thiazines in obstetrics, in which they assessed the patients' response after one dose of the drug under test and demonstrated a significant difference between the phenothiazines and the placebo.

These present trials were, however, designed to assess therapy under normal labour ward conditions, which is a more realistic method than the single-dose test. So far as promazine was concerned the double-blind trials confirmed the safety suggested by a pilot study and showed it to be an effective agent for controlling agitation and potentiating analgesics in labour. An anti-emetic effect was also shown.

Maternal tachycardia was the only adverse effect, but this did not appear to have any clinical significance. Hypotension is a recognized risk of phenothiazine administration, but although no serial blood-pressure readings were made there were no cases of clinical hypotension in the 785 patients in the series treated with promazine.

Summary

Three consecutive controlled clinical trials of promazine (sparine) were carried out on 1,565 maternity cases in the same unit. The first, a retrospective toxicity study of 993 consecutive cases, confirmed the safety of promazine suggested by the literature, despite a tendency towards maternal tachycardia. The reduction in vomiting from 5% to 1% and a corresponding reduction in the need for intravenous fluids suggested a powerful anti-emetic effect in the promazine group.

In the first double-blind trial of 280 cases subjective relief was assessed by the average condition of the patient at various stages of labour. This method failed to demonstrate any significant difference between placebo and promazine groups.

In a second double-blind trial of 292 cases subjective relief was assessed at a fixed time after each drug administration. The results showed a significant difference between the promazine and placebo groups (see Table IV).

Taking all dosage levels, 58.5% of promazine cases and 36.1% of placebo cases showed marked improvement in pain. The corresponding figures for "mental state" were 63.2% for promazine cases and 36.2% for placebo cases.

The methods of conducting and interpreting the results of obstetric trials are discussed in some detail.

In conclusion it is suggested that promazine, with its tranquillizing, analgesic-potentiating, and anti-emetic properties, is a useful adjunct to therapy in labour. Statistically, no increased risks were noted to mother or child and it appears that this phenothiazine derivative is a valuable addition to the therapeutic agents used in hospital obstetric practice.

I would like to express my thanks to Mr. D. M. Stern and Mr. C. W. F. Burnett for encouraging these clinical trials and for their criticism and advice in the final assessment of results. I would like to thank Dr. Brian Cromie for his constant assistance and advice throughout this work, also the nursing staff of the Queen Mary Maternity Unit, and in particular Miss M. Green, who maintained the high standard of efficiency in recording results throughout. In conclusion I would like to acknowledge the co-operation of John Wyeth & Brother Limited in providing the necessary materials.

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AMPHETAMINE AND PHENMETRAZINE ADDICTION

PHYSIOLOGICAL ABNORMALITIES IN THE ABSTINENCE SYNDROME

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Amphetamine addiction is common, though the readiness with which such addiction develops is not as widely recognized as one could wish. Those addicted often take large quantities of short-acting barbiturates as well, and of the tablets containing both, "drinamyl" (dexamphetamine sulphate 5 mg. with amylobarbitone, 32 mg.), popularly known as "purple hearts," is in most common use. A popular substitute or equivalent for amphetamine is phenmetrazine ("preludin") "known in London as 'sweeties' . . . available in any quantity . . . at the rate of £1 for 24 tablets" (Kellock, 1962). This compares with the price of £1 for 25 tablets among Edinburgh factory-workers (Case 4 below). Experience of addiction to these drugs (Bell and Trethowan, 1961) in New South Wales led Trethowan (1962) to emphasize the progressive deterioration in character associated with such addiction. He also pointed out that to claim, as many do, that they are drugs not of addiction but only of "habituation" is to engage in a semantic quibble.

The Interdepartmental Committee appointed by the Ministry of Health and the Department of Health for Scotland (1961), though remarking that in 1959 there were no fewer than 5,600,000 prescriptions for preparations of amphetamine and phenmetrazine, "formed the impression that . . . abuse is not widespread." The committee drew a distinction between addiction and habituation, partly on the grounds of "physical dependence on the effects of a drug" in the case of addiction and "absence of physical dependence and hence of an abstinence syndrome" in the case of habituation.

