Exhibit P-76

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THE CLASSICAL CONDITIONING OF SLEEP AND WAKEFULNESS

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Summary—Using a metronome beat as conditioned stimulus three cases are described in which this stimulus was presented in close temporal contiguity with experimentally-induced sleep or waking. Drugs or fatigue consequent upon sleep deprivation were used as unconditioned stimuli for sleep. One of the subjects was an anxiety neurotic, one had narcolepsy and the third was a student volunteer. No EEG indication of conditioned sleep was obtained but there was evidence of conditioned relaxation in the anxiety neurotic and conditioned arousal in the other two cases.

INTRODUCTION

SLEEP as a provoked response in human subjects has received surprisingly little attention in the English-speaking literature. Yet the notion that sleep should be susceptible to conditioning is fully consistent with most contemporary theories regarding this form of behaviour. As Hebb (1949) has pointed out, "The conditions that produce sleep are not merely negative: The fact is, that some stimulations contribute positively to sleep and sleep is reinforced by learning". That such learning can take the form of classical conditioning has been demonstrated experimentally in animals (Pavlov, 1928; Clemente *et al.*, 1963).

Attempts to condition sleep in man are confined almost entirely to the Soviet Union. Beilin (1952) reported on 204 patients treated by reflex sleep in the Makarov Hospital. Using heat, light or sounds as conditioned stimuli and sedative drugs as unconditioned stimuli, he induced up to 17 hr sleep a day in his patients, even after the drug had been replaced by placebo. Similar work has been reported by Chukhrienko (1952), Gorbatsevich (1955) and Davidenkov (1954).

In Germany, Marchand (1954) conditioned 20 patients to sleep in response to a buzzer. Hypnotic suggestion was used as the unconditioned stimulus, which makes it difficult to know whether the sleep he produced was the result of conditioning or hypnotic suggestion.

Our own work in this area was done in the context of Behaviour Therapy. Some forms of treatment under that heading, notably desensitization in fantasy, rely very heavily on the patient's ability to relax, relaxation being regarded as a state incompatible with anxiety. We have, however, found some patients quite unable to benefit from the usual methods of progressive relaxation as described by Jacobson (1938) and adapted by Wolpe (1958). For such patients, and others afflicted by sleep disorders of various kinds, conditioned reflex sleep (or its antecedent relaxation) seemed to offer some promise.

Our procedure was essentially this. The sound of a metronome was repeatedly paired with the onset of sleep. In some of the cases to be reported sleep was induced by injection of a fast-acting barbiturate. In others, the spontaneous onset of sleep in normally fatigued or sleep-deprived subjects was used as the response to be conditioned. In one case, that of a narcoleptic patient, the procedure was reversed, so that waking rather than sleep was paired with the auditory stimulus. A few cases illustrative of our procedure will be described in detail.

CASE STUDY 1

The first is that of a 35 yr old man with a 10 yr history of anxiety-phobic symptoms accompanied by severe hyposomnia. He had taken sodium amytal gr. 3, nightly for many months, and occasionally required additional sedation in the daytime to counteract his feelings of anxiety and panic. A journalist by profession, he was obliged to abandon his job six months before conditioning treatment began.

Procedure

In the pre-acquisition phase the patient was asked to listen to a metronome set to 58 beats/min, which he himself activated whenever he was ready to go to sleep. The possible effect this stimulus might have had on the patient's arousal system prior to conditioning was monitored on the EEG. The record showed no change in response to the metronome. A test of salivary responsiveness described by Corcoran (1964) was also administered. It was given on the assumption that greater relaxation after sleep conditioning might lead to increased parasympathetic activity and hence greater output of saliva in presence of the conditioned stimulus.

The acquisition trials, of which there were 16, consisted of metronome 58 beats/min for three min, followed by the injection of methohexitone, which led to muscular relaxation and narcosis in about 70 sec. Following each injection, the patient woke spontaneously after about 10 min. The acquisition trials were interspersed by three test trials, in which saline was injected instead of the barbiturate. All trials were monitored on the EEG.

