Drug Treatment of Disease

INSOMNIA

BY

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The purpose of this article is to discuss drugs used for insomnia. That they should form only a small part of treatment must be stressed, but the wider aspects of the problem, though of great importance, cannot be encompassed in this account. It must be noted that insomnia is one of the few states which we are called upon to control without, as a rule, any certainty that it exists. We have to accept the patient's statement that he is sleepless, but the extent of his insomnia can be determined only in the minority who are under observation in hospital. Wakefulness in the night is almost always exaggerated, though in good faith.

In the British Isles, about one in every ten prescriptions issued under the National Health Service is for barbiturates and other hypnotics. It seems improbable that justification exists for this state of affairs.

Physiology

For the human subject sleep at frequent intervals is a biological necessity. Third-degree methods of interrogation have shown that deliberate and protracted prevention of sleep can bring about a complete collapse, both mentally and physically. The insomnia which we are called upon to treat is never of this degree and duration, and is very rarely harmful. This is a point of importance to be stressed to the patient.

Many people are worried about insomnia, not because they fail to sleep at all, but because they cannot sleep when they get to bed. In other words, the conventional nocturnal rhythmicity is lacking. No fundamental law dictates that each person shall sleep from, say, six to eight hours at night. Such a habit is purposely cultivated from childhood onwards. With it is associated a series of virtually conditioned reflexes. Superimposed upon the natural physical and mental tiredness is all the ritual of preparing for bed—the bringing of the evening's activities to a conclusion, the retirement to the bedroom, the undressing, the donning of night attire, the soft light of the room, the warmth of the bedclothes, the quiet, the contentment, the relaxation, and finally the oblivion. Anything calculated to disturb this accepted procedure can defer sleep, be it a strange house, unaccustomed cold or heat, anxiety and worry, or distractions and noise outside. The alleviating of insomnia calls for much more consideration and advice than the mere proffering of a mentally obliterating drug. Despite extensive physiological research, the precise mechanism of sleep remains undiscovered.

Pharmacology

Drug treatment of insomnia remains essentially empirical. What it does, in effect, is: (1) subdue cortical activity, such as anxiety, and (2) depress the nervous system generally so that the threshold is raised to external stimuli, notably noise. What is important is that these effects should be achieved without attendant danger, either to the vital centres of the brain or to the rest of the body. The simple act of taking a tablet at bedtime may itself become incorporated in the ritual, so that it can never be discontinued.

Soporific concoctions are not exclusively a modern delict. Apothecaries in past centuries ventured their potions, of which the mandrake is but one example, upon those tortured by sleeplessness. Lacking though many of these brews may well have been in pharmacological potency, there is

little doubt that they quite often brought about the desired result. Of the older remedies, however, one of unquestionable effect is still available—namely, alcohol. On the central nervous system this behaves not as a stimulant but as a depressant. Its progressive action from the higher centres downwards carries the subject through stages similar to those seen in general anaesthesia—induction, excitement, anaesthesia, medullary depression—the second of these being regarded as a release phenomenon. Small doses of alcohol may thus conspire to that dreamy state characteristic of anaesthetic induction and so serve as a prelude to sleep. Too much can easily give rise to excitement and thwart the purpose for which it is taken. This possibility notwithstanding, a little strong drink taken on retiring may serve in some people, especially the aged, as an appropriate “night-cap.” Large draughts of weak liquor like beer, on the other hand, are to be avoided, if only for the reason that an overloaded stomach is disturbing and an overloaded bladder later may be more so.

Chloral and Paraldehyde

Trichloroacetaldehyde, $\text{CCl}_3\text{CH}(\text{OH})_2$, or chloral hydrate, is a relatively simple chemical compound which is quite easily synthesized. It was introduced as a hypnotic by Liebreich in 1869 with the idea that, in the body, it might be converted to chloroform, CHCl_3 —at that time well on its way to becoming established as an anaesthetic. In fact it is now recognized that chloral hydrate undergoes reduction in the tissues to trichlorethyl alcohol, the substance ultimately responsible for the effects on the central nervous system.

Pure chloral hydrate is a crystalline substance with a pungent smell and bitter taste. Applied externally it is an irritant, even to the extent of causing vesication. Strong solutions are similarly irritant to the alimentary mucosa, so that vomiting and purging may occur. More dilute solutions are less troublesome in this respect, but, even when sweetened, they are unpalatable, for the burning taste is very difficult to disguise. Yet after oral administration absorption of this drug is rapid and a therapeutic dose can maintain hypnosis for six to eight hours. What is more, the therapeutic ratio is very wide, so that only with very excessive doses does medullary depression occur. The cardiovascular system also escapes damage. There is consequently a good deal to be said in favour of chloral hydrate, on grounds of both efficacy and safety. Its taste is the outstanding drawback and even this may be a deterrent to habituation. Unlike the barbiturates, chloral preparations cause no “hangover.”

