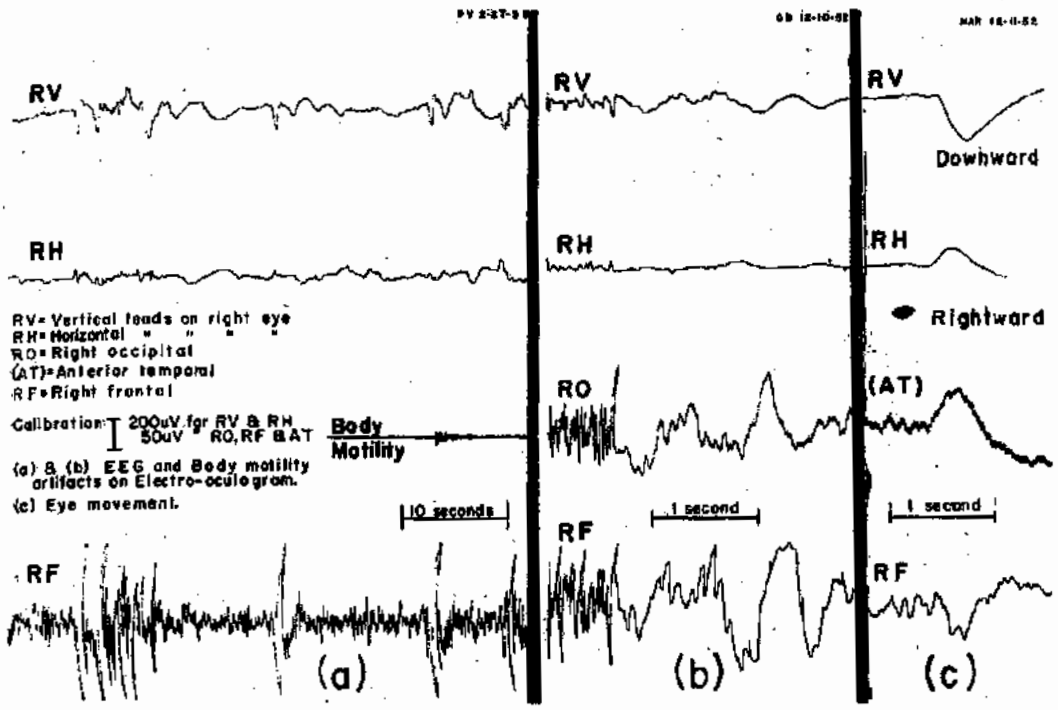

FIG. 1. Record exhibiting typical artifacts and an eye movement on the electro-oculogram (EOG). (*a*) and (*b*), EEG and body movement artifacts on the right vertical (RV) and right horizontal (RH) EOGs. (*c*), Voluntary movement of the right eye in an oblique direction while the lids were shut. EEG leads: right occipital (RO), right frontal (RF) and anterior temporal (AT).

RESULTS

Two types of eye movements were observed. First, there was a slow, lateral movement similar to that seen in sleeping infants (12) and in adults during sleep (4, 7) and anesthesia (6). A single excursion of this type was usually completed in 3–4 seconds; the highest frequencies were in the order of the respiratory rate, i.e. 15/min., whereas the lower frequencies were less than 1/min. Frequently these movements are binocularly asymmetrical. The second type of ocular activity was characterized by rapid, jerky motions of relatively short arc and by completion of a single rotation in about 1 second. This second type of eye movement during sleep was initially described in preliminary reports (13, 14) and is definitely distinguishable from the pendular, oscillatory motions representative of the first type of ocular activity. Inasmuch as a nomenclature describing these movements is lacking, the first type of movement will be referred to as *slow eye movement* and the second type as *rapid eye movement*.

Slow Eye Movement. The uncertainty of identification of these movements from the EOGs alone required direct observations to be made simultaneously with the EOGs on six male subjects including a 10-year-old boy.

Slow eye movements were seen at the onset of sleep and together with and after every body movement throughout sleep. When the subjects were awake and when the alpha rhythm was definite (subjects presumably relaxed) these lateral movements were especially prominent. However, these motions were not discernible despite the presence of alpha waves when the subjects were aware of the observer's presence. In the latter situation, the lids usually quivered and it seemed that an effort was being exerted to keep the eyes closed.

Figure 2 depicts the relationship of ocular motility to body motility during the course of a night's sleep. The quantity of slow eye movement was denoted in relative degrees: 3—frequent movement and high amplitude of the EOG; 2—less frequent but definite

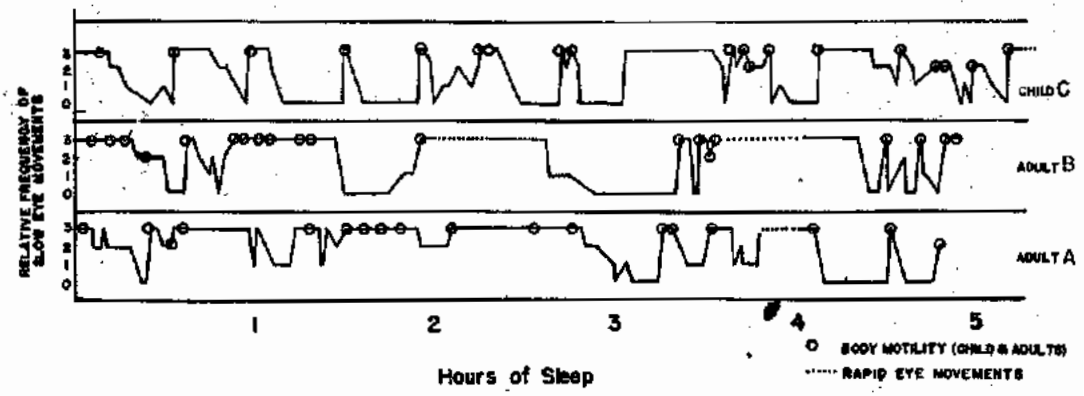

FIG. 2. Relationship of slow eye movements to body motility during sleep. *Solid line* represents level of slow eye movement frequency. *Circles* indicate occurrence of overt bodily activity.

movement and low amplitude of the EOG; 1—questionable movement on the bases of both direct observation and the EOG; 0—no discernible movement.

The ocular motility curve was based on judgments of the continuous EOG as well as from direct observations of the lids for one or more minutes during approximately each successive 5 minutes.

Eye movements were frequently present in the absence of overt body motility but were always observed in the company of each body movement. Periods of complete muscular quiescence were relatively few; the mean duration of such intervals of inactivity was 24 minutes, 55 seconds, disregarding a few intervals of 15 minutes or less which were questionable. This figure was not significantly different from the 23.4-minute mean for comparable periods of ocular and body inactivity of sleeping infants (12). The slow eye movements persisted for an average of 4 minutes after a body movement which preceded a long period of inactivity. However, the termination of the quiescent periods was usually abrupt and marked by slow eye movement occurring at about the same time as a body stir. This gradual decline and sharp rise of slow eye movement were also similar to the pattern of ocular activity observed in the infants.

The EEG during the long periods of ocular quiescence revealed delta waves or definite 12–14/sec. spindles or a combination of both. Although eye movements were never observed in the presence of a predominant delta pattern, some slow eye movements were occasionally seen concurrent with 14/sec. spindles which appeared outside of those long periods of ocular inactivity.

Rapid Eye Movement. Fifty-three series of observations were made on 23 adult males, a 10-year-old boy and 2 adult females.

From 1 to 5 hours (average, 3 hr.) after the onset of sleep, the first group of rapid eye movements appeared simultaneously in both eyes. They persisted for a variable duration, disappearing and then reappearing, until about 20 minutes later the last cluster of movements could be discerned. After 2 hours of ocular quiescence (including slow eye movement) there usually occurred another period of rapid eye movement which did not differ significantly in duration from the first period. Again, about 1½ hours later, a third period of such movement sometimes appeared. With longer sleep, a fourth period of rapid eye movement appeared. The interval between successive eye movement periods was progressively shorter. Table 1 discloses the results for sleep undisturbed by either auditory stimulation or presence of the observer. Results for 29 additional experiments (not indicated in table) were essentially the same; they included sleep which may have been disturbed. There was a possibility that the onset of the second period of rapid eye movements was hastened by a half-hour in the disturbed sleep.

There was a high degree of correlation between the number of rapid eye movement periods and the duration of sleep. For sleep lasting from 4 to 6½ hours there were an average of 1.7 periods of eye movement compared with

an average of 2.5 periods for sleep of 6½–9 hours. The difference of the means was significant at the 0.01 level of probability. Only four subjects failed to reveal rapid eye movements, and that was presumably because their sleep was of too short duration, lasting less than 4½ hours in all those cases.

The most characteristic feature of the EEG at the time of the rapid eye movement *period* was the low voltage pattern observable both in the frontal and occipital leads; delta rhythm of the usual amplitude was never seen. Rhythms from 7 to 15/sec. which extend from the alpha through the sleep spindle ranges could be recognized by careful perusal of a 20-minute record. However, the outstanding frequencies fell into the theta (4–7/sec.) and beta (15–22/sec.) ranges. A sample record illustrating a simultaneous EEG and electro-oculogram is shown in figure 3. A qualitatively similar EEG pattern was frequently evident before and after a rapid eye movement period. Since almost all ranges of brain wave frequencies can be found at any time during sleep (15), a quantitative analysis would be necessary to ascertain more exactly whether shifts have taken place in the brain wave continuum before, during and after a rapid eye movement period.

The graphs in figure 4, constructed from two experiments, show the interrelationship of EEG pattern, respiratory rate and rapid eye movement periods. The brain wave patterns were estimated manually at critical times and designated as follows: *1*—low voltage; *2*—low voltage, plus a few 12–14/sec. spindles; *3*—clearly defined 12–14/sec. spindles with a low voltage background; *4*—spindles, plus delta waves; *5*—mainly delta waves. Clearly defined alpha waves, especially after body movements, were ignored.

The rapid eye movement periods appeared concurrently with a low voltage brain wave pattern, but the latter was not always accompanied by the eye movements.

Respiratory rates before, during and after rapid eye movement periods were calculated from 15-minute intervals in each situation for 14 experiments involving 10 subjects. In all the cases examined there was a well defined shift of inter-respiratory cycle duration to higher frequencies during the eye movement periods. The mean respiratory rate increased approximately 20%, and this was significant at the 0.001 level of probability. Figure 4 shows clearly that certain peaks of respiratory rate were associated with the eye movement periods.

TABLE 1. DURATION AND TIME OF APPEARANCE OF RAPID EYE MOVEMENTS IN UNINTERRUPTED SLEEP*

Exp.	Av. Dur. of Eye Mvt. Period	Time of Appear. of 1st Period	Time of Appear. of 2nd Period	Time of Appear. of 3rd Period	Duration of Sleep
MH 1–23	14′ 27″	4:25′	1:43′		7:20′
MH 1–29	9′ 50″	4:42′			6:07′
NG 2–2	10′ 53″	2:40′	1:55′	09′	6:14′
NG 2–4	15′ 12″	1:39′	2:30′		5:53′
DA 2–6	19′ 15″	3:29′			5:48′
DA 2–7	27′ 37″	2:54′	2:53′		6:38′
NK 1–30	15′ 38″	4:24′	1:39′		8:06′
ID 1–10	29′ 30″	1:40′	3:45′	58′	8:12′
ID 2–21	23′ 30″	2:57′	2:36″		5:53′
AD 2–9	29′ 12″	4:16′	2:27′		7:48′
AD 2–16	27′ 30″	3:52′	2:43′		7:30′
DY 2–13	16′ 07″	2:27′	1:13′	3:14′	9:08′
FB 2–18	14′ 35″	2:58′	1:45′	1:41′	6:45′
JL 2–20	28′ 50″	2:44′	2:04′	1:11′	6:54′
Mean.....	20′ 08″	3:14′	2:16′	1:26′	7:01′

* The time of appearance of the first group of rapid eye movements is noted in hours and minutes after retiring. The onset of subsequent eye movement periods is calculated from the onset of the period occurring previously and is similarly in hours and minutes.

A similar increase of the heart rate was likewise observed. Here the computations were based on the average rates for 30-second intervals distributed throughout an eye movement period and accounted for 25–60% of the total duration of that period. Rates were also determined for equivalent durations immediately preceding and following the eye movement period. The mean heart rate during the presence of the eye movements (based on seven experiments with six subjects) was approximately 10% higher than the control periods. The difference between the means was significant at the 0.001 level. There was no significant difference between the mean heart rates for the periods just before and after the eye movements.

The histograms (fig. 5) illustrate the relationship between the rapid eye movement periods and the relative amount of body

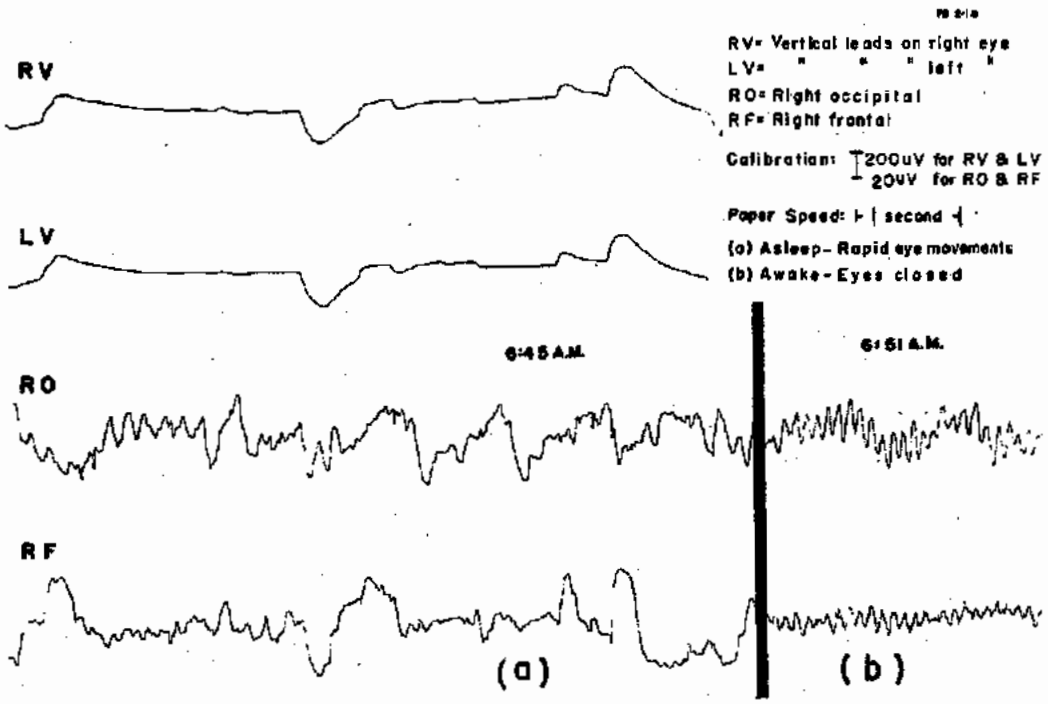

FIG. 3. (*a*) Record exhibiting rapid eye movements and concomitant EEG pattern. Leads: right occipital (RO), right frontal (RF), vertical on right eye (RV) and vertical on left eye (LV).

motility during the night's sleep. Body motility was judged for each successive 5 minutes; any such interval having even a single body movement was categorized as one of movement. Thus, in a half hour there would be a maximum of six periods of body movement. From eight observations on six subjects it was apparent that rapid eye movement periods were concomitant with increases in body motility. However, by charting the ocular and body motility over shorter intervals, one could recognize the presence of eye movements, for, say 5 minutes, in the complete absence of gross body motility.

The peculiar rapid eye movements suggested the possibility that they might be associated with dreaming. Consequently, 10 subjects in 14 experiments were interrogated after intervals with and without rapid eye movements, care being taken that the EEGs in both situations were at least superficially similar. To confirm that the individuals were not awake, they were presented with an auditory stimulus of above the waking threshold intensity for 1 second. Failure to respond to two such stimuli separated by an interval of 1 minute was accepted as additional evidence of sleep. The subjects were awakened by voice and asked whether dreaming was recalled, and if so, to describe in a few words the dream content or any visual imagery which could be remembered. The replies were recorded and classified as follows: +, definite recall of dream content; −, no recall of dreaming; 0, uncertain, *or* remembered dreaming, but could not recall content. The interrogation usually did not extend over half a minute.

Twenty out of twenty-seven replies, from individuals who were awakened after rapid eye movements had been observed, yielded detailed dream descriptions in contrast to 19 out of 23 replies from persons awakened in the absence of eye movements, which revealed complete failure to recall dreaming. Using a 2 by 2 table of analysis, a comparison of the ratios of recall, and failure to recall under the two conditions produced a chi square of 15.9. Thus the recall of dreaming was associated with the prior occurrence of rapid eye movements at a probability level of less than 0.01.

On several occasions incoherent mumbling and groaning accompanied the rapid eye

movements. Once, however, muscle action potentials and movement artifacts so obscured the EOG, which was exhibiting typical rapid eye movements at the time, that the observer entered the subject's room to investigate. The subject was lying restlessly with the lids shut and the eyes moving violently. The clearly interpretable vocalization revealed a nightmare which the subject later claimed to have had frequently at home.

No sex differences with respect to the ocular activity and concomitant phenomena were noted in this study. Rapid eye movements appeared in the child and were apparently no different from that seen in adults. However, there was the suggestion that the child's slow eye movement and body motility behavior bore a closer resemblance to the regularity of the rest-activity cycles than did the adult pattern.

DISCUSSION

The ocular imbalance manifested by the slow eye movements may be related to a loss of fixational ability stemming from the supra-segmental depression accompanying sleep or extreme relaxation. The disintegration of muscular control cannot be attributed to mere closure of the lids inasmuch as perfect fixation (10) can take place while the eyes are closed. Furthermore, drowsy subjects (16, 17) and encephalitics (18) exhibit ocular imbalance even while the eyes are still open.

It has been suggested that slow eye movements may be causally related to the alpha rhythm (5, 6) or due to 'diffuse inhibition' of the cortex before the inhibition has embraced the whole brain (7). The former hypothesis is not supported since the slow eye movements are observable in the absence of an 8–12/sec. rhythm. In addition, these eye movements are frequently binocularly asynchronous while the rhythms of the occipital lobes of both hemispheres are synchronous during sleep (Gibbs and Teplitz cited by Cress and Gibbs., ref. 19, 1949). On the other hand, slow eye movements are commonly observed in conjunction with the cortical depression concomitant with anesthesia. This depression may be due to absence of stimulation rather than to active

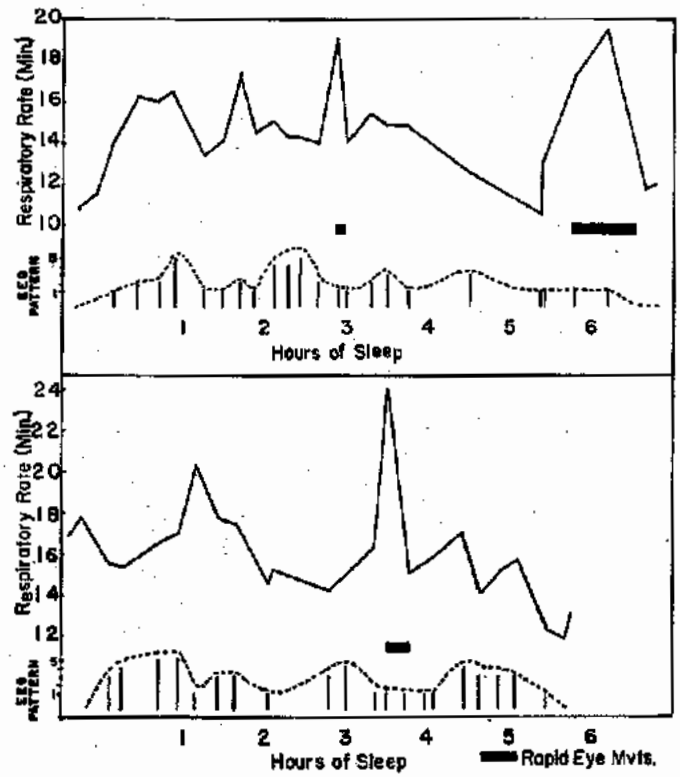

FIG. 4. Changes in respiratory rate and EEG pattern during sleep, and the time of appearance of rapid eye movements. The EEG pattern represents deepest sleep at 5 and the lightest sleep at 1. Explanation in the text.

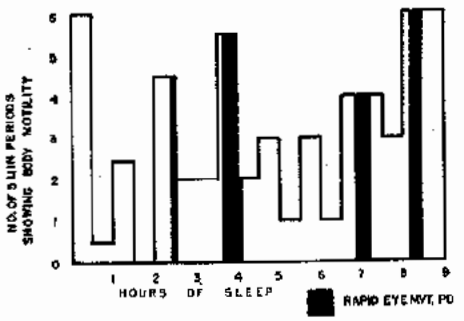

FIG. 5. Relationship of rapid eye movement periods to body motility during sleep. *Vertical bars* represent the degree of body movement. *Shaded areas* indicate occurrence of rapid eye movements.

inhibition. It would appear that activity of the cortex is necessary to *prevent* the occurrence of slow eye movements. Thus in sleep or relaxation there may be a functional regression to an infantile level at which the eyes are poorly coordinated and move asymmetrically and asynchronously.

There appeared to be a parallelism between the slow eye movements and peripheral muscular tone. The eye movements were coincident with overt body movements and persisted for varying durations, either disappearing gradually until there was no longer any discernible motility, or else remaining until the occurrence of another body movement. Action potentials from a limb muscle have been shown to decrease gradually in frequency during the transition from wakefulness to sleep (20). It is therefore likely that changes in skeletal muscle tone which would otherwise be undetected without instrumentation can be readily recognized during sleep by direct observation of the eyes and lids.

In the absence of the supra-nuclear control necessary for extremely fine integration of neural activity, the muscular tone of antagonist muscles waxes and wanes incoordinately. Due to the unusual relationship of the extra-ocular musculature to the orbital socket, these changes in muscle tone are manifested by smooth, gliding rotations of the eyeball. Unequal tone in other muscle groups as in a limb would not be easily observed since a limb is not usually suspended in sleep to allow free movement. Also, at any particular moment there is probably a relatively higher tone in the extra-ocular muscles than in the limb musculature.

In contrast to the slow eye movements which appeared to be passive drifts entirely lacking in fixations, and frequently binocularly discoordinate, the rapid eye movements seemed to be active or 'driven' movements as evidenced by the short time for execution, the abrupt, fixational characteristic and the binocular synchrony. The rapid eye movements may be symptomatic of depression of one of the highest levels of integration inasmuch as complex processes such as dreaming are still present. Furthermore a high degree of CNS development is necessary for occurrence of the rapid eye movements since young infants (12) reveal only slow eye movements in their sleep.

Since the rapid eye movements did not occur randomly, there is an indication that they were associated with a particular level of CNS activity. The concomitant increase in heart and respiratory rates points to a state of heightened irritability. The progressively closer appearance of rapid eye movement *periods* is reminiscent of the scheme of auditory threshold fluctuations (21) which depicted higher and higher sensory (excitatory) levels at progressively shorter intervals during sleep.

The similarity of the rapid eye movement patterns of all the subjects suggests a 'uniformity' of behavior which could be due to functional removal of a high cortical level during sleep just as individual variations of the alpha index disappear in sleep (22) so that there is then a homogeneity of all brain rhythms.

The involuntary motor discharge represented by the rapid eye movements, the low voltage brain wave pattern and the loss of consciousness which sleep entails resemble the abnormal signs associated with epileptoid conditions. There may be a factor common to the neural activity in both sleep and in pathological conditions of the waking state. Davis *et al.* (23), for instance, have reported that certain brain waves resembling pathognomic focal slow wave disturbances appear spontaneously during the sleep of normal persons for no assignable cause.

The evidence for the association of the rapid eye movements with dreaming, or at least the

recall of dreaming, is strong. There will, of course, always remain some doubt as long as subjective report is ultimately needed to ascertain the occurrence of dreaming. Previous EEG studies are in accord with the present findings. Blake, Gerard and Kleitman (24) and Loomis, Harvey and Hobart (25) found an association of a low voltage EEG with the recall of dreaming just as in this study the predominant brain wave in conjunction with the rapid eye movements was of low voltage. Furthermore, the former investigators found the greatest recall of dreaming in the 'Null Period' which corresponds to the 3rd and 4th hours of sleep when the first appearance of a rapid eye movement period would be expected.

The increased body motility which always accompanied the eye movements is in agreement with the observations of Monge (26) that individuals suffering from mountain disease complain of both restless sleep and disturbing dreams.

Depths of sleep curves based on various sensory thresholds and on heart rate (27) disclose one or more periods of lightening of sleep which would correspond temporally to the presence of rapid eye movement periods. Finally, there are the observations of Ohlmeyer and co-workers (28) which described periodic penile erections during sleep wherein the range of the mean durations for the erection periods was from 18.1 to 28.2 minutes. This compares favorably with the mean duration of the rapid eye movement periods which was approximately 20 to 25 minutes.

Although no attempt was made to secure a thorough account of the recalled dream events during the extremely brief interrogation, there were reports revealing strikingly vivid visual imagery, especially after the subjects were awakened following the eye movements. It is indeed highly probable that the rapid eye movements are directly associated with visual imagery in dreaming.

The duration of the rapid eye movement *period* might suggest that a single dream lasts about 25 minutes. It is nevertheless possible that a period may encompass more than one dream. Max (29), who found that action potentials from the limbs of deaf mutes were associated with the recall of dreaming, recorded potentials in one instance for $2\frac{3}{4}$ minutes before awakening the sleeper. Had the subject been undisturbed, those potentials may have endured even longer. The fleeting mental states accompanying unconsciousness (30) and hypnosis (31) should not be identified with dreaming since those conditions are not identical with sleep. Also, the data at hand do not support the contention that dreams last throughout sleep (32) or that they 'regulate' the depth of sleep (33). The regularity of occurrence of eye movement periods, furthermore, makes it unwarranted to assert a causal relationship between emotion, mental conflict or external stimulation with the onset of dreaming although those factors conceivably modify dream content. If anything, such prosaic events as the diurnal fall in body temperature or increase of proprioceptive impulses from the periphery may be the direct cause of CNS changes which manifest themselves as dreaming.

SUMMARY

Eye movements during sleep were studied in 26 adults and 1 child by means of electro-oculograms and direct observation. Simultaneous records were obtained of EEG, respiratory rate, heart rate and body motility. Slow, drifting movements of the eyes were found to be prominent during the relaxation at the onset of sleep as well as with every overt body movement throughout sleep. The frequency of these movements declined gradually after each body movement; several times during the night, especially when delta waves were evident, the slow eye movements were not discernible. The mean duration of the periods of complete ocular quiescence was 24 minutes, 55 seconds which was practically the same as for similar periods of ocular inactivity observed for infants in another study. It was suggested that the slow eye movements reflected changes in skeletal muscle tone. Because of the unique anatomical arrangement of the extra-ocular musculature, loss of supra-nuclear fixational control enabled the discoordination of antagonist muscles to be observed as overt movements of the eyes.

A new type of ocular activity termed 'rapid eye movements' was also observed to occur in sleep. These movements, confirmed by motion pictures, were binocularly synchronous, rapid

and jerky. They appeared in clusters of about 20 minutes duration. The first cluster appeared from 1 to 5 hours (3 hr average) after retiring, a second cluster about 2 hours later and additional groups of eye movements at still closer intervals, depending on the length of sleep. Concomitant with the appearance of the rapid eye movements was a statistically significant increase in heart rate (10% average) and respiratory rate (20% average), a typical low voltage EEG pattern from the frontal and occipital areas, increased bodily activity including facial movements, and occasionally vocalization. Through interrogation of the subjects and from other indications, it is believed that the rapid eye movements were involved in the visual imagery accompanying dreaming.

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The Development of the Diurnal (24–hour) Sleep-Wakefulness Rhythm in the Infant

by

N. KLEITMAN and G. ENGELMANN, Chicago

From continuous actograms and protocols kept by their mothers on specially designed forms, the incidence and duration of sleep was followed in 19 infants, from the 3rd to the 26th week of life, under family home conditions. Even the earliest records revealed a diurnal disparity, the mean group duration of night sleep being 8.4 hours, as against 6.4 hours for day (usually 8 A.M.—8 P.M.). Up to the 12th week, the total duration of sleep was *unchanged*, or slightly increased, but the night portion rose to 10.1 hours, at the expense of a corresponding fall in day sleep. For the succeeding 14 weeks, the duration of night sleep was *unchanged*, or slightly increased, but the day fraction continued to decrease, reaching 3.6 hours, for a total of 13,8 hours per 24 hours. Thus, not only were our objectively obtained figures much lower than those hitherto reported, but there was no marked diminution of sleep during the whole period of observation. The adjustment of the sleep-wakefulness pattern manifested itself mainly in a progressively more pronounced diurnal periodicity, culminating in one long unbroken period of night sleep and short morning and afternoon naps.

Prof. Dr. Nathaniel Kleitman and Dr. Theodore G. Engelmann
Chicago, Ill.
University Department of Physiology

Kleitman N, Engelmann G. The development of the diurnal (24-hour) sleep-wakefulness rhythm in the infant. *Acta Med Scand Suppl.* 1955;307:106.

THE EFFECTS OF SLEEP AND LACK OF SLEEP ON THE CEREBRAL CIRCULATION AND METABOLISM OF NORMAL YOUNG MEN [1]

By RENWARD MANGOLD, LOUIS SOKOLOFF, EUGENE CONNER, JEROME KLEINERMAN, PER-OLOF G. THERMAN, AND SEYMOUR S. KETY

(From the Department of Physiology and Pharmacology, Graduate School of Medicine, the Department of Anesthesia, Hospital of the University of Pennsylvania, and the Harrison Department of Surgical Research, University of Pennsylvania, Philadelphia, Penna.)

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Numerous hypotheses have been elaborated in attempts to explain the puzzling phenomenon of sleep. Thus sleep has been attributed to arterial anoxemia, to cerebral ischemia or anoxia, or to a generalized narcosis on the basis of one or another metabolic alteration. Little information is available, however, on the subject of cerebral metabolism and function during natural sleep. This might be explained to a great extent by the difficulties inherent in any experimental investigation during so labile a state as physiological sleep. Moreover, reasonably quantitative techniques for measuring the blood flow and oxygen consumption of the brain in unanesthetized animals and in man have become available only recently. Early attempts (1) to obtain at least qualitative information on the cerebral blood flow in man during sleep by means of brain plethysmography through trephine holes have yielded contradictory results. Later attempts with better methods of recording (2) have suggested a decrease in cerebral blood flow on passage from the waking state to short or long periods of sleep. More recently, Gibbs, Gibbs, and Lennox have attempted to obtain a better understanding of the cerebral circulation during sleep by means of the thermoelectric flow recorder (3). They found no significant alteration in cerebral blood flow during short periods of sleep in four epileptic patients. Unfortunately, arterio-cerebral venous oxygen differences were not measured simultaneously, and no information on the important question of the oxygen consumption of the brain was obtained.

Recently developed methods permit a more quantitative determination of the cerebral blood flow and oxygen consumption during natural sleep. It was to obtain such information as well as to test some of the previously proposed hypotheses that the present study was undertaken.

[1] This investigation was supported in part by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

METHOD

Attempts to measure cerebral blood flow by means of the nitrous oxide technique (4) during sleep were made in approximately fifty, healthy, young, male volunteers varying in age from 17 to 36 years. In order to facilitate the induction of sleep under the conditions of the study, the subjects had remained awake for a period of approximately 20 hours, or about six hours beyond their normal bed-time, prior to the study. They are, therefore, referred to as "fatigued." Except for making the subjects as comfortable as the procedure would allow, no drugs or other special methods for inducing sleep were employed. The studies were performed in the early morning hours, most often between 4 and 6 A.M., when the tendency to fall asleep after a prolonged period of wakefulness is generally greatest (2). In most cases the subjects had been fasting for several hours; a few had eaten a light meal approximately two hours prior to the study.

In each study the subject was placed in the supine position, the needles were inserted in the internal jugular bulb and the femoral artery, needle electrodes for EEG recording were placed in the scalp, and a mask was strapped on the face. The subject was then permitted to rest in this position for about thirty minutes to permit any physical and emotional disturbances attending the introduction of the needles to subside. At this point the first or control blood flow determination was performed. The room was then darkened and quieted, and the subject, still in the same position, was given an opportunity to fall asleep. During this period the subject was usually permitted to breathe room air through a valve connected to the mask. In a few cases compressed air was fed from a tank into the mask through a reducing valve in an effort to minimize the waking effect of the gas flow associated with the nitrous oxide procedure. The state of wakefulness or sleep was followed by means of continuous EEG recordings in the adjacent room from the four to eight scalp electrodes previously inserted. These recordings were made continuously throughout the study

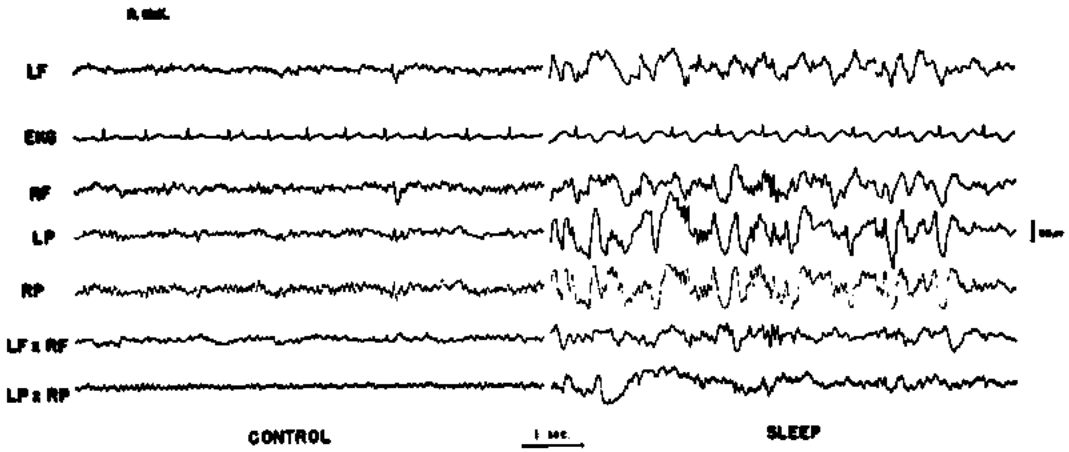

FIG. 1. ELECTROENCEPHALOGRAPHIC PATTERN DURING SLEEP

including the periods during which cerebral blood flow measurements were being made. The mental state or level of sleep was evaluated by means of the EEG record on the basis of the classification of Gibbs and Gibbs (5) as well as by clinical observation including movements, snoring, and response to whispered commands. In no case was the subject considered asleep until after the appearance of the characteristic sleep spindles and delta waves in the EEG record (Figure 1). When, on the basis of all these criteria, the subject was considered to be in a relatively steady state of sleep, a cerebral blood flow determination was made. The above procedure was followed in all the cases in Tables IA and IB except two (P. O. and McK.) in which the order was reversed, sleep occurring throughout the first determination of cerebral blood flow and the control determination performed after the subjects had been awakened and kept awake for 45 and 55 minutes, respectively.

In approximately fifty attempts an uninterrupted state of sleep of sufficient depth and duration to fulfill all the criteria was achieved in only six cases. A large number of studies was discarded because independent review of the EEG record failed to confirm the presence of a steady state of sleep throughout the period of cerebral blood flow determination or revealed momentary episodes of sleep rhythms during the control period. In some of those cases in which sleep did not occur, a second cerebral blood flow determination was made under exactly the same conditions as the first to form a group of "consecutive fatigued controls" with which to study the variation between two consecutive determinations in the same individual done under identical conditions but separated in time by an interval approximating that between the control and sleep determinations.

In all the studies mean arterial blood pressure was measured with a damped mercury manometer attached to the femoral arterial needle. Blood oxygen and carbon dioxide contents were determined by the manometric method of Van Slyke and Neill (6). Total hemoglobin concentration in arterial blood was measured in the Evelyn photometer according to a modification of the method of Evelyn and Malloy (7). Measurements of blood pH were made anerobically at room temperature by means of a glass electrode and Cambridge potentiometer and corrected to 37° C. by the factors of Rosenthal (8). Cerebral oxygen consumption, cerebral vascular resistance, and cerebral respiratory quotient were calculated as previously described (4). Blood carbon dioxide tension was computed by means of the nomograms of Peters and Van Slyke (9).

RESULTS

In Tables IA and IB are presented the data obtained in the six subjects on whom complete sleep studies could be made. The results obtained in the consecutive fatigued control studies in 13 subjects are presented in Tables IIA and IIB.

It is apparent that during sleep cerebral blood flow (CBF) is increased, rising from 59 during the control state to 65 cc. per 100 g. per min. during sleep ($p < 0.01$) while no such statistically significant change in CBF was found in the consecutive fatigued controls. The rise in CBF occurred in sleep despite a significant fall in mean arterial blood pressure (MABP) from 94 mm. Hg to 90 mm. Hg ($p < 0.05$). The series of consecutive studies on fatigued but awake subjects showed a significant blood pressure change in quite the opposite direction, rising from a mean of 90 mm. Hg in the first to 96 mm. Hg in the second determination ($p < 0.01$). This systematic change in MABP between two consecutive control determinations does not explain, however, the decrease found in sleep since the sleep series was a mixed one, sleep sometimes occurring in the first but more often

TABLE IA

Cerebral circulation and metabolism during sleep

Subject	Age	Interval *Min.*	MABP *mm. Hg* C*	MABP *mm. Hg* S†	CBF *cc./100 g./min.* C	CBF *cc./100 g./min.* S	$CMRO_2$ *cc. O_2/100 g./min.* C	$CMRO_2$ *cc. O_2/100 g./min.* S	$(A\text{-}V)O_2$ *Vol. %* C	$(A\text{-}V)O_2$ *Vol. %* S	CVR *mm. Hg / cc./100 g./min.* C	CVR *mm. Hg / cc./100 g./min.* S	Cerebral R.Q. C	Cerebral R.Q. S
E. R.	21	66	79	74	79	85	3.8	5.1	4.80	6.01	1.0	0.9	0.83	0.96
R. M.	28	30	107	95	45	48	2.6	2.3	5.70	4.75	2.3	2.0	0.94	0.86
S. W.	23	23	95	91	67	72	3.6	3.4	5.35	4.75	1.4	1.3	0.81	0.86
P. O.	23	45	99	96	54	61	3.5	3.1	6.51	5.12	1.8	1.7	0.93	1.02
H. K.	26	42	97	95	53	56	3.6	2.8	6.75	6.00	1.8	1.5	1.18	1.00
McK.	25	55	88	87	57	68	4.0	3.8	6.94	5.59	1.5	1.3	1.04	1.04
Mean	24.3	44	94.2	89.7	59.2	65.0	3.52	3.42	6.01	5.37	1.63	1.45	0.96	0.96
Stand. Error	±1.02	±6	±3.9	±3.4	±4.9	±5.3	±0.20	±0.39	±0.35	±0.24	±0.18	±0.15	±0.06	±0.03
p‡	—	—	<0.05		<0.01		>0.7		>0.1		<0.01		>0.9	

* C—Control—fatigued but awake.
† S—Sleep.
‡ Determined by method of paired comparison.

TABLE IB

Blood constituents during sleep

Subject	Hemoglobin concentration *Gm. %* C*	Hemoglobin concentration *Gm. %* S†	Blood O_2 content *Vol. %* Arterial C	Arterial S	Int. jugular C	Int. jugular S	Blood CO_2 content *Vol. %* Arterial C	Arterial S	Int. jugular C	Int. jugular S	Blood pH Arterial C	Arterial S	Int. jugular C	Int. jugular S	Blood CO_2 tension *mm. Hg* Arterial C	Arterial S	Int. jugular C	Int. jugular S
E. R.	14.43	14.55	18.90	19.58	14.10	13.57	47.06	46.83	51.04	52.62	7.31	7.29	7.24	7.27	47	50	60	58
R. M.	15.06	15.06	19.09	19.28	13.39	14.53	45.22	45.81	50.55	49.87	7.43	7.40	7.36	7.34	37	39	46	48
S. W.	14.25	14.43	19.81	19.97	14.46	15.22	50.31	51.28	54.65	55.38	7.33	7.34	7.30	7.30	49	49	56	57
P. O.	13.95	14.43	18.70	18.78	12.19	13.66	49.70	49.15	55.78	54.37	7.35	7.36	7.31	7.29	46	45	56	58
H. K.	14.94	14.86	20.98	20.58	14.23	14.58	52.14	54.63	60.13	60.62	7.35	7.35	7.31	7.31	49	51	60	61
McK.	13.16	12.81	19.01	18.38	12.07	12.79	51.67	51.28	58.86	57.10	7.35	7.38	7.33	7.36	48	44	56	51
Mean	14.30	14.36	19.42	19.43	13.41	14.06	49.35	49.83	55.17	54.99	7.35	7.35	7.31	7.31	46.0	46.3	55.7	55.5
Stand. Error	±0.28	±0.33	±0.35	±0.33	±0.43	±0.36	±1.10	±1.33	±1.60	±1.51	±0.02	±0.02	±0.02	±0.01	±1.9	±1.9	±2.1	±2.0
p‡	>0.6		>0.9		<0.1>0.05		>0.3		>0.7		>0.9		>0.7		>0.7		>0.8	

* C—Control—fatigued but awake.
† S—Sleep.
‡ Determined by method of paired comparisons.

TABLE IIA.—*Cerebral circulation and metabolism in consecutive control determinations in normal fatigued but awake subjects*

Subject	Age	Interval Min.	MABP mm. Hg I*	MABP mm. Hg II†	CBF cc./100 g./min. I	CBF cc./100 g./min. II	$CMRO_2$ cc. O_2/100 g./min. I	$CMRO_2$ cc. O_2/100 g./min. II	$(A\text{-}V)O_2$ Vol. % I	$(A\text{-}V)O_2$ Vol. % II	CVR mm. Hg / cc./100 g./min. I	CVR mm. Hg / cc./100 g./min. II	Cerebral R.Q. I	Cerebral R.Q. II
J. R.	27	110	86	97	63	66	3.0	2.9	4.70	4.37	1.4	1.5	0.74	1.10
A. A.	24	80	90	94	48	50	2.6	2.8	5.52	5.55	1.9	1.9	0.98	1.04
G. M.	22	70	82	86	54	53	3.0	3.3	5.63	6.28	1.5	1.6	0.98	0.94
R. O.	25	49	100	103	49	41	3.6	2.9	7.31	7.01	2.0	2.5	1.08	1.11
H. R.	24	120	81	102	52	48	4.0	3.3	7.62	6.86	1.6	2.1	0.95	0.99
J. D.	28	103	102	104	88	62	3.9	3.7	4.48	6.02	0.9	1.6	0.87	0.98
S. C.	19	125	87	89	56	68	3.7	3.4	6.57	4.77	1.6	1.3	0.86	1.15
T. F.	23	50	95	94	41	37	3.4	2.9	8.27	7.95	2.3	2.5	1.00	0.86
R. W.	22	83	88	100	77	74	3.8	3.8	4.96	5.19	1.1	1.4	1.00	1.08
W. O'D.	18	45	109	110	100	78	5.2	4.3	5.23	5.46	1.1	1.4	0.98	1.04
J. W. D.	29	120	80	86	61	57	2.8	4.2	4.66	7.47	1.3	1.5	0.81	0.94
P. T.	24	100	89	89	88	78	4.9	4.5	5.64	5.71	1.0	1.1	1.05	1.00
L. B.	22	90	83	94	66	68	3.6	3.8	5.45	5.65	1.3	1.4	0.82	0.98
Mean	23.6	88	90.2	96.0	64.8	60.0	3.65	3.52	5.85	6.02	1.46	1.68	0.93	1.02
Stand. Error	±0.9	±8	±2.5	±2.1	±5.3	±3.8	±0.21	±0.16	±0.34	±0.29	±0.12	±0 12	±0.03	±0.02
p‡	—	—	<0.01		>0.1		>0.4		>0.5		~0.01		<0.05	

* I—First control. † II—Second consecutive control. ‡ Determined by method of paired comparison.

TABLE IIB.—*Blood constituents in consecutive control determinations in normal fatigued but awake subjects*

Subject	Hemoglobin concentration Gm. % I*	Hemoglobin concentration Gm. % II†	Blood O_2 content Vol. % Arterial I	Arterial II	Int. jugular I	Int. jugular II	Blood CO_2 content Vol. % Arterial I	Arterial II	Int. jugular I	Int. jugular II	Blood pH Arterial I	Arterial II	Int. jugular I	Int. jugular II	Blood CO_2 tension mm. Hg Arterial I	Arterial II	Int. jugular I	Int. jugular II
J. R.	13.65	14.03	18.18	19.09	13.48	14.72	49.25	49.25	57.73	54.03	7.36	7.38	7.34	7.32	45	44	54	54
A. A.	13.48	13.39	18.56	18.57	13.04	13.02	49.78	49.42	55.17	55.20	7.46	7.47	7.41	7.36	37	37	45	50
G. M.	13.48	13.48	18.60	19.20	12.97	12.92	50.24	51.34	55.74	57.23	7.44	7.43	7.38	7.36	39	40	49	52
R. O.	15.08	15.29	20.89	20.88	13.58	13.87	44.22	46.04	52.05	53.81	7.37	7.37	7.34	7.34	40	42	50	51
H. R.	13.73	14.03	19.50	19.08	12.64	11.46	46.20	44.73	52.73	51.82	7.42	7.40	7.36	7.36	38	38	48	48
J. D.	14.75	14.66	20.23	20.49	15.75	14.47	49.06	47.71	52.94	53.59	7.40	7.40	7.35	7.36	42	41	49	49
S. C.	15.08	14.66	19.85	18.95	13.28	13.98	48.25	47.86	53.89	53.57	7.39	7.34	7.34	7.32	41	46	52	53
T. F.	16.14	16.27	22.31	22.13	14.04	14.18	47.28	46.78	55.56	53.62	7.40	7.39	7.36	7.33	42	42	53	53
R. W.	12.55	12.72	17.58	18.06	12.62	12.96	47.84	46.95	52.81	52.33	7.48	7.38	7.47	7.38	34	41	38	45
W. O'D.	13.10	13.27	17.89	18.28	12.66	12.82	49.22	48.80	54.35	54.56	7.42	7.41	7.38	7.40	40	40	47	46
J. W. D.	14.24	14.24	19.65	19.47	14.99	12.00	52.35	49.87	56.24	56.74	7.34	7.36	7.33	7.31	51	46	56	56
P. T.	13.10	13.48	18.18	18.31	12.54	12.60	49.25	49.57	55.17	55.27	7.43	7.44	7.36	7.33	39	39	50	54
L. B.	13.65	13.86	18.79	19.27	13.34	13.62	45.83	46.56	50.32	52.09	7.35	7.33	7.28	7.30	43	46	52	52
Mean	14.00	14.11	19.25	19.37	13.46	13.28	48.37	48.07	54.21	54.14	7.41	7.39	7.36	7.34	40.9	41.7	49.5	51.0
Stand. Error	±0.28	±0.26	±0.37	±0.32	±0.27	±0.27	±0.59	±0.51	±0.56	±0.46	±0.01	±0.01	±0.01	±0.01	±1.2	±0.8	±1.3	±0.9
p‡	>0.1		>0.3		>0.5		>0.3		>0.8		~0.2		>0.05		>0.3		<0.05	

* I—First control. † II—Second consecutive control. ‡ Determined by method of paired comparison.

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TABLE III

Comparison between normal rested and normal fatigued young men

Subject	Age	MABP *mm. Hg*	CBF *cc./100 g./min.*	$CMRO_2$ *cc. O_2/100 g./min.*	$(A\text{-}V)O_2$ *Vol. %*	CVR $\frac{mm.\ Hg}{cc./100\ g./min.}$	Cerebral R.Q.	Hb concentration *Gm. %*	Blood O_2 content *Vol. %*		Blood CO_2 content *Vol. %*		Blood pH		Blood CO_2 tension *mm. Hg*	
									Arterial	Int. jugular	Arterial	Int. jugular	Arterial	Int. jugular	Arterial	Int. jugular
Normal rested controls—11 cases																
W. C.	24	95	49	2.8	5.74	1.9	0.75	13.43	18.49	12.75	48.59	52.92	7.42	7.37	40	48
H. K.	20	88	42	2.2	5.25	2.1	0.84	13.85	19.61	14.36	48.66	53.09	7.44	7.39	38	46
R. C.	20	78	74	3.8	5.19	1.1	0.95	12.72	16.28	11.09	51.01	55.92	7.40	7.36	43	51
J. D. G.	22	91	80	3.8	4.77	1.1	1.08	13.94	19.29	14.52	49.20	54.36	7.41	7.35	41	51
E. L.	23	87	60	4.0	6.62	1.5	0.89	13.73	20.07	13.45	49.65	55.51	7.40	7.36	42	51
T. C.	24	88	49	2.9	5.97	1.8	0.84	12.18	17.12	11.15	46.55	51.58	7.45	7.39	35	44
L. H.	25	78	35	3.2	9.29	2.2	0.97	15.15	20.53	11.24	45.09	53.15	7.37	7.30	41	55
A. McC.	22	85	50	2.7	5.36	1.7	1.03	16.90	21.16	15.80	43.42	48.92	7.33	7.28	43	57
D. F.	19	85	54	4.3	7.89	1.6	0.92	15.08	19.56	11.67	43.90	51.19	7.34	7.28	42	56
L. H.	19	83	69	4.5	6.51	1.2	0.91	16.16	19.88	13.37	48.37	54.29	7.35	7.30	46	57
N. Y.	22	93	41	2.5	6.11	2.3	0.95	17.16	21.86	15.75	47.53	53.31	7.39	7.35	43	52
Mean	21.8	86.5	54.8	3.34	6.25	1.68	0.92	14.57	19.44	13.20	47.45	53.11	7.39	7.34	41.3	51.6
S.E.	±0.63	±1.7	±4.3	±0.23	±0.40	±0.13	±0.03	±0.50	±0.49	±0.53	±0.73	±0.60	±0.01	±0.01	±0.9	±1.3
Normal fatigued controls—25 cases																
M. S.	36	95	70	5.0	7.15	1.4	1.07	14.23	20.20	13.08	49.19	56.83	7.38	7.32	44	57
J. F.	25	107	56	4.2	7.45	1.9	0.91	13.48	19.38	11.93	51.23	58.02	7.39	7.37	44	53
T. I.	24	90	60	3.4	5.60	1.5	0.90	13.10	18.92	13.32	48.12	53.27	7.44	7.33	38	52
A. P. H.	17	89	70	3.2	4.56	1.3	0.82	12.35	18.13	13.57	50.06	53.99	7.40	7.38	42	47
S. D.	22	81	60	4.4	7.24	1.4	0.96	13.86	19.10	11.86	42.67	49.60	7.35	7.32	40	49
S. S. K.	34	98	57	3.7	6.45	1.7	0.96	13.65	18.86	12.41	44.96	51.15	7.31	7.27	45	56
J. Fr.	26	79	74	4.2	5.69	1.0	0.94	12.35	17.00	11.31	48.29	53.61	7.41	7.34	39	50
P. K.	22	83	62	3.4	5.59	1.3	0.95	13.89	18.80	13.21	52.28	57.57	—	—	—	—
H. K.	26	97	53	3.6	6.75	1.8	1.18	14.53	20.98	14.23	52.14	60.13	7.35	7.31	49	60
E. R.	21	79	79	3.8	4.80	1.0	0.83	14.03	18.90	14.10	47.06	51.04	7.31	7.24	47	60
S. W.	23	95	67	3.6	5.35	1.4	0.81	13.86	19.81	14.46	50.31	54.65	7.33	7.30	49	56
R. M.	28	107	45	2.6	5.70	2.3	0.94	15.09	19.09	13.39	45.22	50.55	7.43	7.36	37	46
J. R.	27	86	63	3.0	4.70	1.4	0.74	13.65	18.18	13.48	49.25	57.73	7.36	7.34	45	54
A. A.	24	90	48	2.6	5.52	1.9	0.98	13.48	18.56	13.04	49.78	55.17	7.46	7.41	37	45
G. M.	22	82	54	3.0	5.63	1.5	0.98	13.48	18.60	12.97	50.24	55.74	7.44	7.38	39	49
R. O.	25	100	49	3.6	7.31	2.0	1.08	15.08	20.89	13.58	44.22	52.05	7.37	7.34	40	50
H. R.	24	81	52	4.0	7.62	1.6	0.95	13.73	19.50	12.64	46.20	52.73	7.42	7.36	38	48
J. D.	28	102	88	3.9	4.48	0.9	0.87	14.75	20.23	15.75	49.06	52.94	7.40	7.35	42	49
S. C.	19	87	56	3.7	6.57	1.6	0.86	15.08	19.85	13.28	48.25	53.89	7.39	7.34	41	52
T. F.	23	95	41	3.4	8.27	2.3	1.00	16.14	22.31	14.04	47.28	55.56	7.40	7.36	42	53
R. W.	22	88	77	3.8	4.96	1.1	1.00	12.55	17.58	12.62	47.84	52.81	7.48	7.47	34	38
W. O'D.	18	109	100	5.2	5.23	1.1	0.98	13.10	17.89	12.66	49.22	54.35	7.42	7.38	40	47
J. W. D.	29	80	61	2.8	4.66	1.3	0.81	14.24	19.65	14.99	52.35	56.24	7.34	7.33	51	56
P. T.	24	89	88	4.9	5.64	1.0	1.05	13.10	18.18	12.54	49.25	55.17	7.43	7.36	39	50
L. B.	22	83	66	3.6	5.45	1.3	0.82	13.65	18.79	13.34	45.83	50.32	7.35	7.28	43	52
Mean	24.4	90.9	63.8	3.70	5.94	1.48	0.94	13.86	19.18	13.27	48.41	54.20	7.39	7.34	41.9	51.2
S.E.	±0.9	±1.9	±2.9	±0.14	±0.22	±0.08	±0.02	±0.18	±0.23	±0.19	±0.51	±0.54	±0.01	±0.01	±0.9	±1.0
p*	>0.05	>0.1	>0.05	>0.1	>0.3	>0.1	>0.6	>0.1	>0.5	>0.8	~0.3	>0.2	>0.9	>0.8	>0.6	>0.8

* Determined by method of significance of difference between two means.

in the second of the two determinations. It seems warranted to conclude that the decreased MABP is associated with the phenomenon of sleep. The elevation of the blood pressure in the second of the consecutive controls was probably the result of the growing discomfort on the part of the subject from lying in the same position for a prolonged period.

Since CBF increased despite a decreased MABP, cerebral vascular resistance (CVR) must have fallen in sleep, as indicated in the change in its calculated value from 1.6 in the control determinations to 1.5 mm. Hg per cc. per 100 g. per min. during sleep ($p < 0.01$). On the other hand, CVR rose from a mean of 1.5 in the first to 1.7 mm. Hg per cc. per 100 g. per min. in the second of the consecutive control determinations ($p \sim 0.01$). The fall in CVR observed in sleep is probably associated with the phenomenon of sleep and, for the same reasons discussed in relation to the MABP, cannot be explained simply by the systematic difference in CVR found to exist between two consecutive control determinations.

Cerebral arterial-venous oxygen difference and cerebral oxygen consumption (CMR_{O_2}) showed no significant changes in either the sleep or the consecutive control studies. Cerebral R. Q. did not change in sleep, but the mean value, 1.02, in the second of the consecutive control determinations significantly exceeded the mean value, 0.93, obtained in the first determination ($p < 0.05$), a finding for which no reasonable explanation is at hand. Arterial hemoglobin concentrations, arterial and cerebral venous oxygen and carbon dioxide contents and pH did not change significantly in either group. Arterial and internal jugular carbon dioxide tensions (pCO_2) were not significantly altered by sleep although it is interesting and possibly significant to note that these values were appreciably higher in the sleep group, even in their control state, than in the fatigued group which could not sleep during the studies ($p < 0.05$ and $p < 0.02$, respectively). Similarly, the mean values for arterial and internal jugular blood pH were significantly lower in both determinations of the sleep group than in the fatigued group which failed to sleep ($p < 0.05$, respectively). In the consecutive control studies arterial pCO_2 remained unchanged, but the mean value of cerebral venous pCO_2, 51 mm. Hg, in the second determination significantly exceeded the mean value, 50 mm. Hg, in the first determination ($p < 0.05$). This finding is probably related to the tendency for the CBF to decrease in the second determination.

