ACTION OF DIETHYLAMINOETHYLPHENOTHIAZINE (2987 RP, DIPARCOL) AND MYANESIN ON TONE AND REFLEX REGULATING CENTRES OF THE NERVOUS SYSTEM

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THE mode of action of drugs used for the treatment of Parkinson's disease in man is not fully understood yet. It is now assumed that the nicotinolytic action of these drugs bears some relation to their therapeutic activity.[1] However, it seems desirable to work out more detailed information on the pharmacology of these substances.

For that purpose experiments were carried out on cats, using a method which proved to be of value in the determination of the action of drugs on interneurons of the Central Nervous System:[2,3] the animals were anesthetised with either Dial (0·5 c.c./kg. of the commercially available solution, intraperitoneal†) or with Chloralose (80 mg./kg. intravenous). The knee jerk was elicited at regular intervals (every 10 sec.) with an automatically driven hammer.[4] Electrodes, covered with insulating material except for the tip, were inserted into the brain stem using a simplified Horsley-Clark instrument. For unipolar stimulation rectangular impulses of a frequency 100 per sec were used. According to the site of stimulation, three different types of effects could be observed in these experiments during the period of central stimulation: inhibition and facilitation of the knee jerk as known from the work of Magoun, *et al.*, were most frequently encountered. Occasionally a hypertonus of the quadriceps muscle with repetitive components or clonus following each reflex contraction was observed as the result of the stimulation. The rise of tone was usually not accompanied by any alteration of the tension developed by the phasic reflex These effects lasted only for the period of actual stimulation, usually ½ to 1 minute. The drugs were injected intravenously. The position of the electrode was verified at the end of the experiment macroscopically. The points which on stimulation gave facilitation or inhibition of the phasic reflex contraction coincided with the regions indicated by Lindsley, Schreiner and Magoun,[5] *i.e.*, basal diencephalon, pontile tegmentum, certain parts of the bulbar reticular formation and lower reticular formation respectively. When rise of tone was observed, the tip of the electrode was always found to be situated near the vestibular nuclei in the medulla.

In these experiments the action of Diparcol‡ as a representative for anti-Parkinson drugs was compared with the well-established action of Myanesin.[2,3] If Diparcol was injected in a dose of at least 20 mg./kg., a block of the interneurons involved in the facilitation or inhibition of the monosynaptic test reflex (*i.e.*, knee jerk) could be observed. Following the injection of such a dose (usually given in at least two portions, each 10 mg., at an interval of 5 minutes), the inhibition as well as the facilitation of the knee jerk, on stimulation of the appropriate points in the brain stem, became gradually reduced and finally disappeared completely. Fig. 1 gives an example of the action

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† Ciba Ltd., Bale

‡ We are obliged to Specia, Paris, for kindly supplying the compound.

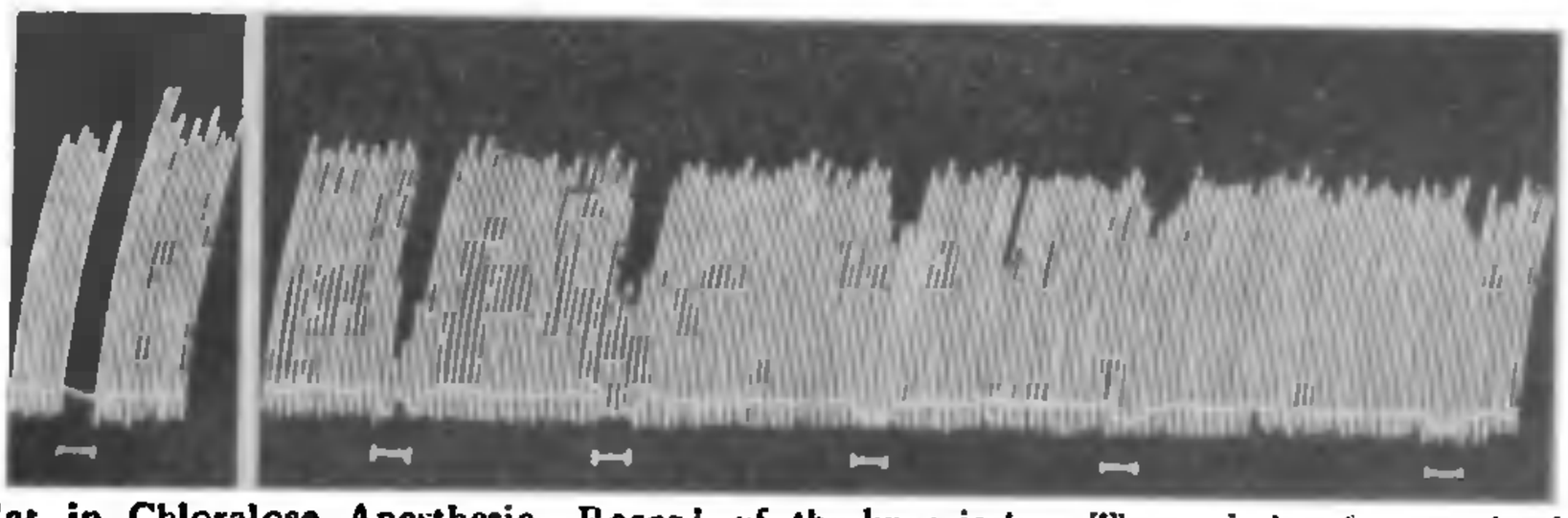

FIG. 1. Cat in Chloralose Anesthesia. Record of the knee jerk. The periods of central stimulation are indicated at the bottom of the record. 20 mg./kg. Diparcol were injected intravenously between the first and the second part of the figure. The injections were given in 10 mg./kg. doses, at an interval of 5minutes. The right part of the record starts with the end of the second injection.