For adults it is convenient to prescribe chloral mixture *B.N.F.*, $\frac{1}{2}$ fl. oz. (14 ml.) well diluted with water to be taken at night, this dose containing 20 gr. (1.2 g.) chloral hydrate with syrup of orange. This preparation supersedes the old draught of chloral *B.P.C.*, or haustus chloralis, $1\frac{1}{2}$ fl. oz., which contains the same amount of drug but in liquid extract of liquorice. There is no rationale at all in combining a bromide with chloral hydrate in a hypnotic mixture. For children there is the chloral elixir for infants *B.N.F.*, with 1 gr. (65 mg.) in each 60 minims (3.5 ml.), flavoured with syrup of blackcurrant. The dose can be adjusted according to age. The *B.P. Codex* also includes a chloral and potassium bromide mixture for infants which is not to be recommended.

Dichloralphenazone is a complex of chloral hydrate and phenazone which has recently been devised. It is the active

constituent of "welldorm" tablets, each of which contains 10 gr. (650 mg.) of the substance. The usual dose for an adult is two tablets before retiring, swallowed whole with a draught of water. The unpleasant taste of chloral hydrate is entirely absent, and even if the tablets are chewed they are only slightly bitter. Limited experience suggests that they are as effective, dose for dose, as ordinary chloral hydrate. No claim is made that the phenazone component is analgesic.

Paraldehyde (CH_3CHO)₃ is a polymer of acetaldehyde (CH_3CHO). Safe and effective as the drug may be, its taste and persistently penetrating smell preclude its oral administration in the ordinary course of practice. It is best avoided in cases of gross hepatic disease. In febrile states it is prone to cause excitement. There are occasions, however, when it is of considerable value. For instance, nocturnal bronchial asthma, temporarily relieved by adrenaline, may be followed by sound sleep if paraldehyde is then administered. This use is not to be confused with the intramuscular injection of 5 ml., so useful in overcoming status asthmaticus.

Furthermore, for the seriously ill patient (for example, with heart failure or carcinomatosis) who is unable to sleep except fitfully from full doses of chloral or barbiturate, the administration of 10% paraldehyde in saline (enema paraldehydi B.P.C.) in a dose of 30 ml. of the enema per stone of body weight (4.7 ml. per kg.) will almost always prove highly effective. It should not be given to a patient heavily narcotized with morphine or heroin, because the superimposed depression on the respiratory centre may be dangerous. It may be given with advantage at night just as the therapeutic effect of an opiate is beginning to wear off.

Ureide Derivatives

Urea is pharmacologically inactive towards the central nervous system, yet a number of its derivatives are depressants. Thus:

Monoureides

Diureides

Barbituric acid itself is not active, but many of its derivatives, formed mainly by substitution on the terminal $>\text{CH}_2$ grouping, are potent. These are the barbiturates.

Carbromal B.P. is a white, odourless, crystalline powder which is practically tasteless. The official preparation is carbromal tablets B.P., usually containing 5 gr. (0.32 g.) each. The dose is 1 to 3 tablets—that is, 5 to 15 gr. (0.32–1 g.) at night. The hypnotic response is mild and of fairly short duration, but acute overdosage is unlikely to occur. Repeated administration, however, may give rise to itching of the skin, erythema, pigmentation, and widespread purpura from increased capillary permeability. Habituation occasionally arises, usually in subjects of inadequate personality. Its main value is for the light sleeper or as a weak substitute to be used in breaking the barbiturate habit. It is to be found in a wide range of proprietary preparations on sale to the public; it is not scheduled as a poison.

Bromvaletone is a mild and safe hypnotic. It appears in various proprietary sleeping tablets and tranquillizers. "Persomnia" contains carbromal and bromvaletone. Apronal ("sedormid"), the prescribing of which has been almost completely discontinued, is a fairly feeble hypnotic

and can give rise to thrombocytopenic purpura, which is more dangerous than the relatively rare purpura of carbromal.

Barbiturates

Most of the barbiturates are white crystalline solids with a slightly bitter taste. The free acids are sparingly soluble in water, but the sodium salts dissolve readily and tend to be absorbed more rapidly from the gut. With a few exceptions, like the sulphur-containing compounds, they can be taken by mouth in tablet or capsule form. Their action is almost entirely confined to the central nervous system, the higher centres appearing to be subdued first of all. But the medulla is soon involved and respiratory depression may follow. Death from overdosage is due primarily to respiratory failure, with cardiac failure ensuing in consequence. Both alcohol and paraldehyde potentiate the action of barbiturates. Such a conjunction may be dangerous.