In Table III, comparison is made between the results obtained in 25 awake but "fatigued" normal young men and those observed in 11 normal rested young men studied similarly by the same group of investigators. The values obtained in the rested subjects agree closely with those previously reported by Kety and Schmidt (4). These data are taken from the control values of various experimental procedures provided that the control determinations were made first. Thus the fatigued group includes also the first of the consecutive control determinations in Tables IIA and IIB and the control values of those sleep cases in Tables IA and IB in which the control determination was first. On the basis of this comparison, no significant differences between fatigued and rested subjects could be found although the mean value for CBF, 64, in the fatigued group exceeded the mean value, 55 cc. per 100 g. per min., in the rested group by an amount approaching statistical significance ($p < 0.1 > 0.05$).

DISCUSSION

These findings are of interest because of their pertinence to certain theories which have been advanced from time to time toward an explanation of the phenomenon of natural sleep. A number of these theories have in common the postulate that sleep is associated with and caused by a diminution in the gross nutrition or metabolism of the brain.

Quite recently, Doust and Schneider have elaborated a theory which ascribes sleep to arterial anoxemia and its resultant cerebral anoxia (10). On the basis of a downward drift in the readings of an ear oximeter, these authors concluded that arterial oxygen saturation progressively decreased during the process of falling asleep and reached levels as low as 87 per cent during deep sleep. The lack of an attempt to confirm this surprising result by more direct techniques and the absence of similar observations on non-sleeping controls leaves open the possibility, however, that it may have been one of the artifacts sometimes associated with indirect oximetry. Our findings (Table IB)

that both the oxygen content and hemoglobin concentration of arterial blood were normal during the control period and remained unaltered during sleep make unlikely any hypothesis which attributes a causal role to arterial anoxemia.

If not the first, then certainly one of the earliest recorded theories of sleep attributed this phenomenon to an ischemia of the brain. By recording changes in intracranial volume in two subjects with cranial defects, Mosso (1) concluded that sleep was associated with a decrease in cerebral blood volume. Tarchanoff (11) supported this view by observing a blanching of the pial vessels in puppies when sleep occurred. A large number of investigators, however, were unable to corroborate the findings of Mosso or found instead evidence of cerebral vascular engorgement (12–16). None of these observations yielded information on cerebral blood flow which is certainly different from and not necessarily correlated with cerebral blood volume. Only in the case of Gibbs, Gibbs, and Lennox, whose thermoelectric technique would probably have indicated if it did not measure gross changes, had observations related to cerebral blood flow in sleep been made (3). These authors were unable to demonstrate any change during sleep in the function which they studied.

The present studies show a moderate but statistically significant increase in cerebral blood flow associated with sleep. This occurred in the face of the slight but significant fall in arterial blood pressure seen in these subjects and consistently observed by numerous previous investigators (17–19) and was the result, therefore, of a decreased resistance to flow somewhere in the brain. Since the intracranial pressure is usually found to rise during sleep (14, 15), and since the present studies demonstrate no change in hemoglobin concentration in the blood, factors of decreased external pressure or lessened viscosity appear to be ruled out, and it seems warranted to conclude that there is a relaxation in cerebrovascular tone during sleep. This supports previous observations which suggested a cerebral hyperemia during sleep (12–16). The cause of this cerebrovascular relaxation remains obscure. It cannot be attributed to changes in arterial oxygen or carbon dioxide tension since these remained relatively unaltered between control and sleep, nor was it in response to an increase in cerebral metabolism which was also unaffected. The usually plausible hypothesis of a decrease in neurogenic vasoconstrictor tone is rendered less tenable by the failure to demonstrate a normal vasoconstrictor tone in the cerebral vessels of man, or at least one mediated by the known sympathetic inflow to the head (20).

Examination of the data in Table III reveals that the results in normal rested young men were almost identical with those in the original report of the method (4). When considered as a single group, the subjects who had remained awake for several hours beyond their normal bedtime and were, therefore, "fatigued," did not differ significantly in any respect from the rested young men. Within the "fatigued" group, however, arterial and cerebral venous carbon dioxide tensions were significantly higher and pH significantly lower in those subjects who slept than in the subjects who were unable to sleep under the conditions of the experiment (Tables IB and IIB). These differences, indicative of a mild respiratory acidosis, were apparent not only during sleep but even during the control period when the sleep subjects were awake. Comparable changes have been observed previously during sleep (2, 21), and Mills (22) has found elevations of alveolar carbon dioxide tension during the night or early morning irrespective of whether the subjects were awake or asleep. He attributes these changes to a normal diurnal rhythm in alveolar carbon dioxide tension which is independent of sleep. Our results indicate also that the respiratory acidosis can occur in the absence of sleep and that sleep *per se* causes little if any change in carbon dioxide tension and pH of the blood, but they raise an interesting question of whether sleep can occur in the absence of the respiratory acidosis. It was this finding which distinguished the subjects who slept from those who could not sleep under identical experimental conditions. Despite the evidence of respiratory depression, no significant anoxemia was observed in these subjects, nor was it to be expected. As Mills has also observed in his studies (22), the degree of carbon dioxide retention was insufficient to account for any appreciable fall in arterial-oxygen saturation, certainly not to the levels on which Doust and Schneider (10) based their anoxemic theory of sleep.

Another hypothesis on the nature of sleep suggests that this state is some endogenous narcosis associated with an overall decrease in metabolic activity in the central nervous system which permits the replenishment of certain substrate stores presumably depleted by the active metabolism of the waking state. That sleep is quite different from anesthesia or coma is clearly demonstrated by the data on cerebral oxygen consumption (Table IA). Whereas coma (23, 24) or anesthesia (25) are associated with profound decreases in the utilization of oxygen by the brain, this function in sleep is not significantly different from its level in the waking state.

Thus the state of sleep should be added to a growing list of conditions, like schizophrenia (23) and performance of mental arithmetic (26), in which a good correlation between energy conversion and functional activity commonly found in other organ systems appears to be absent. This result is compatible with the current vogue of viewing the brain as a calculating or communicating mechanism which, in contradistinction to machines which do mechanical work, utilizes by far the greater part of its energy requirements merely in keeping its circuits alive and sensitive; the presence of a message, its functional usefulness or rationality adds only infinitesimally to the total load. Equally adequate, however, are hypotheses found more on traditional biological concepts than on electronic analogues. Thus, when the brain is considered as a great number of functional units, many of which may be reciprocally related with regard to activity, then increased activity in one group of units may result in decreased activity in others. Under such conditions, different functions could result in an altered pattern of distribution of the activity without measurable changes in the net overall oxygen consumption of the brain. Or, even more simply, is it not conceivable that the primitive functions of the brain, namely, the regulation of unconscious vegetative functions in the body, consume so much of the total cerebral oxygen requirements that they obscure the metabolic effects of the later phylogenetic functions found in conscious waking behavior, such as thought and reason?

These studies have not elicited, nor were they designed to elicit information bearing on the more subtle functional, biochemical, or electrical alterations in sleep. They do, however, render untenable those hypotheses which attribute this important phenomenon to an anoxemia, to cerebral ischemia, to narcosis, or to a generalized depression in cerebral metabolism.

SUMMARY

1. Studies of cerebral blood flow, cerebral vascular resistance, and cerebral oxygen consumption, as well as mean arterial blood pressure, hemoglobin concentration, blood gases, and blood pH, were made before or after and during natural sleep in six subjects, during two consecutive determinations under identical conditions in 13 subjects, during a state of fatigue in 25 subjects, and also in 11 normal rested controls.

2. The mean values obtained in the rested subjects were almost identical with the original normal values reported for the method.

3. The fatigued subjects showed no differences from the rested controls except for an elevation in cerebral blood flow which approached statistical significance.

4. During natural sleep there was a statistically significant increase in cerebral blood flow, statistically significant decreases in cerebral vascular resistance and mean arterial blood pressure, and no changes in cerebral oxygen consumption, hemoglobin concentration, and arterial oxygen content.

5. The fatigued subjects who slept were distinguished from those who were unable to sleep by significantly higher values of carbon dioxide tension and lower values of pH in arterial and cerebral venous blood even during the control period. These findings suggest some relationship between respiratory acidosis and the process of falling asleep.

6. The results of these studies make less tenable those hypotheses which attribute sleep to arterial anoxemia, cerebral ischemia, or to a generalized narcosis or other depression in cerebral metabolic rate.

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LEARNING DURING SLEEP?

CHARLES W. SIMON AND WILLIAM H. EMMONS
The RAND Corporation

Approximately 22 years of the average man's life is lost in sleeping. Economically minded persons and harassed students have long searched for some means to use this time to further advantage. For nearly a third of a century, now, there has been a growing interest in the possibility of trying to learn while one sleeps.

The science fiction writers were among the first to propose sleep-learning as an educational technique. In 1911, a magazine called *Modern Electrics* published a fiction story by Hugo Gernsback (**4**) in which the hero learned during sleep. The process was simple. Upon retiring, the student placed the material to be learned on a machine which played it automatically while he slept. In 1932, Aldous Huxley (**9**), in his *Brave New World*, scoffed at the possibility of improving the *S*'s intellect while he slept, but described the world of the future as one which utilized the sleep period to train the lifelong attitudes of its populations. Other science fiction writers have continued to use the idea of sleep-training in their stories.

Popular news and picture magazines, citing experimental evidence, constantly reinforce the public's interest and misinformation about this osmotic form of education. From time to time, a national news service will release a story telling of some individual who works for a living by day and studies chemistry, operatic arias, or other lessons while sleeping at night. On "People Are Funny," a popular radio stunt show, an audience participant learned a few short sentences and a girl's name while he was apparently asleep on the stage before the audience.

Following closely on the heels of public interest have come the entrepreneurs. Commercial firms have sprung up throughout the country selling recording devices which automatically turn on and off to permit the individual to learn while he sleeps. Impressive publications have been distributed by many of these firms propagandizing their products and extolling the validity and value of sleep-training (**19**, **21**). On the whole, their claims of success for sleep-training have been extrapolations beyond the available supporting data. The majority of claims have been based on distorted facts, statements by unqualified authorities, and armchair hypotheses. Noncritical use of the information, anecdotal evidence, and the citing of inadequate research, much of which will be reviewed in the present paper, have made these commercial publications poor criteria for the support of the validity of the sleep-learning process.

In its constant search for new methods to speed training during national emergencies, the military, too, has tried to sleep-train its personnel. In both the first and second World War, exploratory efforts were made to teach service men Morse code[1,2] during their sleep. A VA Hospital doctor reported the successful use of sleep-training as a supplement to waking-training in a mental health

[1] Comdr. R. R. Humes, USN. Personal communication. January 25, 1954.
[2] L. L. Thurstone. Personal communication. October 19, 1953.

program (20). Unfortunately, most of these incidents have been too inadequately controlled to judge their effectiveness during sleep, and in general their results have not been sufficently striking to justify the extra energy and expense required to carry them out.

It is the scientist who has been slow in investigating these claims for successful sleep-learning. Although psychologists have been concerned with problems of learning from their formalized beginning, there has been relatively little interest in the psychological processes which take place during sleep and a rather skeptical—although untested—attitude toward the value of studying sleep-learning. One of Pavlov's students, Krasnogorski (11), did attempt without success to condition the salivary reflex in a young child during sleep. Recently, however, a resurgence of interest in the problem has occurred. In the present paper the available research on the sleep-learning phenomenon has been collected and subjected to a critical evaluation.

Ten such studies were found. Of these only three have been published (3, 12, 13). Five were academic theses at the master's or bachelor's level (1, 2, 5, 8, 23) of which one was read at an APA meeting (23). The remaining two[2,3] were described in private communications from the authors. Although a number of other references were found, insufficient details were available for an adequate review or else they could not be classified as research under even the broadest definition.

The criticisms in this paper are not for the purpose of belittling these pioneer studies. These criticisms are believed necessary since these studies—many of which are unpublished—are being cited and their conclusions accepted both by the general public and some scientists. Because of the unusual methodological problems in this area of research, a review may help future workers to avoid similar mistakes.

[3] L. LeShan. Personal communication, October 27, 1953.

Description of the Sleep-Learning Studies

The experiments reviewed in this paper are described briefly below. In some of the studies, *Ss* were eliminated for various reasons. Only the number of *Ss* actually completing the experiment is reported.

Thurstone,[2] in 1916, supplemented the waking training of 16 Navy men in a Morse code course with material presented during sleep. The criteria of sleep used in this study are unknown. The *Ss* finished the course three weeks earlier than had been expected. Thurstone concluded that the results "indicated some gain" for the sleep-trained group in their ability to send and receive Morse code.

LeShan (12), in 1942, tried to break the fingernail-biting habit of 20 boy campers, ages 8 to 14, by playing the phrase, "My fingernails taste terribly bitter," through a loudspeaker 300 times a night for 54 nights. The *Ss* were asked if they were awake before turning on the input; if the *Ss* appeared restless, the input was turned off. The nails of the *Ss* in the experimental group and an equal number of *Ss* in a control group were checked every two weeks for eight weeks for signs that the nail-biting had stopped. Since 40 per cent of the experimental group and none of the control group stopped biting their nails, LeShan felt this indicated "the possible therapeutic use of suggestion during sleep."

LeShan[3] in 1943, taught a single *S* a different list of nonsense syllables each morning for 12 days. On the fifth and eighth nights, the list to be learned the next day was repeated 50 times while *S* slept. The criteria of sleep used in this study are unknown. Fifty per cent fewer trials were required to learn the two

sleep-trained lists than to learn the ten *non*sleep-trained lists. LeShan concluded that the sleep-training facilitated learning.

Elliott (2), in 1947, studied the effects of 30 repetitions of a list of 15 common three-letter words during sleep on the per cent saved in learning the list by the anticipation method the following day. Two groups of 20 male college students of equal learning ability spent one night adapting to the laboratory environment. The word list was repeated serially to one group of *S*s while they slept. An EEG record was used as a criterion of sleep. No material was played when the *S* showed "clear alpha patterns" although the EEG was turned off when *E* believed *S* would stay asleep. On awakening the next morning, the two groups learned the sleep-trained list by the anticipation method and were asked if they awoke during the night. The group receiving the sleep-training showed a significantly greater percentage of savings than the control group ($p = .05$).[4] No significant differences between groups were found on the basis of errors or absolute number of trials to learn. Elliot concluded that there is some retention of auditory material during sleep.

Hedges (5), in 1950, tried to improve the speech of three mentally retarded and aphasic children (ages 11, 7½, and 6) by sleep-learning. Short sentences, paragraphs, and simple consonant sounds were played to the children between 433 and 1501 times distributed over 7 to 13 nights. The machine was not turned off if an *S* awoke. The third child required fewer waking lessons to learn the sleep-trained consonant than it had required previously to learn a nonsleep-trained consonant. The babbling of the first child increased. The second child showed no effects. Hedges interpreted this as showing "the possibility of perhaps speeding" the training of the third *S*.

Fox and Robbins (3), in 1952, taught 30 college males and females a list of 25 pairs of English-Chinese vocabulary. The *S*s were divided into three groups, matched on a pretest. Two vocabulary lists were prepared; in the first list, word pairs were matched as they were to be learned on the posttest (the facilitation list), while in the second, they were mismatched (the interference list). These lists were played 15 times to two of the *S* groups approximately three hours after they had retired to go to sleep. The third group—a control—heard only music while they slept. Although *E*s did not observe *S*s during the input period, they disqualified all *S*s who said they had awakened during the night. The facilitation group required fewer trials and the interference group required more trials to learn the posttraining list than did the control ($p < .001$). The *E*s concluded that learning could occur during sleep and could be detected by the savings method.

Leuba and Bateman (13), in 1952, believed that they had taught the words of three songs, 8 to 27 lines long, to a lightly sleeping *S*. Each song, unknown to *S* beforehand, was played to her five times a night for three successive nights as she slept. During the input period, *S* was not observed by *E*, although for three brief periods, *S*'s husband observed no restlessness on the part of the *S*. The *S* claimed she did not awaken during the night. Given only the song title the next day, *S* was able to write the lyrics of two out of the three songs with no errors and of one with only minor errors. The *E*s believed the sleep-training was successful. No learning occurred in a later study during and following the use of sedatives.

Hoyt (8), in 1953, taught ten pairs of English-Chinese vocabulary to his *S*s. Twenty *S*s were matched on a pretest and given one night to acclimate to sleeping in the laboratory. On the experimental night, one group of eight *S*s received twelve repetitions of a list paired in the same manner as that to be learned the next morning (facilitation list). A second group of eight *S*s received a list of comparable words, but with the pairs mismatched (interference list). The remaining four *S*s acted as a control group and received no sleep-training. During the input period, *S*s were observed by *E*.

[4] The p values representing the results of tests of significance are all reported as if they were based on a two-tailed t test, irrespective of what the author used. The p levels greater than .15 were not reported.

If they awoke or heard the stimulus material, they were to turn on a light. If this occurred, or if they stirred, the recording was turned off until *S* lay quiet for a suitable length of time. The next morning *Ss* were asked if they had awakened during the night. Those that had not were given the paired vocabulary list to learn to two correct anticipations. Statistically insignificant differences were found to favor greater savings for the interference group rather than the facilitation group in both the mean number of trials required to learn the list as well as the number of correct responses occurring before the criterion was reached. No comparisons were made with the control group. Hoyt felt that under the conditions of this study, learning during sleep could not be detected.

Stampfl (**23**), in 1953, had six college males learn lists of ten nonsense syllables while acting as their own controls. Different lists were repeated 4, 8, 16, and 32 times on different nights while *Ss* slept, and were learned to one correct anticipation on the morning following the repetition of a particular list. At other times, the same *Ss* were tested on other lists after no sleep-training. Before presenting the stimulus material, *Ss* were asked if they were awake. During the input period they were watched, and if movements occurred, the input was stopped. Since no significant differences were found for savings in either trials or errors between learning sleep-trained and non-sleep-trained lists, no comparisons were made among performances after different numbers of training repetitions. Stampfl felt that the sleep-learning hypothesis was uncertain and improbable.

Coyne (**1**), in 1953, carried out a series of exploratory studies on a variety of psychological problems using from four to six male college students as *Ss*. He believed the results to be generally favorable for sleep-learning. Unfortunately, a statistical error was discovered in Coyne's thesis after he had written his discussion and conclusions which led to a more favorable interpretation of the results than was justified. Although *E* could observe *S* as he slept, he primarily depended on *S* to press a buzzer as soon as he awakened during the night. The problems Coyne studied are described below.

1. An interference list of adjectives was presented 25 times to the sleeping *S*. A similar list was learned to one perfect anticipation the next morning. A control group had no sleep-training. The sleep-trained group did poorer than the control group ($p = .07$).

2. When the first problem was repeated using *S* as his own control, more errors were made on the list which had received the interfering sleep-training ($p = .15$). No difference in savings (trials to learn the posttraining list) was observed.

3. Twenty pairs of numbers and words were presented 24 times during a single 45-minute period to the sleeping *Ss*. These same *Ss* also received another list for the same number of repetitions distributed over a four-hour period. On subsequent mornings, *Ss* were required to answer the appropriate word when given the number found on the list on which they were trained during the night, after that list had been mixed with ten additional new number-word pairs. A greater percentage of sleep-trained words were associated with the correct numbers than those words not trained during sleep ($p = .15$). Distributed sleep-learning resulted in fewer recall errors than did massed sleep-learning ($p = .05$).

4. While the *Ss* slept, one list of adjectives was repeated 100 times; on a different night, another list was repeated 25 times. On the morning following the sleep-training, the list was learned to one perfect repetition. No significant differences were found in performance between the two amounts of training.

5. The *Ss* were required to solve a number of problems by finding *E*'s solution of a concept composed of the correct combination of letters, colors, and their relative positions. The solution to one problem had been repeated 180 times while *S* slept the night before. Insignificant differences were found favoring the performance on the sleep-trained problem.

6. While *Ss* slept, one list of nonsense syllables was presented 30 times begin-

ning at two o'clock and, on a different night, another list was presented 30 times beginning at five o'clock. Since it was discovered that the two lists were of unequal difficulty, comparisons between performance at different times of presentation were not made.

7. During sleep, the contents of a particular picture were described to *S*s 90 times. The following morning, a number of out-of-focus pictures were shown, including the one described during sleep. The degree of focusing required before *S* could identify the pictures was the measure of learning. No significant differences in the case of identifying sleep-trained and nonsleep-trained pictures were found either when *S*s were asked to give unaided responses or when multiple-choice solutions were provided.

Rather than examine each of the ten sleep-learning studies independently, this paper has been organized to discuss them all on the basis of the following categories: experimental design, statistical considerations, methodological considerations, and sleep criteria.

Experimental Design

The use of a control group or of using *S* as his own control is recognized as a necessary procedure in order to know whether a certain experimental effect is real or not. In a number of the sleep-learning studies, however, both of these techniques were conspicuously absent or inadequately handled.

Thurstone (see footnote 2) recognized the inadequacy of his *uncontrolled experiment* teaching Navy men Morse code and attempted to run a second study in order to compare the performance of one group which received sleep-training with another which did not. This study was discontinued, he reported, when it was discovered that ambitious Navy instructors of the control group had been giving extra daytime instruction in order not to be out-taught.

Hedges (**5**) used *no controls* with two of the three speech-defective children he attempted to sleep-train. Since improvement in speech is a maturational problem, even for retarded children, the need for a control was paramount. The increased babbling of the first child may have been independent of the sleep-training and due solely to an additional month or two of growth, although Hedges believed that it took place immediately after the introduction of the sleep-training. Since *S* also received waking-training on the same material, it is impossible to know to what extent one can attribute the increase in babbling to sleep-training. No apparent learning took place with the second *S*. Although Hedges' third *S* acted as his own control by learning to pronounce one consonant with sleep-training added to his waking-training and another consonant without the sleep-training, this was an inadequate control measure since the experimental design was such that the sleep-trained consonant followed the nonsleep-trained consonant. Any improvement in the latter could be attributed to practice as well as to maturation.

Nor was a control used in the work of Leuba and Bateman (**13**). In this study, *S* presumably had no previous knowledge of the songs played to her during sleep, yet was able to write the lyrics without further training on awakening. If this were the case, any learning which took place during sleep would be a significant improvement, although materials such as songs and poetry probably have some internal predictability. This form of experimental design represents an *implied control*. It is implied that *S* acted as her own control for had she been tested previously, no appropriate responses could have been made, nor could one suspect that matura-

tional factors were operating to produce positive results.

A number of *E*s actually used their *S*s *as their own control*. In LeShan's (footnote 3) second study, he compared the number of trials an *S* required to learn a list with and without sleep-training over a period of days. By having the nontrained periods before and after the sleep-trained periods, the superiority of the sleep-trained lists could not be attributed simply to practice or maturation. On many of his studies, Coyne (1) gave sleep-training to his *S*s one night and no sleep-training on the next, counterbalancing the order for these procedures between two groups of *S*s. However, when the *S* acts as his own control, either the study material which is used under the varying conditions must be carefully equated, or additional counterbalancing must be introduced into the experimental design to correct for the inequalities. No *E* used this counterbalanced design; some made use of the published tables on which similarities and associability of the stimulus material had been previously calculated for the items. Several of Coyne's (1) studies were unanalyzable after he discovered the study material had not been equated.

Four of the experiments were designed to use *separate control groups*. In Elliott's (2), Fox and Robbins' (3), and Hoyt's (8) studies pretesting took place in order to equate the mean performance of the control and experimental groups. LeShan (12) used unmatched groups in his study with fingernail-biting children. The median age of his twenty experimental nailbiters was slightly less than ten years. His control was divided into two groups consisting of eight nailbiters with a median age of nine years, and twelve more nailbiters with a median age of twelve. Some question might be raised concerning LeShan's failure to better equate the experimental and control groups on age, for there is reason to suspect a relation between nail biting and age. Wechsler (25) found a sharp rise in nail biting for boys around the age of twelve; if this is so, there would be a lower probability for the older control group to stop biting its nails than the younger experimental group, thus reducing the effectiveness of the older group as a control.

Two of the experimenters added a *second experimental group* to their design. Fox and Robbins (3) and Hoyt (8) used both a facilitation and an inhibition group in order to obtain a more sensitive indication of the value of sleep-training. Of all of the studies, only that of Fox and Robbins (3) provided the control group with a neutral stimulus—music—for the same amount of time as that in which the experimental group received the verbal test material. If there are any disturbances during sleep due to the stimulus and if these in turn affect recall, such a procedure is a wise one.

Although none of the *E*s were directly concerned with the problem, the use of an *additional control group* to compare results from sleep-training with the equivalent amount of waking-training would have been quite illuminating.

Statistical Considerations

Only five of the *E*s (1, 2, 3, 8, 23) treated their data statistically to see if the sleep-training improved performance significantly. The remaining *E*s used clinical criteria to evaluate the effects of sleep-training.

Although Elliott's (2) results favored the performance of the sleep-trained group over the nonsleep-trained group, he failed to find a significant difference at the 5 per cent

level in the number of trials it took to relearn the training list. Elliott had equated his groups on a pretest, but did not attempt to match the individual *Ss* for the analysis. Since equating tends to decrease differences between means, failure to remove the variance due to *Ss* inflates the error variance and decreases the probability of getting significant differences. When the present authors (**22**) did an analysis of covariance with pre- and posttest scores from Elliott's data, the differences between the mean number of trials to learn a new list by sleep-trained and non-sleep-trained *Ss* were significant below the .05 probability level.

Coyne (**1**) used the *one-tailed t test* to evaluate his data. The wisdom of this treatment is questionable. In order to avoid abuses and controversy, exploratory work should be as cautious in its interpretations of results as it should be daring in attempting new ideas. Using the one-tailed *t* test does not allow for the possibility that differences might be in the direction opposite to that hypothesized (**6**). This is serious in any exploratory work; it is particularly dangerous in sleep-learning studies where one could seriously suspect that the intervening training during sleep might actually hinder normal waking recall.

Half of the *Es* (**2**, **3**, **8**, **12**; footnote 2) used a reasonably large *number of Ss* as compared to the number used in most psychological studies; in the remaining cases, the number was smaller. When the number of *Ss* is small, one might be more critical of accepting the null hypothesis merely because the level of significance was not below the traditional 5 per cent level. For studies as exploratory as these, significance levels of 15 per cent could be arbitrarily considered encouraging. Since the expense in time and money is relatively small, preliminary work in sleep-training should favor fewer Type II errors in order not to reject valuable experimental leads by accepting a false null hypothesis.

Methodological Considerations

A number of *Es* believed that differences in methodology might have been responsible for the divergent successes and failures found in the sleep-learning studies. These and other considerations are discussed below.

Subjects

The majority of the studies employed the traditional college student —male and female—as *Ss*. Thurstone used Navy men and LeShan used young boy campers. Hedges (**5**) bravely attempted to provide sleep-training as a supplement to the waking-training of children who had speech deficiencies and who were suspected of being mentally retarded. None of the *Es* attempted to study the effects of either age or sex on sleep-learning.

The selection of *Ss* may have an effect on whether successful sleep-training results are attained or not. Underwood, while reviewing Fox and Robbins' paper in the *1953 Annual Review of Psychology*, commented that "such low variability [on performance scores] among *Ss* on the test list is rarely found in normal transfer experiments with such material, but this may again only reflect the presence of a highly select and homogeneous sample" (**24**, p. 48). Low within-group variability was certainly in part responsible for the high degree of significance of the differences between the sleep-trained groups and the control.

Whatever the variability of the group, it would appear wiser to

choose individuals who have shown the capacity to learn while awake. Perhaps the effects of sleep-training are so subtle that its benefits will be found only when it is applied to individuals with very high IQ's.

Number of Repetitions

The experiments can be divided into two groups on the basis of this variable—those who gave an exceptionally large number of repetitions of the material during sleep (**5,12**) and those that gave significantly fewer repetitions (**1, 2, 3, 8, 13, 23**; footnote 3). The large number of repetitions were actually spread over a number of nights and ranged from a total of 433 times over a period of eight nights to 16,200 times over a period of 54 nights. The smaller number of repetitions ranged from 8 to 180 times, with one study (**13**) playing the material five times per night for three successive nights. More repetitions were characteristic of the field as opposed to the laboratory studies. Both groups obtained both positive and negative results, although the tasks were varied sufficiently so that direct comparisons could not be made. LeShan's (**12**) study, in which 40 per cent of the experimental group stopped biting its nails, represented a successful example where a great deal of repetitious training seemed to have affected a semi-involuntary behavior.

Stampfl (**23**) and Coyne (**1**) found no differences when they tried to study the effects of different amounts of repetitions on sleep-learning. Actually since neither *E* used a non-sleep-trained group as a control, neither could conclude that any sleep-learning took place at all in this phase of their study. Coyne (**1**) suggested that in his study there may have been no greater differences in savings after one hour of repetitions than after four hours because the material was simple enough to be learned in one hour and additional practice could not improve it. This is a reasonable hypothesis, as is its antithesis—that during sleep, learning is sufficiently slow so that little is learned even after four hours of repetitions. Sleep-learning, if it is to occur at all, may require that an extremely large number of stimulus repetitions take place. It will be important to evaluate sleep- versus waking-training from the standpoint of economy of both time and effort.

Presentation

The manner in which the study material is presented to the sleeping *S* has been considered by some *E*s as critical to the success or failure of the training. Two dimensions of this variable are the time of presentation and the order of presentation.

The problem of *presentation time* is an important one since during the sleeping period, time is related to some extent to the depth of sleep, which in turn may be related to trainability. Deeper sleep tends to be more prevalent in the early period of sleep, while lighter sleep tends to occur later (**18**). Of course, the levels vary considerably throughout a normal night's sleep.

Coyne (**1**), studying the effects of presenting the material at different times during the sleep period, failed to equate his lists beforehand and could draw no conclusions from his results. He recognized that presentation time might be inversely related to the amount retained. He suggested, however, that this was due to the recency of the presentation to the recall period. It is interesting to speculate whether or not the Jenkins-Dallenbach interference effect (**10**) occurs within the sleep period for materials presented during sleep.

The differences Coyne found between massed and distributed learn-

ing might also be accounted for on the basis of presentation time. Although he concluded that distributed sleep-learning was superior to massed sleep-learning, there is no way to determine whether this was so because of the spacing of the training or because some of the distributed inputs occurred during the period just before waking—often a light drowsy state—while the massed inputs occurred only during the deeper and possibly less receptive period.

The *order* in which the material was presented during sleep may also affect the results of sleep-training. In a waking state, serial learning has been shown to be easier than learning material presented in a varying order (7). Thus, if any learning takes place in sleep, a serial presentation would more probably increase any positive effects which might occur. Also, if the sleep state is one in which no mental organization takes place, this would favor the learning of only the more organized serial presentation.

Hoyt (8) and Stampfl (23) varied the order in which their material was presented and failed to find that any sleep-learning took place. Fox (3), LeShan (12), Elliott (2), and Leuba (13) believed they found evidence of successful sleep-learning. Thurstone probably varied the order of his material, but his *S*s were practiced over a period of months so that the effects of presenting the material in a varying or an unvarying order may have been minimized.

The varying presentation order in Hoyt's study was methodologically different in one major respect from that used in Stampfl's study. Since the former study used paired-associate material, varying the order in which the pairs were presented would have less effect than it had in the latter study where the order of words in a list was varied during sleep-training, even though they had to be recalled serially during the waking period. Any positive effects of sleep-training in the latter case may have been neutralized by the negative effects built up through nonserial learning.

Training Problems, Materials, and Mode of Input

The types of psychological problems studied by the majority of sleep-training investigators have been quite limited. With the exception of Coyne's (1) work on concept formation and perceptual sets and LeShan's (12) and Hedges' (5) therapeutic studies, the remainder of the research has been involved with training problems which require the memorization of word lists. It is unlikely that all types of problems are suitable for sleep-training, although exploratory studies should examine many rather than a few possibilities.

Of the material used in the studies requiring verbatim recall, the degree of meaningfulness ranged from lists of nonsense syllables through short words to foreign language vocabulary. We know that the more meaningful the material, the easier it is to learn in the waking state (7). Stampfl (23) suggested that this might explain why his results with nonsense syllables were poorer than Elliott's (2) who used a list of adjectives, and why Fox (3), using a Chinese-English vocabulary, got even more striking results. This does not seem to be a critical variable, however, for Hoyt (8), using the same Chinese-English vocabulary as Fox (3), got negative results, while LeShan (footnote 3) and Coyne (1), using nonsense syllables, got positive results.

All of the *S*s used an auditory input. This is certainly the most obvious technique and would appear to be the most economical; however, other sensory channels need not be

ignored. It may be necessary to flash lights on closed eyelids or to apply tactual stimuli to the fingertips in code in order to "reach" the sleeping *S*.

Techniques and Measures of Retention

The techniques used to measure the retention of training material can have considerable influence on the amount of material recalled. However, in the present studies, there did not appear to be a pattern of successes or failures consistent with the technique used.

A number of *E*s did not require the verbatim recall of the verbal material presented during sleep. Instead, they evaluated retention on *S*'s ability to *use the material* in posttraining tasks or on an *observed change* in *S*'s behavior after the training. LeShan (12) examined his *S*s' fingernails every two weeks to see if the children had stopped biting their nails. This technique might have been slightly more objective had the examiner not known which children were and were not receiving the sleep-training. Hedges' (5) clinical evaluations of his children's speech improvement required even more subjective judgments. Because of the very complexity of this measure, Hedges wondered whether it was sensitive enough to detect improvement. Coyne (1), in several studies, had his *S*s describe an out-of-focus picture, the identity of which had been given to them during sleep, and to determine *E*'s solution of concepts composed of the correct combination of certain stimulus variables, the answer to which had also been provided during sleep. Thurstone's *S*s were evaluated on their ability to send and receive Morse code. Both Coyne's and Thurstone's results could be quantified.

Leuba (13) gave his *S*s the titles of songs played during sleep and required them to *recall unaided* the lyrics. Positive results were claimed for sleep-training in this study.

The *savings method* has been used by a majority of *E*s (1, 3, 8, 23; footnote 3), for they believed it to be a more sensitive measure of retention. Stampfl (23) believed that although material could not be consciously recalled at any moment, its presentation during sleep may have still modified the nervous system sufficiently to make learning easier and a savings effected. However, use of the savings technique may confuse the measure of retention with a measure of the ability to learn since both are confounded within the same performance score. None of the *E*s using the savings measure compared the time to relearn a list with the time it took the same *S* to learn an equivalent list presented after sleep. Comparisons with the original list presented before sleep are not sufficient. The positive transfer which occurs from the pretest to the posttest—the phenomenon of "learning how to learn"—may account for some of the apparent savings which several researchers believed they found. However, Stampfl (23) gave three practice lists to be learned before the experiment in order to bring *S*s' learning curve closer to its asymptote and thus reduce the "learning to learn" effect.

A still more sensitive technique for measuring retention is that of *recognition;* at least in Luh's (16) classical study this was so after a two-day interval between training and the posttraining test. Coyne (1) used this technique in the form of a multiple-choice test for one of his exploratory studies on perceptual set, but still failed to get positive results. Hoyt (8) told of an exploratory study in which he presented a single number-word pair to a sleeping *S* who was under constant observation for a total

of 11 hours on three successive nights. On awakening after the third night, *S* was given the number and asked to pick the correct word from a group of ten. He was unable to do this correctly. A major difficulty with the recognition method is that it must be corrected for chance guessing. With words, however, this correction for chance is difficult since all words do not have an equal probability of being recognized (17).

Variations in the score used to measure retention have failed to consistently differentiate success and failure in sleep-learning. Many of the *E*s (1, 2, 8, 23; footnotes 2, 3) used the *number of trials* to learn posttraining material to one perfect repetition as a measure of retention. Hoyt (8) required that the lists be learned to two perfect anticipations; this may tend to make his results slightly more reliable. Some *E*s (1, 2, 8, 23) also used as measures of retention the *number of errors* or correct responses made on the first trial or later trials, or on cumulative trials. Where the *S*s performance was used to measure retention, the measure was characteristic of the task, e.g., Coyne used the extent of focus of the projector as the measure of performance in his perceptual set study. The measure that is used may determine in part the results which are found. For example, Coyne (1) noted that the measure by trials often favored the opposite results than those favored by the measure by errors. Error measures generally lead to less conclusive results than those measured by trials. This situation does occur in waking-research and need not be contradictory, although it certainly affects the conclusions drawn as well as the practical applications of the results.

Before final conclusions can be drawn concerning the feasibility of sleep-learning, more recall techniques should be tried. Simon and Emmons (22) discuss this while considering the possibility of secondary cerebral storage mechanisms for material introduced during sleep.[6]

Sleep Criteria

Perhaps the most damaging criticisms of the sleep-learning studies to date have been the inadequate control of sleep and the criteria used for defining sleep. So elusive is the process of sleep from the psychological standpoint and so little is known about the actual physiological mechanisms which cause sleep that the problem of determining whether *S* is asleep is to a great extent a semantic one. Although both direct observation and *S*'s subjective report are reasonably reliable for deciding if *S* has been asleep over a block of time, neither can be considered sufficient to know if *S is* asleep at any moment in time. Therefore, the care with which *E* determines the sleep condition of his *S* at the time of the input is highly important and determines the degree of confidence which one may place in the conclusion that learning during real sleep is or is not possible. Some *E*s (1, 2, 3) eliminated

[6] Dr. Bernard Fox, in a private communication (26 June 1954), described his attempt to use hypnosis as a means of facilitating the recall of sleep-trained material. A 55-year-old man was brought to a point where deep hypnosis was possible. In his normal sleep he was presented with a list of ten words repeated for a half-hour. During this period, *S* was observed and the input turned off whenever he moved. The next morning, he was unable to recall any words unaided. When he was hypnotized, he made only one association which *might* have been related to one of the words. Still under hypnosis, he recognized fewer words than would be expected by chance when the ten were interspersed randomly in a group of thirty. Neither reading the words aloud nor making him choose by a forced-choice method produced any more positive results.

S from the experiment if he awoke or said he heard the stimulus. Other *E*s (**12, 23**) shut off the stimulus until *S* went back to sleep.

In four of the studies (**2, 3, 8, 13**), *E*s *asked Ss after the training if they had awakened.* This is an unsatisfactory criterion of sleep for experimental studies since it is a common experience to awaken during the night, perform a number of rational acts before retiring again and remember nothing the next day (**8, 18**). Hoyt stated that one *S* was observed to awaken during the night, leave the laboratory to go to the bathroom, and later return to bed. The next morning, *S* remembered nothing about it. In two of these studies (**3**; **13**) *E*s were not even present to *observe Ss* as an added check.[6]

In one experiment (**3**) the *time of night* was considered a partial criterion of sleep; training was applied during the period when studies have shown sleep to be at its deepest. However, published sleep curves are based on statistical averages and cannot be used to predict accurately the sleep characteristics of the single individual. Individual sleep curves vary considerably from time to time during the night (**15**).

Two of the *E*s (**12, 23**), *before presenting the stimulus material, asked Ss if they were asleep.* Since LeShan's (**12**) *Ss* were adolescent boys in camp, naive as to the purpose of such questioning, one may wonder if asking them if they were asleep would be a sufficient check. It has been observed that even willing *Ss* often fail to respond to such questions, although they admit hearing them later. Another major difficulty with this technique is that *S* may actually have been asleep when the test question was asked, but later would awaken sufficiently to hear the subsequent input. In these studies, no systematic check was made to be sure that *Ss* did not awaken *after* the initial test, except to note if they moved.

Coyne (**1**) and Hoyt (**8**) had their *Ss press a button whenever they awoke* in order to stop the input of training material. This method alone is not sufficient since it has been found that often the desire as well as the ability to do this is not present although *Ss* are able consciously to hear and understand the material. Since much of the material used in these studies was short and specific, even a few seconds of waking presentation would have been sufficient to allow *Ss* to hear and learn much of the stimulus while awake.

Stampfl (**23**), LeShan (**12**), and Hoyt (**8**), in addition to asking their *Ss* if they were or had been awake, also *noted whenever they moved,* and turned off the machine at that time. This criterion of sleep is not completely satisfactory since EEG records indicate that sleep may lighten to almost a wakening state before movement occurs, as well as afterwards, or when there has been no movement at all (**15**). Hoyt (**8**) found that two of his *Ss* said they had awakened but showed no observable movements, while three subjects said they had not awakened but showed from two to six movements each. This suggests that the criteria of asking and noting movements did not correlate very well. In Hedges' (**5**) study, the parents occasionally observed the children to see whether

[6] Fox stated "if any *Ss* in the group of 30 actually did wake up without reporting it, then the number was probably distributed about equally throughout the groups. Moreover, since all *Ss* with one exception show effects in the expected directions, it is clear that the results cannot be explained on the bases of a few *Ss* in each group who awakened but failed to report doing so" (**3**, p. 78). It may be on the basis of many.

or not they awoke during the sleep-training; two children awoke. In the first case the number of training repetitions were not counted for the time *S* was awake. However, without a waking control, this correction is meaningless. The other *S* awoke while the recording was playing and began drowsily to follow the instructions given on the record. Hedges felt this aided the progress observed in that case.

Elliott (2) used the *electroencephalogram* to determine the *S*'s sleep level. Independent workers using a variety of techniques have established a significant correlation between the brain wave patterns and the depth of sleep (14). Because the writers believe that properly evaluated electroencephalograms represent the most objective, continuous, and practical on-the-spot indicator of sleep depth available, Elliott's (2) positive results—often quoted by the commercial firms in support of their claims for sleep-learning—are quite noteworthy. An examination of his sleep criterion revealed one major flaw, i.e., Elliott did not keep the EEG running during the entire training period. Therefore, no continuous check was made of the *S*'s sleep level while the stimulus was being played. The EEG was turned on at the beginning of the training and kept on until *E* believed that sleep would remain deep enough; then he would shut it off for the remainder of the half-hour stimulus period. With Elliott's data, a correlation of −.39 was found between the amount learned and the amount of monitoring. This was not significant at the 5 per cent level but in a direction which suggested that more savings occurred with less monitoring. The writers (22) also compared the amount of savings made by a group of Elliott's five *S*s who were monitored nearly all of the training time with the savings of the remaining fifteen *S*s who were monitored on an average slightly more than a fourth of the time, and never more than 54 per cent of the time. For the first group, the average savings in trials to learn was 27.5 per cent; for the second group, the average savings was 45.0 per cent. The difference of 17.5 per cent was highly significant below the 2 per cent level of significance and we can conclude that when a thorough check of the sleep condition was made with the EEG during training, considerably less savings took place.

That any savings occurred for the groups monitored nearly 100 per cent of the time might be accounted for in two ways without assuming that learning actually occurred during sleep. First, the apparent savings may be simply an effect of the "learning how to learn" phenomenon discussed earlier in the section on "Methodological Considerations." Second, Elliott stated that whenever an alpha pattern was "clearly" present he concluded *S* was awake and turned off the input machine. In so doing, he quite likely permitted many of his *S*s to listen while they were already awake since movement, tenseness, or the opening of the eyes may sometimes block a clearly established alpha.

The expense of the EEG equipment negates its widespread use. This does not mean that without it, however, adequate sleep-learning studies cannot be done. The use of a combination of the criteria and continuous monitoring may be sufficient to insure some rough but adequate control of *S*'s sleeping condition. It is interesting to note that Hoyt (8) and Stampfl (23), finding negative results, were the two *E*s using the

greatest number of multiple and continuous criteria.

The continuity of monitoring cannot be overemphasized; for in spite of wishful thinking to the contrary, *Ss* do awaken while the input is being presented. Two out of three of Hedges' (5) *Ss* awoke. As many as half of Coyne's (1) *Ss* awoke in some of his studies. Elliott (2) reported that six of his *Ss* awoke. Only two out of sixteen of Hoyt's (8) *Ss* in the experimental group failed to awaken during an input period. LeShan (12) also stated his *Ss* awoke, but did not specify how many. One-fourth of Fox's (3) *Ss* awoke, and were eliminated from the study.

The conditions under which *Ss* sleep can influence to some extent the soundness of their sleep. Elliott (2) and Hoyt (8) required *Ss* to sleep in the laboratory one night previous to the experiment. Any sleeplessness occurring on this first night probably induced a deeper sleep on the second. Hedges (5), Fox (3), and Leuba (13) used *Ss* while they slept in their own homes, while Thurstone (footnote 2), LeShan (12), and Stampfl (23) used *Ss* who had been sleeping in familiar "homes away from home" for some time.

Although most of this discussion has centered around the problem, Was the sleep state deep enough?, Stampfl (23) and Leuba (13) suggested that there is an intermediate point between waking and deep sleep that is optimal for sleep-learning. Some negative results, they believed, may have been obtained because *S* was too *deeply* asleep. Whether this is true or not is an experimental question for future *Es* to answer.

Summary and Conclusions

Ten sleep-learning studies were reviewed. Many of these have been cited uncritically by commercial firms or in popular magazine and news articles as evidence in support of the feasibility of learning during sleep. A critical analysis was made of their experimental design, statistics, methodology, and criteria of sleep. All of the studies had weaknesses in one or more of these areas.

It is highly speculative whether or not the studies reviewed in this paper have presented any acceptable evidence that learning during *sleep* is possible. The inadequate control of a number of experimental variables makes the validity of the conclusions drawn by many of the *Es* unwarranted. The conditions under which the results were found tend more to support the contention that some learning takes place in a special kind of waking state wherein *Ss* apparently do not remember later on if they had been awake. This may be of great practical importance from the standpoint of economy in study time, but it cannot be construed as *sleep-learning*. More carefully controlled experiments in the future may provide us with a clearer answer to the question," "Can one learn during sleep?," as well as to provide comparative data between waking and resting learning from the standpoint of economy of time and effort. The problem is partially confounded by an inadequate definition of sleep.

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THE RELATION OF EYE MOVEMENTS DURING SLEEP TO DREAM ACTIVITY: AN OBJECTIVE METHOD FOR THE STUDY OF DREAMING

WILLIAM DEMENT[1] AND NATHANIEL KLEITMAN[2]

Department of Physiology, University of Chicago

The study of dream activity and its relation to physiological variables during sleep necessitates a reliable method of determining with precision when dreaming occurs. This knowledge, in the final analysis, always depends upon the subjective report of the dreamer, but becomes relatively objective if such reports can be significantly related to some physiological phenomena which in turn can be measured by physical techniques.

Such a relationship was reported by Aserinsky and Kleitman (1) who observed periods of rapid, conjugate eye movements during sleep and found a high incidence of dream recall in *Ss* awakened during these periods and a low incidence when awakened at other times. The occurrence of these characteristic eye movements and their relation to dreaming were confirmed in both normal *Ss* and schizophrenics (4), and they were shown to appear at regular intervals in relation to a cyclic change in the depth of sleep during the night as measured by the EEG (5).

This paper represents the results of a rigorous testing of the relation between eye movements and dreaming. Three approaches were used: (*a*) Dream recall during rapid eye movement or quiescent periods was elicited without direct contact between *E* and *S*, thus eliminating the possibility of unintentional cuing by *E*. (*b*) The subjective estimate of the duration of dreams was compared with the length of eye movement periods before awakening, reasoning that there should be a positive correlation if dreaming and eye movements were concurrent. (*c*) The pattern of the eye movements was related to the dream content to test whether they represented a specific expression of the visual experience of dreaming or merely a random motor discharge of a more active central nervous system.

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Method

The *Ss* for the experiments were seven adult males and two adult females. Five were studied intensively while the data gathered from the other four were minimal with the main intent of confirming the results on the first five.

In a typical experiment, *S* reported to the laboratory a little before his usual bedtime. He was instructed to eat normally but to abstain from alcoholic or caffeine-containing beverages on the day of the experiment. Two or more electrodes were attached near the eyes for registering changes in the corneoretinal potential fields as the eyes moved. Two or three electrodes were affixed to the scalp for recording brain waves as a criterion of depth of sleep. The *S* then went to bed in a quiet, dark room. All electrode lead wires were further attached to the top of the head and from there to the lead box at the head of the bed in a single cord to minimize the possibility of entanglement and allow *S* a free range of movement. The potentials were amplified by a Model III Grass Electroencephalograph in an adjoining room. The electroencephalograph was run continuously throughout the sleep period at a paper speed of 3 or 6 mm. per sec. which allowed easy recognition of eye-movement potentials. A faster speed (3 cm./sec.) was used for detailed examination of the brain waves although the slower speed permitted at least an approximate

TABLE 1

SUMMARY OF EXPERIMENTS

Ss	Nights Slept	Awakenings	Average Nightly Awakenings	Average Sleeping Time
DN	6	50	8.3	7:50
IR	12	65	5.4	4:20
KC	17	74	4.4	6:00
WD	11	77	7.0	6:30
PM	9	55	6.1	6:20
KK	2	10	5.0	6:00
SM	1	6	6.0	6:40
DM	1	4	4.0	7:00
MG	2	10	5.0	6:10
Totals	61	351	5.7	6:00

estimation of the gross pattern. The criteria of eye-movement potentials and their differentiation from brain wave artifacts have been discussed at length elsewhere (1, 4).

At various times during the night *Ss* were awakened to test their dream recall. The return to sleep after such an awakening invariably took less than 5 min. Table 1 is a summary of the experiments showing the number of nights each *S* slept and the number of awakenings. In all, 21% of the awakenings fell in the first 2 hr. of sleep, 29% in the second two, 28% in the third two, and 22% in the fourth two.

RESULTS

The occurrence of rapid eye movements.[3]—Discrete periods during which their eyes exhibited rapid movements were observed in all nine *Ss* every night they slept. These periods were characterized by a low-voltage, relatively fast pattern in the EEG. The interspersed periods in which rapid eye movements were absent showed EEG patterns indicative of deeper sleep, either a predominance of high-voltage, slow activity, or frequent, well-defined sleep spindles with a low-voltage background. No REM's were ever observed during the initial onset of sleep although the EEG always passed through a stage similar to that accompanying the rapid eye movement periods occurring later in the night. These findings concerning associated EEG patterns were identical with previous observations on uninterrupted sleep (5).

An accurate appraisal of the mean duration of the REM periods was impossible since most were terminated artificially by an awakening. However, those that were not so terminated varied between 3 and 50 min. in duration with a mean of about 20 min., and they tended to be longer the later in the night they occurred. The eyes were not constantly in motion during such periods; rather, the activity occurred in bursts of one or two, up to fifty or a hundred movements. A single movement was generally accomplished in .1–.2 sec. and was followed by a fixational pause of varying duration. The amount, pattern, and size of the movements varied irregularly from period to period.

The REM periods occurred at fairly regular intervals throughout the night. The frequency of occurrence seemed to be relatively constant and characteristic for the individual. DM and WD averaged one eye-movement period every 70 min. and every 75 min. respectively. KC averaged one eye-movement period every 104 min. The other *Ss* fell between these two extremes. The average for the whole group was one REM period every 92 min.

Despite the considerable disturbance of being awakened a number of times, the frequency and regularity with which REM periods occurred was almost exactly comparable to that seen previously in a study of uninterrupted sleep (5). If the awakening occurred during a NREM period, the return to sleep was never

[3] In most of the remaining text the following abbreviations will be used: REM's (rapid eye movements) and NREM's (no rapid eye movements).

associated with REM's, nor was the time of onset of the next REM period markedly changed from that which would have been expected in the absence of an awakening. An awakening during an REM period generally terminated the REM's until the next period, and the sequence of EEG changes, excluding the brief period of wakefulness, was the same as that following an REM period that ended spontaneously. Exceptions occurred when *S* was awakened during an REM period in the final hours of sleep when the period was likely to be quite long if uninterrupted. On these occasions, the REM's sometimes started up again when *S* fell asleep. It seemed as though a period of heightened CNS activity had not run its normal course and, although *S* was able to fall asleep, he continued to dream.

Eye movement periods and dream recall.—For all awakenings to elicit dream recall, the arousing stimulus was the ringing of an ordinary doorbell placed near the bed and sufficiently loud to ensure immediate awakening in all levels of sleep. The *S*s then spoke into a recording device near the bed. They were instructed to first state whether or not they had been dreaming and then, if they could, to relate the content of the dream. When *S* had finished speaking *E*, who could hear their voices, occasionally entered the room to further question them on some particular point of the dream. There was no communication between *S* and *E* in any instance, it must be emphasized, until *S* had definitely commited himself. The *S*s were considered to have been dreaming only if they could relate a coherent, fairly detailed description of dream content. Assertions that they had dreamed without recall of content, or vague, fragmentary impressions of content, were considered negative.

TABLE 2

INSTANCES OF DREAM RECALL AFTER AWAKENINGS DURING PERIODS OF RAPID EYE MOVEMENTS OR PERIODS OF NO RAPID EYE MOVEMENTS

S	Rapid Eye Movements		No Rapid Eye Movements	
	Dream Recall	No Recall	Dream Recall	No Recall
DN	17	9	3	21
IR	26	8	2	29
KC	36	4	3	31
WD	37	5	1	34
PM	24	6	2	23
KK	4	1	0	5
SM	2	2	0	2
DM	2	1	0	1
MG	4	3	0	3
Totals	152	39	11	149

The awakenings were done either during REM periods or at varying increments of time after the cessation of eye movements during the interspersed periods of NREM's. The *S*s, of course, were never informed when awakened whether or not their eyes had been moving.

Table 2 shows the results of the attempts to recall dreams after the various awakenings. The REM or NREM awakenings for PM and KC were chosen according to a table of random numbers to eliminate any possibility of an unintentional pattern. For DN, a pattern was followed: first three REM awakenings, then three NREM awakenings, and so on. WD was told he would be awakened *only* when the recording indicated that he was dreaming, but REM and NREM awakenings were then interspersed randomly. The type of awakenings for IR was chosen according to the whim of *E*.

The *S*s uniformly showed a high incidence of dream recall following

REM awakenings and a very low incidence of recall following awakenings during periods of NREM's regardless of how the awakenings were chosen. In particular, DN was not more accurate than the others although there was a pattern he might have learned, and WD was not less accurate although he was deliberately misled to expect to have been dreaming every time he was awakened. Over a narrow range, some Ss appeared better able to recall dreams than others.

Table 3 compares the results of the first half of the series of REM awakenings with the last half. Practice was certainly not a significant factor as only one S showed any degree of improvement of recall on later nights as compared with the early ones.

The incidence of dream recall dropped precipitously almost immediately upon cessation of REM's. In 17 NREM awakenings that were done within 8 min. after the end of a REM period, 5 dreams were recalled. Although small, this was a much higher incidence of dream recall than occurred when the NREM awakenings followed the end of REM periods by *more* than 8 min. In the latter category only 6 dreams were recalled in 132 awakenings.

TABLE 3

COMPARISON OF FIRST HALF OF SERIES OF RAPID EYE MOVEMENT AWAKENINGS WITH SECOND HALF

S	First Half		Second Half	
	Dream Recall	No Recall	Dream Recall	No Recall
DN	12	1	5	8
IR	12	5	14	3
KC	18	2	18	2
WD	19	2	18	3
PM	12	3	12	3
Total	73	13	67	19

In general, Ss were best able to make an emphatic statement that they had not been dreaming when the NREM awakenings were done during an intermediate stage of sleep as indicated by a brain-wave pattern of spindling with a low-voltage background. When aroused during a deep stage of sleep characterized by high-voltage, slow waves in the EEG, Ss often awoke somewhat bewildered. In this state they frequently felt that they must have been dreaming although they could not remember the dream or, on the other hand, that they had not been asleep at all. They sometimes had a great variety of feelings to describe—such as pleasantness, anxiety, detachment, etc., but these could not be related to any specific dream content.