Addiction to these drugs is common in Edinburgh, and it is our purpose to demonstrate that *physical dependence* and characteristic, persisting, and easily measurable "physical" or physiological abnormalities form part of the *abstinence syndrome.*

Two Varieties of Sleep

Amphetamines have been much used for preventing sleep, and have been shown to act upon the reticular formation (Hiebel *et al.*, 1954). In recent years there have been considerable advances in knowledge about sleep, and it has now to be recognized that there are two principal kinds of sleep (Oswald, 1962, 1963), which have been called the "fore-brain" and "hind-brain" (or "paradoxical") phases of sleep respectively by Jouvet (1962). Human "fore-brain sleep" is accompanied by high-voltage slow waves and spindles in the electroencephalogram (E.E.G.), ocular repose, and incomplete relaxation of skeletal muscle. Human "hind-brain sleep" is accompanied by bursts of conjugate rapid eye movements (R.E.M.s) and an E.E.G. of fairly low voltage (Fig. 1) somewhat similar to that of drowsiness but with periods of characteristic "saw-toothed" waves of 2–3 c./s. "Hind-brain sleep" is accompanied by diminution of remaining muscle tone in the cat (Jouvet, 1962) and in the human (Berger, 1961). When volunteers are awakened from this kind of sleep they report *having just been dreaming* — for example, Dement and Kleitman (1957a) and Berger and Oswald (1962b).

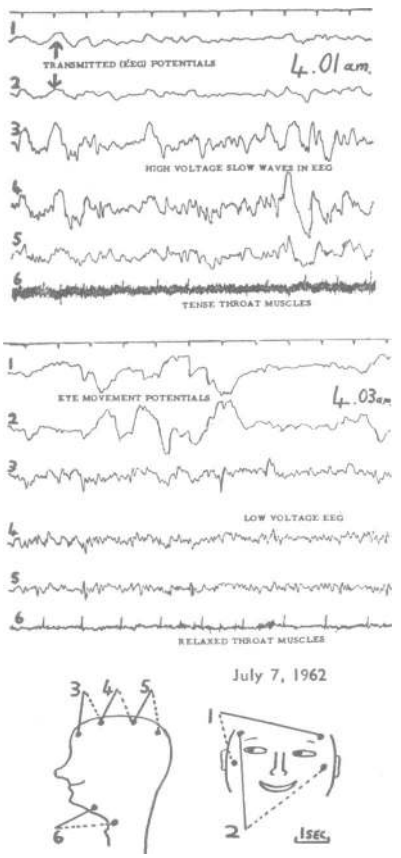

FIG. 1.—To illustrate the differences between the two kinds of sleep (Case 1)—namely, the change from an E.E.G. high-voltage slow-wave pattern, unrelaxed muscles, and motionless eyes, to a low-voltage E.E.G. with relaxed muscles and jerky rapid eye movements. The muscle trace in the upper excerpt is thick because of innumerable little muscle spike potentials; in the lower trace only a few occur, particularly with respiration (the E.C.G. is also visible). The E.E.G. waves are all irregular except for a group of three consecutive waves of about 2.5 c./s. visible in channels 3 and 4 just *before* the main eye movement burst—these precursors are the rhythmic "saw-toothed" E.E.G. waves. Amplification was 6 mm. per 50 microvolts for the E.E.G. and twice this for the throat channel and half for the eye channel; time constants 0.3 sec.

Human "hind-brain sleep" does not appear except after prior "fore-brain sleep." It recurs cyclically, occupying four to six discrete periods of the night. The transition from "fore-brain" to "hind-brain" sleep is abrupt. Though the reverse transition is usually also abrupt, sometimes it can be determined only to within the nearest couple of minutes. In order to obtain a sharply determinable measure of duration, one may note the "R.E.M.-time" by recording the duration of the period from the first to the last rapid eye movement in any period of "hind-brain sleep," subtracting the duration of any interruptions (generally following a major movement, when the E.E.G. may briefly become that of "fore-brain sleep" with "spindles" or that of wakefulness) and determining the sum for the whole night. This may then be expressed as a percentage of the total sleep time.

In man the first episode of "hind-brain sleep" occurs about one to one and a half hours after falling asleep, lasts a few minutes, then ceases. In about a quarter of instances, and especially in some individuals, no actual R.E.M.s occur during the first episode though they do in later episodes during the night.

It seems we need a fairly fixed proportion of each kind of sleep, experimental deprivation of "hind-brain sleep" being followed by a compensatory increase when opportunity allows—for example, Dement (1960) and Berger and Oswald (1962a)—though never approaching the values reported below. Retrospective examination of records from a previous study (Oswald *et al.*, 1963) in which it was shown that barbiturates reduce the R.E.M.-time, also suggests a compensatory increase early in succeeding nights when the drug was not administered.