Pharmacologically the barbiturates may be classified according to their duration of action:

Long-acting—e.g., barbitone, phenobarbitone.

Medium-acting—e.g., amylobarbitone, amylobarbitone sodium, pentobarbitone, butobarbitone.

Short-acting—e.g., cyclobarbitone, quinalbarbitone.

Ultra-short-acting—e.g., thiopentone, thialbarbitone.

To give a long-acting substance like phenobarbitone as a hypnotic is misguided. For patients who have difficulty in getting off to sleep a short-acting drug is usually chosen. For those on the other hand who fall asleep promptly but wake in the early hours of the morning, a medium-acting compound is preferable, if given at bedtime. Alternatively the short-acting quinalbarbitone may be taken on waking in the night. The ultra-short-acting barbiturates are used as intravenous anaesthetics.

The barbiturates presented in colourful capsules require no effort in prescribing and appeal strongly to patients. But overdosage, accidental or deliberate, is a real danger and accounts for many deaths annually. In theory only a week's supply should be prescribed, but this is impracticable. In any case, a determined suicide can save supplies for his terminal adventure, or indeed avail himself of the gas oven. It is our duty to warn the patient of the danger of these drugs and to advise that they be kept in a cupboard inaccessible to children. A common complaint is of "hang-over" in the morning. The explanation of it eludes us. Some patients take barbiturates nightly and yet suffer no depression in the day. Others are conscious of mental slowness and fatigue starting about 2 p.m. and lasting for 3–4 hours. Irritability, prolonged reaction-time, and lack of zest can usually be detected in the confirmed barbiturate consumer. Repeated dosage may give rise to skin rashes, and habituation is common. Despite their wide usage, therefore, the barbiturates have obvious shortcomings. To add to the confusion they are presented in great variety, with a multiplicity of proprietary names and often in a series of combinations. Their relative merits are not easy to ascertain. There is much to be said for restricting the prescribing of barbiturates to those listed in the *British National Formulary*.

Because all barbiturates are Schedule IV poisons the prescription must state in every case the name and address of the patient, the total quantity of the preparation ordered (the total number of capsules or tablets and the strength of each), the dose, the full signature of the prescriber, and the date.

Other Hypnotic Drugs

Glutethimide ("doriden") is a synthetic compound, chemically α -ethyl- α -phenylglutarimide, which is distinct from the barbiturates. It acts as a moderately powerful hypnotic, a therapeutic dose given by mouth having an onset of action within half an hour and lasting for about six hours. Tablets of doriden each contain 0.25 g. of the active principle, and the dose is one to two tablets at night. Clinical trials suggest that this preparation therapeutically is the

approximate equivalent of cyclobarbitone. Side-effects reported include nausea, skin rashes, and, occasionally, excitement. It seems a reasonable alternative to the barbiturates, with probably less likelihood of respiratory depression and certainly less "hangover." Experimentally, this drug is of great interest, for its analogue β -ethyl- β -methyl glutarimide or bemegride ("megimide") is a stimulant to the central nervous system.

Methylprylone ("noludar"), whose active constituent is chemically 3:3-diethyl-2:4-dioxo-5-methylpiperidine, is a depressant of the central nervous system. Clinical experience in Great Britain is so far limited, but a clinical trial suggested that it was therapeutically of the same order as butobarbitone and amylobarbitone sodium. The dosage is one to two tablets, each containing 200 mg., at night. No side-effects have so far been reported.

Thalidomide ("distaval") is another non-barbiturate hypnotic, discovered and developed in Germany and so far not widely tried in Great Britain. It is too early yet to say that habituation and addiction do not occur. Tablets of "distaval forte" each contain 100 mg. thalidomide. The dose for hypnosis is one tablet at night. Side-effects and toxicity are said to be absent, but there is some suggestion of interference with thyroid activity.

Many drugs might be termed indirect soporifics in that by removing a disturbing symptom nocturnal sleep follows. For instance, intestinal hypermotility with rapid filling of the colon is much commoner in the brain-worker than in those of gluttonous habits. Here dry extract of belladonna 60 mg. (1 gr.) at night, or better tricyclamol chloride ("lergine," "elarine chloride") 50 mg. may calm excessive gut movement and provide undisturbed sleep. Drugs which relieve pain and cough fall into the same category.