Results

Although no EEG changes were noted during the test trials, the patient showed sudden clinical improvement after the fourteenth acquisition trial. The metronome, which had seemed highly unpleasant to him in the pre-acquisition control period, was now experienced as soothing and soporific. At his request, he was provided with a bedside metronome to take away with him, and this he used daily for several weeks to induce sleep or relaxation. On several occasions his blood pressure was taken before and 10 min after use of the metronome. The decrement in blood pressure following stimulation is plotted as a function of time in Fig. 1. Control-readings of blood-pressure changes were taken in the absence of metronome stimulation, showing two out of five changes to be in the direction of increased blood-pressure.

Changes in salivation after conditioning were in the expected direction, i.e. incremental, suggesting that some degree of parasympathetic facilitation had occurred.

The patient was eventually provided with a portable metronome which can be worn behind the ear. Seven months after termination of the experiment, during which he has received other forms of Behaviour Therapy, he is still using this device to calm himself when he feels anxious or upset. He requires next to no sedation, is out of hospital and has a part-time job.

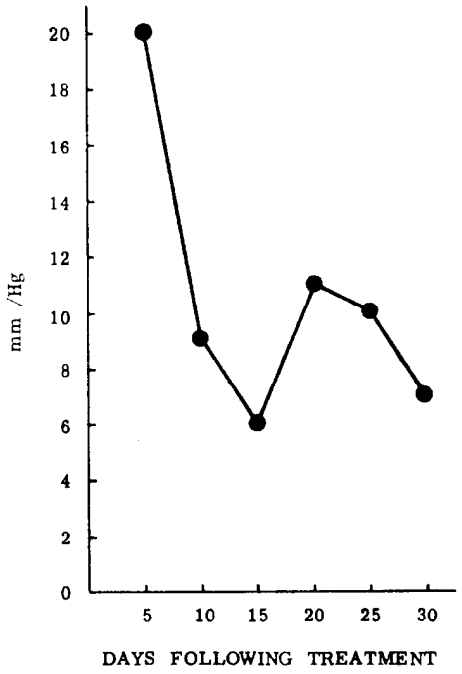

FIG. 1. Drop in blood pressure following use of metronome.

Discussion

Though clinically successful, we cannot fully account for the fact that no EEG evidence of drowsiness or sleep was obtained during the test trials. It is possible that this may have been due to medication effects in line with Sterling and Miller's (1941) observation that conditioned responses in cats, established under anaesthesia, could not be evoked until the effect of the drug had worn off. For practical reasons it was not possible to obtain an EEG from this patient after termination of the experiment.

There may also have been pharmacological reasons of another kind for our failure to elicit more positive evidence of conditioning in this case. In order to produce narcosis rapidly, a depressant drug was used and it is well known that such medication impairs conditionability. Hence, a number of in-patients, as well as some student volunteers, were asked to use a metronome before going to sleep at night. Earlier tests on these subjects had shown the metronome not to affect their EEG record. The purpose of repeatedly pairing the auditory stimulus with the onset of physiological sleep was to explore the possibility that signs of drowsiness or sleep rhythms might appear on the EEG in response to the tone once it had acquired the properties of a conditioned stimulus. This did not occur, although one volunteer received ninety paired stimulations of tone and sleep over a three-month period.

CASE STUDY II

Procedure

On the assumption that one conditioning trial every 24 hr was perhaps not enough to establish the conditioned reflex, it was decided to increase the number of paired stimulations very markedly. This was accomplished by asking a sleep-deprived subject to activate the

metronome by pressing a button whenever he was awake during the night. On reaching Stage B sleep on the EEG muscular relaxation caused the subject to relinquish the button and thereby discontinue the metronome. He was then allowed two minutes sleep in Stage C before he was awakened and asked to resume pressing the button. In this way seventy-six paired stimulations of tone and sleep were brought about in the first night, and sixty-five in the following night.

Results

On subsequent test trials, after S had recovered from sleep deprivation, the expected soporific effect of the metronome was investigated. Far from causing sleep, however, the metronome seemed to keep S awake. When allowed to sleep without metronome stimulation, the subject consistently experienced immediate wakefulness on reaching C stage sleep. Regrettably, we have not yet had an opportunity to repeat this observation.

CASE STUDY III

Since wakefulness seemed to be more readily conditioned than sleep, a 30 yr old artist with intractible narcolepsy associated with cataplexy, sleep paralysis and hyposomnia was treated using the technique described.