Most of the instances of inability to recall dreaming after awakenings during REM periods occurred in the early part of the night. Of 39 negative reports in the entire study, 19 occurred after awakenings during REM periods falling in the first 2 hr. of sleep, 11 after REM awakenings during the second 2 hr., 5 in the third 2 hr., and 4 in the last 2 hr. There was no such variation relating to awakenings during the interspersed periods of ocular quiescence, the incidence of dream recall being uniformly low, regardless of whether the early or late part of the night was being considered.

Length of rapid eye movement periods and subjective dream-duration estimates.—If the length of the REM periods were proportional to the subjectively estimated duration of the dreams, it would further help to establish the relatedness of the two and would give some information about the rate at which dreaming progresses.

At first, Ss were awakened at

TABLE 4

RESULTS OF DREAM-DURATION ESTIMATES AFTER 5 OR 15 MIN. OF RAPID EYE MOVEMENTS

S	5 Minutes		15 Minutes	
	Right	Wrong	Right	Wrong
DN	8	2	5	5
IR	11	1	7	3
KC	7	0	12	1
WD	13	1	15	1
PM	6	2	8	3
Total	45	6	47	13

various increments of time after the REM's had begun and were requested to estimate to the nearest minute the amount of time they had been dreaming. This proved to be too difficult, although the estimates were always of the same order of magnitude as the lengths of the REM periods, and were occasionally exactly right.

A series was then done in which *Ss* were awakened either 5 or 15 min. after the onset of REM's and were required on the basis of their recall of the dream to decide which was the correct duration. The 5- or 15-min. periods were chosen on the basis of a random series. Table 4 shows the results of these awakenings. All *Ss* were able to choose the correct dream duration with high accuracy except DN. This *S*, however, made most of his incorrect choices by estimating 15 min. to be 5 min. This is consistent with the interpretation that the dream was longer, but he was only able to recall the latter fraction and thus thought it was shorter than it actually was.

In addition to depending on the amount of actual dreaming, the lengths of the dream narratives were undoubtedly influenced by many other factors as, for example, the loquacity or taciturnity of *S*. However, the lengths of the dream narratives still showed a significant relationship to the duration of REM periods before awakening. Table 5 shows the correlations between minutes of REM's and lengths of dream narratives for each *S*. The number of words in the narrative was the measurement of length. Of the 152 dreams recalled, 26 were not included because poor recording did not allow complete transcription. Dream narratives recalled after 30 or as much as 50 min. of REM's were not a great deal longer than those after 15 min. although *Ss* had the impression that they had been dreaming for an unusually long time. This was perhaps due to inability to remember all the details of very long dreams.

Specific eye-movement patterns and visual imagery of the dream.—The quality and quantity of the REM's themselves showed endless variation. There was much or little movement, big or small movements, and so on. As has been stated, the movements occurred in bursts of activity separated by periods of relative inactivity. However, the brain-wave stage during the whole period remained the same whether there was much or little movement at any given moment of the period.

It was hypothesized that the movements represented the visual imagery of the dream, that is, that they

TABLE 5

CORRELATION BETWEEN DURATION OF REM PERIODS IN MINUTES AND NUMBER OF WORDS IN DREAM NARRATIVES

Subjects	Number of Dreams	*r*	*P*
DN	15	.60	$< .02$
IR	25	.68	$< .001$
KC	31	.40	$< .05$
WD	35	.71	$< .001$
PM	20	.53	$< .02$

corresponded to where and at what the dreamer was looking. An attempt to account for every movement by having *S* state chronologically in what directions he had gazed in the dream proved futile. The *Ss* could not recall the dream with such a high order of detail and precision.

In a slightly different approach, *Ss* were awakened as soon as one of four predominant patterns of movement had persisted for at least 1 min. and were asked to describe in detail the dream content just before awakening. The four patterns were: (*a*) mainly vertical eye movements, (*b*) mainly horizontal movements, (*c*) both vertical and horizontal movements, and (*d*) very little or no movement. The prevalence of the horizontal or vertical components was determined by placing leads both vertically and horizontally around the eyes.

A total of 35 awakenings was accumulated from the nine *Ss*. Periods of either pure vertical or horizontal movements were extremely rare. Three such periods of vertical movements were seen. After each of these the dream content involved a predominance of action in the vertical plane One *S* dreamed of standing at the bottom of a tall cliff operating some sort of hoist and looking up at climbers at various levels and down at the hoist machinery. Another *S* dreamed of climbing up a series of ladders looking up and down as he climbed. In the third instance the dreamer was throwing basketballs at a net, first shooting and looking up at the net, and then looking down to pick another ball off the floor. Only one instance of pure horizontal movement was seen. In the associated dream *S* was watching two people throwing tomatoes at each other. On 10 occasions *Ss* were awakened after 1 min. of little or no eye movement In these, the dreams all had the common property that the dreamer was watching something at a distance or just staring fixedly at some object In two of these awakenings in different *Ss* the patterns were the same, as follows: about a minute of ocular inactivity followed by several large movements to the left just a second or two before the awakening. Both instances, interestingly enough, were virtually identical as regards dream content. In one case *S* was driving a car and staring at the road ahead. He approached an intersection and was startled by the sudden appearance of a car speeding at him from the left as the bell rang. In the other, the dreamer was also driving a car and staring at the road ahead. Just before the awakening he saw a man standing on the left side of the road and hailed him as he drove past.

In the 21 awakenings after a mixture of movements *Ss* were always looking at things close to them, objects or people. Typical reports were of talking to a group of people, looking for something, fighting with someone, and so forth. There was no recall of distant or vertical activity.

In order to confirm the meaningfulness of these relationships, 20 naive *Ss* as well as 5 of the experimental *Ss* were asked to observe distant and close-up activity while awake. Horizontal and vertical electrodes were attached. The eye-movement potentials in all cases were comparable in both amplitude and pattern to those occurring during dreaming. Furthermore, there was virtually no movement, as indicated by the eye potentials, when viewing distant activity, and much movement while viewing close-up activity. Vertical eye-movement potentials were

always at a minimum except for the upward movements accompanying blinking, and in a few cases when *E* tossed a ball in the air for them to watch.

Discussion

The results of these experiments indicate that dreaming accompanied by REM's and a low-voltage electroencephalogram occurred periodically in discrete episodes during the course of a night's sleep. It cannot be stated with complete certainty that some sort of dream activity did not occur at other times. However, the lack of recall and also the fact that the brain waves were at the lightest level of sleep only during REM periods and at deeper levels at all other times, makes this unlikely. The few instances of dream recall during NREM periods are best accounted for by assuming that the memory of the preceding dream persisted for an unusually long time. This is borne out by the fact that most of these instances occurred very close, within 8 min., after the end of REM periods.

Other workers have attempted to relate dreaming to physiological phenomena during sleep. Wada (12) felt that dreaming and gastric contractions occurred simultaneously. However, this conclusion was based on only seven awakenings in two *S*s. One was unable to recall dream content although he felt he had been dreaming and the other remembered dream content in 3 of 4 awakenings. Scantlebury, Frick, and Patterson (11) also studied gastric activity and dreaming. They felt, on the basis of three instances of dream recall out of seven awakenings, that the two were probably related, but judiciously stated that "the exact time during which a dream occurs is elusive of record." The occurrence of dreaming during a series of foot twitches occurring immediately after the onset of sleep was postulated by McGlade (9). However, he based this conclusion mainly on dreams recalled on the morning after the experiments which is highly unreliable, and only 3 out of the 25 *S*s studied exhibited foot twitches.

Incidental observations have been made on the occurrence of dreaming by investigators studying brain waves during sleep (2, 3, 6, 7, 8). All stages of brain waves were related to dreaming in these five papers, but no mention was made of whether or not actual dream content was recalled, and the number of reports by sleepers was generally very small.

In other studies of dreaming, excellently reviewed by Ramsey (10), attempts were made to localize dream activity by simply awakening *S*s at various times during the night. In general it was found that dreams might be recalled at any time during the night, but that most were recalled in the later hours of sleep. This would correspond to the statistical incidence of REM's as previously reported (1, 4), and is also consistent with the finding in this study that, even when the awakenings occurred during REM periods, recall was still more difficult earlier in the night.

It was stated herein that all *S*s showed periods of REM's *every* night they slept. This was also the case in another briefly reported series of experiments involving 16 *S*s who were observed a total of 43 nights (5). It is felt on the basis of these and other studies which are unreported that periods of REM's and dreaming and the regularity with which they occur are an intrinsic part of normal sleep. In view of this, the failure to observe REM's in occasional *S*s reported in earlier work (1, 4) deserves some consideration. One explanation is that the recording was done by sampling rather than continuously. If the REM periods were shorter than usual, they may have occurred in the intervals between the samples, thus escaping observation. Another explanation is that a lower amplification of the REM potentials was employed which, although usually adequate, did not clearly record very small movements. A third possibility is that the dreams of these *S*s happened to be the sort, such as watching

distant activity, in which eye movement was at a minimum. Since the association of the characteristic low-voltage, non-spindling EEG was not realized at the time and thus could not aid in identifying this sort of period, they very likely would have been overlooked.

There was nothing in the experiments reported in this paper to indicate that the dreams occurred instantaneously, or with great rapidity, as some have supposed. Rather, they seemed to progress at a rate comparable to a real experience of the same sort. An increment in the length of REM periods was almost invariably associated with a proportional increase in the length of the dream. This could not have occurred if dreaming were instantaneous, since any length of REM periods would then easily accommodate a virtually infinite amount of dream activity.

It seems reasonable to conclude that an objective measurement of dreaming may be accomplished by recording REM's during sleep. This stands in marked contrast to the forgetting, distortion, and other factors that are involved in the reliance on the subjective recall of dreams. It thus becomes possible to objectively study the effect on dreaming of environmental changes, psychological stress, drug administration, and a variety of other factors and influences.

Summary

Regularly occurring periods of REM's were observed during every night of experimental sleep in nine adult *Ss*. A high incidence of dream recall was obtained from *Ss* when awakened during REM periods and a very low incidence when they were awakened at other times. A series of awakenings was done either 5 or 15 min. after the REM's (dreaming) had begun and *Ss* judged the correct dream duration with high accuracy. The pattern of the REM's was related to the visual imagery of the dream, and the eye movements recorded in analogous situations while awake corresponded closely in amplitude and pattern to those observed during dreaming.

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THE OCCURRENCE OF LOW VOLTAGE, FAST, ELECTROENCEPHALOGRAM PATTERNS DURING BEHAVIORAL SLEEP IN THE CAT

WILLIAM DEMENT, M.D.[1]
Department of Physiology, University of Chicago, Chicago, Ill.

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During the recording of EEG's from sleeping cats for other purposes, it was noticed that patterns generally associated with wakefulness occasionally appeared even though the animals remained asleep. A review of the literature pertaining to brain wave studies in normal cats disclosed only two passing references to this phenomenon. Derbyshire *et al.* (1936) reported the occurrence of slow waves in the EEG of two unanesthetized sleeping cats, but noted further that "at other times, when sleep was apparently less tranquil, judging by twitching of the vibrissae, there were only small rapid waves, as in the alert waking state". Hess, Koella, and Akert (1953) mentioned that apparently sleeping cats might show an absence of sleep potentials, but felt that in such instances the animals had probably been aroused by stimuli which were unnoticed by the experimenters.

It was decided to investigate the problem further for two reasons. The normal occurrence of a waking type of EEG in the sleeping animal would bear significantly on the interpretation of what has been called "activation" of the EEG, and, an EEG sleep cycle with regularly occurring periods of low voltage, non-spindling patterns has been observed in humans (Dement and Kleitman 1957b) and it would be of interest to see if similar changes occurred in another species during a lengthy period of sleep.

METHOD

Twelve adult cats were used in this study. In order to increase the likelihood that they would fall asleep during the recording sessions, they were first kept awake for 1-3 days. This was accomplished by putting them in a cage whose bottom was flooded with several inches of water. A platform was in the cage and the only way the cats could avoid getting wet was to sit on the platform which, however, was too small for them to lie down or completely relax. They were released periodically for exercise and feeding, and when they seemed sleepy, they were taken to the laboratory for brain wave studies. This was usually done in the evening when external noise was at a minimum. A feeding was always administered just before the recording session to further ensure somnolence.

The recording electrodes were small needles which were inserted into the scalp and held in place by small pieces of tape. In two animals, cortical electrodes were used. These were small steel wires insulated, except for the tip, which were inserted through burr holes in the skull until they rested on the dura and then fixed in place with dental cement.

The recording was done while the animals were unrestrained in a wire cage in a closed room. A Grass Model III four-channel electroencephalograph was used and the cats could be observed at all times through a glass window.

Several of the cats were very tame and seemed to be completely unconcerned with the experimental procedure. They would sleep in the same room with the equipment and experimenters and could thus be observed very closely during the presence of different EEG patterns. As a rule, however, isolation was necessary as the animals remained alert if they could see or hear the experimenters.

RESULTS

Three distinct phases of EEG recording and concomitant behavior were seen in all cats

[1] Postdoctoral Public Health Service Research Fellow of the National Institute of Neurological Diseases and Blindness.

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together with brief transitional episodes. Although records were taken from several scalp areas, no attempt was made to distinguish subtle regional differences, and the following remarks apply to the EEG as a whole.

Awake. The behavior of the cats varied widely from pacing about the cage to lying in a supine, crouching position. The records during this phase showed only varying amounts of muscle potential except in the two cats with implanted electrodes who exhibited quiet. They ceased to react to external noises unless the latter were quite loud. No muscle potentials were present, and slow waves and spindles dominated the EEG. With appropriate gains, the records from scalp and implanted electrodes were virtually identical.

Asleep with waking patterns. At certain times, in the absence of behavioral arousal or gross movement, the EEG changed from slow wave, spindle patterns to low voltage, fast rhythms. Concomitant with this latter phase

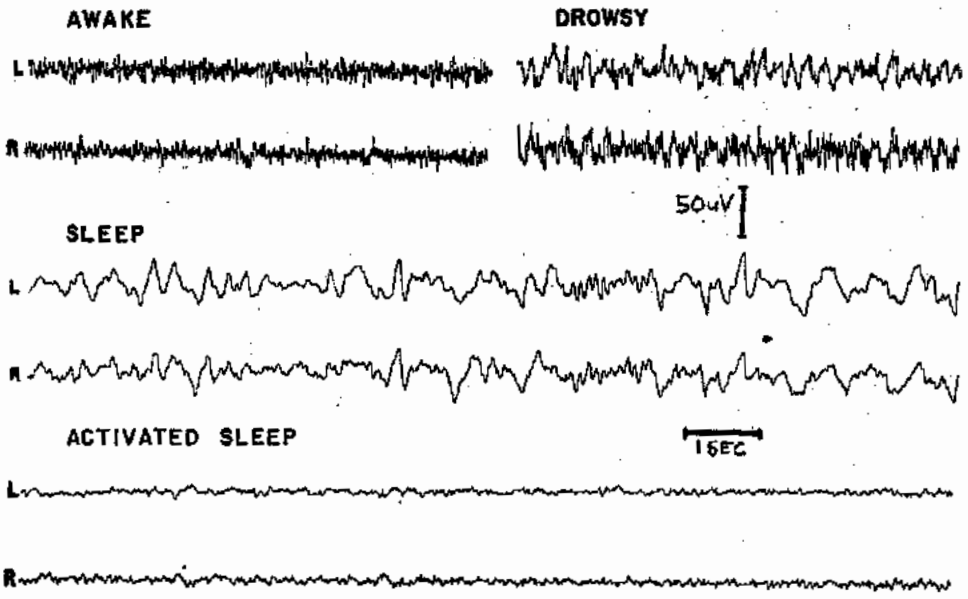

Fig. 1

Sample recordings from one cat using scalp electrodes. L stands for the left frontal electrode referred to the left occipital. R stands for the right frontal referred to the right occipital. AWAKE — a flat record dominated by muscle potentials. DROWSY — slow waves appear as cat's head begins to droop, still some muscle activity. SLEEP — a few minutes later cat completely still and unresponsive, showing slow waves and spindles. After about 10 min. the record changes spontaneously to ACTIVATED SLEEP, a low voltage, fast pattern with no muscle potentials. During the time represented by the latter tracing, the cat was completely still and unresponsive, but usually records of this EEG phase contained many artifacts resulting from the twitching movements described in the text.

typical waking patterns. Often the cats closed their eyes while lying in this crouched position but waking patterns or muscle potential persisted until the head began to droop. In the scalp recordings, the muscle potentials diminished as the cats relaxed at which time the EEG patterns became discernible. If the animals remained quiet, sleep patterns usually appeared.

Asleep. The cats were invariably in a position of complete relaxation and entirely were considerable amounts of twitching movements of the legs, ears, and vibrissae, and occasional tail movements. However, the cats remained in a completely relaxed sleeping posture throughout and were unresponsive to minimal external noises that ordinarily attracted their attention when awake. There was also complete absence of muscle potentials, an excess of which characterized the record of the wakeful animals. The limb and ear twitches were seen in the tracings as slow

wave movement artifacts. In addition to the twitches, close observation of the cats that were not isolated revealed that there was considerable movement of the eyeballs. This was easily discerned on occasions when the eyelids were slightly separated, and could be inferred at other times from squirming, vermiform passive movements of the lids as the cornea rotated beneath them. In the two cats with implanted electrodes, the low voltage, fast EEG pattern seen during behavioral sleep was virtually indistinguishable from the patterns recorded during wakefulness. Since the muscle potentials obscured the EEG from the scalp leads of the other animals when awake, a direct comparison between the two phases could not be made. However, at high gains, the low voltage, fast patterns taken from scalp leads during sleep were similar to those recorded during wakefulness from implanted electrodes.

Figure 1 shows examples of the various EEG patterns. It should be noted especially that the "drowsy" record taken while the cat still was quite responsive and sitting completely relaxed, showed waves that were slower and of greater amplitude than those seen during "activated" sleep. The latter term is used in a purely descriptive sense.

Auditory arousal thresholds. Although one could infer the presence of sleep or wakefulness by observation, it was decided to employ a more precise test. In three cats, auditory arousal or response thresholds were determined during the presence of the various EEG patterns. A loudspeaker was placed near the cage and a 1000 cycle tone was sounded for 5 sec. If no response was obtained the intensity was increased and in approximately 30 sec. the stimulus was repeated. This procedure was continued until the tone evoked an appropriate response. When the cat was awake the threshold was considered to be the intensity at which it looked investigatively toward the loudspeaker. During sleep, an abrupt change to waking behavior accompanied by the appearance of muscle potential was considered an adequate response. The intensities were calibrated in terms of voltage across the loudspeaker.

The threshold when the cat was awake or just beginning to doze with a slight drooping of the head and the appearance of 5-8/sec. waves in the EEG, was invariably quite low, less than 0.5 V. During behavioral sleep with low voltage fast patterns, the threshold ranged quite widely from 1 to 10 V. When classical sleep patterns were present, the range was about the same but tended to average a little higher.

EEG changes during prolonged sleep. Nine of the cats slept for periods of 2-3 hours. During this time, in each cat a regular alternation between phases was observed. The usual sequence was that the cat would, after a certain amount of pacing about, settle down and assume a sleeping position. Slow waves and spindles appeared and this phase predominated without significant change for about 10 min. Then a spontaneous change to a low voltage, fast EEG occurred which persisted without change for about 10 min.

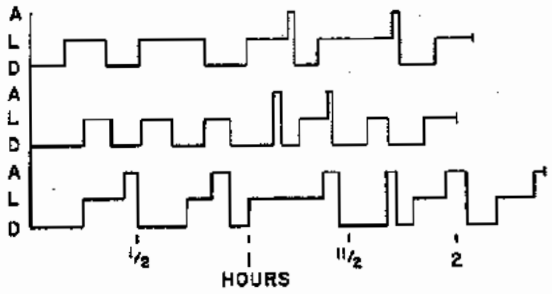

Fig. 2

Continuous plotting of EEG phases for three recording sessions in three different cats. A, L, and D stand for awake, light sleep (activated sleep, low voltage fast patterns), and deep sleep (slow waves and spindles) respectively.

and was accompanied by the twitching movements described above. After this, there was often a brief awakening during which the cat might shift position and meow a few times. Then it would fall asleep and the slow waves and spindles would reappear, and the sequence would be repeated. Many times the low-voltage fast EEG simply reverted to the slower patterns without an awakening. The sleep time was just about divided equally between the two phases which alternated with marked regularity. Figure 2 shows a con-

tinuous plotting of the 3 categories of recording for several different sleep periods. The length of the above described sequence seemed to be somewhat characteristic for individual cats and the changes were apparently independent of external stimuli. Of course, a very loud noise would awaken the cats and disturb the sleep pattern but these were always accidental and quite rare.

It might also be mentioned that when observed on several occasions, the experimenter's house cat showed alternating periods of sleep characterized by complete stillness or the numerous twitching movements described previously and these alternations were of about the same duration as seen in laboratory cats. It was felt, on this basis, that sleep deprivation had not markedly changed the time course of the sleep alternations in the laboratory animals.

DISCUSSION

The salient feature of this investigation was that in the course of normal sleep, cats invariably showed many periods of low voltage, fast EEG patterns which resembled those ordinarily associated with alert wakefulness. It cannot be stated with certainty that they were *exactly* like the patterns of alert wakefulness, but in the cats with implanted electrodes this seemed to be the case. Furthermore, the low voltage, fast sleep patterns seen in this study were at least more active than the patterns associated with relaxed wakefulness and drowsiness. Clark and Ward (1945) described trains of regular 6 per sec. waves in the "dozing" cat, and, in an extensive study, Hess, Koella, and Akert (1953) concluded that 5-8 per sec. bursts characterized the waking "rest-rhythm" of normal cats. Even with scalp electrodes, rhythms could be discerned while the cats were still awake although their heads were beginning to droop, that were slower and of greater amplitude than the low voltage, fast, sleep patterns.

The change from high voltage, slow rhythms to low voltage, fast activity, whether spontaneous or artificially produced, has been called "activation" of the EEG, and is generally concomitant with behavioral arousal. This "activation" has been elicited experimentally by stimulation of the brain stem reticular formation (Moruzzi and Magoun 1949). Since an activated EEG was generally considered to be more or less exclusively associated with wakefulness, it was concluded that one of the functions of the brain stem reticular formation was to arouse the organism and maintain it in an alert state.

It was seen in this study that the change from slow, high voltage patterns to an activated EEG often took place in the absence of behavioral arousal, and that although this activation persisted for many minutes, the auditory arousal threshold remained elevated. On the other hand, relatively slow patterns seen in drowsiness were associated with a much lower auditory threshold. Thus, although behavioral arousal in normal cats seems to be invariably associated with activation of the EEG, the reverse need not occur.

Rinaldi and Himwich (1955) and Wikler (1952) have reported the observation of sleep EEG patterns in the face of behavioral wakefulness after the administration of atropine. It would seem that the brain stem reticular formation has at least two distinct and separable actions; an ascending effect on the cortex which results in EEG activation and is presumably necessary for optimal cortical functioning, and a descending effect which is more closely associated with overt behavioral arousal. In the experiments of Rinaldi and Himwich, and Wikler, it may be assumed that the ascending influence was blocked by atropine leaving the descending effect (behavioral arousal) intact. This is also compatible with the fact that completely decorticate dogs (Kleitman and Camille 1932) and monkeys (Woolsey 1956) show alternating periods of behavioral sleep and wakefulness. Since in sleep, an EEG activation occurs without behavioral arousal, it may be concluded that the brain stem effect is, in this instance, predominantly ascending. In the often described arousal from sleep, as by a loud noise, both ascending and descending effects must be elicited.

It was also found that the low voltage, fast patterns during sleep showed a marked regularity in their occurrence. Periods of low voltage EEG patterns have been described in human sleep (Blake and Gerard 1937; Henry 1941). It is only recently, however, that their functional significance has been appreciated. Records taken from many nights of undisturbed sleep (Dement and Kleitman 1957b) showed that such patterns occurred every 90 min. on the average, as part of a sleep EEG cycle, and persisted approximately 20 min. They were further found to be significantly associated with dreaming. Thus, in humans, the "activation" of the EEG in the face of behavioral sleep nonetheless resulted in a change of consciousness, i.e., the initiation of dream activity.

The question of whether any animal other than man experiences dreaming seems unanswerable since it is a subjective experience and can be known only by a verbal or written communication from the dreamer. However, certain subjective states can be attributed to animals if they consistently exhibit objective behavior patterns which are like or similar to behavior seen in man concomitant with communicable subjective experiences, or if the behavioral patterns are meaningfully related to stimuli which ordinarily evoke strong affective states in humans, such as painful and pleasurable stimuli. Consequently, animals are said to experience anxiety when they tremble, crouch, whine, defecate, exhibit disorganized motility patterns, etc., in response to unavoidable painful stimuli.

Along this line there is considerable anecdotal evidence that animals dream. A hunting dog sleeping before the fire begins to make running movements, barks as it does when in the field, and if awakened, seems somewhat startled and disoriented. The immediate inference is that the dog was dreaming of chasing a rabbit or other game.

If cats dream at all, it certainly seems that these regularly occurring periods of a low voltage, fast EEG must represent the times of its occurrence. In addition, the cats showed behavioral phenomena usually connected with dreaming in animals; leg movements, etc., concomitant with the activated EEG. They also exhibited rapid, jerky movements of the eyeballs which have been definitely associated with dreaming in humans (Dement and Kleitman 1957a). A final correlate is that the periods of low voltage EEG during sleep in both cats and humans were associated with an elevated auditory threshold (Dement and Kleitman 1957b).

Regardless of the presence or absence of dreaming, the regular fluctuation in brain wave patterns suggests a definite "sleep cycle" such as has been observed in humans. The length of the cycle would appear to be much shorter in the cats, but this is compatible with their higher basal metabolic rate as compared to humans and their relatively shorter cardiac and respiratory cycles. The presence of such a "sleep cycle" in both cats and humans suggests the possibility that it may be common to all animals possessing more highly developed central nervous systems.

It may be emphasized, in view of the findings discussed in this paper, that the activity of the brain stem activating system is not confined to arousal and maintenance of the waking state, and that the functions and interactions of the brain stem and cortex during sleep as well as wakefulness need further clarification.

SUMMARY

The EEG and behavior of twelve adult cats were observed during lengthy intervals of normal sleep. All animals showed many periods of a low voltage, fast (activated) EEG in the face of continued behavioral sleep as indicated by absence of muscle potentials, relaxed posture, unresponsiveness, and elevated auditory threshold. These periods alternated regularly with periods during which the recordings were dominated by slow waves and spindles. The former EEG phase was concomitant with many twitching movements of the limbs, vibrissae, and ears, while the latter was generally associated with complete stillness on the part of the animals.

RÉSUMÉ

L'EEG et le comportement de 12 chats adultes ont été observés pendant des périodes prolongées de sommeil normal. Tous les animaux ont montré de nombreuses périodes d'activité électroencéphalographique de bas voltage et rapide, donc des signes d'activation, malgré la continuation de l'état de sommeil. La continuation du sommeil a été mise en évidence par l'absence de potentiels musculaires, une attitude relâchée, une absence de réponse à des incitations extérieures et une élévation du seuil auditif. Ces périodes alternaient régulièrement avec d'autres pendant lesquelles les tracés étaient dominés par des ondes lentes et des fuseaux ("spindles"). Pendant la période durant laquelle l'EEG montrait une activité rapide de bas voltage beaucoup de secousses musculaires des extrémités, des vibrisses et des oreilles ont été observées, tandis que pendant la période dominée par des ondes lentes et des fuseaux les animaux sont restés parfaitement tranquilles et n'ont montré aucun mouvement.

ZUSAMMENFASSUNG

Das EEG und das Verhalten von zwölf ausgewachsenen Katzen wurde beobachtet während längeren Perioden normalen Schlafes. Bei allen Versuchstieren wurden manche Perioden von niedergespannter, hochfrequenter (aktivierter) EEG-Aktivität festgestellt, obgleich das Verhalten des Tieres Andauern des Schlafes anzeigte. Dies wurde objektiviert durch das Fehlen von Muskelaktionspotentialen, die erschlaffte Körperhaltung, Nichtbeantwortung von Reizen und erhöhte Hörreizschwelle. Diese Perioden wechselten regelmässig ab mit anderen während denen das EEG dominiert war durch langsame Wellen und Spindelaktivität. Während der erstgenannten Phase traten oft Gliederzuckungen auf und ähnliche Bewegungen der Vibrissen und der Ohren, währenddem die Tiere in der zweitgenannten Phase sich vollkommen still verhielten.

The author wishes to acknowledge the generous assistance of Prof. K. L. Chow who implanted the cortical electrodes in two cats and also made available several of the normal cats used in this study.

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A PERSISTENT DIURNAL RHYTHM OF LUMINESCENCE IN GONYAULAX POLYEDRA[1]

J. WOODLAND HASTINGS AND BEATRICE M. SWEENEY

Division of Biochemistry, Noyes Laboratory of Chemistry, University of Illinois, Urbana, Illinois, and Division of Marine Biology, The Scripps Institution of Oceanography, La Jolla, California

The photosynthetic marine dinoflagellate, *Gonyaulax polyedra,* emits a brief flash of light (duration, about 90 milliseconds) when stimulated by agitation. It is one of the many organisms responsible for the luminescent display sometimes observed in the ocean at night when the water is disturbed (see Harvey, 1952). Previous studies with this organism (Haxo and Sweeney, 1955; Sweeney and Hastings, 1957a) have shown that the luminescent response to stimulation varies rhythmically in a diurnal fashion. Cultures grown in natural illumination, or in artificial lights with alternating light and dark periods of 12 hours each (= LD), display a much greater luminescence during the dark period (Fig. 2).

When LD cultures are transferred to a dark chamber, the rhythm continues but its amplitude decreases progressively. By action spectra studies, it has been found (Sweeney, Haxo and Hastings, unpublished data) that this decrease in amplitude arises from the need for light in the organic nutrition of *Gonyaulax,* via photosynthesis. This finding prompted the search for constant environmental conditions under which the endogenous rhythm would persist, without the loss of amplitude which occurs in continuous darkness.

The possibility of maintaining the cells heterotrophically was explored, but the consistently negative results obtained indicated that *Gonyaulax* is an obligate photo-auxotroph. Continuous bright light inhibits the rhythmic fluctuations in luminescence, and it has not been possible to separate, by using light of different colors, the photosynthetic requirements for light from the inhibitory action of light on rhythmicity. It has been found, however, that if LD cultures are placed in a continuous dim light, the rhythm of luminescence persists without loss of amplitude. It has thus been possible to investigate in some detail the nature of this endogenous rhythm.

Materials and Methods

G. polyedra has been maintained in a modified sea water medium described previously (Sweeney and Hastings, 1957a). The growth rate is dependent upon light, temperature, and the concentrations of mineral nutrients. The maximum growth rate which we have measured is one division per day, but under the condi-

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Hastings, J. W., and B. M. Sweeney. 1958. *Biol. Bull.* 115: 440-458. Reprinted with permission from the Marine Biological Laboratory, Woods Hole, MA.

tions used in the experiments to be described the rates were always less than this. The illumination was provided by "cool white" fluorescent lamps, the intensity being measured in foot-candles with a Weston illumination meter.

The experimental procedure was as follows: stock cultures were maintained in Fernbach flasks containing 1500 ml. of medium. In preparation for an experiment, 2-ml. aliquots from these cultures were pipetted into each of several hundred test tubes at cell densities between 2000 and 7500 cells per ml. All tubes were then subjected to the appropriate conditions of light and temperature. To measure the luminescence at any given time, two tubes were removed, assayed, and then discarded. The cells were stimulated to luminesce by bubbling air through the cell suspension, and the resulting phototube current was accumulated on a capacitor. Luminescence is expressed in terms of the total amount of light emitted during one minute of stimulation, at the end of which time essentially all luminescence has ceased. Additional details of the light measurement procedure may be found elsewhere (Sweeney and Hastings, 1957a).

Results

Demonstration of the persistent rhythm. A persistent rhythm of luminescence may be observed if cells which have been kept for a time under LD conditions are transferred to continuous dim light (about 100 foot-candles). A typical example of the persistent rhythm under conditions of constant light and constant temperature is shown in Figure 5. In similar experiments, we have continued measurements for as long as 14 days; the rhythmic pattern continues undamped during this time. At the light intensity used in such experiments there was little growth.

The natural period of the rhythm. The period of the rhythm is measured by the time between successive maxima in luminescence. When the cells are subjected to alternating light and dark periods on a daily (24-hour) schedule, the period of the rhythm is 24 hours (Fig. 2). Under conditions of constant illumination, however, the rhythmic changes have a period which is close to, but not necessarily exactly 24 hours. Pittendrigh and Bruce (1957) have referred to this as the *natural period,* or the innate period of an endogenous rhythm when light and temperature are held constant.

The natural period in *Gonyaulax* is a function of at least two environmental factors, light intensity and temperature. The effect of light intensity upon the period is illustrated in Figure 1. Cells were placed in continuous light at three different intensities, and it is evident that the natural period was shorter at higher intensities. These experiments also illustrate the light intensity dependence of the inhibitory effect of continuous illumination upon the rhythm. At the two higher light intensities the amplitude of the rhythm was progressively damped, while at the lowest light intensity no marked damping of the amplitude of the rhythm was evident.

The effect of temperature upon the natural period is not large but, contrary to expectation, the period becomes longer rather than shorter as the temperature is raised (Hastings and Sweeney, 1957b). At 16° C. the period was found to be 22.8 hours while at 26.7° C. it was 26.5 hours. A Q_{10} of less than 1.0 is unusual, and the results were interpreted as evidence for a compensation mechanism which functions to keep the period approximately temperature-independent.

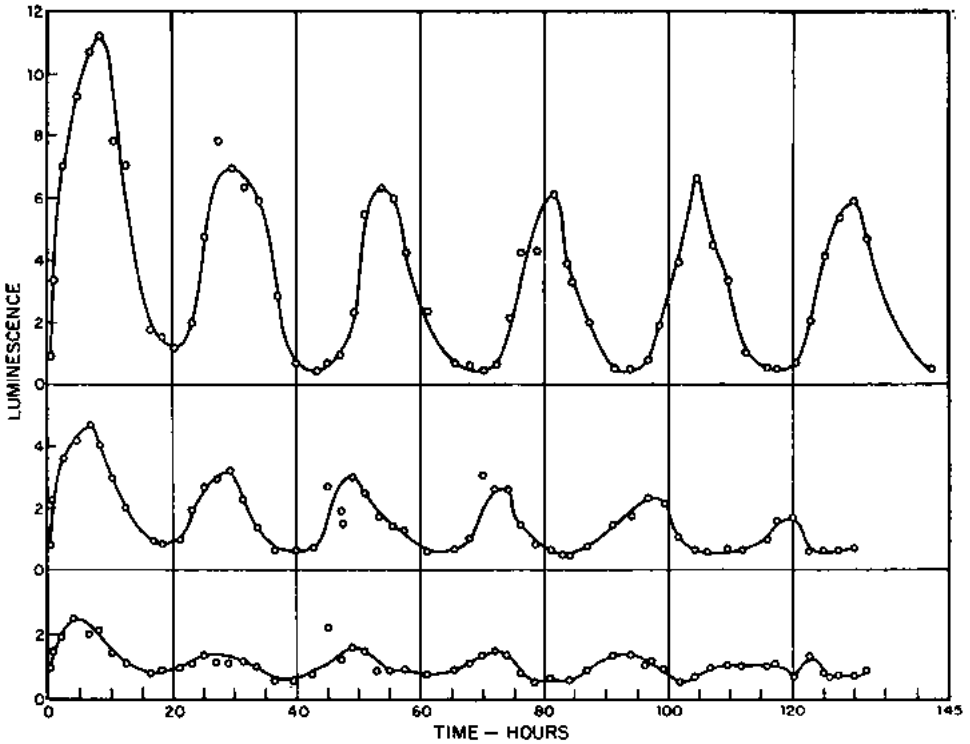

FIGURE 1. The effect of light intensity upon the natural period at constant temperature (21° C.). The cells were grown in LD conditions (800 foot-candles during the light period). The beginning of the experiment, shown on the graph as 0 time, fell at the end of a normal light period. At this time, some cells were placed in the dark, and others in light of 120 foot-candles (upper curve), 380 foot-candles (middle) and 680 foot-candles (bottom). The average periods were as follows: 680 foot-candles, 22.0 hours; 380 foot-candles, 22.8 hours; 120 foot-candles, 24.5 hours; dark, 24.5 hours (not shown on graph; one period measured).

In view of the relatively small temperature effect, the period of this rhythm may be characterized as essentially temperature-independent.

The endogenous nature of the diurnal rhythm. The persistence of the rhythm of luminescence under conditions of constant temperature and light intensity indicates that the mechanism of the rhythmicity is endogenous. Several other experiments serve to support this conclusion.

Figure 2 illustrates one of many experiments in which the phase of the rhythm was shifted by changing the time at which the light and dark periods occurred. In such experiments the phase (*i.e.*, the solar time at which the maximum in luminescence occurs) may be shifted so that it will bear any desired relationship to the solar day. In cultures which are subsequently transferred to constant conditions of dim light or darkness, the phase of the persistent rhythm is related to the previous light and dark program rather than to solar time, or any other factor. Changes in the phase of the endogenous rhythm have not been observed when light and temperatures were held constant.

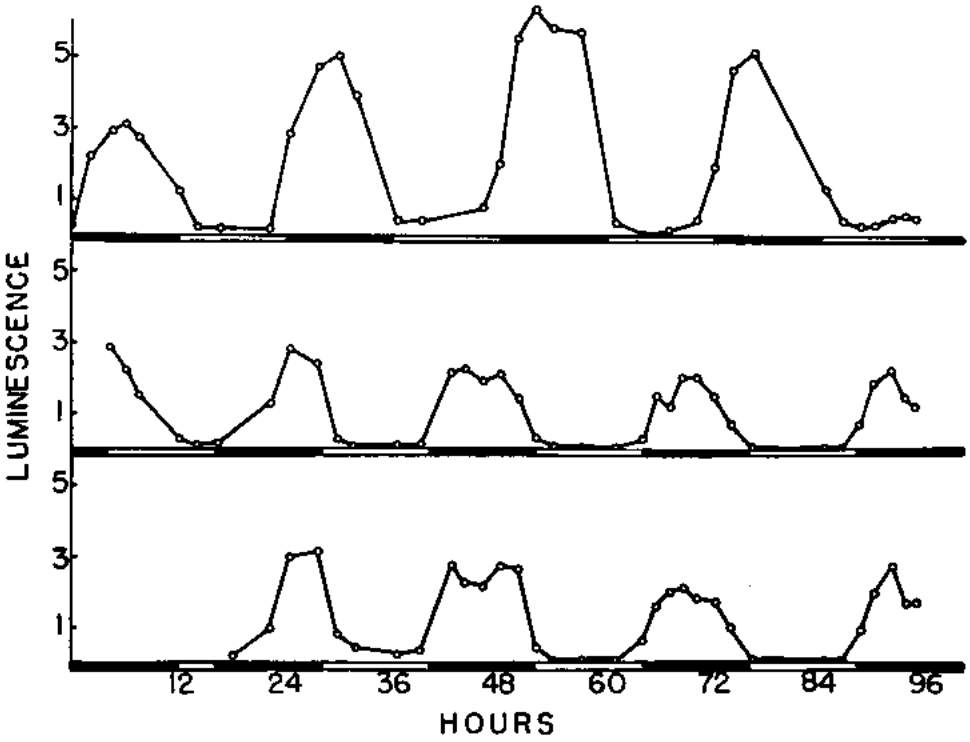

FIGURE 2. This experiment illustrates the effect of changing the solar time at which the light and dark periods occur. The upper curve shows the pattern of luminescence changes in an LD culture which had been on the schedule indicated for some time. The black bars on the time axis indicate dark periods. The lower two graphs illustrate the effect of imposing upon cultures (which were previously on the schedule shown in the top graph) an LD schedule in which the light and dark periods were at a different time of day. The new schedules were started at zero hours on the graph. Temperature, about 26° C. Light intensities used, about 250 foot-candles.

A series of experiments has been carried out from which it is evident that pre-treatment with diurnal light and dark periods (*i.e.*, one dark plus one light period equals 24 hours) is not necessary in order to demonstrate an endogenous rhythm. That is to say, there is no evidence that a "learning" or "memory" process is involved. For example, cells have been exposed to "non-diurnal" light and dark periods which together add up to greater or less than 24 hours, followed by conditions of either constant light or constant dark. An experiment of this sort is shown in Figure 3. In this experiment, cells were exposed to alternating light and dark periods of 7 hours each for about 100 hours. During this period the luminescence changes were quite evidently governed by these light and dark periods so that there was a maximum in luminescence every 14 hours. At the end of this treatment, some cells were placed in constant dim light and others in darkness. In both cases a diurnal rhythm with a period of approximately 24 hours was evident. The 14-hour cycle had not been "learned," even though it had been

possible to entrain the luminescence rhythm to the 14-hour cycle. A difference between those placed in darkness and those in dim light was that the amplitude of the rhythm in darkness progressively decreased as a result of the lack of light (see introduction).

Similar experiments have been carried out in which the alternating light and dark periods were 6 hours each, 8 hours each, and 16 hours each, giving cycles of 12, 16 and 32 hours, respectively. The results were similar to those shown in Figure 3. After about 100 hours of such a non-diurnal light-dark cycle the cells were placed in constant dim light and a rhythm of luminescence having a period close to 24 hours was evident.

Another series of experiments has shown that it is not necessary to pre-treat the cells with any sort of alternating light and dark periods in order to demonstrate endogenous diurnal rhythmicity. As mentioned previously, if cells are grown in continuous bright light (*ca.* 800–1500 foot-candles) there is no detectible rhythmicity. Cells maintained in this way for several months, or for as long as several years, have been found to exhibit a diurnal rhythmicity when they are placed in darkness (Haxo and Sweeney, 1955; Sweeney and Hastings, 1957a). The phase of the rhythm which is initiated when the cells are moved from bright light to darkness is independent of the solar time, and related only to the time at which the light-to-dark transition is made.

A similar result was obtained when cells which had been grown in bright light for almost one year were merely transferred to dim light. This experiment is

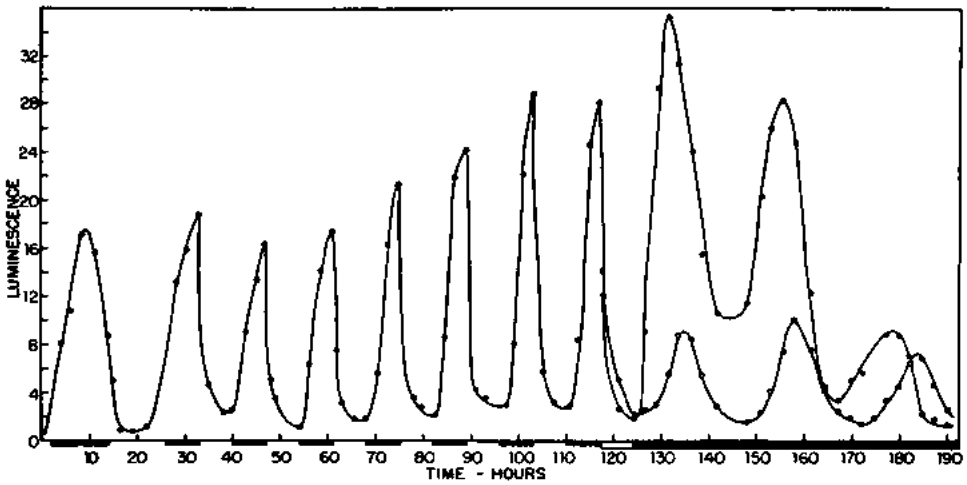

FIGURE 3. This illustrates the entrainment of the luminescence rhythm to a 14-hour cycle and the manifestation of an endogenous diurnal rhythm when the cells are placed in constant conditions subsequent to the treatment. Dark periods are indicated by black bars on the time axis. The cells were on an LD schedule previous to the time when the 14-hour cycle was started (at 26 hours). Light intensity throughout the 14-hour cycling was 800 foot-candles. At 117 hours some aliquots were removed from the dark and placed in constant light at 230 foot-candles. The luminescence changes in these cultures are shown by the circles. From 124 hours on, the other aliquots were left in the dark and the luminescence changes are plotted with solid dots. Temperature, 21° C.

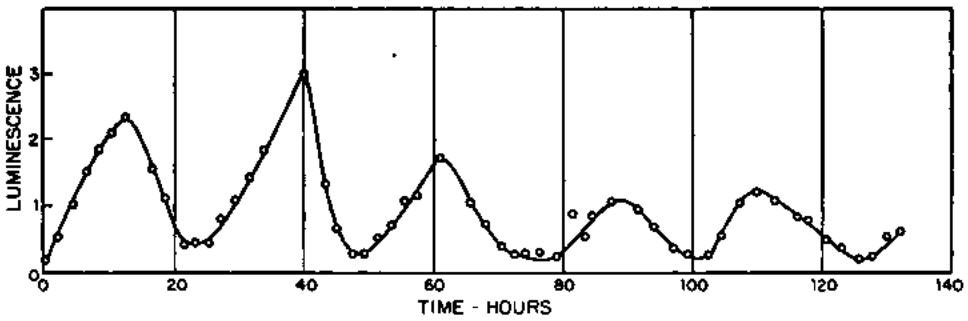

FIGURE 4. The initiation of an endogenous diurnal rhythm of luminescence by means of a one-step change in illumination. Cultures which had been grown in bright light for one year were moved from bright light (800 foot-candles) to dim light (90 foot-candles) at the time indicated on the graph as 0 hours. Luminescence measurements were made approximately every two hours thereafter. Temperature, 21.0° C. Average period, 24.5 hours.

illustrated in Figure 4. It differs from the previously mentioned experiment (in which cultures were moved from bright light to darkness) in that the amplitude does not decrease with time, since light is available for the nutrition of the cells. The precise phase relationship to the time of transfer from bright light is somewhat different, but here also it is not related to solar time.

Phase shift by light perturbation. It is clear from Figure 2 that the phase of the rhythm may readily be shifted by an appropriate manipulation of the light and dark periods to which the cells are exposed. It is not necessary, however, to expose the cells to a new light-dark cycle in order to reset the phase of the rhythm. A single exposure to a different light intensity can result in a stable phase shift. Pittendrigh and Bruce (1957) have discussed the significance of phase resetting of biological rhythms by single light perturbations. If rhythmicity results from an innate oscillatory mechanism characterized by its own natural period, and the phase (but not the period) is determined by the sequence of light and darkness, then it is to be expected that non-repeated light changes should suffice to change the phase. The perturbation therefore need not contain any information concerning period.

The experiment shown in Figure 4 illustrates phase setting by a single step-type light perturbation. The phase of the previously aperiodic cells was determined by the time at which the light intensity was changed. The shifting of phase in already rhythmic cultures is evident in the experiments shown in Figure 3. The entrainment of the rhythm to a 14-hour cycle may be explained by assuming that each transition, either from darkness to light or from light to darkness, serves to shift the phase, so that repetitive phase resetting occurs.

A phase shift in the *Gonyaulax* rhythm by single light perturbations has also been demonstrated in other ways. Figure 5 illustrates a shift in the phase of rhythmic cells which were given a single exposure to either bright light or darkness. The phase shift which results in such experiments has been found to be stable since, in experiments where measurements were continued for an additional 48 hours, the phase difference between the controls and the treated cells remained unchanged.

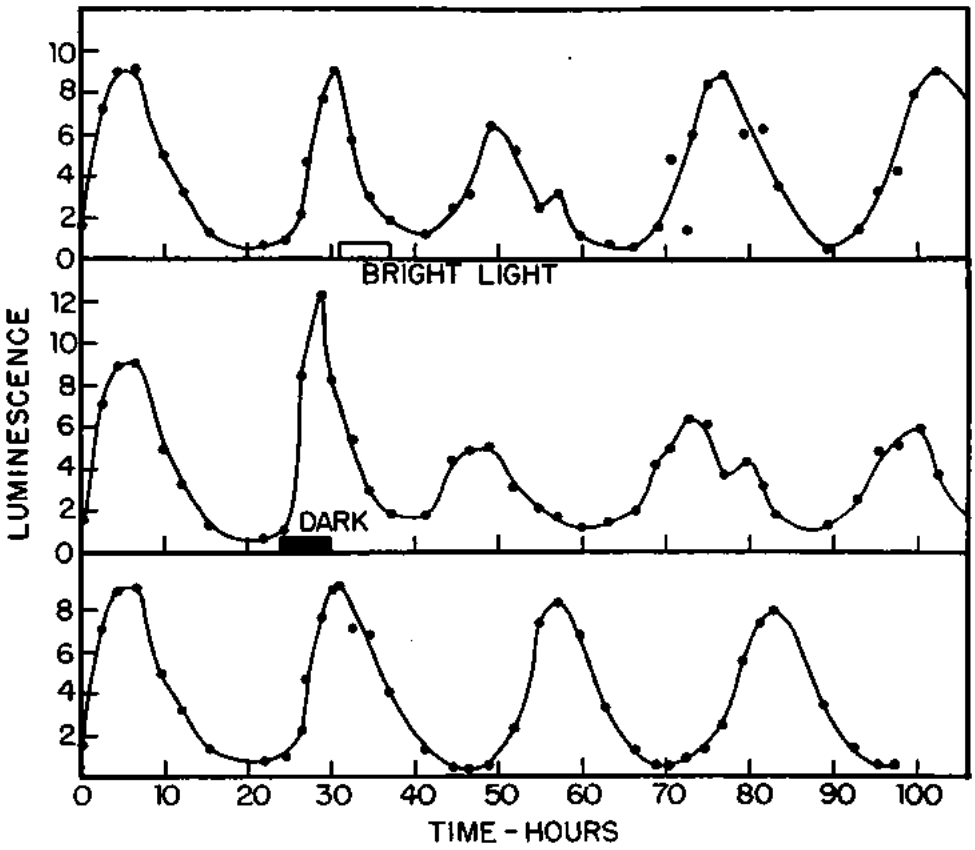

FIGURE 5. This experiment illustrates a phase shift in the rhythm following changes in light intensity. Cells previously kept under LD conditions were placed at constant temperature (23.5° C.) and constant light intensity (100 foot-candles) at the end of a 12-hour dark period. Two days later (zero time on the graph) measurements of luminescence were begun and the endogenous rhythm was apparent. Some cultures (upper curve) were transferred to bright light (1400 foot-candles) for a period of 6 hours and then returned to the previous condition (100 foot-candles). Other cultures (middle curve) were transferred to darkness for 6 hours and returned to dim light at 200 foot-candles. The time at which treatment was given is indicated by bars on the time axis. In both cases a marked phase shift in the rhythm is evident. The control (lower curve) was left in dim light all the while. Average period in control: 25.7 hours.

Figure 6 shows another technique which has been used in the study of phase shifting by single perturbations. Rhythmic cells were placed in the dark and, at a later time, received an exposure to light. Although the amplitude of the rhythm decreases over the next few days, the times at which maxima in luminescence occur are evident, so that the phase may be determined. The number of hours by which the phase is shifted would be expected to be some function of both the magnitude of the perturbation, and the time in the old cycle at which it is administered. The technique of interrupting darkness by light has been used to investigate these parameters.

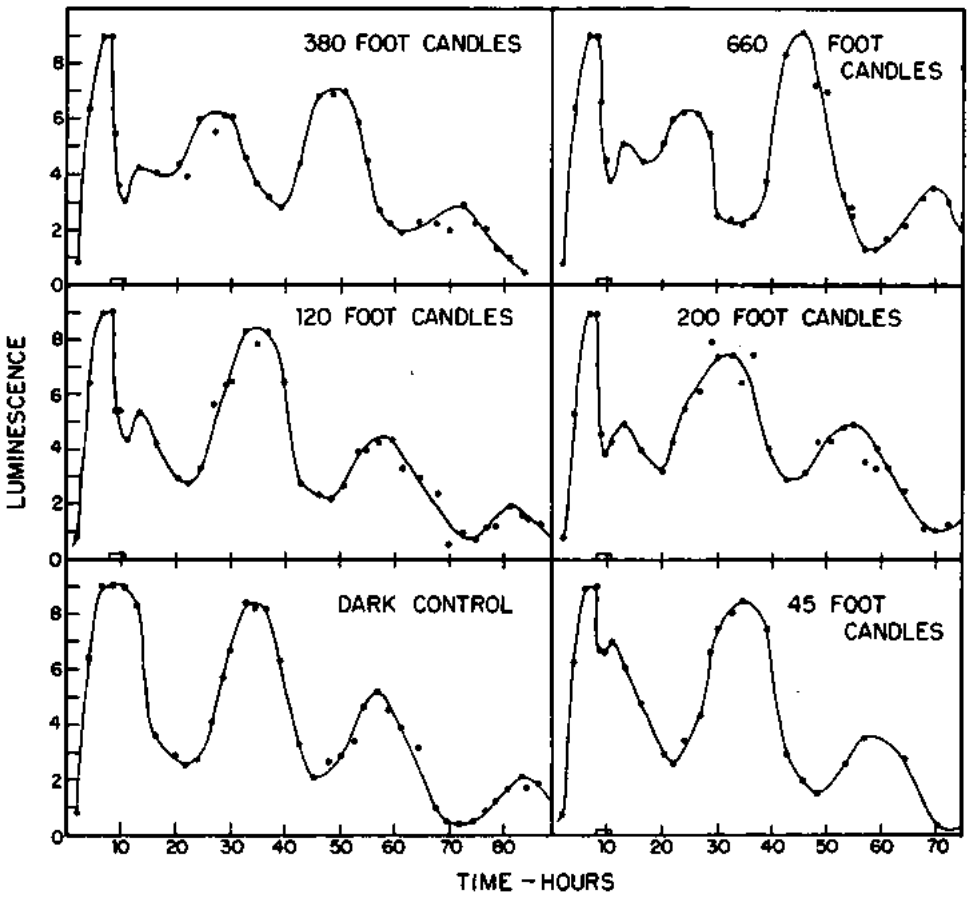

FIGURE 6. This illustrates phase shifting in a rhythmic culture by a single 2½-hour exposure to light, and the effect of intensity upon the magnitude of the phase shift. Prior to the time shown on the graph, all cultures were in LD conditions, and "two hours" on the time axis was the end of the last 12-hour light period. All cultures were put in the dark at that time and the control was left in the dark thereafter. The remaining cells were exposed to a 2½-hour illumination beginning 6 hours after the light-to-dark transition (indicated by the rectangle on the time axis). Following this 2½-hour illumination they were returned to darkness for the remaining time. The intensities used are shown in the figure. A 2½-hour exposure to 1400 foot-candles (not plotted) was found to be no more effective than the exposure to 660 foot-candles (Fig. 7). Temperature during experiment, 21° C.

The effect of varying the light intensity was determined in experiments such as the one shown in Figure 6. The amount of phase shift was found to increase with increasing light intensities, up to a "saturation" value of about 800 foot-candles. This relationship is illustrated in Figure 7, and the stability of the resetting is shown by plotting on the same graph the phase shift measured at each of the subsequent cycles. Several experiments of this sort have been carried out and the same type of relationship has been observed. The quantitative values obtained in separate experiments were somewhat different, however, and the reason for this variation has not been determined.

The magnitude of the perturbation may also be changed by varying the duration of light exposure. In an experiment similar to that shown in Figure 6, the duration instead of the intensity was varied. All exposures (at 800 foot-candles) were started simultaneously, six hours after the cells were placed in darkness. A longer exposure to such a light perturbation was found to be more effective than a shorter exposure. The amount of phase shift was found to be proportional to the duration of the exposure, up to a maximum phase shift of about 11½ hours, which was achieved with 2½ hours exposure. The relationship between phase shift and duration might be expected to be different, depending upon the time in the old cycle at which the perturbations were given, as discussed below. This aspect has not been studied, however.