As emphasized at the outset, it is more important to inquire into the causes of sleeplessness than to give drugs. Such simple matters as exercise, type of meal, quantity of fluid taken in the evening, and so forth may have an important bearing on a natural approach to insomnia.

Finally, tranquillizers are not suitable as soporifics.

THE ART OF CONSULTATION

FIFTH JAMES MACKENZIE LECTURE

On November 22 the College of General Practitioners held its annual meeting in the Great Hall of B.M.A. House. During the morning Dr. G. F. ABERCROMBIE delivered the College's fifth James Mackenzie Lecture, taking as his subject "The Art of Consultation." The general theme of his lecture, said Dr. Abercrombie, was that the family doctor must learn to manage, not only the patient and his relations and friends, but upon occasion his specialist colleagues also. The family doctor must remain in control unless, with the patient's consent, he delegated his authority temporarily and for some special purpose.

A Stroll down Harley Street

Inviting his audience to accompany him on a stroll down Harley Street, he said they would listen respectfully when the talk was of Pancoast's syndrome or Schimmelbusch's disease, but they would not be impressed by statisticians. As a family doctor, he was not concerned with percentages, but only with people one at a time. The average expectation of life without operation might be so-and-so, but that was not the point. The point was what would happen to his particular patient. How his heart still warmed to the surgeon who wouldn't operate. And they should take kindly to the surgeon who said, "It is rather a good idea to regard the husband as one of the physical signs," and to the physician who wrote, "But you know her better than I do, and if you have any other view I hope you will let me know."

The art of consultation was not simply a question of sending a patient away for a second opinion. It was the careful

selection of the man who by training and temperament was the most suitable for the matter in hand. His position in the profession, his standing in his specialty, his skill, his appearance, his manner, and his gift of tongues had all to be considered. When Dr. Abercrombie began in practice they knew their men pretty well, for they met them in person at every opportunity. His partner made it perfectly plain to all his patients that, if they wished, a consultation would immediately be arranged, but also that, if he himself felt the need for a second opinion, no objection should be offered. In that way, he had met many physicians and surgeons from hospitals other than his own, and had learned a great deal from them.

Absolute Equality

When a consultant and a general practitioner met, no matter how distinguished the one or how obscure or diffident the other, they met on terms of absolute equality, the one to give, the other to receive, but not necessarily to adopt, the advice tendered. The consultant had to be careful here. He should be patient while the practitioner told his tale; he should not wave away, as of no account, the x-rays that had been brought; and he should not, with a brisk, "Well, I don't think we need discuss this together, need we?" deprive the practitioner of the opportunity to consider what was to be said to the patient, before it was said. Beyond all doubt a consultation was of immense value to the general practitioner, for it afforded him priceless opportunities of keeping up to date.

Consultations were arranged, generally speaking, either for information or for action, though often of course for both purposes. Dr. Abercrombie then gave some admirable examples of the first, often the "reassuring," type. "These men," he commented, "gave their opinions with absolute assurance. I may have had an idea, but their reasons were so convincing that they converted the idea into a certainty." Such opinions were first class; there was nothing woolly about them. He then recounted a rather different experience.

"A lady, 14 weeks pregnant, and her 4-year-old daughter, simultaneously developed German measles. The mother knew all there was to be known at that time about pregnancy and German measles, and I immediately obtained confirmation of the diagnosis from a dermatologist. Thence to an obstetrician, who, though clearly in favour of terminating the pregnancy, asked that his opinion be confirmed by a colleague. The second was just as hesitant as the first, and I had finally to take her to a physician before the operation could be done. This physician simply said, 'You can't do anything else.'"

Often, of course, one got no help at all from a consultation. Harley Street, in his experience, was reluctant to confess itself stumped. "It would be better sometimes if it did, and the exceptions are refreshing."

A Chance for the College

Cases of cancer of the breast were always distressing, for if at all possible there had to be a mutilating operation. The question was, "How much?" and the practitioner would know his surgeons well enough to be able to forecast what operation any of them would recommend in an individual case. The practitioner's responsibility was not lessened but rather increased thereby. But at any moment now, it seemed, continued Dr. Abercrombie, some pharmaceutical firm would announce a new drug for the treatment of cancer, and, if the history of antibiotics and of tranquillizers was any guide, that announcement would be followed within a matter of months by a dozen such discoveries. Their College would then have an immense opportunity if they were ready for it. "Have we a plan for the immediate investigation of such new remedies?" Their new building was to be alongside the Royal College of Surgeons and the Imperial Cancer Research Fund. They ought now, in anticipation of something revolutionary in the treatment of cancer, to have a consultation with those bodies, and prepare a scheme for assessing the value of new therapy.