Physiological Abnormalities on Amphetamine and Phenmetrazine Withdrawal

Six addicts admitted for drug withdrawal between June and November, 1962, were studied. It is difficult to persuade such patients to enter hospital, and if one stops their drugs abruptly they may discharge themselves. They were therefore allowed to continue their drugs briefly in order to allow a doctor–patient bond to develop, strong enough to sustain them on drug withdrawal. Their nocturnal sleep was studied, either by whole-night recordings of the E.E.G. and eye-movements, and sometimes muscle tonus, or, in a few instances, by recordings of the first two hours of sleep only. The first appearance of "sleep spindles" at about 14 c./s. in the E.E.G. was taken as the time of sleep onset.

Silver disk electrodes containing electrode jelly were fixed to the face near the outer canthi with adhesive plaster, in order to record eye-movement potentials, and to the scalp with collodion in order to record the E.E.G. (Fig. 1). Electrodes thus fixed are not noticeable after the first few minutes. A paper-speed of 1.5 cm./sec. and time constants of 0.3 sec. were used. Patients slept in a bedroom away from the E.E.G. room. In all, 88 recordings, running over some 24 miles (39 km.) of paper, and of which 83 were whole-night recordings, were made on 60 nights. Sometimes we recorded from two patients concurrently. Recordings generally began around 11 p.m. and ceased around 7.30 a.m., depending on when the patient woke spontaneously or was awakened by outside noises or by the patient sharing the room.

Case Reports

Case 1.—A 41-year-old woman. Given her usual 10 drinamyl daily from admission on June 1. First sleep recording on June 8. No drinamyl on June 14, 15, 25, and 26, and it was finally stopped on July 5. Withdrawal (Fig. 2) was followed on each occasion by a dramatic rise of R.E.M.-time to values far exceeding those reported or encountered previously.

Case 2.—Married woman of 20. Admitted August 15; four tablets of "durophet" (50 mg. of amphetamine) permitted daily. Durophet stopped August 20. Fig. 3 shows the same kind of withdrawal effect as was seen in the other patients.

Case 3.—A 40-year-old woman. Permitted drinamyl, 15 tablets each morning till stopped on July 18. On July 20 dexamphetamine sulphate, 50 mg. each morning, begun. This stopped on August 9, and on August 11 only 30 mg. daily was resumed (comparable to doses often prescribed on "therapeutic

grounds"). On August 20, 45 days after admission, drugs ceased. Figs. 4 and 7 show the effect of drug withdrawal. On September 22 she was in unusually good spirits; her urine was therefore examined for amphetamines, but no trace of these was found. The examination, kindly carried out by Dr. J. D. Crombie, involved extraction, vacuum concentration, and one-way paper chromatography in a butanol/acetic-acid/water system, the spots being visualized with diazotized *p*-nitro-aniline reagent. This method has proved a sensitive qualitative detector with other such patients.

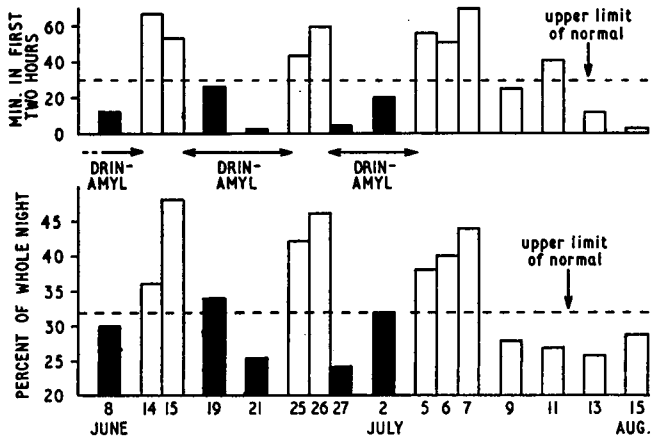

FIG. 2.—Case 1. At the foot, from left to right, are vertical blocks indicating the percentage of the whole night's sleep spent in rapid-eye-movement periods (R.E.M. time). The solid blocks indicate nights following days on which she received her drinamyl, and the empty blocks nights following days without drugs. At the top the number of minutes made up of R.E.M.-period sleep within the first two hours of sleep is similarly indicated. The rise in the values whenever the drug is stopped can be seen. The values of 48% (whole night, June 15) and 70 min. (first two hours, July 7) were far above values hitherto reported or any encountered by us. The horizontal time scale is not linear.

