drugs in eighteen out of the thirty-two cases, often in combination with other analgesics.

Since etorphine did not cause vomiting it was especially useful in patients suffering from nausea or vomiting with their regular, oral analgesic. Use of etorphine made it possible for these patients to be maintained on oral medication, often to the end.

REFERENCES

BLANE, G. F. (1967). Absence of respiratory depression in the new-born rat after maternal administration of etorphine by the sublingual route. *J. Pharm. Pharmac.*, **18**, 781–782.

BLANE, G. F., BOURA, A. L. A., FITZGERALD, A. E. & LISTER, R. E. (1967). Actions of etorphine hydrochloride (M99). A potent morphine-like agent. *Br. J. Pharmac. Chemother.*, **30**, 11–22.

DENEAU, G. A. & SEEVERS, M. H. (1964). Evaluation of new compounds for morphine-like physical dependence in the Rhesus monkey. *Minutes of 26th Meeting of Committee on Problems of Drug Dependence*, Addendum 1, p. 3.

DOBBS, H. E., BLANE, G. F. & BOURA, A. L. A. (1969). Uptake of etorphine and dihydromorphine after sublingual and intramuscular administration. *Eur. J. Pharmac.*, **7**, 328–332.

The mechanism of the reversal of the effect of guanethidine by amphetamines in cat and man

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The reversal of the effects of guanethidine by amphetamines is well known (Day & Rand, 1962), but the mechanism of the antagonism is unclear. The effects of amphetamines on the release of guanethidine in cat and man have therefore been examined.

The isolated cat spleen perfused with oxygenated Krebs was labelled with a solution containing ^{3}H-guanethidine (10^{-6} g/ml) for 20 min and then washed out with drug-free Krebs solution. Collections (2 min) of the effluent perfusate were assayed for noradrenaline and ^{3}H-guanethidine before and during splenic nerve stimulation at 30 Hz for 10 s at 30 min intervals. This dose of guanethidine caused just-complete block of the splenic response to nerve stimulation during the first stimulation period after wash-out.

In four experiments an intra-arterial injection of dexamphetamine (20 μg) reversed the blocking effects of guanethidine. The times of the injection varied, being before the second, third, fifth and sixth stimulation periods after washing out guanethidine, at which times the response of the spleen was reduced by 50–90%. The injection of dexamphetamine did not cause splenic contraction but produced a striking increase in the resting output of guanethidine without releasing noradrenaline. The lack of splenic response despite the release of large amounts of guanethidine indicates that under these conditions guanethidine has no post-synaptic agonist properties. When the spleen was subsequently stimulated, the release of both noradrenaline and guanethidine was enhanced. The noradrenaline/guanethidine ratio of samples obtained during stimulation was greater after (1·7) than before (0·7) dexamphetamine reversal. This is probably a result of blocking the reuptake of noradrenaline to a greater extent than that of guanethidine. Both reduction of the extravesicular

concentration of guanethidine and block of reuptake of noradrenaline could contribute to the reversal of blockade by dexamphetamine.

The effects of amphetamine on the excretion of guanethidine in man have also been examined. It has been shown that, after the administration of 50 μCi of ^{3}H-guanethidine intravenously in man, the urinary excretion follows a bi-exponential course. The late exponential phase occurs after about 5 days following the injection and has a half-time of decay of 5·7 days. In three subjects, the administration of amphetamine 10 mg t.d.s., 8 days after the ^{3}H-guanethidine injection, caused a pronounced increase in the rate of excretion of ^{3}H-guanethidine. This implies that in man, as well as in the cat, amphetamines can enhance the removal of guanethidine from its site of action and may explain, at least in part, the mechanism of this drug interaction in man.

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REFERENCE

DAY, M. D. & RAND, M. J. (1962). Antagonism of guanethidine by dexamphetamine and other related sympathomimetic amines. *J. Pharm. Pharmac.*, **14**, 541.

The effect of nitrous oxide on reaction time and cerebral evoked potential

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There is evidence that certain later components of the electroencephalographic evoked response recorded from the vertex of the scalp reflect the levels of attention and alertness of the subject. Satterfield (1965) showed that the evoked response to an attended stimulus was of greater amplitude than that to an unattended stimulus. Similarly, the evoked response to signal stimuli is enhanced when the subject is required to discriminate between relevant and irrelevant stimuli during a prolonged visual vigilance task (Haider, Spong & Lindsley, 1964). Nitrous oxide, having depressant effects on central nervous system function, would be expected to decrease alertness and hence diminish the evoked response. In an earlier experiment, in which click stimuli were used to which the subject was not required to respond, diminution of all evoked response components between 40 ms and 240 ms after the stimulus occurred (Lader & Norris, 1969).

The experiment investigates the action of nitrous oxide further by examining its effects on reaction time performance and the evoked response to the reaction time stimulus. The experimental situation used is essentially similar to that in the study by Bostock & Jarvis (1969) in which the evoked response was found to vary according to the speed of reaction time, one component in particular, thought to relate to level of alertness, augmenting with slower reaction times. The subject is instructed to press a key as quickly as he can in response to the onset of a tone presented at random intervals through a loudspeaker behind his head. Fifty stimuli are presented at each dose level of nitrous oxide. The electroencephalogram is sampled and digitized every 2 ms for a 500 ms epoch after each stimulus. These data are stored together with the subject's reaction time on the Linc-8 computer digital magnetic tape. Averaging of the responses and analysis of the data is carried out off-line