The effect of varying the time in the cycle at which the perturbation is given has been studied by again using a procedure similar to that used in the experiments shown in Figure 6. Cells grown in LD conditions were transferred to a dark

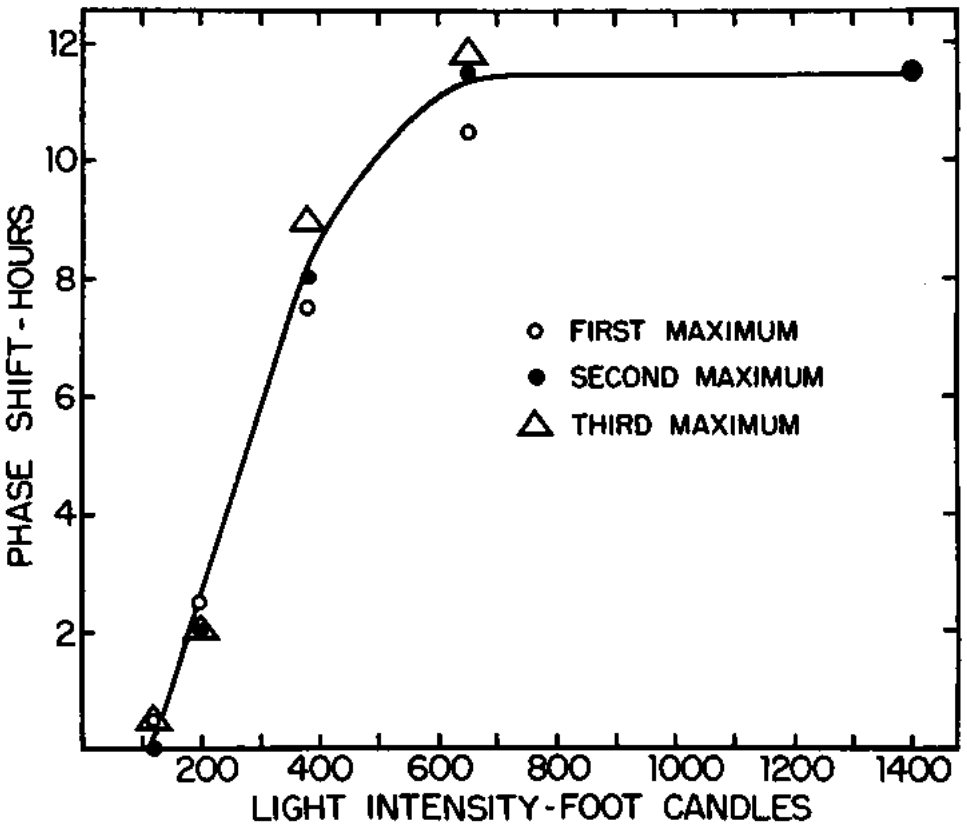

FIGURE 7. The relationship between the intensity of a single 2½-hour light perturbation and the number of hours by which the phase is shifted. Data taken from the experiments shown in Figure 6. Different symbols, as marked on the graph, give the phase difference between the control and the experimentals, measured at each of the three maxima in luminescence subsequent to the perturbation.

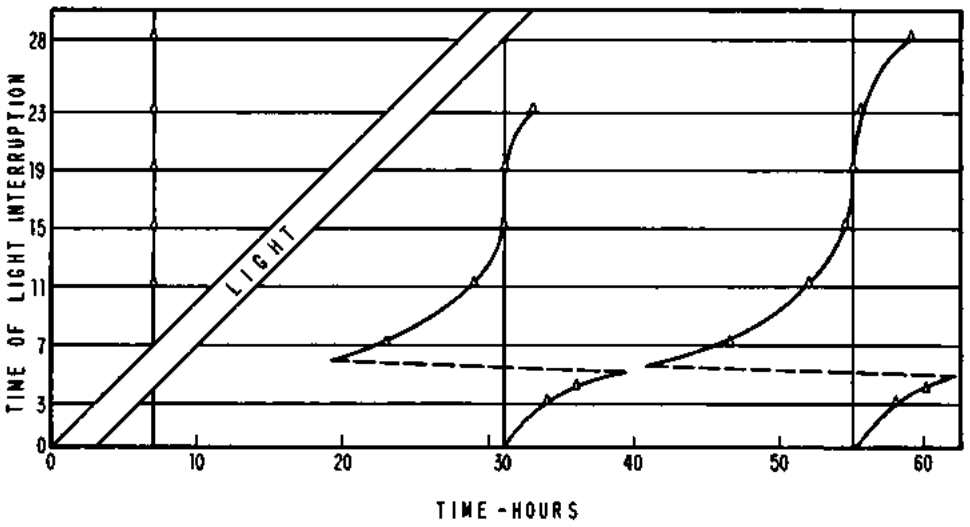

FIGURE 8. The effect of light perturbations (1400 foot-candles for 3 hours) given at different times during the cycle, upon the phase of the endogenous rhythm. Cells which had been kept under LD conditions were placed in the dark at zero time on the graph, which was the end of a 12-hour light period. The times at which the maxima in luminescence occurred in the control, which remained in the dark all the while, are indicated by vertical lines. In the experimentals, a triangular symbol shows a time at which a maximum in luminescence occurred, and thus represents phase. The experiments were carried out in a way similar to those illustrated in Figure 6. Each horizontal line represents a different experiment. For example, the line at 11 hours on the ordinate was an experiment in which a maximum in luminescence occurred at 7 hours. A light perturbation was begun at 11 hours and terminated at 14 hours. Maxima in luminescence occurred subsequently at 29½ hours and 52½ hours. The other experiments are represented in a similar way. The relationship between the time in the cycle at which the light perturbation was administered and the number of hours by which the phase was changed may be better visualized by rotating the figure by 90°.

chamber at the end of a light period. At regular time intervals thereafter, some of the cells were removed and exposed for three hours to light at an intensity of 1400 foot-candles, and then returned to darkness. Times at which exposures to light were made were selected so that the experiment served to scan somewhat more than a full 24-hour cycle. A control received no exposure to light, and the times at which maxima in luminescence occurred in this control are indicated by the vertical lines in Figure 8.

The results of the experiments are summarized in Figure 8. First of all, it may be noted that the new phase, following a light perturbation, was not directly related to the time at which the light perturbation was administered. That is, the maxima in luminescence did not occur at a fixed time interval following the light treatment. If that had been the case, the symbols indicating phase would fall along a line at 45°, parallel to the lines representing the times at which light exposures occurred. This latter type of result was obtained in experiments mentioned previously (Figure 4, for example) where a rhythm was initiated in an arrhythmic culture, and the phase was determined only by the time at which the light intensity was changed.

Secondly, it is apparent that the sensitivity to light perturbations was greater during the first 12 hours (Fig. 8) than during the second 12 hours of the cycle. During the first 12 hours a rather pronounced phase shift resulted, whereas during the second 12 hours there was little or no phase shift. In other longer term experiments it has been found that this variation in sensitivity continues in a rhythmic way. It may therefore be stated that, in general, the cells are maximally sensitive to a light perturbation at a time when luminescence is near maximum, and that this sensitivity declines to a minimum at a time when luminescence is minimum.

Finally, however, it may be noted from Figure 8 that a light exposure given before the maximum in luminescence results in a phase delay, so that the time between the light perturbation and the subsequent maximum in luminescence is greater than 24 hours. On the other hand, a light exposure given after the maximum in luminescence results in a phase advance, such that the next maximum in luminescence occurs in less than 24 hours. This difference is illustrated by the light perturbations which start at three hours and at seven hours in Figure 8.

Perturbation by mechanical stimulation. It is of interest to consider the nature of the cellular component or components which, being modified as a result of the light perturbation, result in the observed phase shift. If perturbation by means other than light also resulted in a change in the components of the rhythmic mechanism, then a phase shift would be similarly expected. It seemed possible that mechanical stimulation might be effective in this regard. Consequently, a perturbation experiment was carried out, in which air was bubbled through the cell suspensions instead of exposing the cells to light (Fig. 9). No phase shift occurred; the cells which had been stimulated retained the same phase as the unstimulated controls.

The experiment also shows that it is possible to modify the concentrations of compounds which are involved in the luminescence rhythm without having any effect upon the phase of the rhythmic mechanism itself. It was found previously (Hastings and Sweeney, 1957a) that the rhythm of luminescence involves a daily variation in the amount of extractable components of the luminescent system (luciferin and luciferase). Mechanical stimulation causes the luminescent reaction to occur, so that one would suppose that the concentrations of components in the luminescent system (and other biochemical systems coupled to it) might be changed. In fact, the apparent effect of stimulation is similar to the effect of light; the luminescence decreases to a low level in both cases. But since no phase shift occurred following stimulation, it does not seem likely that the luminescent system could be directly involved in the basic rhythmic mechanism, although it is clearly coupled to such a mechanism. Moreover, it is evident that there is no feedback from the luminescent system to the system controlling the phase of the rhythm. From previous evidence we had suggested that the luminescent system might itself constitute an autonomous chemical oscillation (Hastings and Sweeney, 1957b). The results described above, however, favor a hypothesis which proposes a basic mechanism of cellular rhythmicity to which various physiological and biochemical processes, such as luminescence or cell division (Sweeney and Hastings, 1957b; 1958), could be coupled.

Cellular interaction. Since all the experiments which have been described are carried out with large cell populations (4000–15,000 cells per tube), the ques-

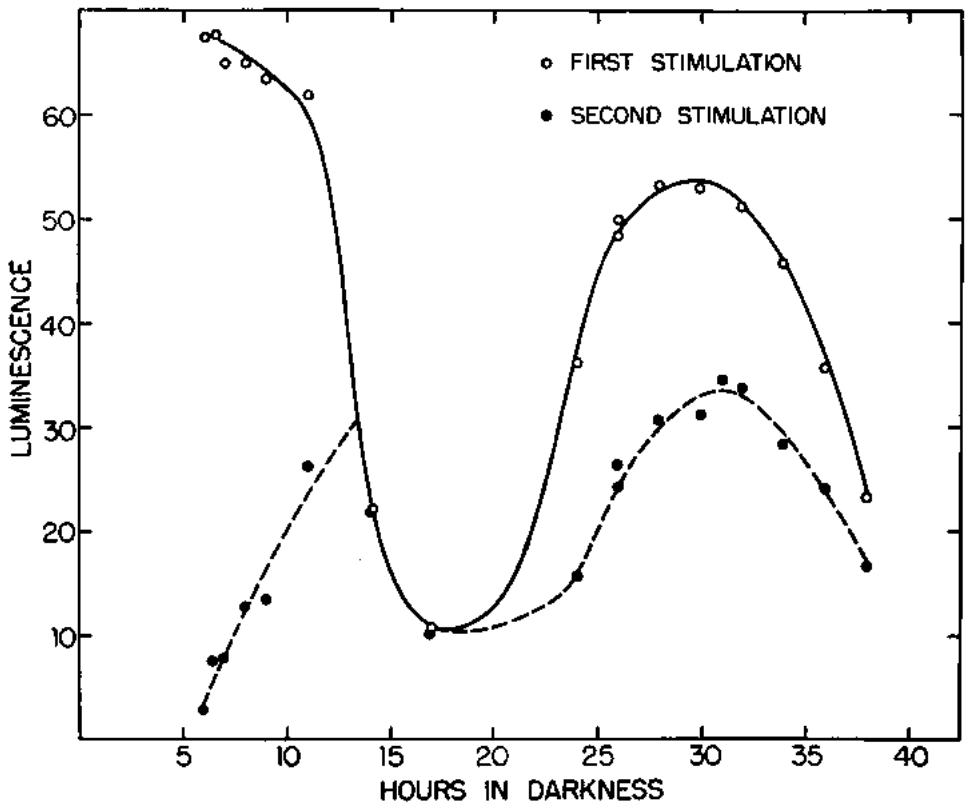

FIGURE 9. The effect of perturbation by mechanical stimulation upon the phase of the rhythm. Previous to the time shown, all cultures were in LD conditions, and zero time on the graph was the end of a light period. At this time all aliquots were placed in the dark. Six hours later a large number of aliquots were stimulated by bubbling air, but were not exposed to light. The luminescence changes of both these and the controls were determined through the subsequent maximum in luminescence. No significant change in the phase of the stimulated cultures was observed.

tion arises as to whether or not some cellular interaction might occur. Since the rhythmic mechanism involves fluctuations in the concentrations of chemical components within the cells, it is conceivable that certain diffusible compounds might escape into the medium, and that their concentrations might also fluctuate in a diurnal fashion. The importance of such a phenomenon would be evident if the supposed compound or compounds could function, as in a feedback mechanism, for stabilizing the frequency and/or phase of the rhythm. It is also possible that some other phenomenon, such as cellular motility, could be involved in such a feedback mechanism. This latter possibility seems unlikely, however, in view of the fact that mechanical stimulation, with its attendant violent motion and disturbance of cellular motility, did not result in a phase change.

An experiment in which this question was investigated is illustrated in Figure 10. Two cultures were maintained under LD conditions for several weeks with

their phases different by 5 hours. Samples were pipetted from each culture and moved to constant dim light at the end of a dark period. After each had been under constant conditions for several days (their phases still being different by

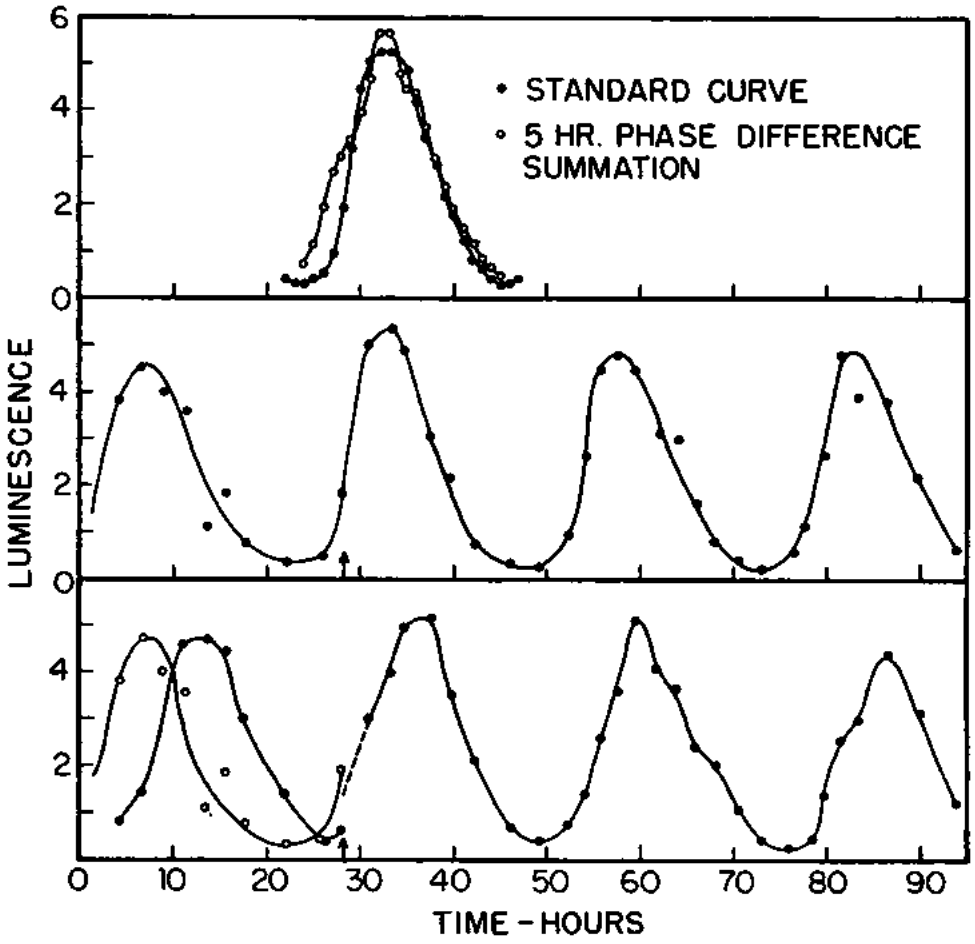

FIGURE 10. The effect of mixing two rhythmic cultures which were out of phase with one another. Cultures which had been in constant dim light for several days, having a 5-hour phase difference as shown (bottom curves), were mixed at the time indicated by the arrow. The rhythm continued, with a phase having its maximum at a time precisely halfway between the maxima of the two original cultures. The middle curve shows the result of mixing cultures having the same phase, done at the time indicated by the arrow. No change of phase was observed. The upper graph shows the result which would be theoretically expected upon mixing two cultures 5 hours out of phase, on the assumption that no interaction was involved. Two "standard" luminescence curves, which were measured from a culture which had not been mixed, were summated with a 5-hour phase difference. For purposes of comparison, the resultant curve is plotted on the graph along with the original standard curve, the latter having been displaced by 2½ hours on the time axis and normalized to the calculated curve. It may be seen that the shape of the calculated curve does not differ greatly from that of the original "standard" luminescence curve.

5 hours), the cultures were mixed in equal proportions, and the luminescence changes in the mixed cultures were measured.

If two typical curves showing the luminescence rhythm are summated, the phase of the two curves being different by five hours (75°), the resultant curve differs only slightly in shape from the original curves (Fig. 10, top). The maximum of the resultant curve lies precisely midway between the maxima of the two original curves.

In the actual mixing experiment, the maximum in luminescence of the mixed cultures occurred halfway between the maxima of the two separate unmixed cultures. Moreover, the shape of the curve from the mixed cultures was very similar to that which was obtained when the measured luminescence of the separate cultures was summated. The mixing experiment therefore indicates that no cellular interaction was involved.

Discussion

The subject of persistent endogenous rhythms has been recently reviewed by Harker (1958), Pittendrigh and Bruce (1957), and Bünning (1956). These reviewers, as well as other authors, have taken the view that the property of rhythmicity may be a nearly universal feature of organisms. This view is derived, largely, from the observation that endogenous rhythms are extremely widespread, having been reported from a large variety of both plants and animals. Furthermore, Pittendrigh and Bruce develop the generalization that most, if not all organisms can measure time; that they possess clocks. They consider that the basic mechanism evolved early, and that it has been retained in the course of evolution as a part of the adaptive organization of all organisms. Their use of the word "clock" refers to the basic mechanism involved in cellular rhythmicity, and the essential properties of this mechanism are considered to be similar in different organisms.

Pittendrigh and Bruce (1957) thus distinguish between the clock as the basic mechanism, and the persistent rhythms which are presumed to be controlled by the clock. Other authors (Brown, Hines, Webb and Fingerman, 1950; Stephens, 1957a; Harker, 1958) have similarly concluded that an overt persistent rhythm may be distinguished from an underlying mechanism, and our studies with *Gonyaulax* give support to this thesis. For example, since it was found that concentrations of compounds taking part in the luminescent reaction could be changed without shifting the phase of the rhythm, it is probable that the luminescence rhythm does not in itself constitute the basic mechanism. Furthermore, we have recently reported a persistent rhythm of cell division in *Gonyaulax* (Sweeney and Hastings, 1957b). The luminescence rhythm and the cell division rhythm have essentially identical properties. Moreover, we have not been able to demonstrate a phase shift in one rhythm which is not accompanied by a similar phase shift in the other rhythm. These findings give additional support to the hypothesis that one basic mechanism controls both rhythms.

The identity and physico-chemical nature of the presumed basic clock mechanism in persistent rhythms remains undefined. But if the properties of this basic mechanism in *Gonyaulax* may be deduced from the rhythm of luminescence, then it is evident that the mechanism possesses essential clock-like properties; the

period is not greatly affected by environmental factors, but the phase is labile to resetting by the appropriate external changes. We may note, in addition, that light emission in *Gonyaulax* is clocked so that it is maximal during the night phase, when it is visible; and without environmental inhibition, luminescence is minimal during the day phase. However, since the possible utility of the light emission is not known, the functional significance of clocked luminescence is not apparent.

Many of the characteristics of the rhythm of luminescence which we have described are similar to the characteristics of persistent rhythms in a variety of other organisms, ranging from other unicellular forms to mammals. The comparisons outlined below do not pretend to be complete, but they serve to illustrate the point. The remarkable similarities found support the view of Pittendrigh and Bruce (1957), that the basic mechanism involved in rhythmicity is the same in all organisms.

Practically all the persistent diurnal rhythms described have natural periods which are close to but different from 24 hours. This includes rhythms in *Drosophila* (Pittendrigh, 1954), *Uca* (Webb, Brown and Sandeen, 1954), *Oedogonium* (Bühnemann, 1955a), *Euglena* (Bruce and Pittendrigh, 1956), and many others. The natural period may range, in different organisms, from about 21 to 27 hours. In fact, significant differences in the natural periods in different individual mice are well documented (Pittendrigh and Bruce, 1957).

Studies of rhythms in a variety of organisms, including the bee (Wahl, 1932), *Uca* (Brown and Webb, 1948), *Avena* (Ball and Dyke, 1954), *Drosophila* (Pittendrigh, 1954), and *Euglena* (Bruce and Pittendrigh, 1956), have shown that in each case the period is nearly the same at temperatures which differ by 15° C., or more. It is interesting to note that the effect of temperature upon the period of the *Gonyaulax* rhythm is similar to that reported by Bühnemann (1955b) for the rhythm of sporulation in *Oedogonium*, in that the apparent Q_{10} for both is less than 1.0. Two cases may therefore be interpreted as the result of an over-compensation in the mechanism responsible for temperature independence (Hastings and Sweeney, 1957b).

Only a few experiments have been specifically designed to detect the effect of different light intensities upon the natural period of persistent rhythms. In those cases which have been reported (see Harker, 1958), the natural period has been found to change no more than an hour or two under different light intensities.

The entrainment of rhythms to periods different from 24 hours has been reported in several organisms, including *Euglena* (Bruce and Pittendrigh, 1956) and *Oedogonium* (Bühnemann, 1955a). In these and other cases, as in *Gonyaulax*, the rhythms return to the characteristic natural period when the organisms are returned to constant conditions.

On the other hand, several experiments have been reported in which rhythmic organisms still continue to show a 24-hour rhythm while being subjected to light-dark cycles which differ from 24 hours. For example, Webb (1950) found that the period of the *Uca* rhythm was not changed while the organisms were subjected to light (95 foot-candles) and dark periods of 16 hours each, and Tribukait (1954) found that entrainment to an imposed light-dark cycle occurred in the mouse only so long as the imposed cycles did not differ greatly from the natural period.

Studies with *Gonyaulax* suggest a possible reason for the lack of apparent entrainment in experiments such as those cited above: the light intensities used may not have been sufficiently bright. In *Gonyaulax,* the luminescence rhythm may be entrained to periods which differ greatly from the natural period. Our interpretation of this entrainment is that repetitive phase resetting results in a period corresponding to the imposed schedule. The importance of light intensity as a parameter in phase shifting by single light perturbations has been documented in experiments with *Gonyaulax*. That it is equally important in entrainment has been shown in an experiment with *Gonyaulax* described elsewhere (Hastings and Sweeney, 1958), in which it was found that entrainment occurred at a light intensity of 800 foot-candles, but not at 200 foot-candles.

Entrainment of rhythms to imposed cycles which are only slightly longer or shorter than the natural period has been discussed by Pittendrigh and Bruce (1957). Their interpretation suggests that the mechanism may be different from that involved in entrainment to cycles differing greatly from the natural period.

The role of 24-hour light-dark cycles in establishing the phase of diurnal rhythms has long been recognized, and experiments with many organisms have demonstrated that, as in *Gonyaulax,* the phase shifts in response to a new light-dark cycle which is out of phase with solar night and day. The fact that the light intensity used in such experiments is of importance has been shown by Brown, Fingerman and Hines (1954).

That non-repeated light perturbations are capable of establishing or changing the phase of a persistent rhythm has been stated as an important generalization only in recent years (Pittendrigh and Bruce, 1957), although some previous studies (Kalmus, 1940; Webb, 1950) do provide examples of the phenomenon. The phenomenon provides another analogy between the characteristics of persistent rhythms and the known properties of physical oscillators. It is well known that a single disturbance or perturbation applied to an oscillating system will quite generally shift its phase without any modification to the period, and the behavior of a simple pendulum is a good example. Pittendrigh and Bruce (1957) have found phase shifts following single light perturbations in persistent rhythms of *Euglena* and *Drosophila*, and the rhythm in *Gonyaulax* provides another example of the phenomenon.

Detailed studies on the effect of the duration and intensity of single perturbations have not yet been reported in other organisms, but it appears that the nature of the phase shift in *Gonyaulax* may differ in one respect from that reported for *Drosophila* (Pittendrigh and Bruce, 1957). Following a single light perturbation in *Drosophila* there may occur "transients," so that the phase is not reset immediately but comes to its stable position only after several cycles. In *Gonyaulax,* on the other hand, phase has been found to be reset immediately. The reason for this difference is not known, but it may be related to the relative complexity of the organisms involved.

With respect to the phenomenon of phase shifting, Bruce and Pittendrigh (1957) have discussed whether the resetting signal is the step-up in light intensity (dawn) or the step-down in light intensity (dusk). Several experiments with *Gonyaulax* have adequately illustrated that the phase is labile to both, so that

neither event may be said to be the timing cue to the exclusion of the other. For example, the experiments shown in Figure 3 illustrate both a light-to-dark transition followed by constant darkness, and a dark-to-light transition followed by constant light. In both cases, the last transition resulted in a phase shift.

The action spectrum for shifting the phase of the luminescence rhythm by a single light perturbation shows relatively sharp maxima in effectiveness at 475 mμ and 650 mμ (Hastings and Sweeney, unpublished). The red maximum, in particular, suggests that chlorophyll acts as a photosensitizer for phase shifting. Since the effects of single light perturbations are essentially the same in plants and animals, we may conclude that in *Gonyaulax* the photosensitizers involved in phase determination are not a part of the basic mechanism of rhythmicity. In animals, also, the photoreceptor pigments of the eye are not a part of the basic mechanism, although they function in phase determination by light. Whitaker (1940) reported that blinded mice possess a natural period of about 24 hours in their activity rhythm, but that the rhythm could not be entrained by 24-hour light-dark cycles to correspond with solar night and day, as in normal mice.

It is known that temperature changes (Pittendrigh, 1954; Stephens, 1957a), and perhaps certain other factors (Harker, 1958) may also serve to establish or reset phase. There is no report, however, that mechanical disturbances can be effective in other organisms in this regard.

The possibility that individuals in a population may entrain each other was suggested by Pittendrigh and Bruce (1957). However, Stephens (1957b) was unable to demonstrate any significant phase modification in individual fiddler crabs when they were placed together with crabs possessing a different phase. A similar result was found in the present studies with *Gonyaulax*.

It is of interest to note that the shape of the luminescence curve obtained in experiments where *Gonyaulax* cultures possessing different phases were mixed is not greatly different from that for the unmixed cultures. Indeed, as already pointed out, this is the expected result of adding two luminescence curves which are five hours out of phase with one another. Thus, a population composed of cells having at least two different phases is difficult to distinguish from the usual experimental populations, in which we have assumed that all cells possess the same phase. This experiment serves to caution us. In a biological rhythm having a sinusoidal shape, measurements from populations may not accurately represent the behavior of individual cells.

We do not know how the luminescence of the individual *Gonyaulax* cell at different times in the cycle compares with that measured in a population. The question is an important one, and there are several possibilities which, in the absence of any relevant data, need not be discussed here. This problem is being investigated utilizing measurements of the rhythm of cell division, where the performance of an individual cell may be repeatedly and relatively easily scored.

Although several suggestions have been made concerning the physico-chemical nature of the basic mechanism involved in persistent diurnal rhythmicity (Pittendrigh and Bruce, 1957; Hastings and Sweeney, 1958), none has received any substantial support. It is hoped that information concerning the extent and kind of biochemical changes associated with the rhythms will be of value in understanding this basic problem. Studies of this nature are in progress with *Gonyaulax*.

Summary

1. The characteristics of a persistent diurnal rhythm of luminescence in the dinoflagellate *Gonyaulax polyedra* are described.

2. The light emission upon stimulation, from cultures which are kept in alternating light and dark periods of 12 hours each (= LD), is 40 to 60 times greater during the dark period than during the light period. If LD cultures are placed in continuous dim light (100 foot-candles) a diurnal rhythm of luminescence persists. If LD cultures are placed in continuous bright light (> 1500 foot-candles) the rhythm is damped, and no fluctuations occur in the amount of light emitted.

3. The occurrence of rhythmicity is not dependent upon prior exposure to LD conditions. Cultures which have been grown in bright light for as long as one year show a diurnal rhythm when placed in constant dim light or darkness. Cultures kept in alternating light and dark cycles which are greater or less than 24 hours similarly show a diurnal rhythm when returned to constant dim light or darkness. "Training" or "memory" is therefore not involved.

4. The rhythm can be entrained by light-dark cycles which are different from 24 hours. The period of the luminescence rhythm corresponds to light-dark cycles which have periods ranging between 12 and 32 hours.

5. The period of the rhythm is always close to 24 hours when the cells are kept under constant conditions, but it varies slightly depending upon the temperature and light intensity.

6. The phase of the rhythm under constant conditions is related to the time at which the previous light and dark periods occurred. Moreover, the phase may be shifted by interposing a non-repeated exposure to a different light intensity. The number of hours by which the phase is shifted in such an experiment is dependent upon the intensity and duration of the light treatment, and the time in the cycle when it is administered.

7. Exhaustive mechanical stimulation does not alter the phase of the rhythm.

8. When cultures having different phases were mixed, no evidence was found which would indicate that there was any interaction between them.

9. The evidence presented indicates that the diurnal rhythmicity is the consequence of a basic oscillatory mechanism which is inherent to the cell.

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Recherches sur l'activité électrique cérébrale au cours du sommeil.

Note de M. JOUVET, F. MICHEL, présentée par H. HERMANN.

Il reste beaucoup d'inconnues dans la compréhension des mécanismes du sommeil. Aux partisans d'un centre hypnogénique inhibiteur diencéphalique [von Economo (1) ; W. R. Hess (2) ; W. J. H. Nauta (3)], s'opposent ceux qui admettent la théorie du « sommeil déafférentation » dans laquelle un système d'éveil sous-cortical serait mis au repos par des processus réversibles encore mal connus [Bremer (4) ; H. W. Magoun (5)].

Nous avons étudié l'activité électrique chronique des formations sous-corticales méso-diencéphaliques et du cortex chez des animaux à cerveau intact, porteurs de section du tronc cérébral et enfin chez des chats décortiqués.

Matériel et Méthodes. — Cette note expose des résultats préliminaires obtenus sur 15 chats chroniques dont l'activité électrique cérébrale est observée pendant des périodes de une semaine à trois mois. Sous anesthésie aux barbituriques, des électrodes corticales et sous-corticales sont implantées au niveau des diverses aires corticales et des formations méso-diencéphaliques. Chez certains animaux est pratiquée, avant l'implantation, une section du tronc cérébral au moyen d'une lame orientée stéréotaxiquement. Ces animaux relativement poïkilothermes ont leur température rectale maintenue à 38° grâce au réchauffement de leur cage. Les animaux décortiqués sont opérés en un temps par aspiration et coagulation du néocortex. Une prothèse en résine acrylique est mise en place, du sinus frontal à la crête occipitale et les électrodes sous-corticales fixées à son niveau. Tous les animaux sont placés pour l'enregistrement dans des cages insonorisées. Enfin des contrôles histologiques vérifient la situation des électrodes, l'étendue des lésions du cortex et du tronc cérébral.

(1) C. von Economo, *Ergebn. Physiol.*, 1929, t. *28*, p. 312.
(2) W. R. Hess, *C. R. Soc. Biol.*, 1931, t. *107*, p. 1333.
(3) W. J. H. Nauta, *J. Neurophysiol.*, 1946, t. *9*, p. 285.
(4) F. Bremer, *C. R. Soc. Biol.*, 1936, t. *122*, p. 464.
(5) N. W. Magoun, *Physiol. Rev.*, 1950, t. *30*, p. 459.

Résultats. — I. ANIMAL NORMAL. — Nous avons trouvé lors de l'étude de l'activité électrique de l'animal chronique les fluctuations parallèles des enregistrements corticaux et sous-corticaux qui ont déjà été décrits [Hess et coll. (6) ; M. B. Rheinberger, H. H. Jasper (7)] : a) activité rapide et de bas voltage généralisé au cours de l'éveil (fig. 1 A) ; b) période des « fuseaux » au cours de l'endormissement (fig. 1 B) ; c) ondes lentes 2 à 4 cs, de haut voltage, corticales et méso-diencéphaliques lors du sommeil profond (fig. 1 C).

II. ANIMAL AVEC SECTION DU TRONC CÉRÉBRAL. — A. L'animal, chez qui une section du tronc intéresse de façon bilatérale les voies spécifiques et respecte la formation réticulaire, présente des fluctuations corticales et sous-corticales identiques à celle de l'animal normal.

B. Si la section du tronc cérébral est totale (au niveau du plan frontal A. 7, Horsley-Clark), l'allure du tracé est toute différente : dissociation manifeste de l'activité électrique corticale recueillie en avant de la lésion (activité typique de déafférentation) et en AR au niveau

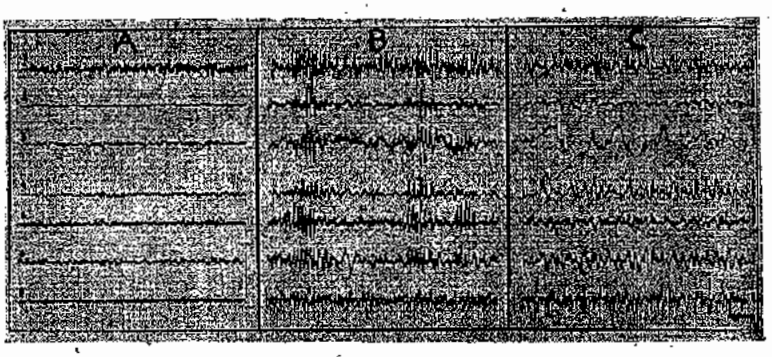

Fig. 1. — Activité électrique corticale et sous-corticale chez le Chat chronique.

A : durant l'état de veille ; B : endormissement, stade des fuseaux ; C : sommeil profond.

1. cortex ectosylvien ; 2. 3. thalamus médian ; 4. formation réticulée mésencéphalique antérieure ; 5. 6. formation réticulée mésencéphalique postérieure ; 7. hippocampe.

Calibrage : 1 sec ; 50 micro-volts.

de la formation réticulée mésencéphalique (F.R.) où l'activité reste rapide de façon permanente quel que soit le comportement de l'animal (éveil par stimulation nociceptive, ou apparence de sommeil).

III. ANIMAL DÉCORTIQUÉ. — A. Décortication totale (intéressant le néo-cortex avec conservation des structures rhinencéphaliques). L'activité des formations méso-diencéphaliques est caractérisée par son micro-voltage et sa rapidité. A aucun moment il n'a été observé d'activité du type fuseaux ou d'ondes lentes. Le tracé est monotone et sans

(6) R. Hess, W. P. Koella et K. Akert, *E.E.G. Clin. Neurophysiol.*, 1953, t. 75, p. 90.
(7) M. B. Rheinberger et J. H. Jasper, *Amer. J. Physiol.*, 1937, t. *119*, p. 186.

aucune variation, même sous narcose barbiturique (fig. 2 A.B.C.). Par contre, l'activité hippocampique est un très fidèle témoin des fluctuations de la vigilance (fig. 2 A.B.C.) ; rapide lors de l'éveil spontané ou provoqué, lente avec des pointes lors du comportement de sommeil, isoélectrique avec des pointes de haut voltage lors de la narcose barbiturique.

L'absence de variations électriques méso-diencéphaliques a été également constatée au cours de l'hyperpnée et de l'injection d'amphétamine et d'adrénaline : l'apnée prolongée entraîne une diminution de voltage sans qu'apparaissent des phénomènes lents.

L'activité évoquée réticulaire (réponses évoquées à des stimuli auditifs) est cependant susceptible de variations car il a été en effet observé une diminution des potentiels évoqués auditifs lors de stimulations nociceptives : phénomène identique à celui obtenu chez le chat normal.

B. Décortication partielle. Il suffit de laisser en place une minime plage de néocortex pour voir apparaître des phénomènes lents méso-

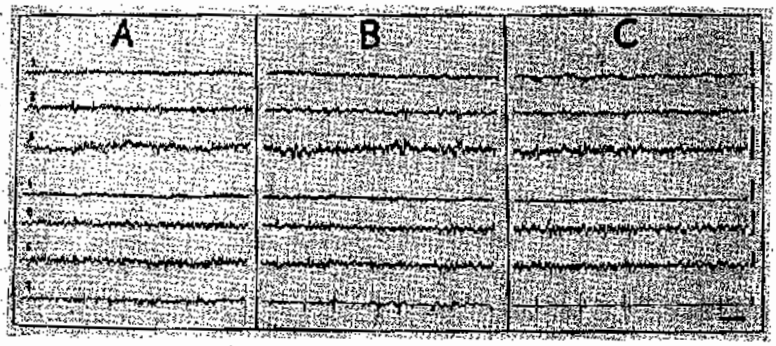

Fig. 2. — Activité électrique rhinencéphalique et sous-corticale chez un chat décortiqué (24 jours après la décortication).

A : éveil ; B : sommeil profond ; C : 80 minutes après l'injection intrapéritonéale de 30 mg/kg de nembutal.

1. 2. formation réticulée mésencéphalique postérieure ; 3. 4. formation réticulée mésencéphalique antérieure ; 5. 6. noyau centre médian du thalamus ; 7. hippocampe.

Calibrage : 1 sec ; 50 micro-volts.

diencéphaliques au cours du sommeil contemporains de l'activité lente de la plage corticale.

Discussion. — Le fait le plus remarquable est l'absence totale, au cours du sommeil, d'activité lente au niveau des formations sous-corticales déconnectées du néocortex.

L'hypothèse d'une « hypersensibilité de dénervation » doit être écartée car l'activité rapide sous-corticale apparaît immédiatement après la décortication ; elle ne s'observe pas chez des animaux à lésion à peu près identique chez lesquels une minime surface corticale a été ménagée. La présence du néo-cortex est donc indispensable pour qu'apparaisse une activité lente au niveau des structures méso-diencé-

phaliques. Ces structures ne sont donc pas capables d'une activité lente autonome soit au cours du sommeil physiologique, soit au cours de la narcose barbiturique. De nombreux arguments expérimentaux permettent d'assimiler l'activité lente recueillie au niveau de la F.R. mésencéphalique à un état d'inhibition active, en particulier nous avons constaté que le seuil électro-encéphalographique d'éveil par stimulation directe de la F.R. mésencéphalique chez l'animal chronique normal augmentait au fur et à mesure du ralentissement du tracé sous-cortical. On doit donc logiquement en déduire qu'une certaine forme d'inhibition réticulaire nécessite la présence du néo-cortex. La topographie de ce système inhibiteur à projection réticulaire n'est pas encore totalement précisée. Rien ne s'oppose en effet à un contrôle direct cortical puisque l'on sait que le cortex isolé est capable d'une activité lente ressemblant à des fuseaux [Bremer (8)]. Par contre on peut également supposer l'existence d'un « centre » diencéphalique antérieur ou rhinencéphalique qui serait à l'origine d'influx se réverbérant au niveau du néo-cortex [H.T. Chang (9)].

A côté de projections corticifuges activatrices du système réticulaire dont l'existence et la topographie a fait l'objet de récents travaux [F. Bremer et C. Terzuolo (10) ; J. D. French et coll. (11)] il faut donc laisser la place à des projections corticifuges inhibitrices entrant en jeu dans les mécanismes de régulation de l'électrogénèse au cours du sommeil physiologique.

La présence d'une activité rapide réticulaire au cours du sommeil physiologique chez l'animal mésencéphalique ou décortiqué et la constatation au niveau réticulaire de réponses évoquées auditives durant le sommeil physiologique du Chat décortiqué infirment donc l'hypothèse de « sommeil déafférentation ». Les structures centrales mésencéphaliques de l'animal décortiqué gardent cependant un pouvoir inhibiteur s'exerçant sur leurs afférences puisque l'on constate une diminution nette d'amplitude des réponses évoquées réticulaires lors de stimulations nociceptives.

Les variations de l'activité électrique rhinencéphalique chez l'animal décortiqué suggère la grande importance de cette structure dans le mécanisme du sommeil, bien qu'à l'heure actuelle aucun argument ne permette encore de dire si cette activité est une cause ou une conséquence du sommeil (*).

(Institut de Physiologie, Faculté de Médecine et de Pharmacie, Lyon. Directeur : M. H. Hermann).

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(8) F. Bremer, *E.E.G. Clin. Neurophysiol.*, 1949, t. *1*, p. 177.
(9) H. T. Chang, *J. Neurophysiol.*, 1950, t. *13*, p. 295.
(10) F. Bremer et C. Torzuolo, *J. de Physiol.*, 1953, t. *45*, p. 56.
(11) J. D. French, R. Hernandez-Pon et R. B. Livingston, *J. Neurophysiol.*, 1955, t. *18*, p. 74.

(*) Les recherches rapportées dans cet article ont été l'objet d'une subvention partielle de l'Office of scientific Research of the air, research and development command, United States Air Force, attribuée par son service européen, sous contrat AF.61 (514) 1206.

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The Effect of Dream Deprivation

The need for a certain amount of dreaming each night is suggested by recent experiments.

William Dement

About a year ago, a research program was initiated at the Mount Sinai Hospital which aimed at assessing the basic function and significance of dreaming. The experiments have been arduous and time-consuming and are still in progress. However, the results of the first series have been quite uniform, and because of the length of the program, it has been decided to issue this preliminary report.

In recent years, a body of evidence has accumulated which demonstrates that dreaming occurs in association with periods of rapid, binocularly synchronous eye movements (*1–3*). Furthermore, the amount and directional patterning of these eye movements and the associated dream *content* are related in such a way as to strongly suggest that the eye movements represent scanning movements made by the dreamer as he watches the events of the dream (*3*). In a study of undisturbed sleep (*4*), the eye-movement periods were observed to occur regularly throughout the night in association with the lightest phases of a cyclic variation in depth of sleep, as measured by the electroencephalograph. The length of individual cycles averaged about 90 minutes, and the mean duration of single periods of eye movement was about 20 minutes. Thus, a typical night's sleep includes four or five periods of dreaming, which account for about 20 percent of the total sleep time.

One of the most striking facts apparent in all the works cited above was that a very much greater amount of dreaming occurs normally than had heretofore been realized—greater both from the standpoint of frequency and duration in a single night of sleep and in the invariability of its occurrence from night to night. In other words, dreaming appears to be an intrinsic part of normal sleep and, as such, although the dreams are not usually recalled, occurs every night in every sleeping person.

A consideration of this aspect of dreaming leads more or less inevitably to the formulation of certain rather fundamental questions. Since there appear to be no exceptions to the nightly occurrence of a substantial amount of dreaming in every sleeping person, it might be asked whether or not this amount of dreaming is in some way a necessary and vital part of our existence. Would it be possible for human beings to continue functioning normally if their dream life were completely or partially suppressed? Should dreaming be considered necessary in a psychological sense or a physiological sense or both?

The obvious attack on these problems was to study subjects who had somehow been deprived of the opportunity to dream. After a few unsuccessful preliminary trials with depressant drugs, it was decided to use the somewhat drastic method of awakening sleeping subjects immediately after the onset of dreaming and to continue this procedure throughout the night, so that each dream period would be artificially terminated right at its beginning.

Subjects and Method

The data in this article are from the first eight subjects in the research program, all males, ranging in age from 23 to 32. Eye movements and accompanying low-voltage, nonspindling electroencephalographic patterns (*4*) were used as the objective criteria of dreaming. The technique by which these variables are recorded, and their precise relationship to dreaming, have been extensively discussed elsewhere (*2, 4*). Briefly, the subjects came to the laboratory at about their usual bedtime. Small silver-disk electrodes were carefully attached near their eyes and on their scalps; then the subjects went to sleep in a quiet, dark room in the laboratory. Lead wires ran from the electrodes to apparatus in an adjacent room upon which the electrical potentials of eye movements and brain waves were recorded continuously throughout the night.

Eye movements and brain waves of each subject were recorded throughout a series of undisturbed nights of sleep, to evaluate his base-line total nightly dream time and over-all sleep pattern. After this, recordings were made throughout a number of nights in which the subject was awakened by the experimenter every time the eye-movement and electroencephalographic recordings indicated that he had begun to dream. These "dream-deprivation" nights were always consecutive. Furthermore, the subjects were requested not to sleep at any other time. Obviously, if subjects were allowed to nap, or to sleep at home on any night in the dream-

The author is on the staff of Mount Sinai Hospital, New York, in the department of psychiatry.

deprivation period, an unknown amount of dreaming would take place, offsetting the effects of the deprivation. On the first night immediately after the period of dream deprivation, and for several consecutive nights thereafter, the subject was allowed to sleep without disturbance. These nights were designated "recovery nights." The subject then had a varying number of nights off, after which he returned for another series of interrupted nights which exactly duplicated the dream-deprivation series in number of nights and number of awakenings per night. The only difference was that the subject was awakened in the intervals between eye-movement (dream) periods. Whenever a dream period began, the subject was allowed to sleep on without interruption, and was awakened only after the dream had ended spontaneously. Next, the subject had a number of recovery nights of undisturbed sleep equal to the number of recovery nights in his original dream-deprivation series. Altogether, as many as 20 to 30 all-night recordings were made for each subject, most of them on consecutive nights. Since, for the most part, tests could be made on only one subject at a time, and since a minute-by-minute all-night vigil was required of the experimenter to catch each dream episode immediately at its onset, it can be understood why the experiments have been called arduous and time-consuming.

Table 1 summarizes most of the pertinent data. As can be seen, the total number of base-line nights for the eight subjects was 40. The mean sleep time for the 40 nights was 7 hours and 2 minutes, the mean total nightly dream time was 82 minutes, and the mean percentage of dream time (total dream time to total sleep time $\times$ 100) was 19.4. Since total sleep time was not held absolutely constant, percentage figures were routinely calculated as a check on the possibility that differences in total nightly dream time were due to differences in total sleep time. Actually, this is not a plausible explanation for any but quite small differences in dream time, because the range of values for total sleep time for each subject turned out to be very narrow throughout the entire study. When averaged in terms of individuals rather than nights, the means were: total sleep time, 6 hours 50 minutes; total dream time, 80 minutes; percentage of dream time, 19.5; this indicates that the figures were not skewed by the disparate number of base-line nights per subject. The remarkable uniformity of the findings for individual nights is demonstrated by the fact that the standard deviation of the total nightly dream time was only plus or minus 7 minutes.

Progressive Increase in Dream "Attempts"

The number of consecutive nights of dream deprivation arbitrarily selected as a condition of the study was five. However, one subject left the study in a flurry of obviously contrived excuses after only three nights, and two subjects insisted on stopping after four nights but consented to continue with the recovery nights and the remainder of the schedule. One subject was pushed to seven nights. During each awakening the subjects were required to sit up in bed and remain fully awake for several minutes. On the first nights of dream deprivation, the return to sleep generally initiated a new sleep cycle, and the next dream period was postponed for the expected amount of time. However, on subsequent nights the number of forced awakenings required to suppress dreaming steadily mounted. Or, to put it another way, there was a progressive increase in the number of attempts to dream. The number of awakenings required on the first and last nights of deprivation are listed in Table 1. *All* the subjects showed this progressive increase, although there was considerable variation in the starting number and the amount of the increase. An important point is that each awakening was preceded by a minute or two of dreaming. This represented the time required for the experimenter to judge the emerging record and make the decision to awaken the subject after he first noticed the beginning of eye movements. In some cases the time was a little longer, as when an eye-movement period started while the experimenter was looking away from the recording apparatus. It is apparent from this that the method employed did not constitute absolute dream deprivation but, rather, about a 65- to 75-percent deprivation, as it turned out.

Nightly Dream Time Elevated after Deprivation

The data on the first night of the dream deprivation recovery period are summarized for each subject in Table 1. As was mentioned, one subject had quit the study. The mean total dream [illegible] on the first recovery night was [illegible] minutes, or 26.6 percent of the [illegible] mean sleep time. If the results for [illegible] subjects who did not show marked [illegible] creases on the first recovery night [illegible] excluded, the mean dream time is [illegible] minutes or 29 percent, which represents a 50-percent increase over the group base-line mean. For all seven subjects together, on the first recovery night the increase in percentage of dream time over the base-line mean (Table 1, col. 3, mean percentage figures; col. 10, first recovery night percentages) was significant at the $p < .05$ level in a one-tail Wilcoxin matched-pairs signed-ranks test (*5*).

It is important to mention, however, that one (S.M. in Table 1) of the two subjects alluded to above as exceptions was not really an exception because although he had only 1 hour 1 minute of dreaming on his first recovery night he showed a marked increase on *four* subsequent nights. His failure to show a rise on the first recovery night was in all likelihood due to the fact that he had imbibed several cocktails at a party before coming to the laboratory so that the expected increase in dream time was offset by the depressing effect of the alcohol. The other one of the two subjects (N.W. in Table 1) failed to show a significant increase in dream time on any of five consecutive recovery nights and therefore must be considered the single exception to the over-all results. Even so, it is hard to reconcile his lack of increase in dream time on recovery nights with the fact that during the actual period of dream deprivation he showed the largest build-up in number of awakenings required to suppress dreaming (11 to 30) of any subject in this group. One may only suggest that, although he was strongly affected by the dream loss, he could not increase his dream time on recovery nights because of an unusually stable basic sleep cycle that resisted modification.

The number of consecutive recovery nights for each subject in this series of tests was too small in some cases, mainly because it was naively supposed at the beginning of the study that an increase in dream time, if it occurred, would last only one or two nights. One subject had only one recovery night, another two, and another three. The dream time was markedly elevated above the base-line on all these nights. For how many additional nights each of these three subjects would have maintained an elevation in dream time

Table 1. Summary of experimental results. *TST*, total sleep time; *TDT*, total dream time.

Mean and range, base-line nights			Dream-deprivation nights (No.)	Awakenings (No.)		Dream-deprivation-recovery nights				First control recovery night		
							First night					
TST	TDT	Percent		First night	Last night	No.	TST	TDT	Percent	TST	TDT	Percent
					Subject W. T. (4 base-line nights)							
	1^h17^m	19.5	5	8	14	1	6^h43^m	2^h17^m	34.0	6^h50^m	1^h04^m	15.6
6^h48^m	1^h10^m–1^h21^m	17.0–21.3										
					Subject H. S. (5 base-line nights)							
	1^h24^m	18.8	7	7	24	2	8^h02^m	2^h45^m	34.2	8^h00^m	1^h49^m	22.7
7^h58^m	1^h07^m–1^h38^m	15.4–21.8										
					Subject N. W. (7 base-line nights)							
	1^h18^m	19.5	5	11	30	5	6^h46^m	1^h12^m	17.8	7^h10^m	1^h28^m	20.2
7^h10^m	1^h11^m–1^h27^m	17.4–22.4										
					Subject B. M. (6 base-line nights)							
	1^h18^m	18.6	5	7	23	5	7^h25^m	1^h58^m	26.3	7^h48^m	1^h28^m	18.8
7^h38^m	0^h58^m–1^h35^m	14.8–22.2										
					Subject R. G. (10 base-line nights)							
	1^h26^m	19.3	5	10	20	5	7^h14^m	2^h08^m	29.5	7^h18^m	1^h55^m	26.3
7^h57^m	1^h13^m–1^h46^m	16.9–22.7										
					Subject W. D. (4 base-line nights)							
	1^h21^m	20.8	4	13	20	3	8^h53^m	2^h35^m	29.0			
7^h22^m	1^h08^m–1^h32^m	17.8–23.4										
					Subject S. M. (2 base-line nights)							
	1^h12^m	17.9	4	22	30	6	5^h08^m	1^h01^m	19.8	6^h40^m	1^h07^m	16.8
7^h04^m	1^h01^m–1^h23^m	16.2–19.3					6^h32^m*	1^h50^m*	28.1*			
					Subject W. G. (2 base-line nights)							
	1^h22^m	20.8	3	9	13							
6^h24^m	1^h17^m–1^h27^m	20.7–20.9										

ond recovery night (see text).

n only be surmised in the absence of jective data. All of the remaining ir subjects had five consecutive re- very nights. One was the single sub- ct who showed no increase, two were aring the base-line dream time by e fifth night, and one still showed arked elevation in dream time. From is admittedly incomplete sample it ppears that about five nights of in- eased dreaming usually follow four or ve nights of dream suppression hieved by the method of this study.

ffect Not Due to Awakening

Six of the subjects underwent the ries of control awakenings—that is, wakenings during non-dream periods. his series exactly duplicated the eam-deprivation series for each sub- ct in number of nights, total number awakenings, and total number of wakenings per successive night. The eam time on these nights was slightly elow base-line levels as a rule. The rpose of this series was, of course, to e if the findings following dream de- ivation were solely an effect of the ultiple awakenings. Data for the first covery nights after nights of control wakenings are included in Table 1. here was no significant increase for e group. The mean dream time was minutes, and the mean percentage as 20.1. Subsequent recovery nights in this series also failed to show the marked rise in dream time that was observed after nights of dream deprivation. A moderate increase found on four out of a total of 24 recovery nights for the individuals in the control-awakening group was felt to be a response to the slight reduction in dream time on control-awakening nights.

Behavioral Changes

Psychological disturbances such as anxiety, irritability, and difficulty in concentrating developed during the period of dream deprivation, but these were not catastrophic. One subject, as was mentioned above, quit the study in an apparent panic, and two subjects insisted on stopping one night short of the goal of five nights of dream deprivation, presumably because the stress was too great. At least one subject exhibited serious anxiety and agitation. Five subjects developed a marked increase in appetite during the period of dream deprivation; this observation was supported by daily weight measurements which showed a gain in weight of 3 to 5 pounds in three of the subjects. The psychological changes disappeared as soon as the subjects were allowed to dream. The most important fact was that *none* of the observed changes were seen during the period of control awakenings.

The results have been tentatively interpreted as indicating that a certain amount of dreaming each night is a necessity. It is as though a pressure to dream builds up with the accruing dream deficit during successive dream-deprivation nights—a pressure which is first evident in the increasing frequency of attempts to dream and then, during the recovery period, in the marked increase in total dream time and percentage of dream time. The fact that this increase may be maintained over four or more successive recovery nights suggests that there is a more or less quantitative compensation for the deficit. It is possible that if the dream suppression were carried on long enough, a serious disruption of the personality would result (6).

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6. The research reported in this paper was aided by a grant from the Foundations' Fund for Research in Psychiatry.

Effects of sleep and waking on spontaneous and evoked discharge of single units in visual cortex.

EDWARD V. EVARTS

Laboratories of Neurophysiology and Clinical Science, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland

Since the discoveries of Berger (6), Adrian and Matthews (2), and Bremer (8–10) concerning the characteristics of cerebral electrical activity associated with sleep and waking, there have been numerous studies of the effects of sleep and arousal on brain potentials in both man and lower animals. In large part these studies have involved macroelectrode recordings of the summed activity of populations of cerebral neurons. In considering the elimination of slow waves from these recordings during arousal, Adrian and Matthews (2) suggested that the slow waves were based on synchronization of the activity of individual neurons, and that their disappearance was the result of the desynchronization of this activity. Reduction of a variety of evoked cortical potentials (4, 11, 13, 14, 16, 18, 21, 27, 34, 49, 50, 54, 58) has also been shown to occur during arousal. The reduction of these evoked potentials has generally been viewed as the result of desynchronization and occlusion. With the advent of techniques which have permitted studies of the activity of individual cerebral neurons, it has become possible to obtain additional data concerning mechanisms underlying the appearance and disappearance of spontaneous slow waves and of evoked potentials in macroelectrode recordings. On the basis of microelectrode recordings, Adrian, who proposed synchronization and desynchronization as the bases for these alterations, was one of the first to question the adequacy of this explanation. In studies of the electrical activity of the olfactory bulb, Adrian (1) observed that a strong olfactory stimulus abolished the spontaneous rhythmic activity of the bulb. He stated that "After a strong olfactory stimulus the rhythm is abolished and it is built up again gradually, but its absence is associated with a reduction in the activity of the olfactory tract and its return with an increase of activity. In this case therefore the break up of the rhythm seems to involve a decrease in the activity of the cells, and it is not merely that their activity is no longer synchronized."