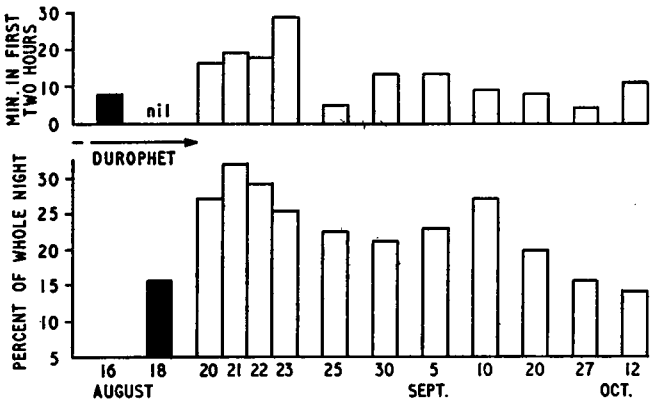

FIG. 3.—Similar to Fig. 2. Case 2. Only the first two hours of sleep recorded on August 16. No R.E.M. period within the first two hours on August 18. Though the rise after withdrawal was less striking than in the other patients, an overall fall of whole-night R.E.M.-time is clearly visible occurring over a seven-week period.

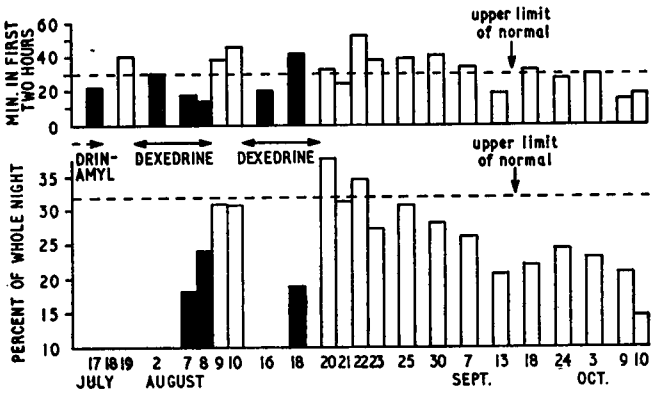

FIG. 4.—Case 3. Only the first two hours of sleep recorded on July 17, 19, August 2 and 16. Receiving only 30 mg. a day of dexamphetamine sulphate August 11–19. The slow return to a steady level within her normal range takes over a month.

Case 4.—A 50-year-old married woman of below-average intelligence. Admitted September 2; permitted eight 25-mg. tablets of preludin (phenmetrazine hydrochloride) until October 8. In the second week after stopping her drug two surprise urine checks were made. Chromatography revealed no trace of phenmetrazine. Fig. 5 shows an effect of phenmetrazine withdrawal similar to that of amphetamine withdrawal, recovery to her probable normal levels of function taking place in three to four weeks.

Case 5.—A 39-year-old married woman. Admitted August 29; allowed nine tablets of drinamyl each morning until September 16. Figs. 6 and 7 illustrate the slow return to normal sleep function after withdrawal.

Case 6.—A 25-year-old single woman. Admitted November 6. Allowed nine preludin tablets daily until November 10. Her sleep was recorded on four nights only. On November 6 and 7 she had no R.E.M.s within the first two hours on either night, but after withdrawal 29 and 26 min. on the 10th and 12th respectively. The whole-night percentage rose from 15.5 (42 min. in 270—Case 4 wakened her early) and 24.3 (112 min. in 461) to 31.7 (170 min. in 536) and 27.5 (123 min. in 448). The delay before the first R.E.M.s fell from 123 and 132 min. to the unprecedentedly low figure of 4 min. on each night.