Procedure

During a pretreatment observation period in hospital, no drugs were given and a careful record of the attacks of cataplexy and the duration of sleep—both diurnal and nocturnal—was compiled.

On retiring each evening, she was requested to press a button while she remained awake and during any periods of wakefulness during the night. This button activated a recording apparatus adjacent to the patient's room. The night nurse kept a sleep chart each night, and the patient completed a questionnaire on waking each morning about the previous night's sleep. When six days of such observations were obtained, continuous EEG recording was performed throughout the day on two successive days. Then for a further two days she was given a miniature metronome worn in an earpiece like a hearing aid and instructed to switch on the tone when she experienced any diurnal drowsiness. This produced no change.

Then the following experimental procedure was carried out. The patient reclined on a bed and held a switch (press button) in her hand, which she was instructed to press. This operated a light bulb above her head. Then narcosis was induced by methohexitone, administered via an intravenous dextrose drip at a rate of 20 mg every 15 sec. The injection was discontinued when the patient ceased operating the light-switch. As soon as the drug took effect, the miniature metronome was switched on and attached to her left ear. The point at which the subject was sufficiently awake to switch off the tone was taken as the end of the session. This procedure was performed 37 times during an eight-day period.

Then, following 24 hr when no experimental stimuli were applied, eight test trials were carried out during an all-day EEG recording session, the patient wearing the earpiece and having been instructed to switch it on when she felt drowsy.

Results

The first four trials produced EEG and clinical evidence of arousal (i.e. return of alpha, etc.). The next three did not prevent sleep, but the last one again produced arousal.

During a further recording throughout the day, the effect of other neutral arousal stimuli was compared with that of the metronome. Attempts to keep the patient awake by repeatedly calling her name when she became drowsy were unsuccessful. A police whistle blown loudly every 30 sec during a 5 min period was ineffective (once the novelty effect had worn off). The patient continued to use the instrument in the ward for another 13 days, and as an out-patient for a further five weeks.

The all-day EEG studies revealed a slight increase in the duration of diurnal wakefulness and a similar reduction in the time spent at various levels of sleep, following the treatment (see Table 1). This applied especially to the day when only the metronome was used. A similar reduction in the duration of diurnal sleep was observed clinically, the average time spent asleep each day during the ten days before treatment being 62·25 min (variation being from 10–97 min), as compared to an average of 39·8 min for the 15 post-treatment days (variation 0–95 min).

TABLE 1. TEMPORAL DISTRIBUTION OF SLEEP AND WAKEFULNESS IN A NARCOLEPTIC PATIENT BEFORE AND AFTER TREATMENT

	Before (%)	After (%)
Awake	72·10	80·23
Stage A	5·00	4·21
Stage B	7·50	5·58
Stage C/D	15·10	5·73
Total time recorded (hr)	11·9	13·1

During her last 15 days in hospital, the patient used the metronome thirty-six times, arousal occurring on twenty-eight occasions. She went to sleep, despite its use, eight times, seven of these being in the afternoons. The duration of the stimulation on each occasion was determined by the subject and varied from 55–410 sec, the mean being 146·6 sec.

There was a subjective improvement in her nocturnal sleep but this was not confirmed by the sleep recordings, nor the nurse's reports. A reduction in the frequency and severity of the cataplexy also occurred. Similar trends were observed during the period of out-patient treatment.

However, although the use of this stimulus often increased her level of awareness, she was reluctant to use it, because its application was associated with a subjective feeling of tension and irritability. In addition, she was sometimes overwhelmed by sudden sleep, going off before she remembered to switch on the metronome, or after she had just switched it off.

CONCLUSION

While no evidence of sleep conditioning was obtained in this set of preliminary studies, findings in the first case reported do suggest that conditioned relaxation can be obtained by our technique. This conclusion is tentative until the result can be replicated on other subjects in whom stimulus generalization effects can be tested. This is necessary in order to establish that response measures of relaxation are, in fact, related to the conditioning of a drug response, and not to some other "symbolic" association between metronome and relaxation. Evidence for the classical conditioning of wakefulness is less equivocal, but also in need of confirmation. That as a result of our procedure in case II a specific EEG stage of sleep became associated with waking may, on further investigation, emerge as an experimental parodigm of certain sleep disorders.

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