Reduction of neuronal discharge in association with abolition of a slow rhythm has also been observed in the cortex. Whitlock *et al.* (58) found that units in the motor cortex which discharged in association with spindle waves show arrest of discharge when the spindle waves are eliminated by arousal. These authors suggested that arousal may be associated with inhibition of discharge in these neurons.

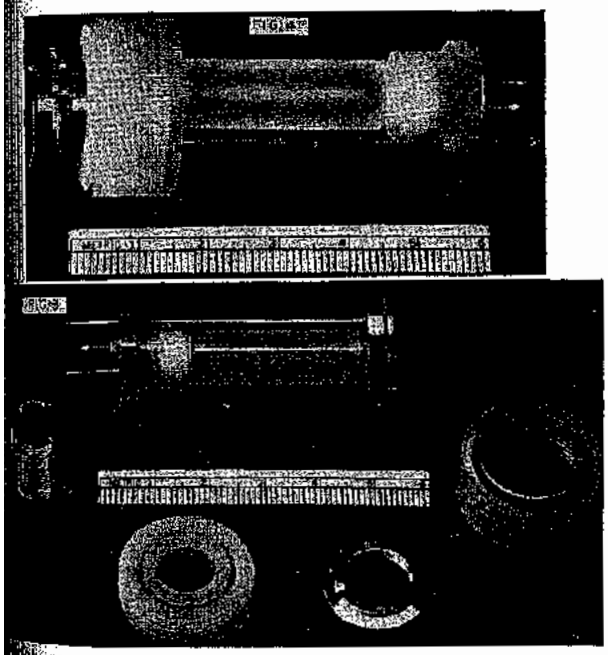
More recently, it has become possible to record the activity of single neurons in intact unrestrained preparations. Techniques devised by Hubel (28) and Jasper (33) allow studies of unanesthetized intact preparations in which observations of behavior may be related to activity of single neurons. It was in this type of preparation that Jasper and his colleagues obtained further evidence that arousal is associated with inhibition of discharge in many cortical neurons. In referring to Ricci's observation on arrest of single unit discharge in the temporal lobe by arousal, Jasper points out that "This can hardly be called 'ascending activation' unless one includes inhibition in the processes activated."

The studies referred to above have indicated the importance of inhibition as one factor underlying differences in cortical electrical activity between sleep and waking. The present study, employing a preparation similar to that employed by Hubel, was carried out to obtain additional information concerning differences in cortical electrical activity during sleep and waking, and to determine the relation of alterations of evoked activity to associated alterations of spontaneous activity.

METHODS

Microelectrodes. Figures 1 and 2 illustrate the type of preparation which was employed; figures 3 and 4 show the components of the system which was used for microelectrode recording. An externally threaded stainless steel cylinder with two projections at its base was placed so that the projections were beneath the skull. A small extension at the margin of the trephine hole allowed

ig. 1. Cat with contact occluders in place.
ig. 2. Cat following attachment of gross electrode cable and roelectrode carrier. The anterior device is the Sheatz pedestal, which are fixed the terminals of electrodes implanted for stimulation of the lateral geniculate radiations and for recording the spontaneous slow wave activity from the cortical surface. The posterior device is the microelectrode carrier. The vertically projecting cylinder contains a piston which may be lowered 30 mm, allowing penetration of deep structures in the brain.



ig. 3. Components employed in fixation and driving of microode. At top is cylinder with hydraulically driven piston, ified after the one developed by Hubel. At left is stainless cylinder whose basal projections are placed beneath the Steel ring at bottom right is screwed down on this cylinder one is firmly held between ring (above the bone) and proons at base of cylinder (beneath the bone). Nylon ring at lower nternally and externally threaded, is attached to steel cylinder eyes as base for microelectrode drive (top) which is held his base by internally threaded collar (right).
ig. 4. Assembled components of microelectrode system.

ections at the base of the cylinder to be placed th the skull. An internally threaded ring was put the cylinder and tightened so that the bone was ed firmly between the projections at the base of the cylinder and the ring. The center of the cylinder was placed at Horsley-Clarke coordinates A_2-L_0 in order to allow penetration of either lateral gyrus. Caution was exercised to avoid injuring the dura, since it was found that the intact dura prevented injury to the subjacent cortex. Electrodes were inserted into the lateral gyrus between Horsley-Clarke coordinates A_4-A_0 and L_2-L_3.

The hydraulically driven micromanipulator, which was modified after that of Hubel (28), was placed eccentrically over the cylinder, allowing the electrode to be inserted at any point on a circle whose radius was 3 mm and whose center was at the center of the cylinder which was fixed to the skull. Oil-filled polyethylene tubes connected to the two chambers of the micromanipulator, and running into a room adjacent to the one in which the preparation was placed, allowed the electrode to be raised or lowered in small steps. Tungsten microelectrodes were prepared according to the method of Hubel (29). Penetration was limited to a depth of 1.8 mm.

Macroelectrode implantation. At the time of implantation of the cylinder which was to carry the micromanipulator, macroelectrodes were implanted for electrical stimulation of lateral geniculate radiations and for recording the spontaneous activity of the visual cortex. The technique of Sheatz (55) was employed in fixation of these electrodes. Three .009 inch diameter enamel-insulated stainless steel wires with tips 1 mm apart were placed in the lateral geniculate radiations bilaterally. The spontaneous slow wave activity was recorded between an extradural electrode at the margin of the cylinder which carried the micromanipulator and an electrode placed in the bone of the occipital crest. The Sheatz pedestal in which the external terminations of these

macroelectrodes were fixed was grounded and served as a reference for the microelectrode.

Experimental conditions. Three days elapsed between the surgical procedures and commencement of recording. Cats were placed in a slowly revolving treadmill during the night prior to recording sessions. In the morning they were fed and placed unrestrained on a soft pad in a 2 ft. x 3 ft. x 3 ft. cage within a sound-proof room equipped with a one-way window. In studies of responses to lateral geniculate radiation stimulation opaque contact occluders (45) were placed in both eyes. These occluders extended well beyond the limbus and excluded all light save that which might reach the retina by penetrating bone, soft tissue, and sclera. Such light as did impinge upon the retina must have been of approximately equal intensity during sleep and arousal. In studies of unit responses to retinal illumination 10 msec. flashes were delivered to the contralateral eye by a small neon bulb which had been attached to a translucent contact occluder. The external surfaces of the contact occluder and neon bulb were made opaque to exclude external light. The pupil was dilated prior to placement of the light source. The ipsilateral eye was covered with an opaque contact occluder. A period of dark adaptation of approximately 30 minutes was allowed prior to the start of recording.

Recording and analysis of data. A flexible lead connected the microelectrode to a Bak amplifier (5) which was suspended above the preparation. The suitably amplified output of the Bak amplifier was displayed on a recurrently sweeping cathode ray beam and recorded on moving film. A time constant of 2 msec. was employed to eliminate slow wave activity from the microelectrode record. Spontaneous slow wave activity from the cortical surface was recorded with an ink-writing oscillograph. Observations concerning the behavior of the preparation were written on the EEG record; such observations are particularly important in studies of sleep and waking, since observation of the EEG alone does not allow distinction between arousal and that phase of sleep in which slow waves are absent (15, 31, 32, 35, 36). Following completion of recordings the EEG and behavioral notes were used to determine presence or absence of sleep. For the present report, analyses of unit activity have been restricted to periods of sleep with pronounced slowing of spontaneous activity and to periods of waking as indicated by the behavior of the cat and by the absence of slowing in the EEG. Unit activity occurring in association with sleep but in the absence of EEG slowing will not be described here. Thus, for the present report, the term sleep will in all cases mean sleep with EEG slowing. Units were selected for analysis only if they were recorded during successive periods of sleep and waking.

Of 286 units studied 90 were observed for sufficiently prolonged periods of sleep and waking to allow analysis of their records according to the criteria indicated above. These 90 units may be divided into two groups. The first group (41 units) was derived from studies of the effects of sleep and waking on responses to lateral geniculate radiation stimulation. The second group (49 units) was derived from studies of effects of sleep and waking on responses to retinal illumination. Of the entire group of 286 units 190 were initially positive and 96 initially negative. In the sample of 90 units selected for analysis 52 were initially positive and 38 initially negative. The initially positive units were, as observed by previous investigators (3, 24, 47, 51), of relatively great amplitude (1–10 mv) and in most cases showed the A-B break of Fuortes *et al.* (23). The initially negative units were rarely greater than 1 mv in amplitude. The inversion of initial sign was commonly observed in the sequence described by Mountcastle *et al.* (47) and by Phillips (51). In presenting the results below no distinctions will be drawn between initially positive and initially negative units. Separate analyses of these two groups have been carried out, however, and have shown that the results to be presented in this report were true of both groups of units. In spite of the qualitatively similar effects of sleep and waking in these two groups of units, comparisons between the groups were consistent with the findings of Mountcastle *et al.* (47) concerning reduced excitability in the initially positive units.

RESULTS

Activity evoked by geniculate radiation stimulation. A previous study in cats with chronically implanted electrodes has shown that the amplitude of the response to lateral geniculate radiation stimulation is reduced during waking as compared to sleep (22). Desmedt and La Grutta (16) have described a similar effect of arousal in the encephale isolé. Reductions of a variety of additional evoked cortical responses by arousal have previously been described by other investigators (4, 7, 13, 14, 16, 18, 21, 27, 34, 49, 50, 54, 58). One purpose

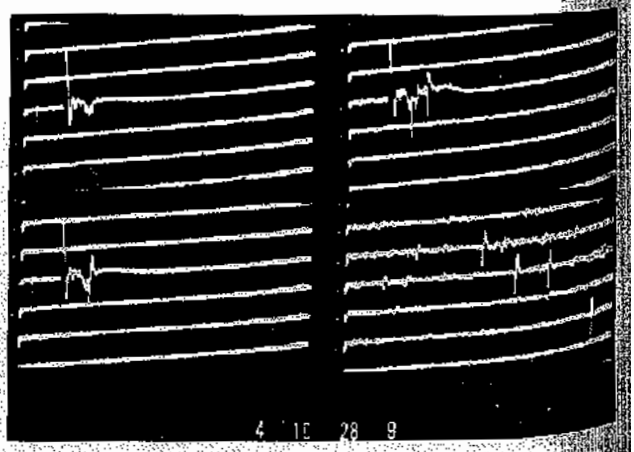


FIG. 5. Response of initially negative unit to lateral geniculate radiation stimulation. Upper left shows shock artifact and evoked response without unit discharge. Lower left and upper right show unit discharging once and twice, respectively, in response to radiation stimulus. Lower right shows spontaneous discharge. Sweep duration is 25 msec. In this and all subsequent illustrations positive is up and time advances from left to right and from below to above.

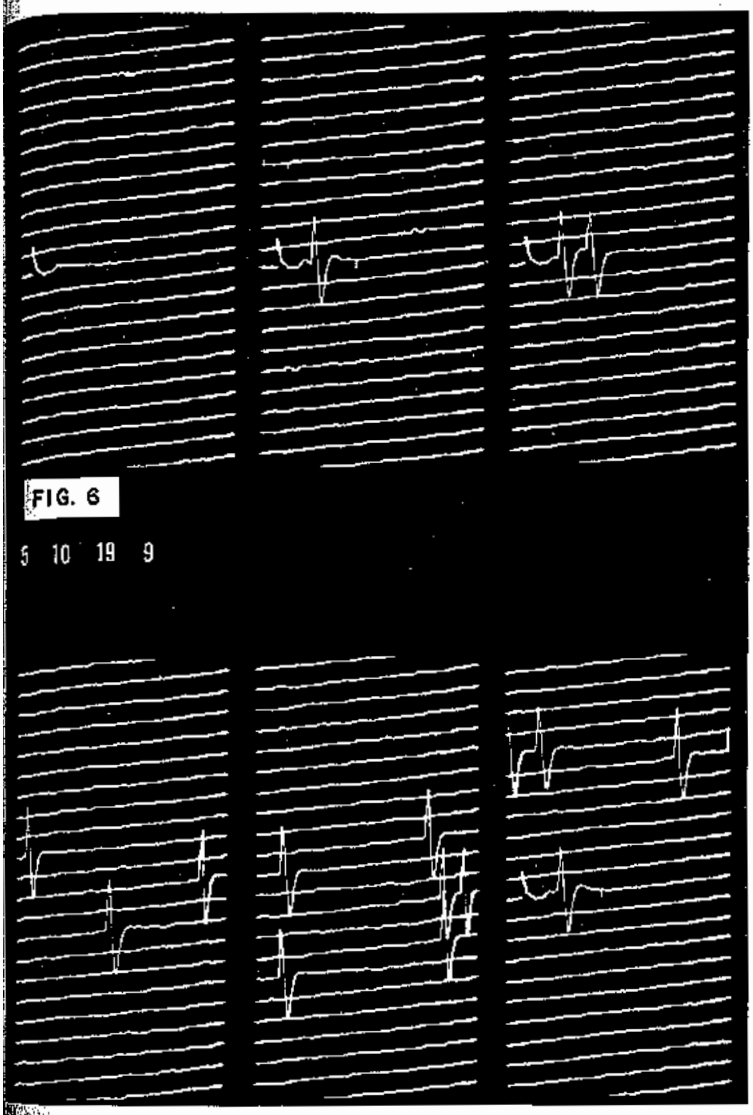


FIG. 6. Response of initially positive unit to lateral geniculate radiation stimulation. Above are shown variations of response to constant geniculate radiation stimulus, which evokes from 0 to 2 spikes. Below are shown spontaneous discharges in absence of geniculate stimulus (left and center) and following response evoked by geniculate stimulus (right). Sweep duration is 25 msec.

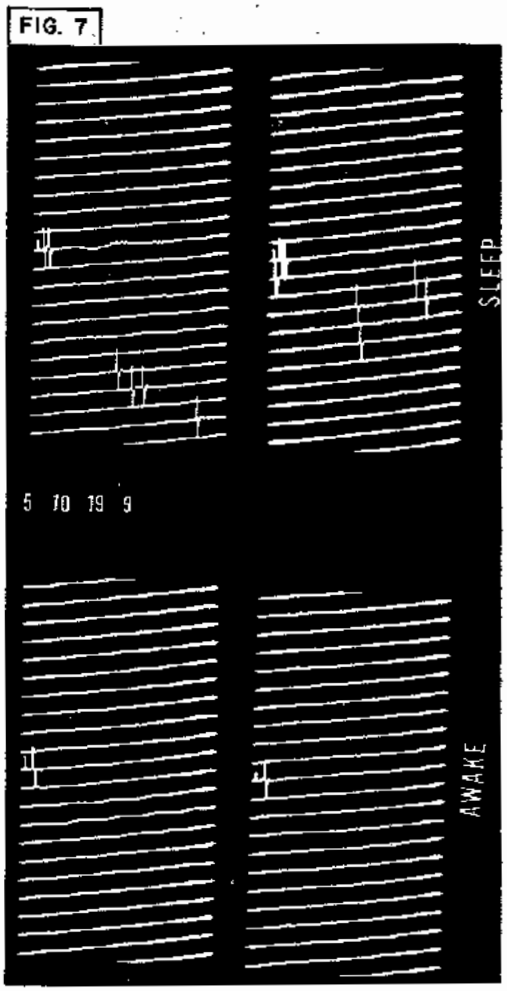


FIG. 7. Reduction of evoked discharge and arrest of spontaneous activity during waking. The initially positive unit illustrated in fig. 6 is shown here (at reduced gain and on 100 msec. sweep) with 2 spikes/stimulus and occasional spontaneous discharge during sleep, and with 1 spike/stimulus and arrest of spontaneous activity during waking.

The present set of observations was to determine the duration of unit activity which might correspond to the above mentioned reduction of the gross response to geniculate radiation stimulation during waking. A possible explanation for this reduction of gross response amplitude might be that the elements whose discharge gives rise to the response have more interstimulus spontaneous activity during arousal than during sleep, and that this greater interstimulus activity causes reduced responsiveness to the synchronous afferent volley. It therefore seemed important to observe the effects of sleep and waking on both spontaneous and evoked activity in the same population of neurons, and to determine the relation of changes in evoked to changes in spontaneous discharge.

Supramaximal stimuli of 30 μsec. duration and 0.5–2.5 ma were delivered to the geniculate radiations ipsilateral to the visual cortex from which unit records were to be obtained. Of the 150 units which were investigated during geniculate radiation stimulation, 63 responded to the geniculate stimulus at latencies of 1 to 6 msec. and had a variety of characteristics which identified them as postsynaptic elements. Of these 63 units 16 were observed during successive periods of sleep and waking, and were therefore analyzed. Figures 5 and 6 show responses to geniculate radiation stimulation in two units, one initially negative, the other initially

positive. Of the 16 units, 9 were initially positive and 7 initially negative. Figure 7 shows representative traces (during sleep and waking) of the initially positive unit shown in figure 6. It is apparent that in this unit there is a reduction of evoked activity and an arrest of spontaneous activity during waking. It is clear, in this case, that reduction of evoked activity during waking is not secondary to increased spontaneous interstimulus activity. Figure 8 presents the results obtained in 15 additional units. Of these 15 units, 11 showed reductions of evoked activity (spikes/stimulus) during waking; 10 of these 11 had associated reductions of spontaneous activity. All of the units showing reductions of 50% or more in evoked activity during waking showed reductions of spontaneous activity.

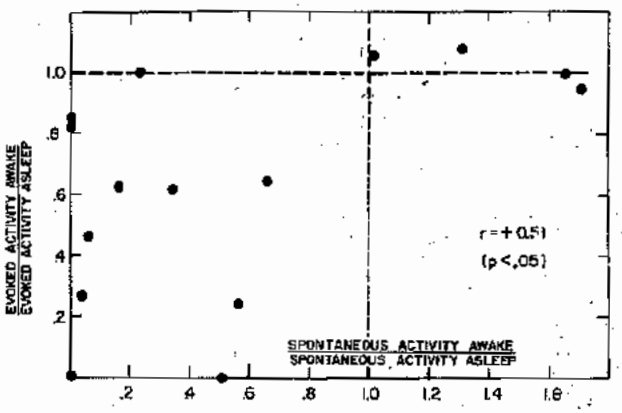
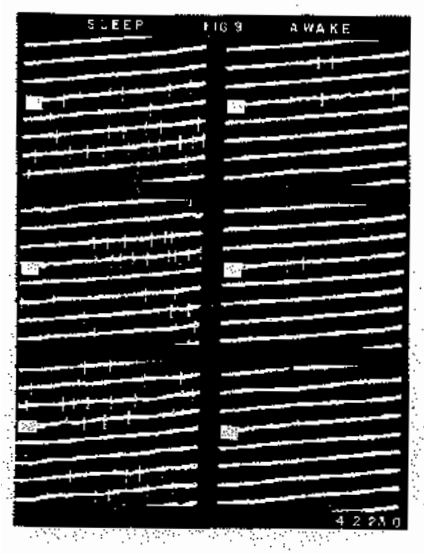
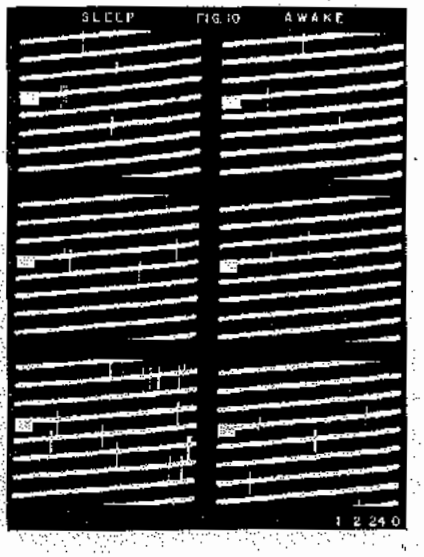


FIG. 8. Effects of sleep and waking on responses to geniculate radiation stimulation. On abscissa is plotted the ratio of spontaneous discharge rate during waking to spontaneous discharge rate during sleep. On ordinate is plotted the ratio of evoked activity during waking to evoked activity during sleep. Points below 1.0 on the ordinate and to the left of 1.0 on the abscissa represent units which had reductions of both spontaneous and evoked activity during waking. Ten units fell into this category. Only 1 unit showed a reduction of evoked activity in association ith an increase in spontaneous discharge during waking.

Activity evoked by retinal illumination. One hundred and thirty-six units were observed during retinal illumination. The photic stimulus was a 10 msec. flash delivered every 2.5 sec. to the contralateral eye. Of the 136 units 84 were initially positive and 52 initially negative. Forty-nine of the group of 136 units were studied during sleep and waking. Of these 49, 17 were regularly excited by the photic stimulus. It is with these 17 units that the present section will deal. Eleven of the 17 were initially positive and 6 initially negative. As mentioned previously, the initially positive units were usually of large amplitude and showed the A-B break, whereas the initially negative units were of lower amplitude and failed to show the A-B break.

For each of these 17 units spontaneous and evoked activity were determined for many presentations of the flash during sleep and waking. As in the case of the results reported in the previous section, it was found that when marked reductions of evoked activity occurred during waking, they were associated with reductions of spontaneous activity. In four of the 17 units waking led to reductions of greater than 50% in the number of





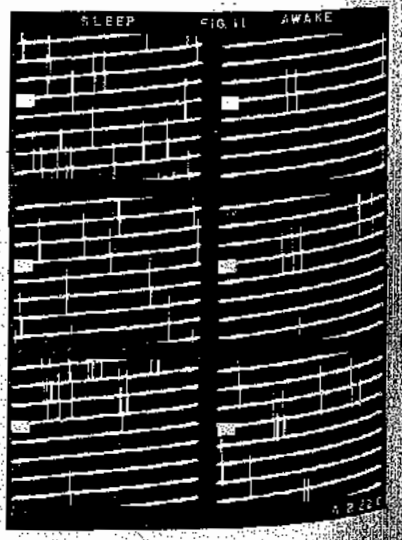


FIG. 9. Reduction of spontaneous activity during waking. The occurrence of a 10 msec. light flash is indicated by white rectangle. During sleep, evoked activity, though shown to be present by statistical analysis of this unit, was obscured by rapid spontaneous discharge. During waking there is marked reduction of spontaneous discharge, and the flash can be seen to elicit two spikes. Sweep duration is 100 msec. Unit is initially negative.

FIG. 10. Reduction of evoked and spontaneous activity during waking. During sleep, the 10 msec. light flash is followed by 1 to 3 spikes. During waking, the flash regularly evokes 1 spike. During waking, the reduction of spontaneous activity is more pronounced than the reduction of evoked activity. Sweep duration is 100 msec. Unit is initially negative.

FIG. 11. Increase in evoked activity associated with decrease of spontaneous activity during waking. During sleep, evoked activity, though present, is of small amount and is obscured by spontaneous discharge. During waking, the flash regularly evokes impulse discharge, and spontaneous activity is reduced. Sweep duration is 100 msec. Unit is initially positive.

es/stimulus. In three of these four units there were more marked reductions of spontaneous activity, e in the fourth there was a slight (20%) increase in spontaneous rate of discharge. Figures 9 and 10 rate the alterations of evoked and of spontaneous ity in two units showing reduction of both evoked of spontaneous activity during waking. It may be that in both of these cases the reduction of spon- eous discharge is more marked than the reduction of ked discharge.

hree of the 17 units showed marked (at least two- d) and consistent increases in evoked activity during king. In these three units there was not a correspond- increase of spontaneous discharge. Figure 11 illus- es the marked increase of evoked discharge which urs in some units during waking. In the unit illus- ed in figure 11, the spontaneous activity showed uction in association with the increase of evoked ivity.

he remaining 10 of these 17 units failed to show ked changes in evoked discharge during arousal. is apparent that units of this sample showed both creases and decreases of evoked discharge with arousal. however, one considers the relation between alteration pontaneous and of evoked activity during arousal, a mewhat more consistent picture emerges. One way to sider the relation of evoked and of spontaneous ivity involves expressing the evoked activity as an teration' of spontaneous discharge rate induced by stimulus. For example, consider a unit which shows average of three spikes in the interval between 20 d 40 msec. after the initiation of the photic stimulus d is thus discharging at a rate of 150/sec. during this ticular interval). If this unit has a spontaneous dis- rge rate of 3/sec., one may say that the stimulus has to a 50-fold increase in the rate of discharge of the It is clear that if the evoked response remains stant while the spontaneous activity is reduced, the ulus will have caused a greater change in the rate of harge of the unit. A similar effect will result from increase in the evoked discharge without change in spontaneous activity. Thus, if, in the example re-

LE 1. *Ratios of Evoked to Spontaneous Discharge ring Sleep and Waking*

nit No.	Sleep	Waking	Unit No.	Sleep	Waking
12	.81	12.65	10-2-27	6.59	5.87
22	1.98	69.94	10-2-11	7.52	5.56
3	2.39	7.87	11-2-26	8.22	9.79
27	2.65	2.48	8-3-2	12.26	20.00
23	3.45	6.02	8-3-1	12.81	14.41
-1	4.72	2.78	118-2-11	15.86	9.12
8-2-11	5.86	2.19	2-3-2	15.89	116.67
3-1	6.07	12.31	5-3-1	16.28	35.50
24	6.48	11.60			

The figures in columns headed 'sleep' and 'waking' are ios of the rate of discharge during a brief interval (usually 0-40 msec.) after the flash to the mean rate of discharge during the 500 msec. prior to the flash.

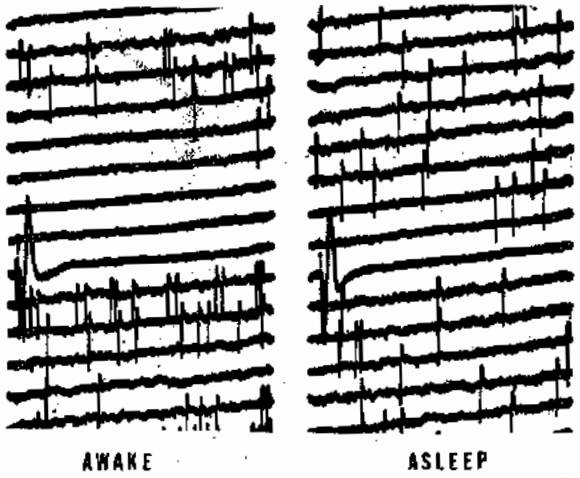


FIG. 12. Inhibition of spontaneous discharge by lateral geniculate radiation stimulus. The slow wave evoked by the stimulus is followed by more prolonged absence of spontaneous activity during waking (left) than during sleep (right). Sweep duration is 100 msec. Unit is initially negative.

ferred to above, the unit shows a reduction of spontaneous activity from 3/sec. to 1/sec. while continuing to discharge at a rate of 150/sec. during the specified interval after the stimulus, the stimulus may be said to have become more effective in 'altering' the discharge rate of the unit. During the period of 3/sec. spontaneous activity the stimulus caused a 50-fold increase in rate of discharge, whereas the same stimulus caused a 150-fold increase in rate of discharge when the spontaneous discharge had decreased to 1/sec. Table 1 lists the effect of the photic stimulus on rate of unit discharge during sleep and waking in 17 units. The table shows the ratio of the rate of discharge in a given interval (usually 20–40 msec.) following the initiation of the stimulus to the rate of discharge prior to the stimulus. It may be seen that for a majority of units this ratio is greater during the waking state than during sleep. In only one unit of the group was waking associated with reduction of this ratio to one-half or less the ratio during sleep. In six of the units the ratio became at least twice as great during waking as it had been during sleep. Examination of the results obtained with responses to electrical stimuli applied to the geniculate radiations reveals a similar trend in the effect of waking on this ratio in the case of these responses.

A detailed statistical analysis of the present results has not been undertaken at the present time due to the relatively small sample which is available. Thus, the data which have been presented must be viewed as merely suggesting that waking is associated with an increase in the ratio of evoked to spontaneous neuronal discharge.

Inhibitory effects of lateral geniculate stimulation on spontaneous activity. A number of investigators have shown that stimulation of a primary thalamic relay nucleus or radiation pathway inhibits the spontaneous activity of units in the corresponding cortical projection area (7,

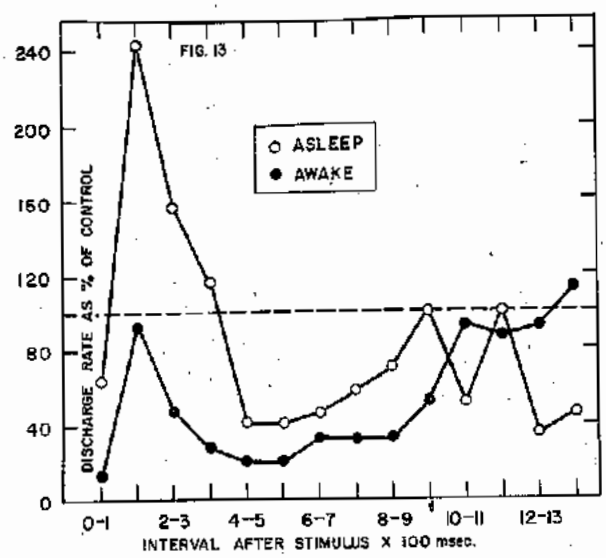


FIG. 13. Inhibition of spontaneous discharge by lateral geniculate radiation stimulus. Rate of spontaneous discharge, as per cent of control rate, is shown for one unit during waking (solid circles) and during sleep (hollow circles). The reduction of spontaneous discharge is more marked during waking than during sleep.

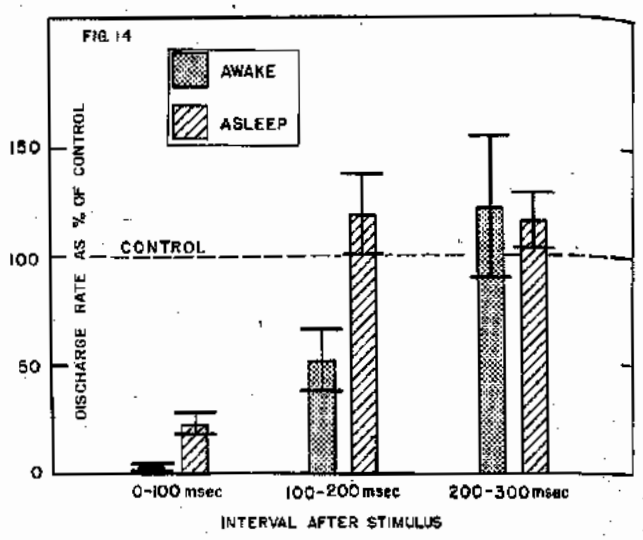


FIG. 14. Averaged results for inhibition of spontaneous activity by geniculate radiation stimulus. The bar graphs show mean rates of discharge, as per cent of control, in 19 units during sleep and waking. The horizontal lines indicate the standard error. Reduction of spontaneous activity was significantly greater ($P < .01$) during waking for the first 2 periods (0–100 msec. and 100–200 msec.).

42, 57); similar inhibitory effects occur following stimuli applied to the cortical surface (7, 37, 39, 52). In view of recent evidence concerning greater activity of inhibitory mechanisms in certain cortical areas during sleep as compared to waking, it seemed worthwhile to determine the effects of sleep and waking on the inhibition of unit discharge in visual cortex induced by lateral geniculate radiation stimulation. Figure 12 illustrates the inhibitory effects of a single geniculate stimulus on spontaneous unit discharge during sleep and waking. Figure 13 is a graphical representation of the inhibitory effect of a single geniculate stimulus during sleep and waking. It is apparent that inhibition is more pronounced during waking than during sleep. The differences in the inhibitory effects of the stimulus on unit activity are consistent with results recently obtained on the recovery cycle of the gross cortical response to lateral geniculate radiation stimulation during sleep and waking (22). In this study, it was found that the recovery curve of this response showed greater subnormality during waking than during sleep. The present observations demonstrate what may be a related phenomenon at the unit level.

Construction of inhibitory curves requires the presence of spontaneous activity. Thus, units which show marked reduction or arrest of spontaneous discharge during waking cannot be used to compare the inhibitory effects of the geniculate radiation stimulus during sleep and waking. Of the 41 units studied extensively during sleep and arousal during electrical stimulation of lateral geniculate radiations, 10 showed arrest or virtual arrest of spontaneous activity during the waking state. Twelve additional units did not provide information concerning differences in the inhibitory effects of the geniculate radiation stimulus between sleep and arousal because their rates of spontaneous discharge were too low to allow determination of the curve on the basis of the number of observations which were available. Inhibitory curves were determined for 19 units during sleep and waking. Figure 14 shows the means and standard errors of the inhibitory effect during periods from 0–100 msec., 100–200 msec., and 200–300 msec. following the stimulus for these 19 units. During the first two of these periods inhibition is significantly greater ($P < 0.01$) during waking. Differences between sleep and waking for the third of these periods (200–300 msec.), and for all remaining points on the curve, are not statistically significant. Inhibition of spontaneous activity was independent of whether or not the unit was excited by the geniculate radiation stimulus, and thus did not represent refractoriness. This independence of inhibition and prior discharge has been previously pointed out by Jung (37).

Spontaneous activity. The spontaneous activity of 90 units was observed during both sleep and waking. Of these 90 units, 48 showed lower rates of discharge during waking than during sleep and 42 showed higher rates of discharge during waking than during sleep. Of the 48 units with reduced activity during waking 17 showed arrest or virtual arrest. The proportion of units showing this marked reduction of spontaneous activity during waking is similar to that observed by Hubel (28) in a previous study of the effects of sleep and waking on spontaneous discharge of units in the visual cortex. Alteration of pattern of spontaneous discharge was observed in many neurons which failed to show marked alterations of over-all spontaneous discharge rates. This alteration of pattern, as previously described by Hubel

(28), takes the form of a reduction of bursts and a general smoothing of the pattern of discharge.

DISCUSSION

Activity has been evoked in units of the visual cortex by two means: electrical stimulation of the lateral geniculate radiations and diffuse illumination of the contralateral retina. Both of these stimuli have certain disadvantages. They were employed because they could be held constant during sleep and waking under the conditions of the present experiment. The electrical stimulus has several disadvantages. First of all, it leads to indiscriminate activation of the radiation fibers and must necessarily obscure the patterns of afferent input which occur in response to physiological activation of retinal elements. Moreover, the characteristics of discharge induced by such a stimulus are entirely dissimilar to that seen in response to retinal illumination. The electrical stimulus gives rise to short high frequency bursts (1–4 spikes) regularly followed by complete suppression of spontaneous activity. Physiological stimulation causes more prolonged discharge of cortical neurons and is not so regularly followed by total elimination of spontaneous discharge. Of advantage, however, are the facts that this stimulus allows positive identification of postsynaptic cortical elements. Changes in responsiveness of cortical elements to such a stimulus may therefore be viewed as the result of changes in cortical excitability and not the secondary result of changes at the level of the retina or lateral geniculate. The photic stimulus, while physiological, has the disadvantage that it is relatively ineffective in exciting discharge of cortical neurons. The results of Hubel and Wiesel (30) show that many cortical units which may be excited by small light sources (either moving or stationary) fail to respond to diffuse retinal illumination.

In spite of the inadequacies of the stimuli employed, the responses which they evoked indicate several alterations of discharge in cortical neurons during waking as compared to sleep. It has been found that reductions of discharge evoked either by flash or by shock are in general associated with reductions of spontaneous activity. This relationship between alteration of evoked discharge and alteration of spontaneous discharge during waking as compared to sleep makes it clear that the reduction of evoked activity is not secondary to increased background activity. In some cases, in fact, reduction of evoked unit discharge was associated with total arrest of spontaneous activity. It would seem that both the reduction of spontaneous discharge and of evoked discharge may result from a higher level of inhibitory input to neurons of the visual cortex during the waking state.

Further evidence of greater activity of inhibitory mechanisms during waking is seen in the more prolonged suppression of spontaneous discharge by lateral geniculate radiation stimulation during waking than during sleep. The basis for the change in inhibitory effects remains to be determined. Several investigators have studied the inhibitory effects of thalamic stimulation (7, 42, 57) and of direct cortical stimulation (7, 37, 39, 52) on unit discharge. The intracellular recordings of Tasaki *et al.* (57) showed that geniculate radiation stimulation led to a suppression of spontaneous discharge, and that this suppression was associated with hyperpolarization of the neuron whose activity was suppressed. Jung (37) has shown that direct stimulation of the visual cortex leads to inhibition of spontaneous unit activity; in these studies it was found that the occurrence of the inhibitory effects was not dependent upon initial discharge of the unit; our observations in this respect confirm those of Jung. In other studies, Jung and Creutzfeldt (40) have shown that inhibition of spontaneous unit discharge occurs in sensori-motor cortex following stimulation at the site of recording or at the corresponding point on the opposite hemisphere. Mechanisms underlying such inhibitory effects have been considered at some length by Phillips (51–53) who found that spontaneous activity of Betz cells could be inhibited either by direct cortical stimulation or by stimulation of the pyramid. Phillips found that surface shocks to the cortex caused hyperpolarization of Betz cells and cessation of spontaneous discharge, whether or not the cells were initially excited by the stimulus. Phillips suggested that the inhibitory effect might be mediated by interneurons analagous to the Renshaw cells of the spinal cord. Branch and Martin (7) observed prolonged inhibition of Betz cell discharge following repetitive stimulation of nucleus *ventralis lateralis*. The mechanism (activation of inhibitory neurons within the cortex) which they propose as underlying this phenomenon would seem to apply equally well to the inhibitory effects observed in the present experiments.

The studies referred to above have demonstrated that inhibitory processes are responsible for the pause in spontaneous discharge which follows direct cortical or thalamic stimulation. The alterations in the duration of this pause of spontaneous discharge of neurons of the visual cortex during sleep and waking indicates that inhibitory processes may be more active during waking than during sleep. This alteration of inhibitory mechanisms during sleep is paralleled by alteration of inhibitory processes by small amounts of an anesthesic agent. The work of Mountcastle (46) and Mountcastle and Powell (48) has shown that afferent inhibition set up by cutaneous stimuli is eliminated by quantities of barbiturate which do not alter the responses of units to excitatory stimuli.

The reductions of evoked discharge which occurred in many units in association with waking may at first glance seem poorly suited to serve perceptual functions. As pointed out by several authors (e.g. 19, 20, 41, 56), however, the detection of a stimulus is based not only on the neuronal activity evoked by the stimulus, but also on the background of spontaneous activity against which the effects of the stimulus must be seen. In the present study, it has been found that many units show

an increase in the ratio of evoked to spontaneous activity during the waking state, whereas a decrease in this ratio is quite rare. The combined results of responses evoked by electrical and by photic stimulation showed that 13 units had a two-fold or greater increase in this ratio during waking, while in only three units was the ratio reduced to one-half or less. This ratio may be thought of as roughly analagous to the signal to noise ratio of communication engineering. It seems possible that the relative increase in evoked as compared to spontaneous activity seen during waking may serve to heighten sensitivity to visual stimuli during the waking state. It should be added that in spite of its occurrence in the absence of external stimulation, spontaneous activity undoubtedly has a variety of functions, as pointed out by Bremer (12) and Granit (25). The analogy between the ratio of evoked to spontaneous activity and the ratio of signal to noise is thus intended to be entirely descriptive.

It has been mentioned that during waking 17 of 90 units showed arrest or virtual arrest of spontaneous discharge. Arrest of activity such as this has been described by Hubel (28) and Jasper (33) and has been investigated in acute preparations by Whitlock *et al.* (58). The latter authors found that discharge of units in motor cortex was arrested during EEG arousal induced by high frequency stimulation of the thalamic reticular formation. Such stimulation also eliminated the high frequency spike discharges which followed application of dilute strychnine to the cortex, but failed to block the discharges induced by concentrated solutions of strychnine. These authors suggested that a possible explanation for the arrest of spontaneous activity seen in these experiments was active inhibition of neuronal elements in motor cortex during arousal.

In the present experiments there is little evidence available as a basis for deciding the sites and mechanisms responsible for reduction of spontaneous discharge in those cases in which it occurred during waking. Equally unexplained are the increases in the rate of spontaneous discharge which occurred in 42 of 90 units studied. It is possible that reductions in spontaneous discharge may reflect changes in active inhibitory processes at a cortical level, alterations in activity in the lateral geniculate, or even in the retina. The observations of Granit (26) and Dodt (17) indicate a possible mechanism for alterations of retinal activity during arousal. Such alterations might be reflected in corresponding changes at a cortical level. Jung's (38) demonstration of the influence of the diffuse thalamic projection systems on activity in the visual cortex indicates another possible origin for some of the effects we have observed. Finally, there is much evidence that alteration of activity in the mesencephalic reticular formation (43, 44, 49) is an important determinant of the alterations in cortical activity associated with sleep and arousal. There are, of course, a number of additional regions of the brain which may be involved in mediating alterations of visual activity. The present investigations cast little light on which of these mechanisms may be involved in the effects which have been described in this report.

In the section on methods it was pointed out that the observations which have been presented were carried out in darkness. Extraneous visual stimulation was eliminated in an attempt to dissociate the effects of waking, per se, from the effect of increased visual input which is ordinarily associated with waking. Unfortunately, equalization of sensory input during waking and sleep was achieved only for the visual modality. During waking the cats often moved. The result was necessarily an increase of cutaneous, proprioceptive, and auditory stimuli, all generated by the cat itself. The studies of Buser and Borenstein (14), and Jung (38) have shown that such nonvisual stimuli influence neuronal discharge in the primary visual system. It seems probable, therefore, that the results obtained in the present studies reflect more than 'pure waking.'

The importance of the behavior associated with sleep or waking in determining patterns of neuronal discharge in these two states has been strikingly indicated in several experiments. For the sensorimotor cortex of the monkey, for instance, Jasper (33) has found that the amount of neuronal discharge is markedly increased during movement. A similar relationship between eye movements and neuronal discharge in the superior colliculus may be seen during sleep. Huttenlocher (personal communication) has made simultaneous recordings of eye movements and unit discharge in the superior colliculus of the sleeping cat. Eye movements (which commonly occur during sleep without EEG slowing) are associated with striking increases in rate of discharge by many units in this region during sleep. These observations make it clear that findings which are obtained in studies of neuronal activity during sleep and waking will depend to a very large extent on the associated behavior of the experimental animal.

SUMMARY

Waking is associated with a reduction of spontaneous discharge rate in a majority of cortical units, and with a prolongation of the suppression of spontaneous discharge by a single lateral geniculate stimulus. In association with reduction of spontaneous discharge there is often a reduction of discharge evoked either by electrical stimulation of ipsilateral lateral geniculate radiations or by diffuse illumination of the contralateral retina. In many units in which activity is evoked, waking is associated with an increase in the ratio of evoked to spontaneous discharge. The increase of this ratio during waking may serve to heighten sensitivity during the alert state.

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Sleep Deprivation, Age, and Exhaustion Time in the Rat

Abstract. Male rats were maintained on a constantly moving wheel in a study of prolonged sleep deprivation. The results obtained revealed a striking negative relationship between age and resistance to exhaustion.

In an earlier study of the effects of prolonged sleep deprivation, six young male hooded rats, 60 days old, were placed on a constantly moving wheel for 27 days. One animal was lost after 17 days. When older animals were tested in a similar manner, it was noted that exhaustion occurred much earlier. This study reports on the relationship of this age variable to exhaustion time.

Six male animals from the following six age groups were obtained from the University of Florida colony: group I, 63 days old; group II, 89 days old; group III, 147 days old; group IV, 170 days old; and group V, 220 days old. At least two litters were represented in each group. The rats were placed, in individual 4½- by 7½-inch cubicles, on wheels, two-thirds submerged in water, which rotated at a constant speed of approximately 2 rev/min. Food trays were placed in each cubicle so that the animals could feed at any time. The rats remained on these wheels continuously except when they were removed for weighing at 24-hour intervals. The total distance covered by an animal during a day was 0.7 mile. The rats, when exhausted, fell from the wheel into the water and were unable to remount the wheel. Animals were removed from the experiment when they fell into the water after being replaced on the wheel three times during a 15-minute period.

Figure 1 shows for each age group the time at which the criterion of exhaustion was reached. The group I (63 day) animals were removed after 9 days although none had reached the exhaustion criterion. It may be recalled, at this point, that 60-day-old rats were run 27 days with the loss of one animal after 17 days. The only difference in the treatment of the 60-day-old rats was that they were kept off the wheel for a longer time (approximately 20 minutes) because several additional measures were taken.

The rats' weight loss and their intake of food while on the wheel were measured. The average percentages of weight retention for each of the five groups after 48 hours were as follows: group I, 95.8; group II, 86.2; group III, 89.2; group IV, 90.6; and group V, 93.3. These averages do not include values for one animal from group V and one from group III that did not last 48 hours. These weight losses, however, give a distorted picture in the case of group I, and to some extent in the case of group II, as these animals are still in a growth gain period; thus these figures may represent a considerable suppression of weight gain. There is a .20 correlation (rank order) between amount of weight lost in 48 hours and terminal exhaustion time in groups II through V. Finally, the overall weight loss for all animals at the weighing before exhaustion was 15.81 percent.

The average change in food intake from the first day on the wheel to the second day on the wheel was as follows for the five groups (in percent): group I, 248.7; group II, 53.4; group III, 99.1; group IV, 88.8; and group V, 45.3. These figures represent the total food intake during the second day divided by the total food intake during the first day in percentage terms. The correlation between the change in food intake and the change in exhaustion time was not significant.

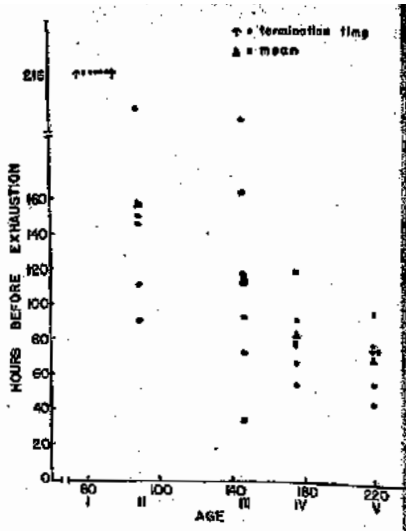

Fig. 1. Exhaustion times of each rat and group means as a function of age. Note that, in group I (age 63 days), runs were terminated after 216 hours.

In conclusion, the data show a clear-cut relationship between exhaustion time and age. Because the amount of activity involved is far below the normal free-run activity of a rat and because the weight loss before exhaustion is certainly within survival limits, it is at least plausible to hypothesize that this exhaustion is related to sleep deprivation (*1*).

WILSE B. WEBB
HARMAN W. AGNEW, JR.
Department of Psychology, University of Florida, Gainesville

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SPECIAL ARTICLES

English Translations Of The First Clinical Reports On Narcolepsy And Cataplexy By Westphal And Gélineau In The Late 19th Century, With Commentary

Carlos H. Schenck, M.D.[1]; Claudio L. Bassetti, M.D.[2]; Isabelle Arnulf, M.D., Ph.D.[3,4]; Emmanuel Mignot, M.D., Ph.D.[3]

[1]Minnesota Regional Sleep Disorders Center, Department of Psychiatry, Hennepin County Medical Center, University of Minnesota Medical School, Minneapolis, MN, USA; [2]Department Of Neurology, University Hospital, Zurich, Switzerland; [3]Stanford Center for Narcolepsy, Stanford, CA; [4]Fédération des Pathologies du Sommeil, Hôpital Pitié-Salpêtrière, Assistance Publique - Hôpitaux de Paris, France

Study Objectives: To publish the first English translations, with commentary, of the original reports describing narcolepsy and cataplexy by Westphal in German (1877) and by Gélineau in French (1880).

Methods: A professional translation service translated the 2 reports from either German or French to English, with each translation then being slightly edited by one of the authors. All authors then provided commentary.

Results: Both Westphal and Gélineau correctly identified and described the new clinical entities of cataplexy and narcolepsy, with recurrent, self-limited sleep attacks and/or cataplectic attacks affecting 2 otherwise healthy people. Narcolepsy was named by Gélineau (and cataplexy was named by Henneberg in 1916). The evidence in both cases is sufficiently convincing to conclude that they were likely each HLA-DQB1*0602 positive and hypocretin deficient.

Conclusions: The original descriptions of narcolepsy and cataplexy are now available in English, allowing for extensive clinical and historical commentary.

Keywords: Narcolepsy, cataplexy, JBE Gélineau, C. Westphal, late 19th century, neurology, history of medicine, sleep disorders, motor dyscontrol, excessive sleepiness/sleep attacks

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To our knowledge, there are no published English translations of the first clinical reports describing narcolepsy (in French, 1880)[1] and cataplexy (in German, 1877).[2] The first author herein (CHS) had a professional translation agency (Berlitz) translate these 2 reports into English, which he then edited, as described below. (A minimum of 2 language experts reviewed each translated manuscript.) These historic documents richly describe recurrent, self-limited sleep attacks and/or cataplectic attacks in 2 otherwise healthy people.

Preliminary comments on the translations are as follows: First, all punctuations and italics come from the original articles. Second, the article by Gélineau was twice as long as the article by Westphal. Third, the translations were edited slightly. Two paragraphs from the Gélineau report that had no direct bearing on the description of narcolepsy or cataplexy were eliminated from the text, as indicated, and placed in an Appendix. Fourth, the Berlitz agency translator of the Gélineau report made this comment: "The original French of this two-part article is written in an unusually loose style for late 19th century scientific reports. It is somewhat like a slightly-edited copying of hasty notes on a physician's note pad. Accordingly, it is difficult to render in smooth English; we have in many cases sacrificed esthetics of style for accuracy." Nevertheless, Passouant, who wrote about Gélineau for the narcolepsy centennial, mentioned that "Throughout his life, Gélineau wrote in a clear, alert, and easy-to-read style."[3] It is evident that Gélineau astutely identified and accurately named narcolepsy; he wrote an impressive set of descriptions on narcoleptic sleep attacks and their contexts, and he provided a detailed and carefully reasoned differential diagnosis and list of treatments. Westphal also correctly described the new clinical entities of cataplexy and narcolepsy. Therefore, both authors, in our opinion, deserve equal recognition for formally identifying narcolepsy and cataplexy.

(At this point the reader may wish to consider going directly to the translations of the original texts found in the final section, before returning to the commentary that immediately follows.)

GÉLINEAU'S DESCRIPTION OF NARCOLEPSY

Dr. Jean Baptiste Edouard Gélineau (1828-1906) at the outset of his report[1] attributed the initial description of narcolepsy to a Dr. Caffe who had published a case 18 years earlier, in 1862. However, a reading of Gélineau's quotes from Caffe's report would instead suggest the diagnosis of obstructive sleep apnea (OSA) as being more likely than narcolepsy. The case involved a 47-year-old man with "an irresistible and incessant propensity to sleep" that had forced him to resign from his job. He was not

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Address correspondence to: Carlos H. Schenck, M.D., Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, 701 Park Avenue South, Minneapolis, MN 55415; Tel: (612) 873-6288; Fax: (612) 904-4207; E-mail: schen010@umn.edu

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reported to have cataplexy, sleep paralysis, or hypnagogic/hypnopompic hallucinations. However, he was reported to have "attitude detached; stupor; mental sluggishness; persistent stoutness; effect on overall health," and his face was "puffy." These descriptions are more indicative of OSA than of narcolepsy. Dr. Caffe was apparently describing an overweight or obese patient when he used the word "stoutness", particularly in the context of "persistent stoutness." (One of the coauthors—IA—reinforced this conclusion in regards to the French word "fort" that describes a person being "overweight" distinctly more so than "strong," both in the 19th century and in the contemporary French language). Although various treatments did not help Dr. Caffe's patient, a stay at a spa did improve his condition. Is it possible that he lost weight at the spa, which would have had a beneficial effect on his presumed OSA?

Gélineau presents a 38-year-old man with a 2-year history of very frequent narcoleptic sleep attacks, totaling up to 200 attacks daily. This man could not speak with Dr. Gélineau for even 30 minutes without falling asleep and constantly needed his 13-year-old son at his side to keep awakening him, so that he could attend to his successful business. A wide array of intense emotional states played a prominent role in triggering his sleep attacks. The description of his initial visit with Dr. Gélineau is a dramatic example. In reading the entire report, a question could be raised as to whether this man—besides his "volatile temperament"--had histrionic personality traits that interacted with his narcolepsy.

Gélineau briefly described cataplexy (which he termed falls or "astasia") and sleep paralysis in his patient but did not comment on the presence of sleep-onset dreaming, dream disturbance, or hypnagogic/hypnopompic hallucinations. He mentioned that his patient had "excellent night-time sleep, waking only once," which argues against the presence of either disruptive periodic limb movements of sleep or REM sleep behavior disorder, conditions now known to be commonly associated with narcolepsy. Cataplexy was the initial manifestation of his narcolepsy. Gélineau's patient was a member of the "mutual aid society," and his card bore the diagnosis, "morbis sacer," Latin for "sacred disease" in reference to epilepsy, which during antiquity had been considered a divine disorder.

Gélineau's male patient reported that his infant child "was conceived in a moment when the illness came over him." Among the various explanations to account for this intriguing comment, the most likely would be either a hypnagogic hallucination or a vivid sleep-onset REM dream, which are common events with narcolepsy that may have accounted for an imagined sexual event. Another possibility is that this man indeed had coitus with his wife while awake that was immediately followed by a sleep attack, and in retrospect he incorrectly recalled the coitus to have occurred during the sleep attack. Also, he may have experienced peri-coital cataplexy.

This patient received many unsuccessful treatments, including bromides, strychnine arsenate, curare, picrotoxin, apomorphine, phosphates, amyl nitrate vapors, hydrotherapy, electricity, and cauterization of the nape of his neck. Gélineau was thus led to comment, "as we both acknowledged that these successes were not in keeping with our mutual efforts, we lost contact, leaving to time and to nature the care of healing or improving this painful neurosis."

WESTPHAL'S DESCRIPTION OF NARCOLEPSY-CATAPLEXY

Westphal had 2 cases that he presented at a Berlin Medical and Psychological Society meeting during 1877 that were then published in the Archives of Psychiatry and Nervous Disorders (for which he was an editor).[2] It is of note that he first chose to speak and write about "larvate epileptic attacks" before he described a patient with cataplectic attacks, and the publication of the former topic was twice the length of the latter topic. Westphal emphasized in italics 2 aspects of his patient's clinical history: "He did not lose consciousness during these attacks," and "persistent night-time sleeplessness must be noted." Westphal clearly grasped that the cataplectic attacks involved loss of muscle tone without associated loss of consciousness, and his comment about sleeplessness may have indicated the presence of disrupted nocturnal sleep that is common in narcolepsy.

In being the first investigator to describe narcolepsy with cataplexy, Westphal was also the first to describe the possible existence of familial cataplexy, as the mother of his 36-year-old male patient had also suffered from longstanding, recurrent episodes of cataplexy and/or sleep attacks that were of milder severity than her son's cataplexy, although "she had been troubled by such attacks frequently earlier on". The observation that some of her attacks occurred when sitting quietly, while sewing or eating, is more suggestive of sleep episodes rather than cataplexy. There was no mention, however, of daytime sleepiness or any other features of the "narcolepsy tetrad."