The fully addicted patients slept remarkably well despite their stimulant drugs. The delay between onset of sleep and the first R.E.M. period tended to fall considerably on some of the first nights after drug withdrawal, thereafter slowly rising (see Table). After withdrawal, patients tended to fall asleep sooner after retiring and the duration

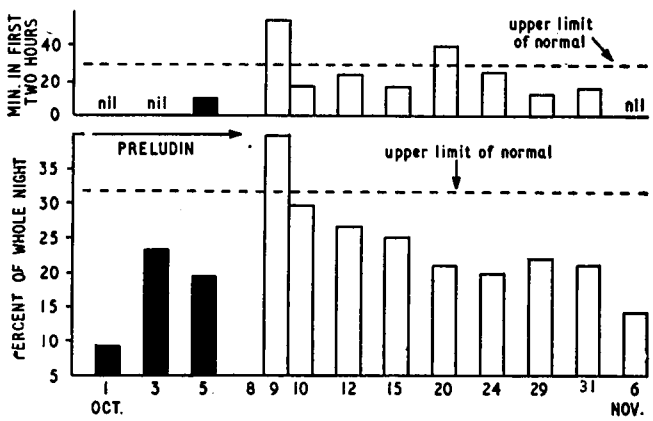

FIG. 5.—Case 4. Showing that withdrawal of preludin in a fully addicted person has the same effects as withdrawal of amphetamine.

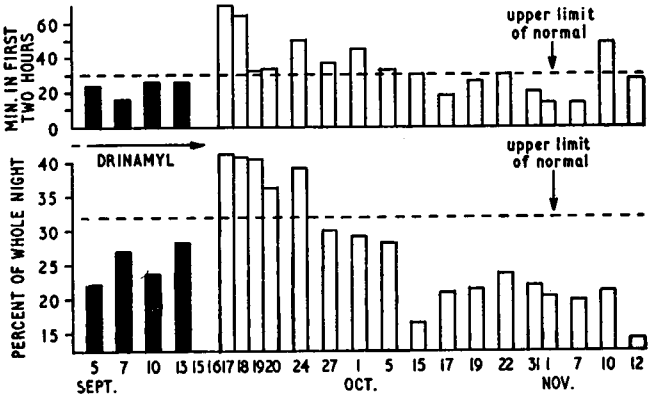

FIG. 6.—Case 5. Shows a similar slow return to normal.

of sleep during the night tended to rise, subsequently to fall again (see Table).

Date	T.S.T.	T.R.T.	Delay
Case 1			
Jun. *8* ..	376	113	71
14 ..	420	148	15
15 ..	494	237	21
19 ..	491	169	23
21 ..	420	107	70
25 ..	456	192	15
26 ..	453	204	12
27 ..	370	90	70
July *2* ..	463	148	79
5 ..	443	168	46
6 ..	480	191	37
7 ..	435	156	37
9 ..	493	138	61
11 ..	444	117	39
13 ..	501	128	42
Aug. 15 ..	251	72	85
Case 2			
Aug. *16* ..			90
18 ..	391	59	147
20 ..	504	137	82
21 ..	530	167	74
22 ..	478	140	72
23 ..	485	123	57
25 ..	466	103	107
30 ..	495	104	81
Sept. 5 ..	537	121	68
10 ..	510	139	62
20 ..	449	89	72
27 ..	410	63	65
Oct. 12 ..	434	61	108
Case 4			
Oct. *1* ..	379	34	154
3 ..	408	93	198
5 ..	395	78	31
9 ..	480	191	51
10 ..	468	138	55
12 ..	419	112	44
15 ..	375	95	82
20 ..	372	78	73
24 ..	336	67	85
29 ..	330	73	98
31 ..	373	78	41
Nov. 6 ..	319	45	164

Date	T.S.T.	T.R.T.	Delay
Case 3			
July *17* ..			52
19 ..			8
Aug. *2* ..			10
7 ..	254	45	61
8 ..	377	91	86
9 ..	430	130	12
10 ..	360	111	9
16 ..			61
18 ..	392	73	69
20 ..	442	166	90
21 ..	455	142	13
22 ..	432	149	16
23 ..	405	110	58
25 ..	435	133	13
30 ..	406	114	45
Sept. 7 ..	392	107	30
13 ..	437	90	50
18 ..	487	106	66
24 ..	452	110	40
Oct. 3 ..	433	111	58
9 ..	480	112	64
10 ..	405	58	68
Case 5			
Sept. 5 ..	430	96	71
7 ..	392	107	51
10 ..	395	94	56
13 ..	397	113	38
17 ..	462	192	11
18 ..	439	180	10
19 ..	499	202	33
20 ..	407	148	9
24 ..	395	155	16
27 ..	374	113	23
Oct. 1 ..	348	102	14
5 ..	340	96	14
15 ..	332	65	42
17 ..	480	100	103
19 ..	434	93	33
22 ..	411	98	34
31 ..	329	73	39
Nov. 1 ..	445	91	35
7 ..	413	84	51
10 ..	482	103	45
12 ..	383	56	86

T.S.T.—Total whole-night sleep time (min.).
T.R.T.=Total R.E.M. time (min.).
Delay=Delay before first onset of R.E.M.s (min.).
Dates in italics = Dates when on drugs.

