1958 ; Takagi, Takashima & Kimura, 1964 ; Rudzik & Mennear, 1965). The ability to inject drugs directly into the brains of conscious rats has permitted a re-examination of the role of these amines in morphine analgesia.

A nociceptive response was induced in rats by a foot-pressure method similar to that described by Randall & Selitto (1957), using a commercially available apparatus (Arnold R. Horwell, Ltd.). A constantly increasing pressure was applied to the dorsal surface of the hind paw, the actual load applied being recorded when the animal made its first escape attempt.

When given alone, intraventricularly, noradrenaline (NA), 10–80 $\mu$g, or 5-hydroxytryptamine (5-HT), 5–20 $\mu$g, did not alter the minimum load at which the animal responded. When 20 $\mu$g of NA was injected intraventricularly 30 min after morphine (8 mg/kg subcutaneously) the analgesic action of morphine was abolished. In contrast, when 5-HT was given after the morphine, it substantially prolonged the analgesic effect.

In a second series of experiments, the rats were pretreated with reserpine (5 mg/kg intraperitoneally) 16 hr before the injection of morphine (8 mg/kg subcutaneously). The analgesic action of morphine was completely abolished. Intraventricular NA (20 $\mu$g) failed to restore the morphine effect ; rather there was some evidence that it induced an increased sensitivity to the nociceptive stimulus. Intraventricular 5-HT (5 $\mu$g) restored the effect of morphine in reserpinized rats to the level observed in morphine-treated control rats. In the absence of morphine, intraventricular injections of NA or 5-HT did not alter the response of reserpinized animals.

All these experiments were repeated giving the amines peripherally. Intravenous injections or infusions of either NA or 5-HT failed to modify the analgesic effect of morphine.

It is concluded that the previously observed antagonism of morphine analgesia in rats by reserpine is related to the depletion of central stores of 5-HT ; the antagonism of morphine by intraventricular NA requires further study.

REFERENCES

HAYDEN, J. F., JOHNSON, L. R. & MAICKEL, R. P. (1966). Construction and implantation of a permanent cannula for making injections into the lateral ventricle of the rat brain. *Life Sci., Oxford*, **5**, 1509–1515.

RANDALL, L. O. & SELITTO, J. J. (1957). A method for the measurement of analgesic activity on inflamed tissue. *Archs int. Pharmacodyn. Thér.*, **111**, 409–419.

RUDZIK, A. D. & MENNEAR, J. H. (1965). Antagonism of analgesics by amine depleting agents. *J. Pharm. Pharmac.*, **17**, 326–327.

SIGG, E. B., CAPRIO, G. & SCHNEIDER, J. A. (1958). Synergism of amines and antagonism of reserpine to morphine analgesia. *Proc. Soc. exp. Biol. Med.*, **97**, 97–100.

TAKAGI, H., TAKASHIMA, T. & KIMURA, K. (1964). Antagonism of the analgesic effect of morphine in mice by tetrabenazine and reserpine. *Archs int. Pharmacodyn. Thér.*, **149**, 484–492.

**Post-operative pain in the assessment of analgesics in man**

R. C. HILL* and P. TURNER, *Department of Clinical Pharmacology, Medical Professorial Unit, St. Bartholomew's Hospital, London E.C.1*

Post-operative pain has been used to assess potential analgesic compounds (Beecher, 1957 ; Lasagna, 1964). We have tested a number of oral analgesics against post-operative pain to evaluate the sensitivity and usefulness of the method for the assessment of potential analgesic compounds. Patients aged between 20 and

75 years who had undergone an operation under general anaesthesia within the previous 48 hours were studied under double-blind conditions, each patient receiving in random order, on request, the active treatment and an identical placebo. The test preparations were substituted for the first two oral analgesics required after operation. Patient volunteers were asked, by means of a multichoice questionnaire, (1) to indicate their initial level of pain immediately before taking the first set of tablets; (2) to rate their pain relief 1 hr after taking each set of tablets and (3) to select their preference, if any, for either set of tablets. Preparations investigated included aspirin and pethidine.

Submission of the results to sequential analysis using the method described by Armitage (1960) showed that it was not possible to demonstrate a significant difference between the test treatments and their corresponding placebo on pain relief if the populations were treated as homogeneous units. When, however, these populations were split into three groups using the initial pain levels as the basis for classification, the sensitivity of the study was greatly increased. Pethidine (100 mg) produced greater analgesia at the more severe pain levels, whereas aspirin (600 mg) had its most significant effect at the mildest level of pain. This difference was confirmed by the mean pain relief scores ($\pm$S.E.) obtained at every level of pain after both drug and placebo. It was also found that with both drugs the number of placebo responses were inversely related to the pain relief obtained. When the patient's preferences were analysed sequentially, similar results were obtained to those using relief scores.

Differences between the two sets of results may be due to the incidence of side effects and their influence on the preference made by the patient. For patients with mild pain the discomfort was often preferred to the side effects produced by the potent analgesic, whereas at the more severe levels of pain the importance of the side effects encountered was relatively small compared with the relief of pain achieved.

The classification of initial pain permits better discrimination between drug and placebo than is achieved using overall comparisons and also enables an estimation of the potency of the drug to be made.

We thank the surgeons of St. Bartholomew's Hospital for allowing us to study their patients. R. C. H. is supported by a grant from Roche Products Ltd.

REFERENCES

ARMITAGE, P. (1960). *Sequential Medical Trials*, pp. 25–47. Oxford: Blackwell Scientific Publications.
BEECHER, H. K. (1957). The measurement of pain. *Pharmac. Rev.*, **9**, 59–290.
LASAGNA, L. (1964). The clinical evaluation of morphine and its substitutes as analgesics. *Pharmac. Rev.*, **16**, 47–83.

## The effect of triflupromazine on the peripheral and central actions of some anticholinergic drugs

R. W. BRIMBLECOMBE and D. M. GREEN,* *Ministry of Defence, Chemical Defence Experimental Establishment, Porton Down, Salisbury, Wiltshire*

Many authors have shown that atropine and other anticholinergic drugs can produce a pattern of slow wave activity in the electroencephalogram (e.e.g.) inde-