Westphal also described repeated sleep attacks in his patient: "At times…these attacks [viz. cataplexy] do cause the patient to fall asleep. The falling asleep appears, as it were, to be an extension or increase of the attack." The patient would also have sleep attacks in public while "strolling around quietly and aimlessly." These descriptions of sleep attacks and cataplectic attacks indicate that Westphal recognized and described narcolepsy with cataplexy before Gélineau, although he did not name these conditions, as did Gélineau for narcolepsy in 1880 and Henneberg[4] for cataplexy in 1916. Whereas Gélineau described narcoleptic sleep attacks in great detail, Westphal only briefly described sleep attacks in a circumscribed manner as an extension of a cataplectic attack or as a consequence of aimless wandering. It is noteworthy that only in 1902 a third author (Löwenfeld) confirmed Westphal's and Gélineau's suggestion that narcolepsy with cataplexy represents a "disease sui generis."[5]

THE HISTORICAL CONTEXT OF THE WESTPHAL AND GÉLINEAU REPORTS

The forceful unification of Germany by Prussia's Otto van Bismark was completed after first defeating Austria and then the French armies during the short 1870 war against Napoleon the Third. Germany was a strong but barely united country. France had lost the Alsace and the Lorraine regions and was separated from Germany both culturally and linguistically. Psychoanalysis was not formally established, as Sigmund Freud had not yet completed medical school, but there was growing interest in the unconscious and in psychological explanations for physical disorders. The pioneering work of Jean Martin Charcot's "Leçons sur les Maladies du Système Nerveux" had just been published, introducing the notion of hysteria.[6] Neurology and psychiatry were still virtually one discipline.

Figure 1—Portrait of Karl Friedrich Otto Westphal (1833-1890) reproduced with permission from www.mrcophth.com/ophthalmologyhalloffame/westphal.jpg

Figure 2—Portrait and signature of Jean Baptiste Edouard Gélineau,[9] reproduced with permission.

ON THE AUTHORS

Karl Friedrich Otto Westphal, born in 1833 in Berlin, was the son of a well-known and wealthy physician. After a European medical education that included studies in Germany, Switzerland, and France, he joined the smallpox clinic at the Berlin Charité hospital to rise to become full professor of psychiatry in 1874. He trained a number of well-known physicians including Arnold Pick and Carl Wernicke. His achievements were numerous and included the first descriptions of agoraphobia;[7] the first description of periodic paralysis; the report of a relationship between tabes dorsalis and general paralysis of the insane, prefiguring the syphilis connection; work on pseudosclerosis; and the first description of the deep tendon reflex. In 1887, two years after Ludwig Edinger, he described the accessory nucleus of the 3rd nerve which bears his name. His picture is that of a well-groomed, bearded aristocratic man with a bow tie (Figure 1). Dr. Westphal died in 1890 and is not frequently credited for his report on narcolepsy-cataplexy,[2] which was linked to the possible forensic implications of sleep attacks.[8]

Jean Baptiste Edouard Gélineau had quite a different career that took place outside of the medical establishment. Born in 1828 close to Bordeaux in the south of France (Blaye, Gascony), he was educated as a navy physician in Rochefort and practiced medicine on ships, studying tropical disorders on his frequent and long travels to the Indian Ocean. He spent the war as a surgeon-major and was decorated for his services.[3,9] With his large muttonchop beard (Figure 2), it is easy to imagine him with the flamboyant and proud character of people born in the country of Cyrano de Bergerac and of The Three Musketeers. Not only was Dr. Gélineau a prolific writer of medical articles and monographs, he also had a great deal of business acumen. Dr. Gélineau was known for his arsenic-bromide tablets to calm neurosis and epilepsy, was involved in coordinating a medical insurance system for older physicians, and founded a successful society of health spas and mineral waters. In 1878, he moved to Paris, to rapidly establish a successful private practice, a position he left only in 1900 to retire as a wine grower, owner of the castle of Saint-Luce-La-Tour and seller of Bordeaux wines (probably thanks to the success of his tablets). Dr. Gélineau's publications are eclectic and cover literature, the history of his native town, commercial ventures, and medical studies. His medical work includes observations on tropical diseases, postpartum psychosis, neurosis, angina pectoris, phobias, deafness, and epilepsy. He is credited for coining the term "narcolepsy" in the attached translated 1880 report,[1] and for forcefully defending it as a disease entity distinct from epilepsy.

Interestingly, Dr. Gélineau also published a monograph in 1880 on agoraphobia,[10] citing Westphal's work on the topic ("agoraphobie des Allemands"). This indicates knowledge of the work of the German physician prior to his own 1880 article or discovered just after his Gazette des Hôpitaux publication. In 1881, Dr. Gélineau wrote a more detailed account on 14 narcolepsy cases in a monograph "De la narcolepsie,"[11] still not citing Westphal's 1877 narcolepsy report. A careful review of the cases reported in the monograph, however, suggests that most, if not all (except the original 1880 case) are not genuine narcolepsy-cataplexy. Whether or not Dr. Gélineau spoke German and if the 2 physicians met or corresponded is unknown, but certainly possible.

ON THE CLINICAL DESCRIPTIONS

There is no doubt that both Westphal's and Gélineau's cases have genuine narcolepsy-cataplexy. Both physicians report on the presence of sleepiness and of strange episodes of either sleep or atonia triggered by emotions, which we now call cataplexy. In both cases, onset was somewhat late in life, 34-36 years old, and abrupt, following what could be considered a psychological insult. Earlier reports of narcolepsy have been attributed to Willis (1672, in "De anima brutorum"), Schindler (1829), Bright (1836), Graves (1851), Caffé (1862), and Fischer (1878),[12] but they in fact described cases of either isolated severe, overwhelming (narcolepsy-like) sleepiness or atypical/ imprecisely described (cataplexy-like) "fits."[12-14] In contrast, the cases described by Westphal and Gélineau are likely to be HLA-DQB1*0602 positive, hypocretin deficient cases.

A missing aspect in these reports is the lack of description of automatic behavior, abnormal dreaming, and sleep paralysis. Hypnagnogic hallucinations in particular had been described in 1848 by Alfred Maury[15] and sleep paralysis by Binns in 1842[16] and by Mitchell in 1876,[17] but were not reported in either Gélineau's or Westphal's case. Nevertheless, the reports of Gélineau and Westphal are remarkable for their diversity and, in both cases, by the certainty of the 2 authors reporting on a new disease entity (later authors erroneously equated "narcolepsy" with every condition associated with severe daytime sleepiness[18]). The descriptions are tainted by their schooling and influenced by their time. Nonetheless, nothing better would be written for many years thereafter, and it could be argued that the next major discovery in narcolepsy was on the association of narcolepsy with REM sleep onset by Vogel in 1960,[19] almost a century later.

In Wesphal's case, the description of the case is mostly focused on episodes of muscle weakness with persistence of consciousness, and in the discussion the author agonized at length on whether these episodes did or did not represent genuine epilepsy, and wisely summarized that it was impossible to conclude for or against this hypothesis. Westphal pointed out correctly the presence of subtle "positive" motor phenomena during cataplexy consisting of "small sporadic nostril contractions" and "slight twitching movements in the face…as were movements of the jaw." The precise observation has been confirmed by electrophysiological recordings.[20] Emotional triggers are also noted but are not very well described ("mental stimulation of seeing two boys fighting in the street"; "any type of excitation"). Laughter and joking, for example, are not reported as triggers. It is in this context to note that Oppenheim, in his 1902 article on "Lachschlag" (syncope with laughing), while discussing the differential diagnosis of spells associated with laughing, did not mention narcolepsy.[21]

Sleep attacks are noted to occur "especially if not engaged in some physical activity, but is sitting quietly, talking or reading" but also "while standing" and "while walking in the street." Sleep attacks while engaged in physical activity are indeed typical although not specific for narcolepsy. A relationship and an association of the muscle weakness episodes with sleepiness is emphasized by Westphal, and considered as an extension of the muscle weakness episodes ("at times, however, these attacks do cause the patient to fall asleep"). The German author did not completely differentiate the sleep attacks from cataplectic episodes, an ambiguity which may have reflected the simultaneous co-occurence of both symptoms in his patient (as can be observed occasionally in narcoleptics). This ambiguity may have also reflected Westphal's uncertainty about the true nature of the sleep attacks. It is of interest to note in fact that in Oppenheim's "Lehrbuch der Nervenkrankheiten," the most important German textbook of neurology at the beginning of the 19th century, such episodes were considered to represent episodes of "psychic immobility" with muscle weakness, rather than "true" sleep attacks.[22] Insomnia and the absence of any response to potassium bromate were also noted by Westphal in his report.

Interestingly, Westphal noted that the patient's mother also suffered from similar episodes, following a head trauma. In this case, however, it is difficult to make a conclusion as maintenance of postural tone is reported, and the episodes may be more reminiscent of absence seizures. Similarly, in the case of Fisher (1878), [12] i.e. a younger case where cataplexy is not described with certainty, a sister is suggested to have had the same condition, to later outgrow it during adulthood.

Further discussion of Wesphal's cases also attest to the rise of "pre-psychoanalytic" ideas, already evident in Westphal's prior studies on "sexual inversion" and homosexuality.[23] Detailed reference to and discussion of the case of Van Zastrow, a famous criminal pedophile evaluated by the author in prison, is made. Contrary to what was generally believed in this time, the author was surprised not to find the criminal epileptic (epilepsy was frequently considered at the time a sign of "mental degeneration"), but rather excessively sleepy, falling frequently asleep in public (the symptom was severe enough that people were laughing about it). A relationship between his sleepiness and his alleged frequent masturbation, repressed homosexuality, and associated shame is suggested, with the prisoner attributing his sleepiness to the "secret vice of masturbation" to which he had become "addicted." Whether Mr. Van Zastrow had obstructive sleep apnea or Kleine-Levin syndrome is impossible to reconstitute, but narcolepsy is not likely.

Dr. Gélineau's report is complementary to Westphal's. Its style is more descriptive, "story telling." A potential head trauma 2 years prior to onset is reported as a possible contributing factor. Whereas Westphal was more interested in the loss of muscle tone and the sleep attacks (as reflected by the title of his communication), Gélineau was fascinated by sleep attacks during active tasks such as eating and by the existence of refreshing short naps. Cataplexy is confused with sleep attacks, but its triggers are very well described, i.e., playing cards (and having a good hand), smiling at someone poorly dressed in the street, being surprised by a sudden danger, and anticipating the pleasure of a good play in the theater. Most telling is the story of this patient going to the zoo of the Jardin des Plantes and "falling asleep" in front of the monkey's cage when everyone was laughing around him. The patient had up to 200 episodes per day, suggesting a form of "status cataplectitus."

Although Gélineau did not formally distinguish cataplexy from sleep attacks, it is of interest to note that in naming narcolepsy he identified "narcolepsy's twofold analogy with drowsiness and catalepsy." Catalepsy, however, involves prolonged maintenance of body posture, which is a form of motor dyscontrol opposite to cataplexy. Gélineau's use of the word catalepsy may refer to the patient maintaining posture during some sleep attacks, which were not cataplectic attacks. Nevertheless, his use of the term "astasia", viz. falling episodes, in relation to narcolepsy prefigured the naming of cataplexy in 1916 by Henneberg, who clearly differentiated sleep attacks from episodes of muscle paralysis triggered by emotions.

A second article follows the initial report where Gélineau excludes potential differential diagnoses including vertigo, epilepsy, agoraphobia, anxiety, meningitis, and sleeping sickness, and to conclude that narcolepsy is a unique disease entity. As mentioned above, Gélineau also wrote a monograph reporting on 13 additional cases, none of whom is likely to have genuine narcolepsy. Gélineau described how decreased brain tissue oxygenation and metabolism in the pons, the "site of emotional regulation and dreams" could occur in selected predisposed patients or was caused, in 2 patients, by too much sex ("Venus' pleasures"). Decreased oxygenation would be precipitated by emotions, considered as consuming too much oxygen and energy. Gélineau also reports on numerous therapeutic attempts. Therapies aimed at relieving a potential vasomotor abnormality, including picrotoxin and amyl nitrate to induce vasodilation, were tried without success. Further trials with apomorphine had no efficacy. Interestingly, he tried to give strychnine (which is now known to block postsynaptic glycinergic transmission, in particular at the spinal motor neuron where it could antagonize REM sleep-induced atonia), but obtained only a transitory effect. Dr. Gélineau finally suggested caffeine to treat the narcoleptic sleepiness (as originally suggested in 1672 by Willis[24]), despite the fact it was of little benefit in his only genuine case. A more potent treatment than caffeine, i.e., ephedrine sulfate, was suggested by Janota and Daniels about 50 years later.[24]

Gélineau considered in his monograph that the sleep of narcoleptic patients was deep and devoid of dreams, which suggests, as emphasized below, that the 13 other cases were probably not narcoleptic. Importantly however, he introduced the still-valid notion of a duality in narcolepsy, that of sleepiness and falls (also called astasia).

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ENGLISH TRANSLATIONS OF THE ORIGINAL REPORTS ON NARCOLEPY AND CATAPLEXY BY WESTPHAL AND GÉLINEAU

Archives of Psychiatry and Nervous Disorders

Vol. VII

Berlin, 1877

"TWO MEDICAL CASES"

Presented at the Berlin Medical and Psychological Society

By Prof. C. Westphal

I. Larvate epileptic attacks many years before the outbreak of a paralytic mental disorder. (pages 622-631).

II. Peculiar attacks associated with falling asleep. (pages 631-635).

II.

Mr. Ehlert, a bookbinder, was admitted to Charité for the first time on July 18, 1871. He has been admitted a few times since then, and is there now. He is 36, and is reported always to have been healthy. Approximately three months before his first admittance, he became ill, he says, as the result of a fit of anger. He had lost his job because of quarreling. After having a few drinks of schnapps (he is reputedly not a drinker), he went home, where he was scolded by his wife. Soon thereafter, he had a brief "fit" (1—1 ½ minutes), characterized by a loss of speech, or at least an inability to express words clearly. His whole body was trembling (the patient called it "agitation"), so that he had to sit down (he reported that he had an "involuntary compulsion to sit down"). This "agitation" is said to have continued throughout the entire evening. He slept well that night. He says that he felt completely fine the next day, but a similar condition (in which he lost his capacity to speak and experienced trembling) occurred thereafter at the least mental stimulation, e.g. once when he saw two boys fighting in the street and had, in his mind, taken sides with one of them. Headaches and other complaints never occurred in these instanc-

es. Thereafter he was employed in a workshop, which was heated even on hot days. He cites these circumstances as the reason for the increased frequency of the attacks. Approximately 10 weeks before his admittance, the attacks changed so that his teeth chattered, speaking was difficult and, if he had anything in his hands, he would have to lay it aside, because he did not have the strength to continue holding it. During these attacks, he was unable to raise his arms. If the attack came upon him while walking or standing, he had to find some means of support, although a cane was sufficient for the purpose. These attacks varied in duration, depending on whether he had exerted himself beforehand. *He did not lose consciousness during these attacks.* He understood everything when spoken to; he was simply unable to respond coherently or fluently. He always had to close his eyes when doing so.

According to the patient, his mother, who had been struck in the head by a falling brick earlier, also suffers from similar attacks. Specifically, her attacks occur while she is sitting quietly, sewing, eating, or while drinking coffee from her saucer, for example. When asked, he expressly stated that these occurrences in his 61-year-old mother were not caused by any type of senility, and that she had been troubled by such attacks frequently earlier on.

I have had the opportunity to observe the attacks in the patient himself on repeated occasions. He had one of these attacks while I was engaged in conversation with him. While he was still speaking, one could see that a certain change had occurred in his facial coloration, his upper eyelids lowered gradually like those of a person falling asleep (during which the eyes roll upward). Then they opened again once or twice, seemingly with great effort, until they finally shut completely, whereupon the patient stopped speaking after murmuring something incomprehensible. His head sank down to his chest, and his brow seemed forcefully knit. Small sporadic nostril contractions were observable, and the patient's appearance was that of a seated person asleep. After a short time (several minutes), the eyebrows relaxed, the patient raised his right arm a few times as if stretching upward, and rubbed his eyes sleepily, like one awakening from slumber. The scene then repeated itself all over again, during which one could observe that, though apparently asleep, the patient hears if one addresses him, since he nods in response to questions directed to him. Afterwards, he also knows everything that was said during the time.

He experiences many such attacks all day long, especially if he is not engaged in some physical activity, but is sitting quietly, talking or reading. However, even when occupied in a physical task he often undergoes these attacks, e.g. while helping wash the dishes. He then sits down on a bench, continues holding the objects that he had in his hand, nods off, and usually returns to his activity a few minutes later. As he says, he has noticed, as corroborated by others, that the attacks certainly usually start at a specific place in a particular situation. For example, from time to time he has to get papers and other objects from the chief attendant's office. Almost always, while standing, he nods off as described above immediately after picking up these objects; he staggers, with his head on his chest and his trunk bent forward like one intoxicated with sleep, from the office out into the corridor. He then proceeds down the corridor, and after taking a few steps the attack is over. He never drops the objects given to him, but he holds them differently. He does not carry them with outstretched arms, as before, but his arms hang down loose. He does not lose consciousness at all during these attacks. He says that when he enters the office, his spirit becomes uneasy, that he feels a kind of anxiety, and it seems to him as though something had happened to him there before.

The attacks always come on suddenly. When he was a porter, he had such an attack when a man was giving him an order. The man thought that he was drunk, and told a policeman who happened to be there that he wanted him arrested. Meanwhile the attack passed, and the policeman was quite amazed when the patient reasonably explained to him that it was a medical condition. The patient still had time to run after the man, and to ask him for the order again. He further related that once, when he was leaning far forward over the table to get something from the other side, he experienced an attack in that position, and that he stayed in that position until it had passed.

His information about the sensations that he has during these attacks is as follows. His eyes close involuntarily, and he cannot keep them open. If he manages to open them for a moment, he sees a bright light, but cannot make anything out distinctly. At the same time, he loses all strength in his limbs and the ability to speak. He cannot move, and must sit or lean on something. He says that he does not feel tired like someone on the verge of falling asleep. In his mind, it is as though he were thinking of nothing at all, as if his thoughts were wandering completely. He could not provide a more specific description of his mental condition. He says that he does not experience any dizziness. He reports that he hears and understands what is said to him during the attack, but only pays attention to it if it interests him somewhat.

At times, however, these attacks do cause the patient to fall asleep. The falling asleep appears, as it were, to be an extension or increase of the attack. He says that if he can stretch, the attacks do not go to that extreme. During visits, one often finds the patient already asleep, and one can observe him for fairly long periods at a stretch in that condition. The image is exactly that of a person sleeping peacefully in a seated position. By simply calling his name, he can always be awakened, is aware that he had been sleeping, and notes particularly that upon awakening he is immediately lively and alert, not drowsy. He has also experienced this actual falling asleep while walking in the street. Most often, he steps into the gutter or runs into a lamppost or a person, whereby he is suddenly awakened. He has also stayed asleep in the street and a passer-by, tapping him on the shoulder, wakes him saying, "My good man, you're asleep!" Occasionally another attack occurs after he walks about another hundred paces. This falling asleep in the street, says the patient, usually does not happen if he has a specific destination, but occurs more often when he is strolling around quietly and aimlessly.

Aside from what has been described above, the patient also has attacks that he characterizes as more severe. I was witness to one, which he says falls into this category. The patient was brought into the room by an attendant walking behind him. The patient was completely limp, his eyes were closed, and he was staggering like an intoxicated person, and had difficulty in maintaining his balance. Then all support was removed, and the patient stood free, with only a slight swaying motion, but did not fall. During this time, slight twitching movements in the face were observed, as were movements of the jaw. The eyes were half shut, and the whites of the eyes, which appeared to be rolled up and to the right, remained visible. Respiration was rapid, with sighing. At times it seemed as though the patient was searching for a chair or a seat to hold himself up, but he only

made motions with his head that corresponded to such a search, and did not use his eyes. Finally, he was able to reach the edge of a bed, which he then held onto. Toward the end of the attack, he murmured, "Chair," and then said immediately, "Professor, please excuse me while I take a seat," with his eyes still half shut and continued rapid breathing. Although the attack had given the observers the impression that the patient had been unconscious, when asked, he said that he had been fully conscious during the entire attack, and knew exactly which attendant had brought him into the room.

No specific indication of the onset of the attack in this or any form can be determined through observation. The patient himself states quite clearly that any type of excitation, even of the most minimal kind, is very often the trigger for the attacks. He says that they often occur immediately after such excitation.

The patient's intelligence leaves nothing to be desired, and his demeanor is generally calm and reasonable, and no particularly violent outbreaks have ever occurred, as far as we know, although he is easily roused.

Finally, persistent *night-time sleeplessness* must be noted. He says that he spends only a very small portion of the night sleeping, and that the night-time disturbances of other patients are a kind of entertainment for him, rather than making him uncomfortable.

During his first stay at Charité (July 18, 1871 to December 22, 1871), he was treated consistently with potassium bromate, but to no avail.

As is clear from the medical history, the patient attributes the onset of these attacks to a significant emotion. It is also noteworthy that his mother at times falls asleep while performing ordinary chores. However, the patient notes that there is a difference, in that his mother does not lose control of her limbs during the attacks, as he does, but that when she is drinking coffee, for example, the hand bringing the full saucer to her mouth remains in that position, whereas it would be impossible for him to maintain such a position.

One is faced with a predicament in attempting to attribute a name to the illness described above. It would be a simple matter to call these episodes "epileptoid" attacks, as well, and I cannot object to the term, if one wishes to lengthen the list of very varied conditions commonly called by that name. This does not advance our understanding at all, however, and the peculiarity of the attacks, to which I need not add any further detail given the exhaustive description above, persists nonetheless.

However, I would like to draw attention to this case not solely for its interesting pathology, great as it may be, but in the interests of forensics. A number of years ago, I collaborated with Messrs. Liman and Skrzeczka on the task of providing an opinion regarding the mental state of the well-known v. Zastrow *) [*) He had committed pederastic rape of a boy, H., and had even made attempts on the child's life.] In the course of the medical examination, as I was attempting to uncover any prior epileptic events, but turned up absolutely nothing, as had been indicated, a chance comment of v. Zastrow struck me, namely that he had often fallen asleep on social occasions, and that he had frequently been laughed at as a result. Since I no longer have in my possession a copy of the opinion in which my relevant notes on this case are kept, I present the case here as reported in the opinion written and communicated by Liman: **) [**) Casper-Liman, Practical Manual of Forensic Medicine. Vol. 1, p. 497, 5th Edition, 1871.]…"he said that he had not noticed anything unusual about himself, and he could only report that following fairly considerable mental exertion, e.g. after fairly extensive reading aloud, he found himself to be half asleep, subject to the derision of those around him. He said that this condition had come over him rather frequently while walking, so that he had to ask directions to find his way. He said that it must be the result of such a secret vice as the one to which he had become addicted (i.e. masturbation)."

In this instance, I was spontaneously reminded of the medical case reported above, and one cannot deny that if additional observations should uncover a fairly common occurrence of such "sleep attacks," then we are in the presence of a pathological manifestation of the nervous system, which, in the exploration of the mental condition of certain categories of criminals, deserves no less consideration than epileptic or epileptoid attacks. It is evident that for the time being nothing less than a disease of the central nervous system can be concluded, and that the question of responsibility in and of itself is not involved.

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"ON NARCOLEPSY"

By Dr. Gélineau

I.

I am proposing the name narcolepsy (from the Greek "narcosis," drowsiness, and "lambanein," to seize, to take) for a rare neurosis, or at least one that has been little known until now, characterized by a sudden, brief, urgent need to sleep, which recurs at varyingly-spaced, close intervals. This name calls to mind narcolepsy's twofold analogy with drowsiness and catalepsy.

Initially, I believed that the case I had observed (reported below) was the only known instance; however, in Dr. Delasiauve's *Journal de medicine mentale*, nos. 8 and 9, vol. II, 1862, I have just read that Dr. Caffe published an initial case of this sleep neurosis in his *Journal des connaissances medicales pratiques* (August 20, 1862). I am pleased to report this case here, as undeniable proof of its existence.

CASE I. "For more than a year," states Dr. Caffe, "I observed an employee of the Grand Cercle, 16 Boulevard Montmartre, who, because of an irresistible and incessant propensity to sleep, was forced to resign his position. This forty-seven year old man was tall and strong, married, and had always lived soberly. He had no history of illness, and the first external sign was heaviness and half-closure of the eyelids. This drowsiness, which varied in severity depending on circumstances, had affected him for more than four years, coming on while he was standing, sitting, lying down, or while walking. If he woke up, he would fall back to sleep immediately. Even the most pressing hunger did little to divert these effects; his face was somewhat pale and puffy; attitude detached; stupor, mental sluggishness; persistent stoutness; effect on overall health.

Various treatments were unsuccessful, and a stay at the spa at Brides served only to improve his condition, but not result in

complete recovery.

Later, after a terrifying emotional experience and illicit excesses (abuse of coitus, masturbation, and alcoholic beverages), he suffered hallucination and meningitic delirium, for which he was intensively treated by Dr. Semelaigne."

CASE II (my own observation). Mr. G., age thirty-eight, a barrel seller with a nervous, volatile temperament, came to my clinic on February 15, 1879.

He had not experienced convulsions in his youth, nor syphilis at a later age. He has two children, the elder of whom, age thirteen, always accompanies him, and the second of whom is only a few months old. G.'s father was nervous, but was free from illness; his mother died of cancer, and his brother of a stomach ulcer. He drinks moderately. Five years ago, he suffered acute rheumatism in the joints and Herpes tonsurans at the same time.

Three years ago, during a heated argument, he received a violent blow of the fist from the other party, to which he responded by striking his opponent with a drill, after which he was physically apprehended by a policeman and imprisoned; it was a deeply distressing incident.

Finally, a short time later, a log fell on his head, although it did not cause any great pain; and I find no sensitivity at that spot nor any depression worthy of note.

For a long time, this individual experienced no consequential phenomena. Only in the past two years, when laughing out loud or when anticipating a good business deal in his profession, he would feel weakness in his legs, which would buckle under him. Later, when playing cards, if he was dealt a good hand he would freeze, unable to move his arms. His head would nod forward and he would fall asleep. He would wake up a minute later. Soon, the slightest emotion—the sight of his barrels, for example—would be enough to bring on sleep, and since then, this urgent need to sleep has bothered him constantly. When he eats, his meal is interrupted four or five times by the need to rest. His eyelids droop, his hands drop the fork, knife, or glass. He has trouble finishing a sentence, falls asleep. Rubbing his eyes to ward off this sensation while seated is of no avail. His hands fall inert, he is overcome, bends forward, and falls asleep. If he is standing in the street, when this need comes over him, he wavers, stumbles like a drunk, hears people accuse him of drinking and make fun of him. He cannot answer them. Their taunting overwhelms him all the more, and he collapses, instinctively avoiding passing carriages or horses by a final effort. When several people then form a circle around him which always happens in Paris, he hears them or perceives them offering sympathy, and their amiability paralyzes him, affecting him even more and preventing him from getting up.

If he experiences a deep emotion, whether painful or joyous, the need to sleep is even more urgent and sudden. Thus, for example, if he is closing a good business deal, if he sees a friend, if he speaks with a stranger for the first time, or if he receives a good hand while playing cards, he collapses and falls asleep. If he goes to the Jardin des Plantes, near the Monkey House, the place where curiosity-seekers, children's nannies, soldiers, and hecklers usually congregate, he falls asleep seeing this whole laughing crowd around him. A bolting horse, a carriage about to cross his path, or the sight of a person grotesquely dressed who causes him to smile is all he needs to suffer an attack.

At the theater, he falls asleep at the mere thought of the pleasure he is going to experience. He falls asleep again when sitting in his seat, and his son has to shake him and pinch him to pull him out of it. Once the actors come on stage, however, the need disappears; he follows the play with great interest, not collapsing for a single instant, unless a poignant act arouses too great an emotion in him.

Bad weather, particularly the approach of a storm, increases the frequency of these sleep attacks; he has experienced up to two hundred per day.

The only way to pull him out of these attacks is to shake him strongly, or to pinch him. When he becomes violently angry, he sleeps less, but longer and deeper. When he wakes up, he walks straight and firmly, until a new sleep attack comes over him a quarter of an hour later.

I will always remember the way he entered my clinic. He was guided and supported by his son, who held him by the arm. No sooner had he passed through the door of my office and turned his eyes toward me, than, frozen, his gaze glazed over, his eyelids drooped, he staggered, stumbled, and fell asleep, onto a chair; his son spoke to him and shook him hard, after which he began to speak to me.

During his sleep, his pulse, which ranges from 66 to 68 ordinarily, immediately drops to 38 to 60. His pupils, which are highly contracted when awake, are slightly less so when he is asleep. His pupils contract once again when they are raised and brought near the light. The attacks last one to five minutes.

In addition, nothing in him gives evidence of a state of illness; he is calm, at ease. He eats well and his night-time sleep is excellent, waking only once. He has coffee once a day and is not constipated. His sexual desires have diminished considerably. I should repeat that he has just had a child; he says, however, that the child was conceived in a moment when the illness came over him.

A member of the mutual aid society, his card bears the diagnosis *morbus sacer*. He has been treated at his home and at Salpêtrière. When he was going there, he fell asleep several times at the door of the hospital, then at the door of the room, and finally, for the third time, confronting the doctor whom he was there to consult. They recommended potassium bromide, subcutaneous injections, hydrotherapy, electricity, and finally, they cauterized the nape of his neck, but, he says, none of this brought any improvement.

When asked to explain his disease and its onset as best he could, he said that he never feels any pain when he is overcome. He merely feels a deep heaviness, an intracranial emptiness, a sort of whirlwind spinning around inside his head, and a heavy weight on his forehead and in back of his eyes. His thoughts dim and fade; his eyelids close half way. He continues to hear, and he is conscious. Finally, his eyelids close completely, and he sleeps. All of this occurs very quickly, so that the normal physiological sleep phase which occurs in progressive periods of five, ten, and twenty minutes, lasts at most a few seconds for him.

If one has him close his eyes and asks him to speak and walk, as is done in cases of ataxia, his voice fades out, he falls asleep and collapses, but without disordered movements. If he enters a dark place, such as a cellar, he also has increased tendency to fall asleep. When he descends a steep street, he has difficulty remaining standing; also, when he pushes a wheelbarrow, with a small cart hitched to him from behind, he pulls it along easily behind him by means of a harness, and he does not fall asleep, probably because his will is more intense at that particular moment.

During his morbid sleep, he never releases any urine or fecal matter. At my office, he has on occasion spoken for a half hour without falling asleep.

His memory is not affected in the least. He is aware of the status of his business, and he is actively involved in taking care of it, but he is always accompanied, because he cannot go out alone without risk of danger. When he works alone, he has fewer attacks than when he is with someone; this is because he enjoys talking, becomes animated and falls asleep.

The intermittent appearance of this illness, its frequency, its lack of resulting injury would place it in the category of a neurosis. The question arises, however, as to whether it should be included under a type already known, or whether it deserves a place apart in this group that is so large and already so numerous? That is what we shall examine.

First, is this a form of *epilepsy*? I do not think so…He does not experience either tonic convulsions or clonic movements. He feels when he is pinched. He is always conscious of what is happening around him. When one shakes him, one can rouse him from his sleep. He does not stammer when he wakes up, and he recovers his intellectual faculties, his senses, and his motility immediately. Moreover, far from overwhelming him, this rest seems to be necessary for him, and appears to give him strength. Finally, his recall is perfect. In addition, potassium bromide, that touchstone of epileptic seizures and epilepsy, has had no positive effect on him. Besides, what epileptic, after one or two hundred spells of dizziness and falls per day, would keep his intelligence and memory intact after two years?

Dr. Semelaigne, however, sought to link his subject's illness to epilepsy. "One symptom," he said, "predominated and masked the others, but their occurrence together is nonetheless significant. Everyone knows that attacks of dizziness can occur for a long time without revealing their true character. Everyone is also aware that such attacks result in drowsiness, mental sluggishness, a weakening of the memory, problems with the brain, stupidity, and moral perversion. – In the absence of attacks of dizziness, or when the attacks cease, intelligence and the moral sense return. That was the situation with M…. --- Certainly, the drowsiness first attracted attention as the predominant symptom, but several times a day he experienced "blackouts", dizziness or pseudo-attacks as they are called. It is generally drowsiness and not stupor which precedes this sort of attack." With regard to the slight cerebral congestion, Dr. Semelaigne says that this is one of the most frequent complications of epilepsy. Finally, the acute meningitic delirium which struck the patient also falls within the "domain of mal comitial".

We reproduce our colleague's opinions in full, but they are not at all convincing. Here is a man who has had continual falls and dizziness for four years, and has never had a full, typical epileptic seizure. He falls, and his drowsiness ceases after the attack; he falls and the *ictus* never causes him to fall stiff, with resultant injuries of the type so common among epileptics. He falls and immediately recovers his wits, his intelligence. Ah! This is because his fall is similar to that of a drunken person or a sleeping child. It is a collapse caused and *preceded* by drowsiness, whereas in the epileptic seizure, sleep *comes after* the fall. Let us add, finally, that Dr. Semelaigne does not mention the one thing that, for us, constitutes the *criterion* of epilepsy from its mildest to its most severe manifestations: the loss of memory, of recollection of what just happened. A subject who remembers and is conscious of what is happening and what happened after an attack of dizziness, an absence, a fall, is not an epileptic.

II.

Can one confuse the affliction from which G. suffers with kenophobia (from the Greek "kenon," the void; "phobeo," I fear), or the fear of open spaces, to use Mr. Legrand du Saulle's term, or agoraphobia, as the Germans put it? Not anymore. Clearly, when crossing a fairly wide street, a square, he is frightened, upset, hesitant. But it is less the view of the open space which affects and frightens him than the fear of being surprised by a carriage, a wagon, or horses. When emotion stops him in his tracks is the moment that sleep overcomes him, and freezes him in place. Also, a person suffering from kenophobia does not fall asleep. He moans, looks about, shouts, makes gestures, calls, and backs away if no one comes to offer him a hand. G., when moved or upset, does not reason or look around; he goes to sleep and falls.

One cannot confuse this affliction with vertigo accompanied by syncope, falling, and the loss of consciousness. First, in the beginning, the objects that surround G. do not appear to him to be moving. Although his eyelids are half closed, he sees them as immobile. When he rocks, the reason is that, since he has stopped seeing, he wants to stretch out to sleep. He does not try to hold himself up by the objects surrounding him, as a dizzy person does. He yields without a struggle. For G., sleep is the rule. For a man experiencing a dizzy spell, syncope is the exception. Finally, what a difference between G., sleeping peacefully, blissfully, his face colored, in comparison to the appearance of a livid, frozen man covered with cold sweat and as pale as death, plunged into syncope!

Dr. Casse had attributed this condition of illness to a *serous and passive congestion of the meninges and of the brain*. I assert that this anatomical injury is difficult to reconcile with an intermittent symptom such as sleep that appears and disappears several times a day. Cerebral circulation does not lend itself at all to such sudden alternating flux and reflux, which are necessary to explain the main sign of the illness, the intermittence of sleep, whereas the idea of a spasm makes it quite easy to explain.

Can this affliction be linked to various degrees of morbid sleep which have been somewhat forgotten in our day, but which the ancients were careful to distinguish in theirs: cataphora, sopor, stupor, coma, carus, and lethargy? The form, duration, and idiotic insensitivity which characterize these last three types make the comparison impossible from the outset.

Perhaps one could associate it with cataphora, and, if one were to consider only the meaning of the Greek words ("kata," down; "pherein," to carry), one would actually believe in a certain analogy between these two types of sleep. But in cataphora, sleep, which is easily interrupted in the case of G., starts again as soon as one stops speaking to the patient. The sleep is continuous, of a certain duration, and does not include long intervals in which the subject thinks, acts, and works. Finally, cataphora would not be prolonged for years without ending in death or recovery.

As for *sopor* or drowsiness, an intermediate stage between cataphora and coma, the difference is even more marked. The patient, lying on his back, sleeps even more soundly, and cannot be awakened without great effort, and exhibits clearly defined cerebral symptoms, cephalalgia, dizziness, loss of memory, akinesia. However, our patient has no symptoms indicating a cerebral illness…and ultimately has more waking hours than sleeping.

Confusion with what the English call "sleeping dropsy," which Dr. Nicolas calls "somnosis" and Dr. Dangaix calls "hypnosis," is

impossible. First, this illness is only found in negroes in equatorial countries, and no cases of it have been observed in our temperate latitudes. However, since that is not in and of itself reason enough to exclude any analogy, let us recall the insistence with which Dr. Nicolas recently (reports from the Academy of Sciences, issue of May 10, 1880) outlined the progressive and fatal evolution of sleeping sickness from initial drowsiness to death. Sleeping sickness, he says, begins with drowsiness that is completely indistinguishable from normal drowsiness, and its progression is marked by increments that start with deep sleep, followed by longer and longer periods of sleep, until finally the patient does not wake up again. I might add that, being familiar with the work of my friend, Dr. Nicolas, I invited him to examine this patient with me, and that, as a qualified judge of such matters, he immediately rejected any idea of an analogy between these two afflictions.

(Paragraph deleted, placed in the Appendix[a]).

I had thought of associating the illness with the particular form of nervous condition that was so well described by Morel under the name *emotive delirium*. I found this idea attractive for a short while. In fact, there is no disputing that G. does have a very obvious degree of emotionality, and that this emotionality provokes the attacks. But what a difference there is in the depth of their effects and the final outcome! Although it is true that the two illnesses appear in response to the slightest of causes, and even the most bizarre, it all adds up to just one effect for G., namely sleep, whereas the scene is quite complex and varied in emotive delirium, accompanied by agitation, anxiety, palpitations, and clouding of the senses, rapid pulse, exaggeration of ideas, and finally automatism. There is nothing of this sort with G. *He falls asleep without suffering*; a subject suffering from emotive delirium shakes at the slightest occasion, complains, and *suffers without falling asleep*.

We also do not believe that it can be considered incipient *ataxia* for short periods, because there are no flashes or jerky movements.

The reduction of strength, motility, and the will in G. also made me think of the *neurasthenic* form of *spinal irritation*. However, on the one hand, the back pain, the sense of fatigue, compression, or burning in the spinal column, is absent, and, on the other hand, he shows no sign whatsoever of the melancholia or hypochondria that accompany irritable weakness and make this type of patient extremely unhappy and quite given to complaining. This man is a happy, talkative individual, who lacks neither strength nor energy, and never worries, and shows fatigue in his limbs only on occasion. All the facts are in contrast to cases of neurasthenia.

Therefore, I feel justified in designating *narcolepsy* as a specific neurosis, little known until now, and it is good to draw the attention of observers to it.

Let us remember what happened with agoraphobia, which was long confused with vertigo. Once identified, many practitioners in every country throughout the world began to recognize it immediately. Perhaps the same will be true for narcolepsy, which we consider a specific neurosis, characterized by the twofold criterion of drowsiness and falling or astasia.

A few words of explanation regarding the cause, the role, and the need for physiological sleep will help us, I believe, explain the pathogenesis of this neurosis.

Whether cerebral function is dependent upon a substantial material, liquid or solid, supplied by the gray matter, or by a molecular movement of the fibers and ganglia of the brain, as soon as there is work or exercise, the result is wear, exhaustion, and loss, and consequent absolute need for repair.

If cerebral activity is a direct function of the amount of oxygen absorbed by the brain and other tissues, and if that amount is greater when awake because the blood reaches the brain more quickly, then the more active this oxidation, the greater the wear on the cerebral substance, the elimination of materials, particularly phosphates, and an exhausting fatigue. This results in a need for a period of rest and calm, during which the brain expends less, and receives the elements needed to make repairs, to store them, as well as a need for frequent pauses during which oxidation and reabsorption are less active. What could better ensure and procure this period of rest, this necessary pause, this indispensable repair, than sleep?

Having said this, let us try to explain the intimate cause of narcolepsy in the case of G. I do not believe that the fall of a piece of wood on his head, by causing a congestive state that is continually renewed on the surface of the hemispheres, has caused it. This intermittent and so frequent state of congestion of the brain is not easier to explain than an intermittent commotion.

As I see it, G. is subject to the laws of two different types of sleep. Thus, like all of us, after the day's fatigue, he feels a need for rest during the first hours of the night, and from nervous habit, and his sleep is then the natural, normal physiological sleep. But during the day, things are quite different. Several times each hour, he is forced to obey a morbid, urgent, and sudden need for narcosis.

Probably, through a special idiosyncrasy, the amount of oxygen accumulated in the nerve centers is in too short supply there, or the oxygen is exhausted too rapidly under the influence of emotions that are too frequent or too strong. The cerebral wear for G. is perhaps greater than in other people, the arterial capillaries too few or too narrow. Perhaps he experiences too rapid an elimination of the regressive products, particularly phosphates.

Whatever the case may be, in this state of relative poverty, the slightest expenditure of strength, the electric influence, a storm, an emotion, constantly subtract from and exhaust his energy, his vitality. On each occasion, he is neuroparalyzed or, to put it better, neurolyzed, which results in the frequent need to sleep, sleep being the greatest and most powerful restorer of the weakened organism. This opinion is shared by Dr. Delasiauve who, early in his journal, wrote that, "exposed to rapid losses, the nervous system needs to be reimmersed in immobility and rest."

Given this explanation, borrowed from physiology, if we try to determine the exact anatomical location of this neurosis, I believe that, supported by the authority of Dr. Vulpian, we can place it in the annular protuberance. "The annular protuberance," says Dr. Vulpian (1), "must be considered the center of association for emotional movements: whether the excitement comes from the brain or from outside (and he lists several examples), in great emotional expressions, in dreams and in crying, the protuberance plays the most significant role. Under the influence of joy, happiness, sadness, distress (which is certainly the case here), or fright, a certain number or most of the active elements of the protuberance are affected and, through an associated excitation of the motor fibers, a harmony of movement breaks out which varies depending on the intensity of their affliction." What a strong argument in support of our cause! In our subject, there is incontestable over-activity of the protuberance, which enters into a spasm, exaggerating its function on the least provocation, and reacting on the other nerve centers. The result is, on the one hand, a momen-

tary paralysis of the cerebrospinal axis, a suspension of nervosity, resulting in astasia and falling and, on the other hand, momentary anemia which, in turn, causes sleep. These two results that constitute narcolepsy are immediate because, in G., there is some sort of shattering of the annular protuberance and cerebral stun.

To complete this observation, I must say something about the treatment that I employed.

Initially, given the appearances and the diagnosis presented to me, and acknowledging the effect of the emotions on the reappearance of these sleep attacks, believing that the spasm of the vessels could cause cerebral anemia common to sleep and to epilepsy, I used picrotoxin, which has the characteristic of preventing the vessels' spasmodic contraction by keeping them in a relaxed state, and I added various bromides to reduce irritability and the reflex action of the cerebrospinal axis.

I must admit that I did not achieve any positive results by using this medication. On the contrary, my patient lost strength and had an increased tendency to sleep. I abandoned that approach.

Along the same lines, I advised that he inhale amyl nitrite vapors poured onto a handkerchief as soon as the narcoleptic attack began. In fact, the amyl nitrite made the intracerebral circulation and the visceral circulation more active, and it expanded the vessels. We did not overlook the fact that G.'s pulse fell even further, clearly causing an intracranial void, a whirlwind blowing in his head. The use of this medication thus seemed to be indicated. It appeared to be successful for several days, and the subject blushed when inhaling it. But its use did not prevent the attacks, and we then abandoned it, convinced that cerebral anemia played no role in the neurosis at hand.

Then I used subcutaneous injections of apomorphine, which are extolled in Germany in cases of convulsive neuroses, initially in very moderate doses, then up to levels causing nausea, without obtaining any positive results.

Then, I decided to turn the symptoms into a medicine, i.e. directly fighting the drowsiness. I placed a seton directly on the nape of the neck, which I maintained, and I prescribed grains of caffeine and caffeine valerianate. He improved slightly, but, being eager for more pronounced results, I was perhaps mistaken in abandoning this medication to consider another idea.

I used strychnine arsenate in progressive doses, and I did not stop until the patient felt tremors in his limbs. I hoped that using this power agent, I would increase the general tone of the economy, fighting the collapses and constant neurolytic exhaustion. At the same time, I had him take phosphates, very tonic food, and warm showers that were revulsant on the spinal column. I even used hypodermic injections of curare. In sum, I did my best to treat the patient aggressively. Nevertheless, I must admit in all humility that by using these methods I barely managed to obtain a few hours of rest and constant work without sleep in the morning and evening. As we both acknowledged that these successes were not in keeping with our mutual efforts, we lost contact, leaving to time and to nature the care of healing or improving this painful neurosis.

Is the ineffectiveness of these remedies one of the characteristics of this neurosis? (remainder of paragraph deleted, and placed in the Appendix[b]).

It is clear from what we have said above that the treatment of narcolepsy is entirely open to study. This is one more point of similarity that it shares with the other neuroses, which are so often the stumbling block of our therapeutic means. Whatever the case may be, I am glad to have been able to present this initial study to my colleagues. I am sure that it will result in further studies, for I have already received from a doctor in Lyon all the elements of a third observation of narcolepsy, which I propose to publish somewhat later.

APPENDIX

a) Moreover, neither Dr. Casse nor Dr. Semelaigne concluded that there was an analogy between the illness of their subject, M., and the sleeping sickness among negro populations. Dr. Semelaigne added, amusingly, "For the time being at least, let us leave sleeping sickness to the negroes. Whites have quite enough other illnesses without that one."

b) In treating M., Dr. Casse used tea, coffee, quinine sulfate, ferruginous agents, purgatives, and Seine baths with running water. A vesicant was applied to the nape of the neck, all to no avail. When the symptoms were even worsened by digestive function problems, heaviness of the head, and more difficult locomotion, our colleague advised the waters at Brides. The highly ozonized mountain air, the action of the waters internally and externally, stimulated his appetite and strength, and the skin regained a livelier color. Finally, after a season followed by a trip to Switzerland, M. returned to Paris much improved, but not entirely cured.

c) The translator of Gélineau's report made an additional comment that "The French words 'voiture' and 'camion' translate as 'carriage' or 'automobile' and 'wagon' or 'truck', respectively, depending on the historical period. Since this article was written at a time when primitive diesel vehicles may well have been coursing the streets of Paris, i.e., at a time when 'voiture' could refer either to horse-drawn or horseless carriages, we have used 'carriage' and 'wagon' to translate these two words, but the reader should be aware that the author might well have had in mind 'automobile' and 'truck.'"

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FROM THE ARCHIVES

Idiopathic narcolepsy: a disease *sui generis*; with remarks on the mechanisms of sleep. By WJ Adie, MD, FRCP. Physician to Out-patients, the National Hospital, Queen Square, (London). (From a Thesis submitted for the Degree of MD in the University of Edinburgh, on February 26, 1926). *Brain* 1926: 49; 257–306 *and* The narcolepsies. By S.A. Kinnier Wilson. *Brain* 1928: 51; 63–109.

'The disease I am about to describe is characterized by . . . attacks of irresistible sleep without apparent cause, and curious attacks on emotion in which the muscles relax suddenly so that the victim sinks to the ground fully conscious but unable to move'. Concerned that the original descriptions of Westphal (1877) and Gélineau (1880) have become confused with all sorts of other sleep disorders, and quoting Sir Clifford Allbutt on 'sticking a label' on a new disease entity, Dr Adie (Fig. 1) describes five personal cases and summarizes those reported by Gélineau (1880), Löwenfeld (1902), Redlich (1915), Hennenberg (1916), Jolly (1916), Mendel (1916), Singer (1917), Stöcker (1918), Stiefler (1918), Noack (1918), Somer (1921, two examples) and Goldflam (1924, with two others having uncontrollable sleep but without falling attacks).

Mis-diagnosed with petit mal epilepsy at Queen Square, Olive P, aged 14, complains that 'when I laugh I cannot stand' . . . and she 'sleeps at inconvenient times'; by chance, Dr Adie comes across Gélineau's description when looking up his preferred diagnosis of 'Lachschlag'. Freda W, aged 19, under the care of Dr James Taylor, has fallen from her bicycle and slept in the middle of the road' . . . and with laughter . . . 'the limbs crumple[d] up'. On learning that a boy cycling from London to visit her home has been killed, Mrs C, aged 42, fell and lay powerless on a couch; now any unpleasant emotion provokes these episodes and she has a morbid fear of being thought dead if found in an attack; 'London consultants' have diagnosed hysteria and epilepsy without convulsions. Captain X, aged 35, sleeps through one of Dr Adie's lectures, as host at his Corps' Mess dinner, and whilst driving his car; unaffected either by danger or excitement during the Great War, with laughter he goes 'floppy all over'. Leslie W, aged 16, sleeps whilst talking to the Matron of the National Hospital.

What can be said of this mysterious disorder usually affecting otherwise healthy males in their teens or as young adults who cannot resist the urge to nod off for a few seconds or longer, sometimes in circumstances conducive to sleep but typically also at inappropriate times? Two soldiers describe sleeping whilst on listening-post duty—an offence carrying the death-penalty—and others have been saved by medical intervention prior to courts-martial. Falling attacks precipitated by emotion, usually laughter but also anger and annoyance and often associated with grimacing, protrusion of the tongue and stammering, usually start later. These also may end in sleep. As the head lolls, the patient may jerk upright a few times so that the unwary diagnose epilepsy or chorea. Gélineau's patient fell down at the prospect of a good business deal or finding that he had been dealt a winning hand at cards; Redlich's patient weakened and became flaccid during coitus.

The terms 'hypnolepsy' and 'Einschlafsucht' have been proposed but Dr Adie favours 'narcolepsy' for the sleep attacks. Rejecting all foreign suggestions ('chute ou astasie' [Gélineau], 'kataleptische Starre' [Löwenfeld], 'kataleptische Hemmung' [Henneberg], 'plötzlicher Tonusverlust' or 'affektiver Tonusverlust' [Redlich] and 'Tonusblockade' [Stern]) and noting that translating Lowenfeld's term as catalepsy will not work (already having meaning in Anglophone medicine), Dr Adie suggests the term cataplexy for the falling attacks. In short, 'two kinds of sudden attack occur, sleep . . . with cause and cataplexy on emotion . . . [such that] anyone possessing this knowledge would be able to recognize a typical case', although transitional states do exist. It follows that sleep attacks and cataplexy have the same mechanism. Apart from non-convulsive epilepsy, the differential diagnosis might include pyknolepsy (originally described, unhelpfully, as 'short narcoleptic attacks' by Friedmann, 1906), hysteria, 'Lachschlag' (Oppenheim, 1902: in which the patient is deeply unconscious during the emotion-induced episode and without sleep attacks), Pickwickian 'Fat Boy' disorder, encephalitis lethargica and cerebral tumour; but the absence of co-existent symptoms and the benign natural history of narcolepsy usually serve to distinguish these conditions.

Beyond his clinical interest, Dr Adie wants to understand the nature of sleep. He has been reading Ivan Pavlov, but not yet 'Conditioned reflexes: an investigation of the physiological activity of the cerebral cortex' based on lectures given in 1924 to the Military Medical Academy in Petrograd (1926), and translated into English by GV Anrep (1927). Here is an exposition of reflexes that are innate to any nervous system, and those that are learned by association between a neutral stimulus and a primitive response; conditioned reflexes fade if not actively habituated and through internal inhibition when the conditioning stimulus is no longer followed by the expected 'reward'. But Pavlov's research has been thwarted by his dogs falling

Fig. 1 William John Adie (1886–1935)

asleep during training or on repetition of the conditioned reflex, although they became alert in response to something new—the orientation reflex. Pavlov considers sleep and internal inhibition as one and the same. Simply stated, the cortex finds any repetitive stimulus dull and so switches off until something novel crops up. The Pavlovian dog, subjected to a familiar routine, shows increasingly long intervals between the sight of food and reflex salivation, and eventually takes a nap in response to stimulation. Internal inhibition has spread throughout the cerebral hemispheres. But a novel stimulus wakes the cortex and restores responsiveness to conditioned reflexes—old and new alike. Sleep and inhibition are one; narcolepsy and cataplexy are part of the same process. At first, attacks are favoured by the lack of extraneous stimuli (... 'sitting before the fire, after a heavy meal, in a warm room, during the rest hour') and then by monotonous challenges. But the patient with narcolepsy who cannot resist sleep in the context of repetitive but familiar stimulation soon wakens when the eyelids are raised, the skin is pinched, or an unexpected sound is heard.

Now, Dr Adie advances the idea that narcolepsy–cataplexy is an 'endocrine–nervous' disorder. The pituitary is reciprocally connected to the 'tween–brain' and, together, these structures regulate temperature, fat, water and sugar metabolism, and sexual activity. 'In symptomatic narcolepsy, I surmise, the primary disturbance is in the [pituitary] gland; in idiopathic and post-encephalitic narcolepsy the nucleus hypophyseus and adjoining structures are at fault'. But why are only certain individuals affected? Much depends on their constitutional state of alertness. Lively Pavlovian dogs sleep more readily than easy-going animals because the former—once restrained in a cage—experience fewer and more monotonous stimuli by comparison with their natural habitat. Narcolepsy is an expression of fatigue in individuals with a constitution that favours the spread of normal inhibitions throughout pathways of the endocrine–nervous system. Sleep is controlled by sub-cortical centres that ultimately inhibit the cortex. Trömner has it that this lies in the optic thalamus, turning off the ascending sensory lights that illuminate the drowsy cortex, and simultaneously inhibit muscle tone down below. Hence, narcolepsy is thalamic. Whilst accepting that thalamic activity may set in motion an inhibitory mechanism, Dr Adie does not see this as related to sensory volleys. Rather, he prefers the evidence—from examples of von Economo's encephalitis lethargica—that the crucial region is restricted to 'the floor of the tween brain in and around the vegetative centres that form a part of the pituitary tween-brain system'. Reflecting that the pendulum of opinion on how the nervous system works has swung from a doctrine of medieval humours to the neural concept of brain function and back to discoveries of the ductless glands... 'it is almost certain that hormones play a part... my study of narcolepsy has taught me that... nervous and endocrine organs work together as equivalent parts of an intimate system'.