Cases 1, 3, 5, and 6 all had some extremely short delays on drug withdrawal. We followed two over a long period, until three consecutive delays within normal limits (Fig. 7). At times, these delays were lengthened by the patient first falling asleep, waking after a few minutes, and so on several times. In addition, when the patient wakens for, say, 20 minutes just as the first R.E.M. period is expected, then R.E.M.s do not appear until the second cycle of the night is due—Case 3, August 20, and Case 5, October 17, delays were lengthened thus.

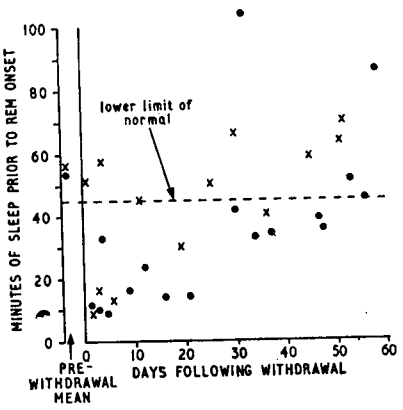

FIG. 7.—Illustrating the occurrence of abnormally short delays before the first onset of a R.E.M. period in the nights following withdrawal of amphetamine preparations. Pre-withdrawal means are based on six nights (Case 3) and four nights (Case 5). The first two post-withdrawal values for Case 3 are also mean values (see Table). Case 3 had one delay outside the normal range as late as the 36th day after withdrawal. Case 5, after 18 and 20 days, still had grossly abnormal values (14 min.), and not till after the 47th day did three consecutive values within normal limits occur. × = Case 3. ● = Case 5.

While patients were receiving the drug to which they were addicted the variables we have measured mostly fell within normal limits. Patients received their drugs in the mornings only, and by nightfall a minor degree of deprivation may have contributed to the three very short delays (Cases 1, 3, and 4, see Table), and to the R.E.M. time of Case 1 on June 19 (whole night) and of Case 3 on August 18 (first two hours).

Discussion

To establish the existence of "physical" dependence on a drug it is necessary to demonstrate some physiological function which is within normal limits in the fully addicted patient but which becomes abnormal upon drug withdrawal, and which returns to normal if the drug is again given. The physiological function we have chosen to measure concerns a basic brain process—sleep, upon the mechanisms of which amphetamine was known to have an action. Fisher and Dement (1962) and Rechtschaffen and Maron (1963) have observed that the decrease in whole-night R.E.M.-time caused by a barbiturate can be significantly enhanced by giving amphetamine with the same quantity of barbiturate. The central nervous systems of our patients had evidently become so accustomed to drugs that a normal pattern of sleep was present. In each case (Figs. 2–6) upon withdrawal a huge increase in R.E.M.-time occurred, reversible by reinstituting the drug (Figs. 2 and 4). Alternatively, the passage of time brought about decline to fairly steady individual normal values. The addicts were therefore dependent on their drugs for normal function.

Each individual has his own mean and usual range of R.E.M.-time values. As a guide we have included in the figures an indication of the upper limits of normal for the population as a whole in so far as they are currently available—from Dement and Kleitman (1957b), Dement (1960), Berger and Oswald (1962a), other unpublished studies in our own laboratory, and Rechtschaffen and Verdone (1963)—in the sense that the following figures are unlikely to be exceeded more than once or twice per hundred instances—namely, 32% R.E.M.-time in the whole night (mean about 20–22%), and 30 minutes R.E.M.-time in the first two hours of sleep (mean under 10 minutes).

The two largest series with volunteers subjected to neither drugs nor experimental procedures are those of Dement and Kleitman (1957b) with 126 nights from 33 volunteers, and Rechtschaffen and Verdone (1963) with 80 nights from 20 volunteers. The former give figures for the delay from onset of sleep to first R.E.M. period as 67 min. (mean) and 45 min. (minimum), and the latter as 84 min. (mean) and 49 min. (minimum). We therefore give the value of 45 minutes as the minimum (Fig. 7), though this is lower than we have encountered in over 70 normal nights. In a co-operative study from two centres in the U.S.A., Rechtschaffen *et al.* (1963) have also observed very short delays of a few minutes between sleep onset and the first R.E.M. period, comparable to those in Fig. 7, in narcoleptic patients (from at least some of whom amphetamine had just been withdrawn), which they state they have never before encountered in the many hundreds of other nights they have, between them, studied.