But not everyone is impressed. Within a year Samuel Kinnier Wilson (Fig. 2), Adie's senior colleague at Queen Square, publishes his account of the narcolepsies: 'recent communications dealing with the subject are reduced in value by ignorance or neglect of previous work... hypotheses are evolved which suffer... fatally... from failure to take all the germane data into consideration... to describe... narcolepsy as a "morbus sui generis" is a nosological error, yet in the communication of... Adie... this regrettably occurs "passim"'. Narcolepsy is no more a single disorder than epilepsy: both are syndromes with idiopathic and secondary causes. The 'vicissitudes that [Gélineau's] conception has undergone' make it proper only to refer to "the narcolepsies"'; and Dr Adie is wrong in allowing the diagnosis in individuals who do not also have falling attacks... 'experience should surely have convinced the neurologist that no good purpose is served by a hard-and-fast schematization of a clinical syndrome—which is all that narcolepsy can possibly be—to fit a conception based solely on an original description'. Kinnier Wilson describes four cases that although having the combination of sleep, or sometimes reveries, and falling attacks '... have nothing else than a purely symptomatic and non-committal significance, and under no circumstances can be used for a "disease"'. POR (aged 24, railway porter), EC (aged 26,

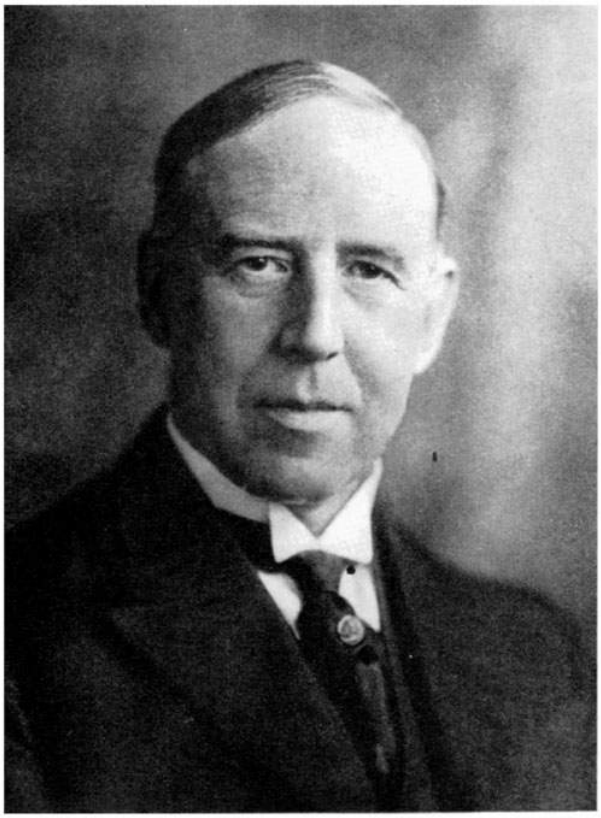

Fig. 2 Samuel Alexander Kinnier Wilson (1878–1937)

bricklayer), TT (aged 41, boilerman), ABCD (aged 18, schoolboy) and HGB (aged 32, business-man) describe their sleep attacks and falling with emotion (Fig. 3). In a famous passage Dr Kinnier Wilson relates how . . . 'I was able to observe an (emotional attack) from beginning to end and to examine the patient's neurological condition during it. Dr Macdonald Critchley, the present Registrar at the National Hospital, was with me at the time . . . testing the knee-jerks I found them completely abolished and . . . Dr Critchley . . . obtained a slight but definite left extensor [plantar] response . . . which I corroborated . . . just as we were finishing . . . the patient said "I'm all right, sir" . . . testing his knee jerks again, I found them active'. Arguing that all examples are symptomatic, Kinnier Wilson considers narcolepsy to consist of recurring diurnal episodes of sleep, with or without toneless attacks, or sleeps of longer duration that straddle day and night and may be continuous (as in encephalitis lethargica and trypanosomiasis). He accepts that, very occasionally, larval or incomplete varieties either of sleep or cataplexy may occur without the other. Transitional variants are seen in which emotion triggers sleep: cataplexy may occur if sleep is prevented; sleep may follow cataplexy; and cataplexy may occur without an emotional trigger. Agreeing for once with Dr Adie, Kinnier Wilson concludes that a common factor

Fig. 3 Facies: Cases 1 (POR; **A**), 2 (EC; **B**) and 3 (TT; **C**) from Kinnier Wilson

must underlie all the clinical phenomena—a not as-yet fully understood inhibitory mechanism responsible both for the sleeping and falling attacks, and both for the narcolepsies and conditions with which they may be confused or indeed

overlap. He lists periodic familial paralysis, catalepsy, nocturnal or sleep paralysis (described by Silas Weir Mitchell), epilepsy (especially reflex forms) and Lachschlag—described on hearsay by Oppenheim and which Kinnier Wilson considers to be cataplexy without narcolepsy, thus scoring another point over Dr Adie who judges these to be different conditions.

In defence of his emerging ideas, Dr Kinnier Wilson identifies the several causes of narcolepsy—traumatic, psychopathological, endocrine, epileptic, toxi-infective, circulatory, tumour-related and those in which no 'Grundkrankheit' is found. People do not die of narcolepsy unless there is an underlying cause. In those situations, pathology in the floor of the third ventricle is usually found; and experimental work (for example by Harvey Cushing on hibernating wood-chucks) also directs attention to a sleep centre in that region although it is obvious that sleep involves alteration in many other distributed physiological functions that cannot be 'localised to grey matter around the back end of one ventricle'. Jabbing again at Dr Adie, Kinnier Wilson politely dismisses Pavlov's work on conditioned reflexes as irrelevant to any understanding of narcolepsy and cataplexy. So what is going on?

The narcolepsies occur only in the daytime, unrelated to nocturnal sleep, and the falling aspect is close to the normal experience of being made 'helpless with laughter'. The tonelessness is reminiscent of the Sherringtonian 'knock-out' blow in which '... the lower jaw conveys concussion to the otocyst [and] reduces in a moment a vigorous athlete to an unstrung bulk of flesh whose weight alone determines its attitude'. Dr Kinnier Wilson therefore considers that labyrinthine stimulation may explain the generalized inhibition of muscle-tone in narcolepsy and cataplexy. More generally, any group of nerve-cells can be activated or inhibited by several categories of ascending or descending impulse, any combination of which may result in the same outcome such that one narcoleptic state may closely resemble another although differing markedly in its exciting elements: 'only in some such way as this can we find a possible interpretation for the diverse narcoleptic symptoms of the psychoneurotic, the post-encephalitic, or the sufferer from cerebral tumour, as well as of the patient whose case is classed as spontaneous or idiopathic'.

Neither Dr Adie nor Kinnier Wilson mention hyposmia in their account of the narcolepsy–cataplexy disorder nor could they predict that a peptide product of the hypothalamus—hypocretin-1 or orexin-A—would emerge as a strong candidate for direct involvement in the pathogenesis. But their struggles with definition and classification, and ideas on mechanism and anatomy, clearly did anticipate contemporary understanding of this curious disorder to which Paul Baier and colleagues now add new details (page 2734).

Alastair Compston
Cambridge

Sleep Research Society®

June 7, 2010

Dear SRS Member,

The initial list of classic articles was assembled by querying the ISI Web of Science database for the most cited articles in the sleep literature from the 1960's and earlier. To this, the members of the 50th Anniversary Task Force added classic articles that had not been picked up by the initial list (e.g., because they were not directly on sleep, such as the paper by Moruzzi and Magoun). The entire Task Force then voted on the articles that they thought were the most important, and the top 25 were selected for inclusion on the CD-ROM.

We could not get permission to reprint a few articles (or permission was too costly), so we added a few more to bring the total number on the CD-ROM to 24.

The entire list of articles that was considered is below, in chronological order.

Sincerely,

Clifford B. Saper, MD, PhD
President
Sleep Research Society

50th Anniversary Task Force Members

Sonia Ancoli-Israel, PhD, *Chair*
Donald Bliwise, PhD
Melissa Burnham, PhD
Mary A. Carskadon, PhD
Sean Drummond, PhD
Gina Poe, PhD
Thomas Roth, PhD, *Classic Papers Project Leader*
Martica Hall, PhD
Robert McCarley, MD
Howard Roffwarg, MD, FAASM
Kenneth Wright, PhD

Extended List of Classic Sleep Research Papers

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The Collected Abstracts Of Research Reports Presented at the First Annual Meeting of the Sleep Research Society at The University of Chicago 25-26 March 1961

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Introduction

By the time of the first, announced gathering of sleep researchers in the United States in Chicago on March 25-26, 1961, modern sleep research, that is, sleep investigations that recognized the existence of two major stages of sleep, had been in progress since the early-to-mid ‘50s. Various forms of communication and informal meetings among investigators were clearly taking place. It was finally agreed that a “formal” meeting be organized. Allan Rechtschaffen hosted the event at the University of Chicago. It was called the “Conference on Research in EEG, Sleep and Dreams.” Thirty six people attended. Their names and places of work are listed below. By the second annual conclave, the group was designated the Association for the Psychophysiological Study of Sleep (APSS). The Association changed its name in the early ‘80s to a more inclusive title, the Sleep Research Society (SRS). The 2010 meeting of the SRS marks the 50th consecutive meeting of this continually growing scientific assemblage devoted to the study of sleep.

You will find below each of the 16 individual abstracts of research presented at the 1961 meeting. They have never been published. The collection is provided here as a historical scientific memento of the very first, organized meeting of the American sleep research community.

It was apparently not customary in the early ‘60s for participants at the annual sleep conferences to submit, before the meeting, abstracts of the research reports they intended to deliver. Only after the presenting investigators returned home did most (but not all) prepare their abstracts for distribution. The abstracts were sent, some quite a few months later, to Dr. Rechtschaffen in Chicago in whose office they were duplicated. A sheaf of mimeographed copies of each of the 16 abstracts was then mailed to each attendee as a record of the research offered at the meeting. Most of the written reports are identified only by a study title and author(s). Many authors did not put the date of the conference, the society’s name, or the meeting location on the abstract. A few of the abstracts are innocent of a study title; they are identified only by author name and an expression such as “Summary of Remarks at…”, “Report to…,” or “Comments by,” indicating the open-discussion atmosphere of the meeting.

Howard Roffwarg, Member,

50th SRS Meeting Committee,

Sonia Ancoli-Israel, Chair

Dr. Rechtschaffen's written advisory to the attendees regarding the abstracts he sent out is reprinted here:

"Following is a set of abstracts of informal presentations made at a meeting of sleep and dream researchers at the University of Chicago on March 25 and 26, 1961. These abstracts are not to be considered as formal publications; they are personal communications of information and preliminary findings among the participants. None of the abstracts is to be quoted or referred to in public without the explicit consent of the author. A list of names and addresses of the participants is appended for the use of those who wish further communication with specific authors."

****

Following in order are:

- A list of the abstract citations
- An alphabetized list of all authors
- A list of the meeting attendees
- The abstracts of research

A specific abstract may be opened directly by clicking either on its citation or on a name in the list of individual authors.

Abstracts by Citation

CLICK ON A CITATION TO VIEW THE ABSTRACT

1. Dement WC. Age Differences: Preliminary Findings. APSS 1961 Mar 25.
   Keywords: age differences;REM sleep
2. Fisher C, Dement WC. Observations on the Dream-Sleep Cycle During the Course of an Acute Paranoid Psychosis. APSS 1961 Mar 25.
   Keywords: NREM and REM sleep cycle;psychopathology
3. Foulkes D. Dream Reports from Different Stages of Sleep. APSS 1961 Mar 25.
   Keywords: dreaming;NREM and REM sleep
4. Goodenough DR. Summary. APSS 1961 Mar 25.
   Keywords: arousal thresholds;dreaming
5. Hamburger W. Summary of Remarks Presented to Conference on Dream Research. APSS 1961 Mar 25.
   Keywords: dreaming;psychoanalytic therapy content
6. Hawkins DR, Wallace C, Puryear H. Relationship of Basal Skin Resistance to Sleep and "Dreaming". APSS 1961 Mar 25.
   Keywords: skin resistance;NREM;REM sleep cycle
7. Kamiya J. Report to the Dream Conference. APSS 1961 Mar 25.
   Keywords: eye movements;skin resistance;arousal thresholds;conditioned introspection
8. Kremen I. Ocular Motility as an Index of Dreaming: Specification of Some Confounding Variables. APSS 1961 Mar 25.
   Keywords: dreaming;NREM and REM sleep;recall bias
9. Opton E. Differences Between Successive Reports of Dreams. APSS 1961 Mar 25.
   Keywords: dreaming;dream forgetting
10. Rechtschaffen A. Summary of Remarks at Meeting of Sleep and Dream Researchers. (Four Parts). APSS 1961 Mar 25.
    Keywords: dreaming;NREM and REM sleep;pharmacology
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    Keywords: dream imagery;eye movements;dreaming
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    Keywords: sleep stage scoring;psychopathology;dreaming;arousal thresholds;EEG
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    Keywords: suggested dreams REM period length
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    Keywords: dreaming;telepathy
15. Verdone P. Variables Relating to Early Visual Memory Reports from Stage One with Rapid Eye Movements. APSS 1961 Mar 25.
    Keywords: dreaming;REM period length;visual memory;eye movements
16. Whitman RM. Drugs, Dreams and the Experimental Subject. APSS 1961 Mar 25.
    Keywords: dreaming;pharmacology

Abstracts by Author

CLICK ON AN AUTHOR'S NAME TO VIEW THE ABSTRACT

Persons Who Attended the Conference on Research in EEG, Sleep, and Dreams
at the University of Chicago, March 25 and 26, 1961

Knight Aldrich, M.D.
Department of Psychiatry
The University of Chicago
950 East 59th Street
Chicago 37, Illinois

Leo B. Arey, Ph.D.
5550 S. Dorchester Avenue
Chicago 37, Illinois

Howard Bagwell
Department of Psychiatry Annex
The University of Chicago
5741 S. Drexel Avenue
Chicago 37, Illinois

Bill J. Baldridge
Department of Psychiatry
Cincinnati General Hospital
Cincinnati, Ohio

E. Douglas Dean
Parapsychology Foundation
29 West 57th Street
New York 19, New York

William C. Dement, M.D.
175 Riverside Drive
New York 24, New York

Charles Fisher, M.D.
65 East 76th Street
New York 21, New York

David Foulkes, Ph.D.
721½ W. Lawrence Street
Appleton, Wisconsin

Marvin Frankel
1451 East 55 Street
Chicago, Illinois

Russell Gardner
1159 East 61st Street
Chicago 37, Illinois

Donald R. Goodenough, Ph.D.
State University of New York
Downstate Medical Center
450 Clarkson Avenue
Brooklyn 3, New York

Walter W. Hamburger, M.D.
Strong Memorial Hospital
260 Crittenden Blvd.
Rochester 20, New York

David R. Hawkins, M.D.
Department of Psychiatry
The University of North Carolina
Chapel Hill, North Carolina

Joe Kamiya, Ph.D.
Langley Porter Neuropsychiatric Institute
401 Parnassus Avenue
San Francisco 22, California

Nathaniel Kleitman, Ph.D.
222 Washington Avenue
Santa Monica, California

Richard L. Koresko
Saint Elizabeths Hospital
Washington 20, D.C.

Irwin Kremen, Ph.D.
Department of Psychology, Michigan State
University, East Lansing, Michigan

Helen Block Lewis, Ph.D.
15 West 75 Street
New York 23, New York

Louise Maron
Department of Psychiatry Annex
The University of Chicago
5741 S. Drexel Avenue
Chicago 37, Illinois

William Offenkrantz, M.D.
Department of Psychiatry
The University of Chicago
950 East 59th Street
Chicago 37, Illinois

Edward Opton, Jr.
Department of Psychology
Duke University
Durham, North Carolina

David E. Orlinsky
5401 Ridgewood Ct.
Chicago 15, Illinois

Persons Who Attended the Conference on Research in EEG, Sleep, and Dreams at the University of Chicago, March 25 and 26, 1961

Herbert B. Puryear
Psychological Services
Department of Psychiatry
University of North Carolina Medical School
Chapel Hill, North Carolina

Allan Rechtschaffen, Ph.D.
Department of Psychiatry Annex
The University of Chicago
5741 S. Drexel Avenue
Chicago 37, Illinois

Howard Roffwarg, M.D.
New York State Psychiatric Institute
722 West 168 Street
New York 32, New York

Arthur Shapiro, M.D.
30 Schermerhorn Street
Brooklyn 1, New York

Frederick Snyder, M.D.
National Institute of Mental Health
Bethesda 14, Maryland

Johann Stoyva
5333 S. University Avenue
Chicago, Illinois

Louis Timmin
5416 S. Woodlawn Avenue
Chicago 15, Illinois
As of July, 1961: Gorgas Hospital
Canal Zone

Harry Trosman, M.D.
Department of Psychiatry
The University of Chicago
950 East 59th Street
Chicago 37, Illinois

Montague Ullman, M.D.
55 Orlando Avenue
Ardsley, New York

Paul P. Verdone
1154 East 56th Street
Chicago 37, Illinois

Roy M. Whitman, M.D.
Department of Psychiatry
Cincinnati General Hospital
Cincinnati 29, Ohio

Harold L. Williams, Major, MSC
Department of Clinical and Social Psychology
Walter Reed Army Institute of Research
Walter Reed Army Medical Center
Washington 12, D.C.

Paul B. Wood
Department of Psychology
University of North Carolina
Chapel Hill, North Carolina

Edward A. Wolpert, M.D., Ph.D.
1801 N. Orleans
Chicago, Illinois

AGE DIFFERENCES

Preliminary Findings

2 subjects ages 20 weeks and 40 weeks: — EEG and eye movements recorded show a high percentage of stage 1 rem (around 40%). The cycles are somewhat shorter than the adult and very regular. Eye movement periods show fairly constant length. There is little difference in cycles and EEG between early and the late part of night; i. e., no diurnal pattern.

3 children ages 2 to 5: — Stage 1 rem percentage dropped markedly 10 to 15%. Marked differences in early and late part of night with typical diurnal patterns.

10 children ages 5 to 15:— Similar to younger children but slightly higher rem percent. Long sleep periods, 10 to 12 hours; high dream time.

Young adults, widely studied group: — Rem time 20 to 25%. There is a suggestion that ages 16 to 20 show higher dream time. 2 subjects, ages 16 and 18, average 28%.

Middle to old age; 4 subjects:— rem percent 10 to 17. High voltage, slow waves, less prominent.

From these preliminary studies there would seem to be a fairly consistent age pattern with high dream time in infancy, low in childhood, a rise at puberty with a gradual decline to old age.

William C. Dement, M. D.

6/27/61

Abstract

Observations on the Dream-Sleep Cycle During the Course of an Acute Paranoid Psychosis

Charles Fisher, M.D. & William C. Dement, M.D.

Investigation of fluctuations in the dream cycle during psychosis.

Dement investigated a group of chronic schizophrenics, who showed the usual cyclic activity, but variations in total dream time were not studied. We recently had an unusual opportunity to obtain EEG and REM recordings on a patient before, during and after the onset of an acute paranoid episode.

The patient, a 25 year old veteran, has been under treatment with one of us (CF) for nearly a year. He was sent from one of the local VA hospitals with a diagnosis of narcolepsy because of a history of some peculiar sleeping spells. Neurological work-up was negative. Psychiatric history revealed that the patient was severely disturbed, probably borderline or potentially psychotic. He showed disturbances of ego functioning chiefly in perception, memory, sense of time and consciousness but, in spite of evidences of serious regressive behavior, at the beginning of treatment and for a long time afterwards there were no manifestly clinical symptoms of psychosis and large areas of ego functioning remained intact.

His dream-sleep cycle was recorded before the beginning of treatment and his total percentage dream time was found to be markedly elevated, averaging over 30%, as opposed to an average of 20% for normal subjects in his age range. He was taken into psychotherapy with the idea of obtaining periodic recordings of his dream cycle in order to observe fluctuations during the course of psychotherapy.

The patient definitely did not have narcolepsy. His illness developed in three phases: the first symptomatic manifestation was sleeping spells. Shortly after beginning treatment these were replaced by a number of fugue states. And finally after about five months of therapy he rather quickly over a period of about ten days entered into an acute paranoid psychosis. He developed the delusion that his wife and mother were spying on him and sending out emissaries all over the city to follow him and ultimately take him to a mental hospital. There he would be placed in a room, abandoned by everyone, and the walls of the room would collapse around him. His paranoid ideas quickly mounted in intensity, reality testing began to break down, and he became increasingly panicky. He began to have visual and auditory hallucinations, would hear his name called in the street, and believed he saw his wife and mother outside the hospital waiting for him. He undertook all sorts of maneuvers to elude his pursuers, checked the hospital entrances and exits carefully before entering, began to run through the streets and hide behind ash cans, and to climb on to roofs and jump from one to another. He imagined he heard the footsteps of his pursuers behind him and would walk on tiptoes to make sure he wasn't hearing his own footsteps, but even with this maneuver he continued this hallucination.

The patient did not involve me in his delusions throughout the course of his psychosis, but continued a clinging positive transference with a persistence of feelings of trust. I cannot enter into a discussion of the genesis of his psychosis. It seems likely that certain events in his life plus unconscious homosexual conflicts stirred up in the transference situation and fears of ultimate rejection by me played an important role. Serious consideration was given to hospitalising him at the time he began to hallucinate but instead it

was decided to attempt to maintain him on an ambulatory basis by placing him on large doses of Stelazine and permitting him to sleep in the laboratory where he always felt comfortable and protected. Fortunately, this course of action worked out. We were able to get recordings of his EEG and REMs over a period of 18 nights, and to observe the effects of Stelazine on his dreaming and on the course of his psychosis.

The slide shows the patient's total dream time percent in the periods before, during and after his acute psychosis. It can be seen that during five separate periods, between May and September, his dream time fluctuated between about 27 and 36%. There was a two month period between September 17 and November 16 where no recordings were made. It was during the latter part of this period that his acute psychosis developed. On the night of the day of November 16th, when he was placed on 20 mgm. Stelazine plus 10 mgm. Artane, his dream time was 59.5%. It is possible that without the Stelazine that day, his dream time might have been even higher. His eye movement and EEG record showed certain unusual features. Normally, the first period of dreaming does not begin until an hour to an hour and a half after the onset of sleep, and the EEG record shows a rapid transition from alpha through Stage 1, without eye movements, into Stages 2, 3 and 4. After about an hour there is a shift to Stage 1 with the commencement of eye movements and the first period of dreaming. In our patient, something quite different occurred which we have never seen before. Within a few minutes he fell into a sleep characterized by Stage 1 EEG and vigorous rapid eye movements began. He was awakened after about 10 minutes of eye movements, and said he had been dreaming. He went back to sleep and the eye movements continued unabated for a period of two and a half hours. Following this prolonged first period of dreaming, the patient went into Stages 2, 3 and 4 of the EEG and had several more normal appearing dream periods, adding up to an additional hour and 22 minutes of dreaming. Altogether there was a total of three hours and 52 minutes of dreaming.

The next day, November 17th, the patient was kept on 20 mgm. Stelazine and that night his dream time was markedly reduced, down to 29.9%, although his total sleep time was also low, only 5 hours and 47 minutes. This night there were only 23 minutes of the initial eye movements at the onset of sleep and the remaining dream cycles were normal. On the 18th the dose of Stelazine was reduced to 10 mgm. and the dream time percent took a marked leap to 45.5%. There were no initial eye movements and the dream cycles were normal in character. The dose of Stelazine was increased to 30 mgm. daily for the next nine days after which it was reduced to 20 mgm. As the figure indicates, the dream time percents decreased and remained approximately at the pre-psychotic level until December 4th, when the recordings were stopped. Since the cessation of recordings, the patient has been on doses varying from 20 to 30 mgm., depending on his condition. The last recordings obtained on this patient about a month ago, showed that his dream time was still elevated, the figures for an eight day period ranging from 27% to 36%.

There is no doubt that there was a marked disruption of the normal dream cycle the first night of recordings, as indicated by the enormously increased amount of dreaming, the initial two and a half hour dream period, and the onset of the latter immediately the patient fell asleep. Within 24 hours there was a marked improvement of symptoms with a decrease in the intensity of his delusions and his panic. His hallucinations disappeared within several days, and have not returned. He has shown progressive improvement during the past six months and is no longer delusional. Since his psychotic episode and while continuing on Stelazine he has become much more amenable to psychotherapy. It seems likely that it was the action of the Stelazine that reduced his dream time in the most dramatic fashion and brought about a marked amelioration of his symptoms.

Dream Reports from Different Stages of Sleep

David Foulkes

Rationale

The apparent consistency of recent findings that dreaming is associated with a particular stage of ocular activity (REMP's) and with a particular stage of EEG activity (stage one) and that dreaming occurs only intermittently during the night suggested the desirability of trying to determine more precisely the objectively recordable point at which dream onset occurs. Such information, it was reasoned, would facilitate an analysis of temporal trends in dream formation. Experimental awakenings made at various intervals after the occurrence of the objective index of dream onset might provide an empirical basis for theorization about the usual sequence of dream development.

Pilot Study

Three subjects were run for 25 nights with experimental awakenings made at and immediately after REM onset, during stage one prior to REM onset, and in presumably pre-REMP stage two. Control awakenings were made in stages three and four and in REMP's well after REM onset. Results indicated that recall (of some specific item of content) was most likely following control REMP awakenings, but also elicited quite often (67% mean subject value) in the early stage one experimental awakenings. Recall figures outside stage one were considerably lower (34% mean subject value) than those within it, but considerably higher than those reported in previous Chicago studies, most consistently so for stage two awakenings. An impressionistic analysis of reports from stage two, pre-REM stage one, and immediately post-REM onset stage one awakenings suggested the operation over this portion of the sleep cycle of a developmental process involving (a) a relative shift from the conceptual to the perceptual mode of experience, (b) a shift from fragmentary and disjointed content to elaborated and integrated content, and (c) increasing distortion and decreasing reality-contact of content. In this respect the results suggested the feasibility of further research directed to the goal of studying dream "formation", though the presence of recall in fairly substantial degree outside REMP's suggested that further research be ~~#####~~ broadened in scope to include the study of possible qualitative differences in mental phenomena during sleep whenever they might occur.

Design

Eight subjects were run for seven nights each, with four awakenings made in each of seven categories of awakening: hypnagogic (after spindle onset); stages three and four; pre-REMP stage two; pre-REM onset stage one; REMP, up to 60 seconds after REM onset; REMP of 2 to 6 minutes duration; REMP of 9-24 minutes duration. Categories were spaced between and within nights so that each category was twice represented "early" within the night and within the series of 7 nights and twice "late" within the night and within the series of 7 nights.

Reports were classified as to whether or not recall was produced (some item of specific content), and as to the nature of the content produced (dreaming or thinking). "Dreams" included all reports containing visual, auditory, or kinesthetic imagery, and the few reports in which the subject felt himself to have an identity other than his own, or to be thinking that he was in a physical setting other than the laboratory. "Thoughts" represented a residual category. However, most reports so classified bore a close resemblance to the usual referent of the term "thought".

A systematic series of questions to which the S could reply yes or no was asked after the S's report at each awakening which produced some content (e.g., "Did you feel any emotion in this dream?"). In addition, Ss filled out, upon awakening in the morning, a rating form for each report they had made during the night. These two sources of qualitative information provided the basic data with which reports from different stages of sleep and ocular activity were to be compared.

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Results

TABLE 1
Recall: REM vs. NREM

* $p < .05$ ** $p < .02$ *** $p < .01$

Recall category	NREM prop.	n	REM prop.	n	Significance	Consistency
Dreaming--content	.54	73	.82	89	8-0-0***	
Thinking--content	.20	27	.05	5	6-0-2*	
Content total	.74	100	.87	94	6-1-1*	
Content plus claims	.87	118	.92	99	5-2-1	
"Nothing at all"	.13	18	.08	8	---	
		136		108		

The column labelled "consistency" gives information on the degree to which the pooled data reflect the data of the Ss considered singly. The first entry gives the number of Ss who show a difference between REMP and non-REMP proportions with a sign identical to that in the pooled data; the second figure gives the number of Ss who show a difference in proportions with a different sign than that in the pooled data; and the third figure gives the number of Ss whose data show identical proportions in the REMP and non-REMP summation of categories. All REMP versus non-REMP differences in this and subsequent tables were tested (two tailed) by the Wilcoxen Matched-Pairs Signed-Ranks test.

Table 1 reveals that recall of some item of specific content was more likely to occur in awakenings during REMP's than in awakenings outside REMP's. This finding is consistent with the results of all prior studies. The high frequency of recall outside REMP's is at variance with the results of all recent published attempts to relate dreaming to EEG activity, with the possible exception of that of Goodenough et al.(1959).

Since the data of Table 1 is pooled over the initial categories of awakening, it might be asked if any one non-REMP category contributed a disproportionate share of the recall in the non-REMP classification. The data of Table 2 show that this is not the case.

TABLE 2
Recall: By Category of Awakening

Awakening category	Thinking content	Dreaming content	Content total	Content plus claims	n
Hypnagogic	.25	.56	.81	.91	32
Stage 3/4	.19	.51	.70	.86	37
Stage 2	.23	.51	.74	.86	35
Pre-REM stage 1	.12	.56	.69	.84	32
Brief REMP	.03	.83	.86	.86	36
Medium REMP	.06	.79	.85	.91	34
Long REMP	.05	.84	.89	.97	38

Although previous investigators have reported wholly unsubstantiated claims of dreaming as "not dreaming", it seemed desirable to distinguish between those times when no specific content was produced but claims of dreaming or thinking were made and those times when the S felt quite definitely that nothing had been "going through his mind" just prior to the awakening bell. Thus Tables 1 and 2 include claims as well as content in the categorization of awakening reports.

It appears that in making awakenings around the time of REM onset we are dealing with the formation of a particular kind of dreams, not of all dreams--if by dreams we mean any mental activity during sleep. While the initial choice of awakening categories served to concentrate attention on awakenings close to

presumed REM onset or soon after REM onset, the procedures of investigation employed should, in view of the recall data, illuminate not only processes of REMP dream formation but also qualitative differences among reports obtained from the whole range of conditions of the human sleep cycle.

Information on the qualitative characteristics of the dreams and thoughts reported by the Ss came from two sources, the responses Ss made to probes during the original dream report and their responses to the morning rating form. Table 3 presents the data for all dimensions which significantly differentiated reports obtained after REM onset from those obtained outside REMP's

TABLE 3

Significant differences in qualitative characteristics of reported phenomena

A: Source--Subject's report at awakening

Query	REM: prop. yes	NREM: prop. yes	Significance
Emotion self?	.50	.32	7-0-1**
Emotion self/others?	.55	.31	8-0-0***
Only one other character?	.34	.57	7-0-1**
More than one part?	.37	.17	6-0-2*
Median judged length ("dreams" only)	(5 min.)	(3 min.)	6-1-1*
Visual?	.90	.66	7-0-1**
Visual Imagery: Clear?	.80	.62	6-1-0*
Any scene shifts?	.63	.33	7-0-0**
Physical movement: self?	.67	.38	7-1-0*
Locomotion: self?	.42	.21	8-0-0***
Locomotion: others	.45	.25	6-2-0*
Manifest work/ school theme	.15	.27	7-1-0*
Continuation of prior dream/thought	.11	.33	7-1-0**
Memory process--undistorted recollection	.01	.17	7-0-0**

B: Source--Subject's response on morning rating form

Dimension	REM: mean score	NREM: mean score	Significance
Activity	2.10	1.38	7-1-0*
Emotion Self	1.41	.91	6-0-2*
Emotion Others	1.19	.72	7-0-1**
Anxiety	1.07	.62	6-1-1*
Scenes (N)	(2.30)	(1.57)	7-1-0**
Scenes clearly visual (prop.)	(.74)	(.52)	8-0-0***
Violence-Hostility	.71	.23	7-1-0**
Distortion	1.68	.75	8-0-0***
Manifest relation to recent event in S's life (prop.)	(.48)	(.73)	8-0-0***

The results in Table 3, both in parts A and B, are given in two groups. It is suggested that the first block in each part includes dimensions of a formal character which differentiate REMP from non-REMP material. The important differences here seem to fit into two general areas: organismic involvement and elaboration. Reports obtained in periods of REM activity showed more organismic involvement in affective, visual, and muscular dimensions and were more highly elaborated than non-REMP reports. The second block of results in both parts A and B includes dimensions which have to do with the relationship between dream and thought content and prior waking experience of the S. These correspondence data show that there is less relationship to the waking life of the S in the REMP reports than in the non-REMP reports. The relatively frequent occurrence of memory processes in spindle and delta sleep was an especially striking result.

Discussion

The near unanimity of recent studies in suggesting that dreaming does not occur in all stages of sleep and ocular activity indicates the desirability of considering whether the present results, which seem to point the the presence of reportable mental activity in all stages of sleep and ocular activity, are artifactual in nature.

First we should examine the Dement and Kleitman hypothesis that dream recall outside REMP's is delayed recall of prior REMP dreams. This seems untenable in light of the fact that in the present study the proportion of recall in stages two, three, and four when there had been no intervening undisturbed REMP since the S was last awake (.72, n=39) was almost exactly comparable to the proportion of recall in these stages when there had been one or more such intervening undisturbed REMP's (.73, n=33).

The considerable and consistent qualitative differences found between REMP recall and non-REMP recall in the present study also make the hypothesis that spindle and delta recall represents memories of prior dreams seem improbable. It is difficult to imagine that the spindle and delta reports represent the end of a series of passive, memorial transformations of REMP material. In addition, when Ss were aware of reporting dreams which had occurred considerably prior to the bell, these dreams retained all the typical characteristics of REMP dreams, and this was true even when a considerable interval of time had elapsed since the last REMP. This last bit of evidence argues that REMP dreams persist, if they do so at all, relatively intact. It seems quite clear, then, that the Dement and Kleitman hypothesis about non-REMP recall must be rejected.

Two other ways in which spindle and delta dreams and thoughts could be something other than what they appear to be suggest themselves. Recall in such circumstances could be of hypnagogic phenomena experienced in low-voltage non-spindling EEG periods while falling asleep. On the other hand, it could represent hypnopompic phenomena experienced between arousal by the bell and full alerting.

Evidence against the hypnagogic hypothesis:

1. The hypnagogic awakenings in the present study which produced reports similar to those from later non-stage one awakenings were made after spindle and delta onset, and on 83% of these awakenings Ss felt that they had been dreaming the material they reported just as the bell rang, rather than sometime before then.

2. Despite broad similarities, there were enough qualitative differences between the hypnagogic reports and reports from later spindle and delta awakenings to suggest that those later reports were not memorial representations of hypnagogic material.

3. Two of the pilot Ss were run for several evenings with a number of hypnagogic awakenings made on each such occasion, the awakenings being made at points ranging from the break-up of continuous alpha to several minutes after spindle onset. Awakenings made during low-voltage EEG activity on falling asleep seemed to produce quite different material (e.g. "lantern slide" phenomena, fleeting progressions of thoughts and images) than that observed in spindling sleep (more extended and self-involved "dreamlets"). This strengthens the conclusion that neither the hypnagogic reports nor the whole class of spindle and delta reports collected in this study consist of memories of material which occurred in stage one while falling asleep.

Evidence against the hypnopompic hypothesis:

1. On those awakenings which had the longest arousal time, recall was very rarely obtained. With maximal opportunity for hypnopompic imagery, no recall at all was the most frequent result.

2. Thus if the spindle and delta recall was of hypnopompic material, that material had to transpire in a very brief moment of time. Median estimated dream lengths were usually shorter for non-REMP categories of awakening than for REMP categories. But in no case did they vary nearly so dramatically from the REMP figures as did the time of non-REMP arousal from the average length of the REMP. And, for stage two awakenings, where arousal took only a matter of a few seconds, dreams were generally estimated to be as long as, and were described as multi-part dreams almost as often as, dreams from awakenings made after REMP's of nine or more minutes duration.

3. The hypothesis might have some difficulty in explaining why the material obtained from one category outside REMP's differed along certain dimensions from that from another such category.

We are (or I am) forced to conclude, then, that the non-REMP recall obtained in the present study is not artifactual in nature. How can the present results be reconciled, then, with those recent studies by investigators of the Chicago group which seem to indicate that dreaming is very unlikely to occur, if at all, outside stage one REMP's?

For one thing, the criterion of recall is quite important here. Dement and Kleitman state that "vague, fragmentary impressions of content were considered negative". Orlinsky's presentation at the conference seemed to indicate that taking the criterion used in this study, rather than that of Dement and Kleitman, one should expect to find recall of ~~###~~ 40% and up outside REMP's. Interest in detailed, coherent dreams is quite understandable, but the labelling of "vague, fragmentary impressions of content" as"no recall" is somewhat unfortunate if the recall results are then used to argue that spindles and delta are very likely associated with a suspension of conscious mental activity. It now seems time to embark upon systematic studies of all aspects of sleep consciousness, whether they are totally "dreamlike" or not.

Another possible reason for the discrepancy between these results and those of prior investigators is the factor of subject set. The ultimate question in this study was not, "were you dreaming?", but "was anything going through your mind?" This question, some of the protocols suggest, picked up material which the "dream" question might have missed. Subjects demonstrated that they considered dreams to be visual, and to be somewhat bizarre. Since non-REMP reports were less often visual and had a higher degree of correspondence with reality, the application of these criteria by Ss would serve to depress recall outside REMP's most severely if the S believed that the E was interested in his "dreams", and in these phenomena along.

Further Comments

Kleitman in his remarks at the conference raised the question as to whether the non-REMP material described above could or should be considered as "dreaming". It would certainly seem to fit a definition which Kleitman himself has proposed: "the act of experiencing apparent sensations and events during sleep, trance, or other unconscious states. Dreams may be confined to a single sensation but more often include incidents and whole chains of connected events in which the dreamer seems to take part."(1960) This definition, one which I would hold is faithful to at least one sense in which the term "dream" is commonly used, does not arbitrarily specify that dreams must include whole chains of connected events, but merely states that they often do. The whole problem of the definition of"dreams"is likely to get quite arbitrary, and since it is a secondary problem, I don't think that it is worth the study we might be tempted to give it. Whatever we call non-REMP recall, so long as we grant that it is not artifactual, it is worthy of more study than it has heretofore been given.

Summary

Ss were awakened from dream periods (defined in terms of Dement and Kleitman's eye-movement criteria) and asked to describe their dream experience. Ss more often believed that they were awake and/or thinking when the awakening was gradual than when the awakening was abrupt. Reports in which the S believed that he had been awakened from a dreamless sleep were more frequent for the first several dreams of the night than for dreams which occurred toward morning. Depth of sleep, as defined by the arousal threshold, also became lighter for successive dreams during the night.

Donald R. Goodenough
July 20, 1961

SUMMARY OF REMARKS PRESENTED TO CONFERENCE ON DREAM RESEARCH

UNIVERSITY OF CHICAGO, DEPARTMENT OF PSYCHIATRY
March 26, 1961

WALTER W. HAMBURGER, M.D.
(Assoc. Prof., Psychiatry, University of Rochester School of Medicine and Dentistry, Rochester, N.Y.)

Dr. Hamburger introduced his remarks by commenting on the central position of the University of Chicago in this research. Not only had Dr. Kleitman and co-workers made the initial observations correlating sleep - EEG - REM - dreams but Dr. Franz Alexander, who had been the first Chairman of the Department of Psychiatry at the University of Chicago, along with Dr. Thomas French at the Chicago Institute for Psychoanalysis had made significant contributions to dream investigation. More currently, under Dr. Knight Aldrich, the Billings' group was one of the most active in on-going research in this field. Therefore, it seemed historically appropriate, as well as geographically convenient, that this first conference was convened at the University of Chicago.

Dr. Hamburger explained that his own dream research utilized the psychoanalytic methodology only, without EEG, tape recorders or digital computers for his data. He defined the psychoanalytically trained observer as the investigative "instrument" and patients in therapeutic analyses as the subjects for investigation. The experimental situation is structured by fifty minute visits three to five times weekly during which the patient-subject free associates over an extensive time period which gives the analyst-observer a baseline of individual data from which to study dreams, as one of many variables.

In pursuing his dream research, Dr. Hamburger said the only instrumentation he used was note paper (provided by his University Medical Center) and a ball point pen (provided by himself). With this equipment he took long hand notes, numbered the patients' visits and after termination of their analyses, enumerated, reviewed and studied the patient-subject's dreams, their associations and interpretations, in a serial manner.

This methodology permits the study of whatever dreams may be spontaneously disclosed WITHIN THE CONTEXT OF ALL THE ANALYTIC MATERIAL before and after a specific dream. Through free association, the investigator is enabled to study the LATENT MEANING TO DREAMS AS WELL AS THEIR MANIFEST CONTENT. Among other things, this method provides an opportunity to study the relation between subject and investigator, both as a contributing element to dream content and as a factor in the remembering or forgetting of dreams.

Dr. Hamburger described this methodologic approach as representative of other clinical investigations undertaken in the practice of medicine. In this situation the analyst may be regarded as a participant-observer who collects and investigates certain data while concomitantly serving a therapeutic purpose. One of the limitations, which applies to the EEG-REM approach as well, is that ONLY REPORTED DREAMS CAN BE STUDIED whereas all forgotten or omitted dreams cannot. Presumably, the EEG-REM method permits of recovering a higher percentage of dreams when the subject is awakened during, or immediately after a dream period. Hopefully, too, there would be less secondary distortion than is known to occur before the delayed reporting of dreams in the psychoanalysts' office.

Nevertheless, Dr. Hamburger had been impressed with the QUALITATIVE similarities of EEG-REM subjects' reported dreams (manifest content only) with his own patient-subjects' dreams. He referred particularly to the publications of the University of Chicago group on "Relations Among Dreams in Sequence". For comparison he quoted three dreams of a psychoanalytic patient (female, 22, unmarried) who had not remembered or discussed very many dreams in her analysis. In her 419th psychoanalytic hour she spontaneously discussed three dreams which had occurred in two preceding nights' sleep. All three dealt in their manifest content with school situations, examinations and proving herself. The patient spontaneously related the three dreams as "...a pattern..."; "...of being tested..." and of "...seeking approval." Subsequent associations indicated that these were feelings directed toward the analyst as the "examiner", and "teacher" and that it was from him that she was seeking approval, partly by remembering these dreams. Dr. Hamburger emphasized such "transference" aspects to investigators as being pertinent to the content of dreams as well as to the remembering and forgetting of dreams.

In his remaining few minutes, Dr. Hamburger summarized his QUANTITATIVE dream studies over the preceding five years. In order to limit the vast number of variables of psychoanalytic material, he had focussed on those repetitive dreams which had food and/or eating symbols in their manifest content (usually in visual sensory modalities). He had studied 320 such dreams in both their manifest form and in their latent meanings throughout the analyses of 5 (female) patient-subjects. The mean incidence of such "food and eating dreams" varied from 9.9 to 18.5% of all reported dreams from the 5 patients, with a combined median of 13.9% (See Table I.)

TABLE I NUMERICAL SUMMARY OF ALL FIVE PATIENTS

Dreams of patients	1	2	3	4	5
Total number	900	571	341	116	491
Number of food and eating	115	57	36	21	91
% food and eating	12.6	9.9	10.6	18.1	18.5
Total hours in analysis	699	744	422	573	514

Although some other analysts had told Dr. Hamburger that this seemed to be a remarkably high incidence of such food and eating symbols, those analysts had not counted the incidence of such dreams. However, in a personal communication, Drs. Dement and Fisher had told him that such an incidence of food and eating dreams was not high in their experience with EEG-REM subjects. Furthermore, after their subjects were "dream deprived", Dement and Fisher had noted an increase in such food and eating dreams, up to as high as 50% of dreams reported by one subject. (Those were the same subjects who, when "dream deprived" developed an increase in appetite and body weight).

Dr. Hamburger had become quite intrigued with his incidental observation that the rate of occurrence of these food and eating dreams decreased as his patients progressed in their analyses,(1,2) (See Fig. 1). This decrease, he told the Conference, was of statistical significance. Time did not permit of his speculations as to the meaning of this decrease. Nor was there time for him to elaborate his interpretation of these dream symbols of food and eating as a reflection of the unconscious oral drives and conflicts of the dreamer. From the RESTROSPECTIVE study of these 320 food and eating dreams, Dr. Hamburger derived the hypothesis that these dream symbols reflected the dreamers' oral drives at the time, whether regarded as fixation or regression. To test such an hypothesis ANTERO-SPECTIVELY, Dr. Hamburger has predicted the incidence of such food and eating dreams at the start of five new patients' analyses. The basis for prediction is Dr. Hamburger's clinical estimate of the patients' oral fixations and potential for oral regression derived from early diagnostic impressions,(3).

At this point it was necessary for the Conference members to turn to the next presentation without discussing Dr. Hamburger's methodology or findings.

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1. Hamburger, W.W. "The Occurrence and Meaning of Dreams of Food and Eating. I., Typical Food and Eating Dreams of Four Patients in Analysis." Psychosom. Med. XX: 1, 1958.

2. Hamburger, W. W. "The Occurrence and Meaning of Dreams of Food and Eating. II., An Example from a Case of Anorexia Nervosa." Presented to Am. Psychoanalytic Assoc., San Francisco, May 10, 1958. (To be published).

3. Hamburger, W. W. "The Serial Study of a Repetitive Dream: A Contribution to Psychoanalytic Research ". Presented to Am. Psychoanalytic Assoc., Atlantic City, May 6, 1960. (To be published).

THE INCIDENCE OF FOOD AND EATING DREAMS
IN RELATION TO TOTAL DREAMS IN ANALYSIS - CASE I.

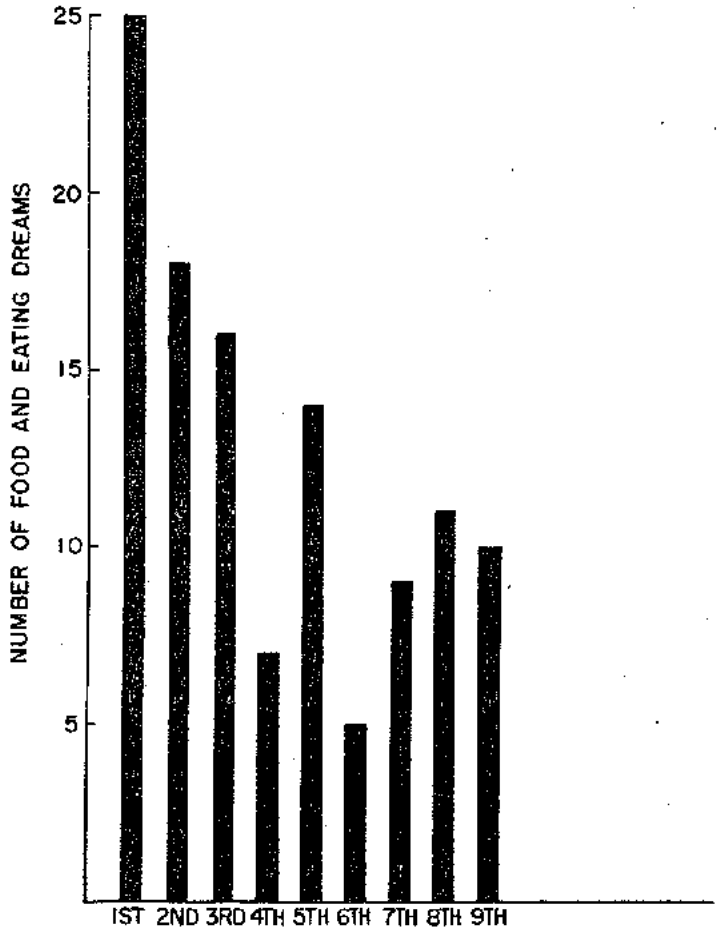

FIG. I

Relationship of Basal Skin Resistance to Sleep and "Dreaming"

Five subjects were studied during 7 nights of sleep utilizing an 8-channel Grass electroencephalograph for the usual EEG and eye movement measurements. In addition, GSR and basal skin resistance were recorded on an instrument made by Texas Instrument Company.

In accordance with the hypothesis that basal skin resistance is a function of level of arousal, it rose as the subject went to sleep, reaching a plateau at stage 3 or 4 as indicated by the electroencephalogram. Paradoxically, during the periods of stage 1 activity with rapid eye movements the basal skin resistance rose and then fell as the subject returned to stages 2 and 4. In every instance, when the subject actually awoke, there was a precipitous fall in the basal skin resistance. In the overall course of the night there was a trend toward a gradual rise in the basal skin resistance with peak rises accompanying stage 1 activity.

Non-specific GSR was recorded but no consistent pattern could be detected when an attempt was made to correlate this activity with levels of sleep.

If this finding of a rise in basal skin resistance during stage 1 is borne out in further studies, it would serve to indicate another way in which this level of sleep is unique. We plan to continue this type of measurement.

David R. Hawkins, M. D. Charles Wallace, M.D. Herbert Puryear

Department of Psychiatry, School of Medicine, University of N. C.

REPORT TO THE DREAM CONFERENCE -- MARCH, 19[illegible] -- CHICAGO, ILLINOIS

Joe Kamiya

University of California Medical Center, San Francisco

First, in the Methods Session the comment was made that the recording of eye movements should be more fully explored, using DC recording. Evidence from my laboratory indicates that the rapid eye movement period usually begins as a gradual increase in slow eye movement from periods of relative quiescence. The slow eye movements are as described previously by Aserinsky and Kleitman, but they are not entirely replaced by rapid eye movements. The REM period is superimposed on increased slow eye movements. The occurrence of non-REM dream reports should be studied in relation to the occurrence of slow eye movements.

To facilitate the study of the slow eye movements it is desirable to have a channel with DC or else some time constant that is of the order of a few seconds, using lower gain than is used for REM recording. Thus far we have observed the slow eye movements only with laterally-placed electrodes but vertically-placed electrodes obviously should also be used.

Another item was a preliminary report on a large number of nights using basal skin resistance. The technique involved a servo-controlled device for automatic balancing of the bridge used in measuring the resistance and a read-out of the basal values as well as a read-out for the more transient GSR's. Our observations so far run contrary to what one might experience from observing base-line GSR's in the waking state; basal skin resistance appears to show more often than not a rise rather than a decline during the rapid eye movement periods. This rise is partly to be accounted for in terms of a general rise in skin resistance that has been observed by several others previously during the course of the night. Therefore, evaluations of whether the rise during rapid eye movement periods are significant, must take into account the longer term rise in skin resistance. Our observations of the over-all trend through the night differ somewhat from those of Titelbaum in that the decline in skin resistance after about two-thirds of the night which they reported is not typical in our records. The most common pattern that we have observed is an approximately linear increase in skin resistance throughout the whole night. However, the data may be reconcilable because most of our nights of observation involved somewhat shorter total sleep time, averaging around six-and-one-half hours.

Other observations have included heart rate, respiration rate, and body movement. Heart rate and respiration rate do increase as previously reported by Kleitman and Aserinsky but our average increase is only about five percent compared to their 10 or 15.

Our EEG and REM observations are based on some 250 nights involving 25 different subjects for 10 nights each. Some of the other physiological measures were taken on around 150 subject-nights.

Body motility seems to show a pattern somewhat different from that reported

by Dement and Kleitman. In our records body motility is not significantly decreased during the rapid eye movement period.

Analysis of the variability of heart rate and respiration rate with respect to the eye movement periods is still in progress. Further, it is not yet possible to report on correlations between these physiological measures and ratings of the verbal report.

Using a criterion that would seem to be roughly the same as those used by Dement and Kleitman in their reports in the JOURNAL OF EXPERIMENTAL PSYCHOLOGY and the EEG JOURNAL, the percent of recall from non-REM periods is about 40 percent. My interpretation of these results of Foulkes' results and of Goodenough's results, and finally of some results emerging from Stoyva's work is that dreaming occurs outside of periods of rapid eye movements, as well as during them, although the rate of recall is decidedly lower during the non-REM periods. The occurrence of a higher percentage of reports of thinking during sleep from these non-REM periods is provocative. But the reports of dreaming that do occur during the non-REM periods must not forgotten. They seem too frequent to be accounted for by explanations based on the idea that dreams occur only during REM periods.

There is no doubt about the strength of the relationship between the occurrence of specific eye movements and the occurrence of specific events in the dream report as recently confirmed by Dement and Roffwarg. We seem to be left with a possibility that some dreams are indexed by the occurrence of eye movements, perhaps most of them, but that others occur without those

In view of the less than perfect co-variations between the occurrence of eye movements and the occurrence of dreaming, it seems that as a most conservative statement one might say that it may be somewhat premature to assume that the interruption of all REMs deprives subjects of all dreaming

A technique was reported for behavioral assessment of a depth of sleep. This technique was developed by Ogden Lindsley at Massachusetts and involves the operation of a thumb switch to reduce the volume of a tone delivered to the ear. If the thumb switch is not operated, the tone gradually rises in intensity over about a 30-second interval until it reaches a steady maximum level of about 100 db. The tone level is inversely related to the rapidity with which the subject operates the switch. If the subject operates the switch at about once every two seconds, the tone level stays near threshold Under these conditions the subject will operate the switch steadily until he falls asleep. At this point he no longer operates his thumb and the tone level goes up to maximum and there it stays for most of the night. At irregular intervals during the night, however, the subject operates his thumb switch for brief periods of time. These occur most typically during periods of body movement and are often accompanied by alpha rhythm. Operation of the thumb switch usually does not occur during sleep spindles or delta at least in the first two nights of operation. (Data obtained after the conference shows that with additional nights the subject begins to operate the thumb switch during slow high voltage, but not (yet) during spindling.)

Lastly, there was described an experiment designed for an experimental behavioral analysis of the process of introspection. It seems desirable to undertake such an analysis inasmuch as the entire field of dream research is dependent on the introspective report. It is postulated that the most central event involved in introspection is the discrimination by the subject of an internal state. To determine whether such discriminatio can be conditioned, using techniques developed in learning experiments, we used as an index of the internal state the EEG alpha rhythm. We do not know at present, of course, except in a gross way, the significance of the occurrence of the alpha burst. However, on the premise that occasions whe alpha was occurring would be discriminable from occasions when alpha burst were not visible in the EEG trace, a conditioning procedure was used. Wit a single ding of a bell from E serving as a signal at each trial, Ss were reinforced for saying "yes" if the ding was presented during a burst of alpha waves, and "no" if given during the absence of alpha. After trainin to nearly 100% correct performance, Ss were able to name the occasions when alpha occurred, without the aid of the bell. Also, after training with these procedures, Ss were able to produce alpha upon command.

Ocular Motility as an Index of Dreaming: Specification of Some Confounding Variables

by

Irwin Kremen

Harvard University

(ABSTRACT of a report presented before the Conference on Research in EEG, Sleep, and Dreams, University of Chicago, March 25 and 26, 1961.)

The studies linking ocular motility to "dream recall" are open to rather serious criticism on methodological grounds. Not the least of these is that data derived from the various scoring systems may be mere classificatory artifact inasmuch as several of the scoring categories were logically arbitrary if not conceptually unsound and unjustifiable moreover either phenomenally or empirically. These scoring systems were hardly more than loose sets of broad categorical statement, lacking entirely in explicit definition of the attributes deemed criterial for "dream recall" and making no provision for the treatment of ambiguous instances.

The study upon which this report is based[1] sought first to determine whether differences in classificatory procedures could possibly account for the reported variation in the incidence of "dream recall" for the NREM condition -- 7% in the study by Dement and Kleitman, 53% in that by Goodenough and his associates for their "dreamer" group. This proved to be highly probable since the incidence for Goodenough's "dreamer" group fell to 21% when the protocols were completely reviewed and the data re-analyzed according to the scoring system used by Dement and Kleitman. These two studies differed, then, over what each chose to consider a positive instance of "dream recall" and the difference turned upon how to treat reports of dream fragments. But both studies excluded from positive designation those claims by Ss that dreaming had occurred prior to experimental arousal if no content was reported as well, and here both erred logically since given the problem of determining whether the REM is associated with dreaming, any test must be based upon the recall of dreaming as an event regardless of content recall. Accordingly, the Goodenough data were recombined with such instances treated as positive dream reports: the NREM incidence for the "dreamer" group rose to 62%. Either way, these analyses point to the possibility of classificatory artifact in the earlier studies, especially for the NREM condition. And if 62% is representative of the actual state of affairs for the NREM-periods, then one would have to conclude that the REM can serve only as a most inefficient index of dreaming. In view of this, an empirical appraisal of the entire situation was deemed necessary and was undertaken with the following procedural improvements among others:

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1. For a fuller account, see: Kremen, I. Dream Reports and Rapid Eye Movements: An Appraisal, Ph.D. Thesis, Dept. of Social Relations, Harvard University, June, 1961.

(i) From the Goodenough protocols, 11 response classes were differentiated and explicitly defined, to form the basis for a very comprehensive Scoring Manual. Three additional response classes were included as controls against false positives. Specific rules were also formulated to handle certain special cases and ambiguous instances. A priori assumptions about the nature of dreaming were avoided. Dream reports were distinguished from reports of hypnagogic imagery on a phenomenal basis, with the difference being taken as that of an impression of having been somewhere or having done something incongruent with one's actual position or actual behavior (sleeping) in space and time. Provision was made for treating certain type cases that might not readily be classifiable given this distinction. Explicit rules were formulated, too, concerning the transformation of raw scores into superordinate positive and negative classes with care being taken to remain on logically tenable ground. Scoring agreement between two raters over three series of protocols was 90% for raw scores, 98% for the positive and negative groupings.

(ii) Based partly on clinical procedures, a special Inquiry Tactic was standardized for each response class, the general aims being to maximize report and minimize ambiguity while gathering the information needed for scoring decisions. The Inquiry Schedule included a special Anxiety Tactic for use when warranted to reduce or forestall buildup of anxiety; included also were tactics for inquiry initiation and termination and a set of general content-eliciting probes.

(iii) Regardless of report or arousal condition, it was mandatory that all report periods be at least three minutes in duration.

(iv) The Arousal Schedule was fashioned about a central set of rules aimed to prevent REM periods from going uninterrupted lest this confound subsequent NREM arousals. Similarly, procedures were devised to space the NREM arousals from the sleep-onset period since dreaming probably also occurs as one falls asleep.

(v) Explicit procedures were fashioned for use in drawing a sample of Harvard undergraduates who would have little trouble sleeping under laboratory conditions and who were still unfamiliar with the phenomenon under study from the wide publicity given it in the popular press.

(vi) Many other precautionary measures were included -- some to preserve subject naivete; others to minimize gross body movement immediately after arousal since movement may tend to dissipate dream recall. Ss were also given a post-experimental interview.

Four separate series of experiments were carried out: 1) a "Biased Series" in which 6 Ss over a total of 8 nights were aroused only during NREM periods while under instructions designed specifically to bias them toward producing dream reports; 2) Series IA with 4 Ss one night each; 3) Series IB with another 4 Ss three nights each; and 4) after some procedural modifications, a final test Series (II), 9 Ss one night each.

For the first three series, the incidence of positive dream report for the NREM condition was 38.2%, 37.5%, and 39.4% respectively. So consistent a finding would hardly seem attributable to chance, and to account for it four possibilities were considered -- unwitting experimenter bias, arousal bewilderment, subject bias, and dreaming. Analysis of the data suggested that the first two were unlikely while the third, subject bias, seemed highly probable for the following reasons: One of these studies involved the experimental creation of a subject bias, i.e., an expectation that arousal would occur only when the investigator had detected "reliable signs of dreaming" on the physiological records, and presumably this contributed some part to the 38.2% positives obtained. In addition, the NREM positives for Series IA and IB were qualitatively indistinguishable from those of the "Biased Series". These reports were marked by hedging, reluctance to say "no", inferential and probabilistic reasoning, labored apologies for inability to recall dream content, considerable indecisiveness, and stereotyped themas. Some reports, too, contained more manifest evidence of a biasing expectancy: for example, "If there is a desire for a dream, then I was dreaming." Finally, a class of report not described in the Scoring Manual was noted, one that appeared trancelike in origin and possibly related to a biasing expectancy. Observation was made also of the contingent conditions of reports best classed as arousal artifacts.

During Series IA, all the NEM arousals led to positive dream reports. But over the three nights of Series IB, the incidence of positive dream reports for the REM condition varied from a high of 75% on the first night to a low of 56% on the second but with some recovery (68%) on the third. Of these negative REM instances, fifty percent occured following certain contingencies that one might expect associated with negative report, such as arousal after body movement or arousal from the generally fleeting first REM-period of the night. The remaining instances of negative report were produced, however, by the three Ss who also reported dreams that were manifestly conflict-laden. And these same Ss developed various patterns of behavior that strongly suggested avoidant or defensive activity, behaviors such as increased response latencies, delay in making a report when aroused, refusal to become sufficiently aroused to make a comprehensible report; clinically as well, these Ss provided numerous expressions of conflict and defense.

On the basis of these observations, several procedural changes were made for a final test Series (II) -- changes in instructions, scheduling, arousal system, and the item order of a single Inquiry Tactic, all aimed toward eliminating the development of response patterns based upon either expectancies or conflict and defense. For this final series the incidence of positive report was 75% and 12% for the REM and NREM conditions respectively, this difference being highly significant statistically ($p < .0001$). An analysis of the small number of instances contrary to the hypothesis disclosed that all but two occurred in a context of conditions specified beforehand as those most apt to be found associated with REM negatives or NREM positives, though not invariably so. Of the two instances not so accounted for, one occurred with violation of an arousal rule and one was actually predicted negative in advance of arousal. Six of the 17 Ss from Series I and II qualified as "non-dreamers" in Goodenough's sense. When the data from these Ss were combined, the REM positive incidence was found to be 76% for all nights of participation, 80% for first nights only.

The following conclusions seem warranted from these data: 1) That the REM is a reliable index of dreaming regardless of how frequently a person ordinarily recalls dreams, an index that can be used with considerable confidence providing certain precautions are taken. 2) That save for the sleep-onset period, dreaming probably occurs only during REM periods which all along in this summary have implicitly included periods of low voltage, random brain wave activity associated with REMs during sleep. 3) That investigators of dreaming must give serious attention to problems of artifact -- be it the result of inquiry, instructions, subject bias, experimenter bias, number of sessions, arousal procedures, or the nature of the subject-experimenter relationship itself.

DIFFERENCES BETWEEN SUCCESSIVE REPORTS OF DREAMS

Edward Opton, Jr.
Duke University

Clinical observations have raised many questions about the forgetting of dreams.[1,2,3] These questions have provoked considerable theorizing but little experimentation. For example, Freud (Freud, 1958) mentions eight theories previously advanced to account for dream forgetting and adds a ninth of his own.

The paucity of empirical studies of the forgetting of dreams probably results from practical difficulties: dreams are hard to obtain and difficult to quantify. Such reports as are obtained are often fragmentary, confused or illogical, and therefore may seem to call for techniques of study different from those developed for use with other types of verbal productions.

The practical difficulties which have made it difficult to study the forgetting of dreams seem less formidable in the light of recent technical advances. The Kleitman and Dement technique (Dement and Kleitman, 957) makes it possible to obtain dream reports much more reliably than was formerly possible and enables the experimenter to control the time interval between dreaming and reporting. I. H. Paul (Paul, 1960) has demonstrated that quantified description of changes during the forgetting of connected, meaningful material (such as dreams) is possible. The Kleitman and Dement technique and an approximation to the Paul method are used in the present study to attack questions about differences among successive reports of dreams.

Three approaches are taken in this study:
1) As a point of departure, two hypotheses were selected:
   a) Repression will be a major factor in the forgetting of dreams.
   b) Later dream reports will show less evidence of regression than earlier reports; that is, later reports will be more developmentally mature.

1. The writer is indebted to Dr. Louis D. Cohen for his help throughout the designing and execution of this study.

2. This research was carried out as part of the writer's Internship in Psychology at the Duke University Medical Center. It was supported by a grant from the Dept. of Psychiatry.

3. In order to conserve space all references, tables and appendices, most footnotes, and much of the text of the original paper have been omitted from this abstract. The complete report may be obtained from the author, Dept. of Psychology, Duke University, Durham, N.C.

2) Empirical relationships are sought within the data in the hope of uncovering hypotheses for future studies.
3) A final aim is to assess the advantages and disadvantages of the method of quantitative analysis of successive dream reports as compared to alternative approaches to the problems of dream memory.

Subjects and Methods

The nine subjects are described in Table 1.

There were two dream reporting conditions. Table 2 summarizes the division of subjects between the two conditions. Five subjects, the "Morning-Afternoon" group in Table 2, placed a Dictaphone beside their beds for periods of one to five weeks. They were asked to leave the machine running all night so as to be ready for the recording of each dream immediately upon waking in the morning. Each dream was dictated again in the afternoon. Only one subject in this group succeeded in reporting more than two dreams; she produced 19 sets of dream reports. Her data are not included in this paper.

Four subjects, the "Night-Morning-Afternoon" group in Table 2, dreamed in a laboratory. All were male university students. They slept on a narrow cot in a sound- and light-proof room from about 11 PM until about 7 AM. These subjects wore EEG electrodes attached to their scalps and faces. Six hours after a subject was asked to go to sleep the experimenter began to monitor the EEG and eye movement recording. Four and one-half minutes after the onset of the first "rapid eye movement" period during monitoring a very loud buzzer awakened the subject. Upon waking, the subject dictated his dreams into a bedside Dictaphone and then went back to sleep. This was the Night dream report. One hour later the subject was awakened again to dictate a Morning report of all dreams he could remember from that night. The subject then left the laboratory. In the afternoon, about eight hours after the Morning report, the subject returned to dictate a third, Afternoon report. There was no experimenter-subject communication during reporting; all instructions were given before the subject retired.

The experimenter scordd the dreams from typed transcripts on a multidimensional scoring system devised especially for this study (Appendix A). The scoring system consists of 11 variables which are scored on each dream report considered as a whole and 35 variables which are scored on each Dream Unit. The Dream Unit (Appendix A) is a grammatically defined group of words, usually 7 to 15 words, which approximates natural conceptual units. The scoring system includes specific kinds of content (e.g., color, sex, relatives), measures of affect (e.g., dreamer's affect), ratings of style (e.g., bizzareness, specified rationality), and ratings of comparisons between successive reports (e.g., forgetting /information loss/).

Results

I. How much is forgotten?

1. There was considerable forgetting between reports. Table 3 summarizes the data on forgetting. The numbers in Table 3 are averages for information preservation from one report to another. A perfectly reproduced Dream Unit would score nine, while a Dream Unit whose content disappeared completely between one report and the next would score zero. The overall average

information preservation score of 3.27 on the zero to nine scale indicates a loss, on the average, of more than half the information in the initial reports.

2. Dreams first reported in the Night condition were forgotten to a greater extent than dreams first reported in the Morning condition. This result is shown in Table 3, and it is even more apparent in the fact that when the data averaged in Table 3 are divided into comparisons of Night (initial reports) with Morning (second reports) and comparisons of Morning (initial reports) with Afternoon (second reports), 66% of the Night-Morning Dream Units scored zero memory, while only 33% of the Morning-Afternoon Dream Units scored zero memory.

3. Very few dreams were completely forgotten. Of the eleven dreams studied, only one, a Night-reported dream, was completely forgotten before the second report. One dream was forgotten between the first and second reports except for a fragment. A similarly low incidence of forgetting dreams completely after the initial report occurred in the 19 dreams of subject E (whose dreams are not otherwise included in this paper).

II. What is forgotten?

4. Forgetting was non-random. If the forgetting of dreams were a random process such as, for example, the random deletion of words, then one would obtain a normal random distribution of scores for Dream Unit Forgetting; the mode would be the same as the mean of the distribution. Table 4 shows a highly skewed distribution with the modal score, zero (memory), accounting for 45% of the Dream Units. In other words, the unit of forgetting tended to be not the individual word, but rather the concept, the 7 to 15 word Dream Unit.

5. Some aspects of dreams remained quite stable through successive reports. For example, in the majority of cases there was no discriminable difference between the initial and second reports on any of the variables: Bizzareness, Arbitrary Continuity, Maximum degree of physical and logical improbability, Maximum degree of social improbability, Familiarity of locale and personnel, Pleasant-unpleasant affect, Activity-passivity of the dreamer, Activity-passivity of dream personnel)

III. Other findings.

6. Forgetting was positively correlated with importation of new material. When forgetting is defined as mean information loss per Dream Unit between a report and a later report, then importation (i.e., secondary elaboration) may be defined as the mean information loss between a report and an earlier report. That is, if a first report contains Dream Units (A,B,C) and a second report consists of Units (A,B,X), then the dreamer has forgotten (C) and imported (X). Table 5 shows the correlations between forgetting and importation per Dream Unit (that is, after removing the covariance due to report length). In the comparison of all first and second reports the correlation is +.70. This correlation rises to +.91 if the total amounts of information forgotten and imported are correlated (without removing covariance due to report length).

7. In spite of the positive correlation between forgetting and importation, there was a net decrease of scorable content between successive reports. The results for the first vs. second reports, shown in Table 6 are representative. Nine of the variables measuring kinds of content tended to occur more often in the first reports, as against only two which tended to occur more often in the second reports.

8. There was no net decrease in the number of kinds of scorable content between Night and Morning reports; the entire net decrease occurred between Morning and Afternoon reports. Table 6 shows that the six variables which tended to decrease in frequency between the Night and Morning reports were matched by six others which tended to increase. Thus, if one were concerned only with having some fantasy material to interpret (as opposed to having an accurate reproduction of the experiental dream), the Morning reports, but not the Afternoon reports, would be as adaquate as the Night reports in this sample of dreams.

9. No evidence for repression as a selective instigator of forgetting was found. It was hypothesized that repression would be a major factor in the forgetting of dreams. To test this it was assumed that the repressive process would tend to remove or distort not only material whose latent meaning was ego-alien, but also manifestly ego-alien aspects of the dreams. It was also assumed that for the subjects of this study bizzare, irrational, sexual, violent, etc., aspects of manifest dreams would be ego-alien, and that defensive processes used to cover up such material would appear in the form of negations, qualifications, doubts, etc. These assumptions made it possible to test the repression hypothesis in the form: as compared to initial reports, later reports will be more rational, more defensive, and better controlled. Table 7 lists the variables relevant to this hypothesis and shows that the data give it no support; in fact there is a slighttrend in the opposite direction.

10. No evidence of more regression in earlier than in later reports was seen. The regression hypothesis was tested by means of two subsidiary hypotheses: a) Vocabulary level will be higher in later reports than in earlier ones; b) As compared with earlier reports, later reports will be more rational, less arbitrary in their continuity, less improbable, and less bizzare.

There was no support for either (a) or (b) in the data. Six dreams had higher vocabulary levels in the second report, but five had lower levels in the second report. The trend of results for (b) was opposite to the hypothesis.

Discussion

This study made use of two techniques not used in other studies of dreams:

1. The method of successive reports of the same dream. The results suggest that in spite of the great reduction in between-dream error variance, the successive reports method is of limited usefulness because of the influence of having given an initial report on what is remembered later. Of the 11 dreams, 10 were still recalled to some extent at the time of the second report. It is the writer's impression that this constitutes considerably better recall than is commonly found in delayed recall of dreams when no immediate or morning report is elicited. Thus, it appears that reporting a dream has an important influence on memory at a subsequent recall (cf. also Bartlett, 1932).

However, there was a good deal of variability in the memory scores. There would seem to be no barrier to studying the differences between dreams the memory of which holds constant between reports as contrasted with those dreams remembered poorly. The present sample is too small for such a study.

2. Comparison of Night reports (REG method) with Morning and Afternoon reports. These comparisons (result No. 2) appear to show less forgetting in the eight hours of activity between Night and Morning reports than in the one hour of sleep between Night and Morning reports. Such a result poses difficulties for both decay and retroactive inhibition theories

of forgetting. One speculation that could account for the results would be that Night-collected dream reports, which are obtained immediately after the experiental dream, are more like the experiental dream than are the Morning-collected reports, and hence Night-collected reports are more susceptible to repression and distortion. Another speculation would be that since the subject giving a Night report knows he is about to go back to sleep, he purposely keeps himself in a less alert state of consciousness while reporting than does the Morning-reporting subject. A drowsy state of consciousness might be inimical to efficient learning during the rehearsal which the reporting provides. Another strong possibility is that the observed differences were simply subject differences, for the two kinds of comparisons use non-overlapping subject groups.

Quantitative measurements on dreams are not new (e.g., Gordon, 1952), but attempts at quantification have been few. The difficulties which beset quantitative handling of data are much the same for dreams as for TAT stories; there are a multitude of potential variables; there is insufficient theoretical or empirical rationale for grouping variables or focusing on a limited sample of variables; and the frequency of occurrence of individual variables is often too low. This study suffers from its share of these problems. However, such obstacles seem at least no more formidable for dreams than for the TAT. It is the author's impression that is is no more difficult to score dreams for their manifest content, affect, and style than it is to do similar analyses on TAT stories.

None of the hypothesized effects of repression was observed. To what extent should this be taken as evidence against the importance of repression in the forgetting of dreams? The answer to this question would depend on knowledge about factors which may have obscured the observation of repression's effects. Theoretically it is the content whose latent meaning is unacceptable which should be most susceptible to repression, but this experiment measured manifest content. The assumption that manifestly ego-alien content is also ego-alien at the level of the latent content may, of course, not hold true. Also, the giving of the initial report probably had considerable impact on the subsequent course of forgetting. If this impact was accomplished by the subject's bringing to bear different (i.e., waking) modes of thought in his reorganization of the dream memories while giving the initial report, than the susceptibility of the dream to repression might be considerably lessened.

Two implications for future research suggest themselves:
1) A larger-scale study should either be a multi-investigator, multi-purpose study or it should use an already extant scoring system. The effort necessary to devise, score, and refine an original scoring system is disproportionate to the results a single investigator is likely to achieve.

2) Future studies on the memory of dreams might well concentrate on the dreams of a single subject, or at the most, two subjects. The arguments for this approach which Skinner (Skinner, 1932) and Sidman (Sidman, 1960) have advanced apply with special force to behavior such as dreams, where highly

individualized cognitive styles may have to be contended with.

Several further studies may be suggested:

1) Unexpectedly, usage vocabulary level did not vary with state of consciousness (that is, with Night, Morning, and Afternoon reporting conditions) in this experiment. A more systematic study of vocabulary usage level and state of consciousness would be interesting.

2) What is the forgetting curve for dreams through the day? This could easily be measured by collecting large samples of dream reports from students in classes which meet at different times of day.

3) The changes from Night to Morning reports were larger than the changes from Morning to Afternoon reports (result No. 2), but due to the design of the study one cannot tell whether this difference should be attributed to conditions or to subjects. It would be interesting to replicate this part of the experiment on a single subject or a single group of subjects.

4) There is a possibility that subjects "learned" their dreams from hearing themselves speaking the dream while making the initial report. Would this learning ability vary as a function of the EEG sleep stage from which the subject had just been roused?

SUMMARY OF REMARKS AT MEETING OF SLEEP AND DREAM RESEARCHERS

Allan Rechtschaffen
The University of Chicago

1. Reports of Mental Activity During Sleep: Allan Rechtschaffen, Paul Verdone, and Joy Wheaton. Seventeen normal subjects spent, in total, 30 nights sleeping in the laboratory. Before bedtime, each subject was told that we would awaken him several times during the night and that we would want to know about the extent and quality of his mental experience during the period of sleep preceding the awakening. The subject was thoroughly briefed as to the kind of information we wished to obtain, so that a minimum of experimenter-subject communication would be required during the awakening period. Awakenings were accomplished by a standard buzzer. Upon awakening, the subject spoke to the experimenter via an intercom and gave a spontaneous report of all he could recall. Following this report a bulletin board at the foot of the subject's bed was illuminated. On this board was an outline of a series of questions about the sleeping mental experience which the subject answered by voice without interruption by the experimenter. The nature of the items in the questionnaire will become apparent as we discuss the results. A total of 186 experimental awakenings from REM and NREM periods were made and analyzed. In each instance, statistical significance was evaluated by Cochran's test. Unless otherwise specified, the results to be described were significant beyond the .05 level of confidence, using a two-tailed test.

a. Subjects reported some specific content of mental experience in 86% of REM awakenings as compared with only 22% for NREM awakenings. Even when specific mental content was recalled during a NREM awakening, recall was generally described as poorer than for REM awakenings.

b. Subjects judged whether they had been thinking or dreaming while asleep, independent of amount of recall. Dreaming was reported in 87% of REM awakenings and 41% of NREM awakenings. In contrast to this, "thinking" was reported for 19% of NREM and only 8% of REM awakenings. When only those reports where the subject was able to recall a specific element of content were considered, "thinking" reports rose to 73% for NREM awakenings and dropped to 6% for REM awakenings.

c. Subjects described 74% of REM experiences as being vivid as compared with only 24% of NREM experiences so described.

d. 61% of REM experiences were described as primarily visual as compared with 40% of NREM experiences. Only 16% of REM experiences were described as having been primarily conceptual as compared with 36% of NREM experiences so described. Frequency of auditory reports was similar for REM and NREM awakenings, being 17% and 13% respectively.

e. Subjects said they experienced some volitional control over their mental processes during sleep in 25% of REM awakenings. This figure rose to 36% for NREM awakenings.

f. 37% of REM experiences were rated bizarre or implausible, while only 6% of the NREM experiences were so rated. While the difference was significant at only the .06 level of confidence, subsequent experience convinces us that this difference is not sampling artifact.

g. NREM experiences were more often described as dealing with the subject's contemporary life, as compared with REM experiences, which more frequently contained places, events, and people associated with earlier periods of the subject's life. The difference here, however, reached significance at only the .08 level of confidence.

h. Finally, subjects judged whether they had been in deep sleep as compared with light sleep, dozing, or awake. 51% of REM awakenings elicited reports of deep sleep as compared with only 25% of the NREM awakenings.

Our impression is that NREM mentation resembles that large portion of our waking thought which wanders in seemingly disorganized, drifting, non-directed fashion whenever we are not attending to external stimuli or actively working out a problem or a daydream.

Not all NREM reports are clearly thought-like. Most often, NREM reports have the qualities of thought plus some of the qualities we usually attribute to "dreams". Whether one wishes to classify such reports as "dreams" is simply a matter of definition. Some NREM awakenings produce reports which are extremely "dreamlike" in every sense of the word.

How can we be sure that NREM reports are not artifactual attempts to please the examiner, memories of earlier dreams, memories of prior waking thought, mentation experienced in the act of awakening, or confabulations? Two lines of evidence suggest that at least some mental activity reported on NREM awakenings did indeed occur during NREM periods. 1) As several investigators have noted, most sleep talking occurs during body movements in NREM periods. Since brain waves during sleep talking are generally obscured by muscle tension, it is difficult to say whether the subject was in a NREM stage at the moment of speaking. However, the subject does seem to be asleep while speaking, because if he is aroused shortly afterwards, he generally cannot remember having spoken or anything he said. The content of the speech often "sounds like" a continuation of ongoing mentation, e.g., occasionally subjects speak in their sleep as if they were giving us an experimental report of some immediately preceding mental activity. 2) One of our subjects occasionally incorporates external stimuli presented during NREM periods in the content of his mentation, thus providing us with a temporal landmark for the mentation. For example, during one NREM period (Stage 2), the following sequence of stimulation was presented: 67 seconds after the subject showed a slight body movement, a 500 cps tone was presented below waking threshold for 7 seconds. This was followed in turn by 27 seconds of no stimulation, a second presentation of the tone, and an additional 32 seconds of no stimulation. Then the subject was awakened by a loud buzzer. He reported that he dreamt he was standing on a rock talking with someone, then:

> "...a little whistling tone that was going on...and then it went off. And they (the other person) said 'Oh, you had better get things over with quickly, because you may have to wake up soon.'...I just said 'Oh!' to this, and I think I heard the whistling noise again....Then the same scene was there for some time, and I was just walking around trying to think of what was going on."

Then the subject described being awakened. On further questioning, he overestimated all the time intervals in the sequence of stimulation, but he maintained roughly the correct relative duration of stimulation and non-stimulation periods.

Apart from differences between REM and NREM reports, we have made the additional observations: a) Recall improves as the night progresses, independent of EEG stage. b) Subjects tend to have poor recall if they report to the lab in a fatigued condition. c) Subjects seldom give reports of nightmares or frankly sexual dreams in the laboratory. We doubt if this represents mere concealment or non-reporting of dream material that was experienced. Our subjects are usually instructed that they do not have to report any dreams that they feel are too personal or embarrassing. However, we ask them to tell us when they are leaving something out; this almost never happens.

2. Motivational Control of Dreaming: Allan Rechtschaffen and Paul Verdone. Twenty experimental subjects spent four nights each sleeping in the laboratory while their EEGs and REMs were continuously monitored. On two of the nights each subject was told that he would be financially rewarded for dreaming as much as possible, and on the other two nights he was told he would be rewarded for dreaming as little as possible; motivational conditions were counterbalanced.

a. Reliability studies indicate that different pairs of independent raters attain reliabilities in the neighborhood of .90 in scoring amount of dreaming per night on the basis of amount of Stage 1 EEG and REM time.

b. Preliminary analyses, based upon absolute amount of Stage 1-REM time, indicate that the motivational variable was not effective in controlling amount of dreaming. Further analyses utilizing corrections for differences in amount of sleep remain to be completed before a final definitive statement regarding the effectiveness of this motivational variable can be made.

c. Individual interviews with each of the subjects were held to gauge the nature of their subjectively experienced motivation, the extent to which they felt motivated, and the degree of confidence they felt in controlling their dreaming. These data are being analyzed to determine what part these variables might have had in the effectiveness or non-effectiveness of the motivational variable.

d. TAT stories and MMPIs were obtained from the experimental subjects to determine whether individual differences in amount of Stage 1-REM time might be correlated with personality variables. These data are in the process of analysis.

e. There is a marked tendency for subjects to dream less on the first night they spend in the laboratory than on any of the succeeding nights. This datum, combined with the paucity of manifestly sexual dreams generally elicited in our experimental situation, suggests the possible operation of a strong vigilance factor.

f. There is a positive correlation between amount of sleep time prior to the first Stage 1-REM period and the length of the first REM period. This suggests that the sleep-dream cycle itself may be largely a "dream-deprivation" phenomenon.

3. The Effect of Dexedrine on the Sleep Cycle: Louise Maron and Allan Rechtschaffen. Various theoretical considerations prompted us to give dexedrine spansules to subjects just before they were put to bed. While many subjects were unable to sleep under these conditions, those who did showed dramatic reductions in the amount of time spent in Stage 1-REM periods as compared with placebo-control nights. When dexedrine spansules were given in combination with nembutal just

before bed time, the subjects were able to sleep. Under these conditions, there was a marked reduction in amount of Stage 1-REM time as compared to a nembutal-placebo control condition. Approximately 40 subject-nights of experimentation on this problem have been completed.

4. Procedural Comments. We have had very good luck with a particular method of attaching electrodes--it takes a bit more time, but it gives 99% assurance that the electrode will stay on through the night. For electrodes on the face and forehead: Clean with acetone or ether. (We have found ether to be slightly less irritating. Cleaning with soap and water is easier on the skin but yields only barely passable resistances.) With a skin marking pencil (the Blaisdell No. 268-T Skin Marking Pencil works fine) draw circles on the sites of electrode placement slightly larger than the electrodes to be used. With "Ace Adherent" (a resinous liquid compound manufactured by Becton, Dickinson & Co., Rutherford, N. J.) paint a thin film on an area about ½ inch wide outside the circumference of the electrode circle. While the film of Ace Adherent is drying, gently rub electrode jelly (we use Cambridge Electrode Jelly, Cambridge Instrument Co., Inc., Grand Central Terminal, New York, N. Y.) into skin within area delineated by skin marking pencil. When Ace Adherent is thoroughly dry, which requires only a few minutes, apply electrode and cover with an elastoplast patch. Duke Laboratories, South Norwalk, Conn., puts out a pre-cut elastoplast patch (what might be called an elastoplast band-aid) which we have found ideal for the purpose. Their size No. 310, which is 1½" x 1 1/8", seems most convenient. For scalp electrodes the adherent method cannot, of course, be used. We simply cover the electrode with a patch of collodion-soaked, double-thickness gauze, and dry. A good quality hand hair dryer works as well as an air hoze and requires three fewer hands.

In the morning, the Ace Adherent is easily removed with acetone. However, the same cleaning effect can be accomplished with a commercial hand cleaning preparation called "Nixx", manufactured by Nixon Laboratories, Inc., Chicago 47, Ill., which involves none of the irritating effects of acetone. One of the disadvantages of the above system is that the adherent-elastoplast combination sticks so well that removal of the elastoplast in the morning is sometimes slightly painful.

Where mild skin irritation has been produced, the use of Nivea cream (Duke Laboratories), applied in the morning, seems to have a soothing effect.

THE SIGNIFICANCE OF EYE MOVEMENTS IN DREAMING

Howard P. Roffwarg,M.D.; Joseph Muzio,A.B.; William C. Dement,M.D.

Evidence from previous work by Aserinsky and Kleitman (1955), Dement and Kleitman (1957) and Dement and Wolpert (1958) suggested that the rapid eye movements occurring during the low voltage, fast sleep EEG phase (Stage 1) were associated with the visual imagery of the dream.

The present study was undertaken in an effort to show that a one-to-one correlation exists between the number and direction of eye movements, and what the dreamer actually "sees" in the dream, as well as how he looks at it.

Twelve subjects slept 38 subject-nights. They were awakened abruptly by an experimenter during Stage 1 sleep after a single or sequence of eye movements. A second experimenter interrogated the subject about the last visual elements in the dream, and then this experimenter made a predictive judgment on the basis of the dream report about the type and direction of the last eye movements. The predictions were then compared to the electrical recordings by two judges.

Of the 121 dreams reported, 77 were vividly recalled by the subjects. In this group, the prediction of the eye movements corresponded exactly, or near exactly, to the electroencephalogram in 80% of the cases. When dream recall was less certain, the correlation fell off to about 50%. Accordingly, where a subject could recall a dream accurately, there was a high probability that the eye movements could be predicted accurately. As the clarity of the dream diminished for the subject, so did the ability of the experimenter to predict correctly.

This study adds to the developing literature about the nature of the

dreaming experience. Other workers, studying respiratory and pulse rates, have shown that dream content is related to the frequency and variability of these autonomic parameters. The dreamer thus "watches" his visual hallucinations and reacts both physically and emotionally to them.

G. H. HYSLOP, M.D. What of color imagery?

REPLY BY DR. ROFFWARG:

Although there are no published reports on the incidence of color dreams in normal subjects when this method is used, it is our general impression that all dreams are in color, but the memory for color is very transient. Thus, while recall of form and content are often retained, color memory frequently drops out by the next morning.

MEETINGS OF RESEARCHERS IN THE FIELD OF
EEG AND DREAMS---University of Chicago
March 27 and 28, 1961

Comments by: Dr. Frederick Snyder
Adult Psychiatry Branch
National Institute of Mental Health
Bethesda 14, Maryland

MEETING OF RESEARCHERS IN THE FIELD OF
EEG AND DREAMS---University of Chicago
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Scoring System and Problems:

Certain of the methodological difficulties involved in the quantitative estimate of sleep stages, especially that of percentage Stage I in total sleep time, have become very conspicuous in a current study attempting to compare the sleep patterns of normals, hallucinating and non-hallucinating schizophrenics.* Our original intention in this study was to make a precise classification and tabulation of time spent in the four stages of sleep as these are defined by Dement and Kleitman. The first difficulty arises from the fact that the sleep of our schizophrenic subjects has proved to be extremely disturbed, with a great deal of fluctuation in the EEG patterns from one stage to another, and quite frequent brief awakenings during the night. This means that a relatively large portion of the records are taken up by transitional patterns for which the proper classification is not obvious at a glance, and which would require a prohibitively laborious task of counting and measuring EEG waves.

So the first implication of this experience is one with which I assume no one will disagree: such quantitative studies demand a much easier and more precise means of quantifying the EEG record than that of visual inspection. Short of becoming involved in the expense and complexities of frequency analysis, we are planning to explore this matter further in terms of the sort of integrated records described by Paul Coleman et al., as well as the frequency count measure reported by David Lester. We hope to hear from other members of this group their thoughts and experiences in the area of automatized record analysis.

The second point is, that since there are such frequent fluctuations in these records, it no longer suffices to use an undefined measure such as Dement's a "fairly long stretch of record". For our purposes we have settled upon the procedure of treating the record as though it were divided into separate segments of one minute duration, then judging each of these in terms of the predominant pattern during that interval. Obviously such a unit must depend upon the questions at issue, and cannot be entirely standardized. For comparative purposes, however, it would seem necessary that the interval of record being judged should be specified.

* Since this study became a matter of subsequent discussion, the following is a brief comment about it. Mr. Richard Koresko, Dr. Robert Feinberg and I have recorded from the sleep of twelve schizophrenic patients over at least five consecutive nights in each case. It was the intention of the study that we would select six patients who were floridly hallucinating , and six who, to all indications, were not hallucinating, but that both groups would be in a relatively acute phase of illness. Despite extensive

By reason of the inordinate amount of labor involved, we have pruned our ambitions for the present to the point of tabulating only the percentage Stage I in total sleep time. Here too we encounter difficulties and these seem to be considerably more serious. Taken together they amount to the question: When does Stage I represent "Dream time" and when is it something different?

I think we all agree that the low voltage random pattern seen at the onset of sleep carries quite different implications from that seen during the REM periods later in the night. Similarly, we share Dement's uncertainties about the period of low voltage random activity frequently seen at the end of an REM period after a gross body movement, usually with little or no rapid eye movement, and merging into Stage II with the gradual onset of spindling. Does this represent "dream time", or is this more like the phenomenon th we see at the onset of sleep? Independently we have arrived at the same surmise mentioned by Jouvet, that the pattern associated with REM and dreaming might be functionally very different from Stage I at the onset of sleep; that it may have nothing to do with depth of sleep, but may be a different kind of sleep. Pertinent to this point, perhaps, is the common observation during dream deprivation awakenings that Stage I with REM does not usually ensue until after the subject has passed thru a brief period of Stage I without REM as well as at least a very brief period of spindling. A second type of observation which leads us to question whether the pattern associated with REM always represents the same 'depth' of sleep is that rather frequently the first REM period of the night does not follow after a gradual transition through Stages II and III, but may take off very abruptly from a characteristic Stage III pattern, even without intervening movement, or other evidence of arousal. Of course these are questions for further empirical study, and at a later point I shall mention some of our own efforts in relation to them.

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screening we were unable to find patients who were quite definitely acute, and at the same time not hallucinating. Those finally selected are probably less 'acute' than the hallucinating group. The latter is relatively 'acute' as hospital populations go, both in terms of the clinical picture and in terms of the historical information which was available to us. Still, they certainly are not as acute as the patient described by Dr. Fisher.

The processing of the data has been delayed by the problems described here, and the eventual results will contain inherent ambiguities for the reasons mentioned. Nevertheless, it seems clear from the data at hand that we will not find gross discrepancies in percentage Stage I time in either group which would clearly distinguish them from the normal. The striking differences are in terms of the disturbances of their sleep, including the REM periods, and the anomalous characteristics of much of their Stage I time.

With regard to the present topic, however, the point is that our schizophrenic patients show many body movements and other evidence of brief arousal even in the midst of REM periods; there are long stretches of record devoid of REM following these; and these frequently merge imperceptibly with stretches of Stage I which are associated with REM. What, then, are we to tabulate as Stage I time, if we aim for an estimate of "Dream time"?

A second problem along these same lines is one which we had occasionally encountered under other circumstances, but which looms very large in the records of these patients. This has to do with the presence of spindles, or at least abortive looking spindles, in the very midst of unmistakable rapid eye movement activity. The usual comment about this is that spindling never occurs simultaneously with REM, but in these records there are many instances of REM occurring within one or two seconds continguity with spindling. Again, there are long stretches of such record from these patients, and how are we to tabulate them?

A further difficulty in calculating percentage Stage I time stems from the fact that our patients frequently present numerous periods of wakefulness interspersed with their sleeping time. Should these be substracted from the total sleep time, or should this be calculated from the time of initial onset of sleep until final awakening, regardless of the discontinuity of sleep in between? The former procedure would seem to be a reasonable one, but doubt about this arises from the appearance of inherent periodicity and self-regulation in the occurrence of REM periods almost independent of the sleeping intervals between them. If this were not the case it would be meaningless to do control awakening during dream deprivation experiments, since these seriously disturb the non-REM sleep.

In summary, the extension of our techniques to the area of sleep pathology raises difficult questions, and perhaps highlights untested assumptions in relation to the sleep of normal subjects. I believe that the theoretical importance of these questions and assumptions demands further empirical work, which will certainly be very difficult and tedious. It would assist greatly in such efforts if we had additional, less ambiguous measures of sleep depth, as well as further, independent correlates of dreaming sleep. These are the ends to which my own interests now turn, and will be the subject of my discussion at a later time.

Session on Research Reports:

When I first became involved in this work I was extremely impressed and intrigued by the regularity of the sleep cycle and the predictability of detailed dream reports from REM periods. I've never ceased to be impressed by these things, but familiarity breeds contempt, and soon I found myself almost equally intrigued by the variations in dream recall during REM period awakenings. Clearly there are circumstances when we can predict little or nodream recall during Stage I periods with REM: the first REM period of the night; certain subjects who almost never recall dreaming; any subjects under specific circumstances such as unusual fatigue. We wondered whether this was entirely due to the vagaries of dream recall, or whether it might not be

possible that Stage I with REM is not always the same state either physiologically or experientially. This idea went together with the hypothesis expressed earlier that REM periods may not represent a 'depth' of sleep, but might be simply a different kind of sleep which can occur on various planes of depth.

With this in mind we have done a small scale study of arousal thresholds in relation to the four sleep stages. From this we are able to confirm that for a given subject on a given night the auditory thresholds for arousal from Stage IV tend to be greater than III, and these tend to be greater than II. However, there is great variability in absolute level of the thresholds from one subject to another, or in the same subject from night to night. It appears that the EEG patterns are a very relative index of depth of sleep, and we must search for other indices which would permit comparative studies of sleep depth among subjects, or in the same subjects under varying circumstances.

The situation with regard to arousal from Stage I is even more complicated. Some subjects ... consistently have auditory thresholds for arousal during Stage I which are hardly higher than their thresholds during the waking stage; other subjects consistently require sound levels equal or greater than the levels required to awaken them from Stage IV on the same night; most subjects vary over the entire range of thresholds quite unpredictably. Perhaps this is entirely a matter of the degree of the dreamers involvement in his dream, or perhaps it tends to support the idea that dreaming may occur at various sleep depths.

The question has led us to investigate the possibility that there might be other physiological measures which would distinguish dreaming from non-dreaming sleep, would be better indices of depth of sleep, and would relate to the vividness with which the dreamer recalls his dream experience. Thus far we have been primarily concerned with respiration, heart rate, skin temperature and the finger plethysmograph. Currently we are extending these efforts to include blood pressure, GSR, oxygen saturation by oximetry, and CO_2 tension of expired air. We can venture a tentative answer to only the first question, whether there are other indices which correlate with the occurrence of REM periods. The answer to this would seem to be positive in terms of all of the indices which we have studied in any detail: Respiratory rate, heart rate, plethysmography and skin temperature, but this answer requires qualification. There are two kinds of changes which characterize the REM periods: (1) A change in average level, which is somewhat inconsistent and would be a poor diagnostic indicator, (2) changes in the variability of the measure from minute to minute, which are much more consistent and characteristic. Of the variables studied the variability of respiration has been by far the most consistent correlate of REM periods. The only discrepancy arises from the fact that the respiration becomes variable shortly prior to the onset of Stage I with REM.

Although the variability of these measures is almost always greater than during non-REM sleep, there is a more striking range of variability among REM periods. Comparing five minute samples of REM sleep one finds threefold differences in the amount of variability of respiratory rate, for example. There is some predictability about this, in that the levels of variability tend to be low during the first REM periods and tend to be highest during the third REM period of the night. This is in keeping with our impression of a similar pattern in the vividness of dream recall over the several dream periods of the night.

The unenviable task remain of attempting to relate such measures to the characteristics of dream recall, as well as to the arousal thresholds,

THE EFFECT OF SUGGESTED DREAMS ON THE LENGTH OF RAPID-EYE-MOVEMENT PERIODS

Abstract of Ph.D. Dissertation

Johann Stoyva

Dr. Joe Kamiya, Sponsor
Dr. Austin H. Kiessen
Dr. Allan Rechtschaffen

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Earlier studies by Schrötter (1912), Rolfenstein (1923), and Nachmansohn (1925) had indicated that subjects could be made to dream on the night following a hypnotic trance about topics suggested by the experimenter during the trance. It was the initial purpose of the present investigation to try to replicate these previous experiments using the new physiological approach to the study of dreaming described by Aserinsky and Kleitman (1955).

Employing post-hypnotic amnesia for a trial trance period as the criterion for selection, the experimenter obtained a total of 16 subjects. On experimental nights the S's were instructed to dream about a given topic, for example, "climbing a tree," in every dream on that particular night. The subjects were then run in the sleep laboratory and dream reports were obtained. Dreams were scored as being in accordance with the suggested topic if the reported content showed a clear connection with the original suggestion; i.e., if there were identical or similar images present. Then for each S, percentage of dream reports in accordance with the suggestion was calculated from the ratio of:

$$\frac{\text{Total number of awakenings which produced reports in accordance with suggestion}}{\text{Total number of awakenings which yielded content of any kind}} \times 100$$

Of the 16 S's, seven produced content reports in accordance with the dream suggestion from 70% to 100% of the time. These subjects reported dreaming about the same theme throughout the night. While there were variations on the basic theme supplied by the experimenter, the original suggestion was still clearly recognizable in each of the successive reports. Of the remaining nine S's, five gave dream reports in accordance with the suggestion for 40% to 60% of the time, and four gave reports in line with the suggestion from 0% to 33% of the time.

In the group of subjects who regularly reported dreaming in accordance with the suggested topic (70% to 100% of the time) it was

observed that there was a marked reduction in the amount of REM time on experimental nights as compared with REM time, for these same subjects on control nights when no post-hypnotic dream suggestion had been operating. In the case of the nine other subjects, who were run for a total of 31 nights, no such reduction was apparent. The seven subjects, constituting the "70%-100%" group were run for a total of 31 nights--19 control nights; 12 experimental nights. When the difference between the experimental and control nights was tested with the Wilcoxon Signed Rank Test for Paired Observations it was found to be significant at the .05 level.

The present study was of interest in that:

1. It confirmed the reports of earlier investigators that subjects could be made to dream on the night following a hypnotic trance about topics suggested by the experimenter during the trance.

2. The use of the new methodology extended the earlier findings by establishing that certain subjects will dream about the suggested topic in every REM of the night, when instructed to do so.

3. In the group of seven subjects who regularly (70% to 100% of the time) reported dreaming in accordance with the suggested topic, there was a reduction in REM time on those nights on which the subject had been given post-hypnotic dream suggestions. This reduction in REM time, or "shortening effect," was of significance in that it established that it was possible for a psychological variable--the pre-sleep verbal stimulation--to influence not only the content of dreams, but to alter the lengths of REM's as well.

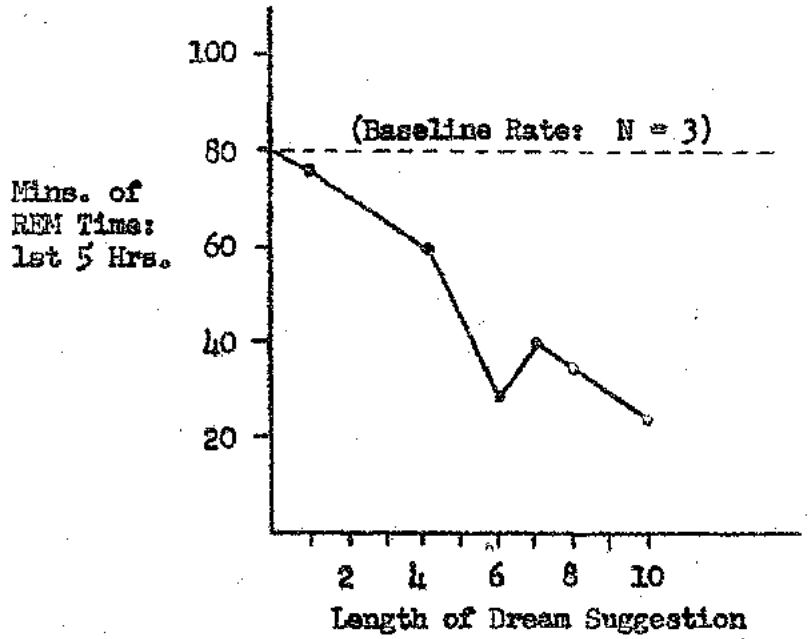
4. When four subjects (all from the 70% to 100% group) were given dream suggestions in the usual manner and run for a total of 18 nights of stage 2,3,4 awakenings, it turned out that almost 50% of the stage 2,3,4 reports obtained were in accordance with the suggested topics. This finding bore upon the problem of the relation between REM mental activity and that occurring in the other stages of sleep. It would seem that subjects make no absolute distinction between the two processes.

5. The shortening effect would seem to be of value for current research on the nature of hypnosis in that it provides a non-verbal indicator of the occurrence of hypnotic, or rather, post-hypnotic hallucinations; i.e., the shortening effect is a response measure which is correlated with the subjects' reports of dreaming in accordance with suggested topics.

Suggested Dreams and the Length of Rapid-Eye-Movement Periods

Johann Stoyva
3-7-61

Subject
CE



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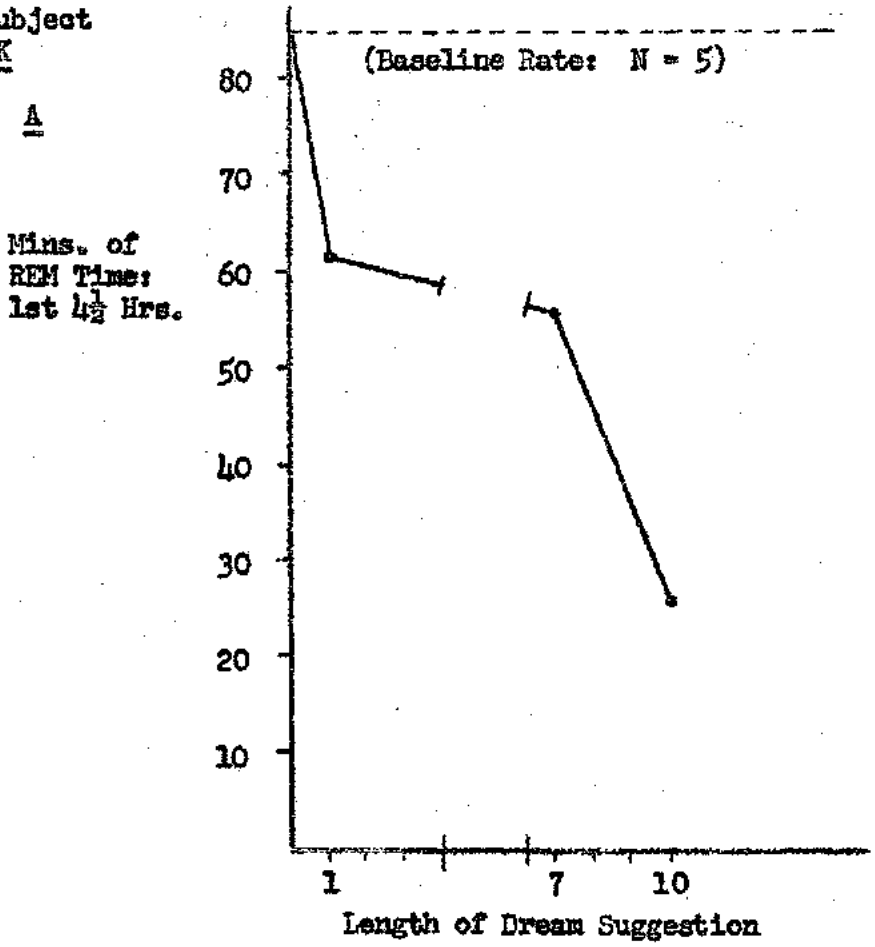

RELIABILITY OF "DREAM" TIME

Raters X & Y

Subj. #	Night #	Rater X	Rater Y	Absol. Diff.
1	1	50	48	2
	2	137	125	12
	3	100	96	4
	4	130	144	14
2	1	85	102	17
	2	87	92	5
	3	101	108	7
	4	137	139	2
3	1	102	122	20
	2	126	125	1
	3	108	116	8
	4	92	103	11
4	1	60	69	9
	2	104	122	18
	3	118	120	2
	4	97	97	0
5	1	94	98	4
	2	89	113	24
	3	117	128	11
	4	92	112	20
6	1	89	76	13
	2	132	125	7
	3	117	125	8
	4	121	115	6
7	1	70	83	13
	2	76	90	14
	3	107	126	19
	4	83	104	21
8	1	144	137	7
	2	164	149	15
	3	175	173	2
	4	157	162	5

$r_{XY} = .90$

Raters X & Z

Subj. #	Night #	Rater X	Rater Z	Absol. Diff.
13	1	53	68	15
	2	100	100	0
	3	79	83	4
	4	80	84	4
14	1	64	62	2
	2	94	90	4
	3	104	92	12
	4	97	92	5
15	1	124	126	2
	2	164	153	11
	3	156	167	11
	4	131	147	16
16	1	69	94	25
	2	96	102	6
	3	84	85	1
	4	113	116	3
17	1	79	105	26
	2	108	89	19
	3	116	96	20
	4	99	99	0
18	1	27	25	2
	2	100	78	22
	3	73	77	4
	4	130	143	13
19	1	57	54	3
	2	87	79	6
	3	114	103	11
	4	110	143	33
20	1	110	111	1
	2	163	169	6
	3	107	113	6
	4	148	149	1

$r_{XZ} = .92$

Combined Data

Absol. Diff.	Freq.	Cum. Freq.	Cum. %
0	3	3	5
1	4	7	11
2	7	14	22
3	2	16	25
4	6	22	34
5	3	25	39
6	4	29	45
7	4	33	52
8	2	35	55
9	1	36	56
10	0	36	56
11	5	41	64
12	2	43	67
13	3	46	72
14	2	48	75
15	2	50	78
16	1	51	80
17	1	52	81
18	1	53	83
19	2	55	86
20	3	58	91
21	1	59	92
22	1	60	94
23	0	60	94
24	1	61	95
25	1	62	97
26	1	63	98
27	0	63	98
28	0	63	98
29	0	63	98
30	0	63	98
31	0	63	98
32	0	63	98
33	1	64	100

A B S T R A C T

The Application of the REM Technique to the Study of Telepathy and Dreaming.*

Ever since Freud's early conjectures on the possibility of telepathic influence upon dream content, there have appeared in the psychiatric literature reports dealing with presumptively telepathic dreams. In New York City in 1947 a number of psychiatrists and psychoanalysts formed the Medical Section of the American Society for Psychical Research for the express purpose of studying the occurrence of the telepathic dream in the therapeutic milieu. One of the chief difficulties inherent in the clinical approach was, of course, that it was limited to those occasional dreams recalled by patients that appeared to be presumptively telepathic, that is, seemed to relate temporally and in content to events in the therapist's life of which the patient could have no normal knowledge nor could such content have been reasonably inferred by the patient.

Beginning with the clinical impression that telepathic dreams may occur and now having at hand experimental techniques making it possible to obtain a high yield of dream recall, it became possible to test the following hypotheses:

(1). Telepathic influence can be detected more frequently in dream content than in waking productions.

(2). When target material is selected on the basis of need, area of conflict, or current anxieties, telepathic elements occur

* This experiment is being conducted on a grant from the Parapsychological Foundation, 29 West 57 Street, N.Y., N.Y.

more frequently than when targets are chosen on a purely random basis.

Two adjoining rooms on the premises of the Parapsychology Foundation were made available for the experiment, one for the sleeping subject and the other housing the agent, the electroencephalograph and the E.E.G. technician. The two rooms were linked by an intercom. The subject reports to the laboratory at his usual bedtime. The electrodes are applied and he is instructed about the general nature and purpose of the experiment. Recordings are taken from the parietal and frontal areas and both external canthi.

In the waking phase of the experiment a randomly chosen target picture is exposed and placed before the experimenter. The subject in the adjacent room is asked to associate to any pictures or images that come into his mind over a ten-minute period. A microphone located at the bedside leads into a tape recorder in the experimenter's room.

In the sleeping phase of the experiment the target picture to be used is exposed to the experimenter after the subject has gone to sleep, and remains in his view throughout the night. The subject is awakened at the termination of each dream episode as near as this can be determined by the electroencephalographic criteria. The awakening occurs over the intercom with the agent asking the subject if he has been dreaming and if so to report the dream.

The first six months have been largely exploratory and devoted to testing the applicability of these particular electroencephalographic techniques to parapsychological research. This involved problems having to do with the selection of subjects, the setting of conditions under which ordinary sensory cues are eliminated, the proper selection and randomization of target material, and the evolution of quantitative techniques for matching target pictures and dream content so that independent judging could take place.

Montague Ullman, M.D.
Douglas Dean
Karlis Osis, Ph.D.

Variables Relating to Early Visual Memory Reports from Stage One with Rapid Eye Movements

Paul Verdone
The University of Chicago

The focus of preliminary work was upon a correspondence dimension of stage one reports, namely, the historical time setting of the manifest content. More specifically, a distinction was made between contemporary setting (CS) and early visual memory (EVM) reports. In order for a report to be considered of the EVM type it had to meet the following two criteria: 1) contain at least one element (i.e., person, place, object, event, or activity) which had not been encountered in reality for at least a month, and 2) have been perceived visually in sleep by the subject (based upon introspective judgment of the subject). All other reports were classified as CS.

Informal observation had given indication that the content of stage one reports moved farther back in time in terms of the personal history of a subject as the night progressed. One possibility was that the simple fact of being in bed longer was a determining variable in producing this effect. Accordingly, the following design was used for each of five subjects: two control nights and two experimental nights with stage one awakenings according to a predetermined schedule. The experimental condition provided for two hours of partial waking sensory deprivation immediately prior to the normal sleep. It was felt that this procedure might result in an earlier appearance of EVM reports as well as in more frequent EVM reports.

An analysis of the resulting 20 subject-nights of data provided no support to the view of a difference between experimental and control nights. On the other hand, the phenomenon of the correlation hypothesized between frequency of EVM reports and cumulative time in bed did seem to be substantiated. Dichotomizing good verbal reports (as judged by the subjects) by cumulative time in bed (using the hour closest to the median as the point of division), the author found more EVM reports in the hours 6-9 than the hours 1-6. The result was significant beyond the .05 level (two-tailed) for blind ratings made by the experimenter, and at the .10 level (two-tailed) for independently agreed ratings only by the subjects and experimenter. The test utilized, which seemed appropriate for the data, was one outlined by Cochran.[1] The difference in levels of significance can probably be attributed to the reduction of total EVM reports from 38 in the first analysis to 24 in the second.

In an attempt to relate the recall of these early memories with other variables a number of analyses were performed. Among the variables studied which showed no relationship with EVM reports were: 1) amount of sleep since last awakening, 2) short (2-5) minutes of stage one with REM preceding awakening versus long (10-20) minutes of stage one with REM preceding awakening, and 3) the subjects' judgments of four characteristics of the reports--vividness, prominence of visual modality, plausibility, and whether the mental activity was "thinking" or "dreaming". Although the data was sparse, there was no indication of marked intra- or inter-individual differences.

One of the variables which did show a relationship to EVM reports was amount of REM. Judgments of the amount of REM for each stage one period correlated positively with reports of EVM reports. The other relationship

which appeared in the data was the positive correlation between EVM reports and good recall. Whereas 40% of all reports were rated as having poor recall, only 10% of EVM reports were so rated.

In summary of the results from the preliminary study, three variables showed a relationship to each other: EVM reports, amount of REM, and judged good recall. In addition, as had been informally observed earlier, all three of these variables showed a relationship to how much cumulative time in bed the subject had had.

On the other hand, the preliminary work did not show a relationship of these variables to the amount of sleep since the last awakening. In fact, there were several clear cases (in different subjects) of EVM reports, with good recall and marked REM, in stage one "on the way down" (i.e., less than five minutes after sleep onset following an experimental awakening); these cases occurred despite a rather prolonged period of wakefulness (in terms of both behavioral and EEG criteria).

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1. Cochran, W. G. Some methods for strengthing the common Chi-square tests. Biometrics, 1954, 10, 417-451. Pp. 443-446.

Drugs, Dreams, and the Experimental Subject

Roy M. Whitman, M.D.

Ten volunteer subjects were monitored throughout forty nights of dreaming. Each of the ten subjects had one night of dreaming as a basal measurement, and one night each after three days on phenobarbital, prochlorperazine or imipramine.

The manifest dream content was scaled in seven areas: hostility, dependency, anxiety, motility, homosexuality, heterosexuality and intimacy. Findings from the dreams were in two major areas: those from the scaling process, and those which revealed the unconscious attitudes and fears that the subjects had towards the experiment itself.

Imipramine significantly decreased the number of dreams per night and significantly increased the expression of hostility per word of the dreams. There was a tendency for prochlorperazine to increase the expression of heterosexuality and phenobarbital to increase the expression of homosexuality in dreams. Nonspecific drug effects noted for all three of the drugs were an increase in the appearance of dependency and anxiety in the dreams and a decrease in intimacy.

Of 111 dreams dreamt over the forty nights, approximately one-third dealt with the experiment obviously, one-third dealt with it in a disguised way, and one-third dealt with other concerns. In this situation of two male experimenters monitoring EEG and eye movements in a room adjacent to the sleeping subjects, male volunteers dreamt largely of castration anxiety and passivity anxiety, and female volunteers dreamt largely of sexual exploitation. There was a striking contrast between their overt cooperativeness and the amount of anxiety about the experimental situation noted in the dreams.