Fig. 7 shows that return to normal can take as long as eight weeks after withdrawal. Utena *et al.* (1959), in Japan, where amphetamine addiction is common, made guinea-pigs into methamphetamine addicts. Animals killed on the 15th day of abstinence still showed abnormalities and probably also the animals killed on the 45th day, in that

there was evidence of a decrease of aerobic and anaerobic *in vitro* glycolytic activity in studies of the animals' brain tissue.

We do not understand the basis of the abnormalities we have observed; for, notwithstanding its fundamental role in our economy, the significance of our need for sleep remains a mystery. We believe this to be the first demonstration of an abnormality both easily measurable and long-persisting (one to two months) in any kind of human abstinence syndrome. Unfortunately we cannot measure another neurophysiological abnormality—namely, that which directly underlies the most significant feature of the syndrome, the *craving*.

After withdrawal of amphetamine, patients describe listlessness, depression, and sleepiness, but cannot easily formulate their craving: "I feel terrible, I miss them so" (Case 4); "I can't get them out of my mind, I think about them all the time" (Case 6). It is this craving that drives them to antisocial acts; to obtain their drugs without prescription from small-time traffickers and unscrupulous pharmacists; to alter, steal, and forge prescriptions; and to call in rotation on different doctors from whom they conceal their addiction. Sometimes it is argued that only "psychopaths" become addicted to these drugs. In our view, many addicts would be better described as young and irresponsible (Case 2) or simply stupid (Case 4).

Case 5 had been an addict for 12 years, obtaining supplies from a pharmacist. For the last eight years she had often visited both her general practitioner and hospital clinics because of Raynaud's disease, without it being realized that she was steadily consuming huge quantities of a potent vasoconstrictor agent. After withdrawal her circulation improved enormously, her nails grew again, and she was delighted—rendering her prognosis relatively good.

Conclusions

Therapeutic indications for amphetamine are to-day becoming vanishingly slight. Diet and not pills should control obesity (*British Medical Journal*, 1961). Amphetamine has not shown itself to be of value in endogenous depression (Hare *et al.*, 1962). Yoss and Daly (1960) recommend methyl phenidate as superior to amphetamine in the treatment of narcolepsy. It has been established by, among others, Kiloh and Brandon (1962) that amphetamine consumption leads to a tendency to increase the dose. Up to 10 times the "therapeutic" dose is common among amphetamine and phenmetrazine addicts. These preparations produce a detrimental effect on the individual and on society. In the former they produce an egocentricity of outlook and impairment of those skills necessary to the conduct of successful social relationships, sometimes physical harm, and occasionally a frank psychosis (Connell, 1958; Beamish and Kiloh, 1960). In paying for the pills, addicts sometimes acquire appalling financial debts. In society, the drugs encourage shady trafficking. Persons taking these drugs certainly experience an intense craving to continue so to take them, and to obtain them by almost any means—these means, it is admitted, are not pursued to the extremes found, for instance, among morphine addicts. Extreme behaviour is unnecessary with the laxity of current controls. We have demonstrated that physical dependence can exist.

The criteria for addictive drugs stipulated in the Report of the Interdepartmental Committee set up by the Ministry of Health and Department of Health for Scotland (1961) are therefore met by amphetamine and phenmetrazine. These drugs, and drugs with comparable actions, such as diethylpropion (Clein and Benady, 1962), are dangerous drugs in fact if not yet in law.

Summary

Evidence is presented to support the view that amphetamine and phenmetrazine preparations are truly addictive, leading to physiological dependence. Six addicts have been studied in whom easily measurable neurophysiological abnormalities appeared upon drug withdrawal.

These abnormalities affected the proportion of nocturnal sleep spent in so-called "hind-brain sleep" (with a characteristic E.E.G., rapid eye movements, and muscle-tension changes). In the abstinence syndrome this kind of sleep began as soon as four minutes (normal about 70 minutes) after onset of sleep, and occupied up to 70 minutes (normal about 10 minutes) in the first two hours and up to 48% (normal about 22%) of a whole night. Return to normal function took place immediately if the drugs were restored, but, if withheld, return to normal took three to eight weeks.

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