of Diparcol on the centrally induced reflex inhibition. In doses below 20 mg./kg., Diparcol was regularly without any significant effect on central facilitation and inhibition respectively.

In the action described so far, Diparcol resembles Myanesin closely,[6] which also abolishes the effect of facilitory and inhibitory stimulation of the brain stem. The striking fact noticed was when the effects of central stimulation of the reticular formation resulted in hypertonicity of the extensor muscles, Diparcol in as low a dose as 5 mg./kg. completely abolished the tonic effect without appreciably interfering with the

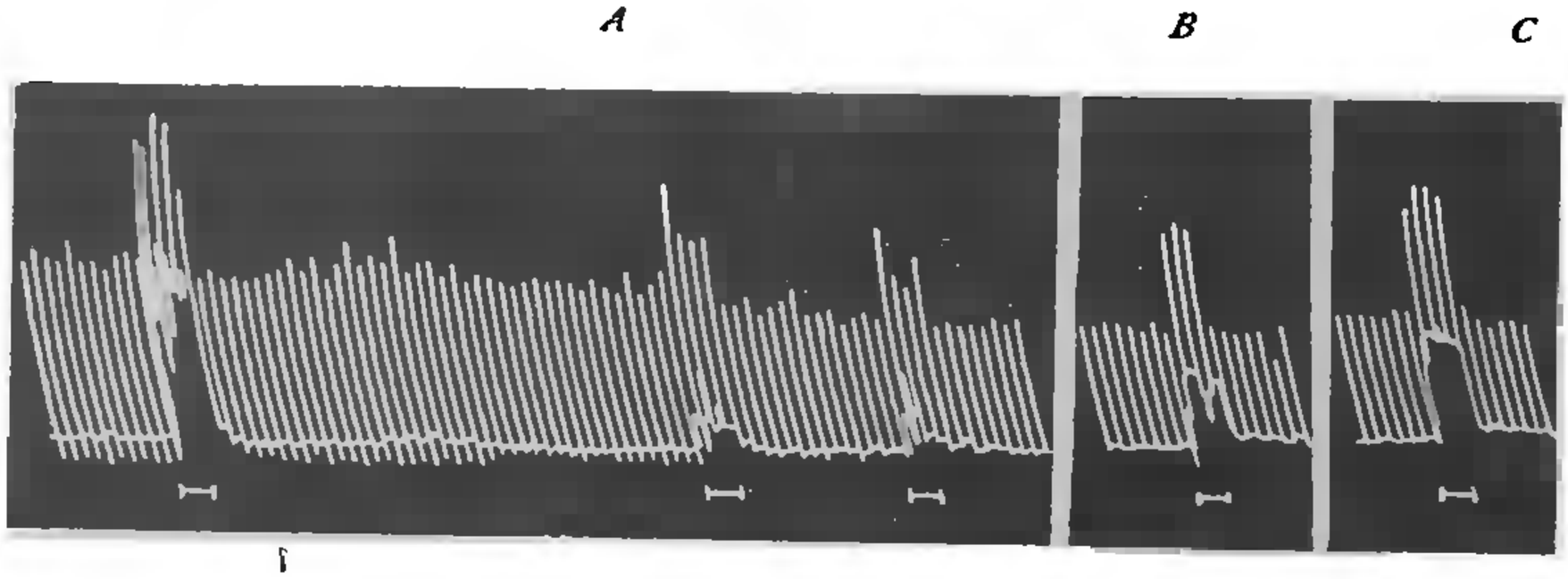

FIG 2. Cat in Dial-Anesthesia, Record of the knee jerk. White marks indicate the periods of stimulation. At the arrow 5 mg./kg. Diparcol are injected intravenously. Record B demonstrates the effect of central stimulation 25 minutes after the injection, record C 40 minutes after the injection of Diparcol.

phasic reflex (Fig. 2). This effect of Diparcol lasted in different experiments from 20-40 minutes. In one instance (cf. Fig. 2), a small facilitation of the phasic reflex became even manifest at a time when the tonic contraction of the quadriceps muscle due to central stimulation was completely suppressed by Diparcol.

Experiments were then performed to demonstrate whether such a difference in the sensitivity of tone- and reflex-regulating areas in the brain stem exists also for Myanesin. In two experiments performed for that purpose, we observed that Myanesin also in a dose of 5 mg./kg. abolishes any centrally induced tonic response. For the blockade of central inhibition and facilitation of the knee jerk however, at least 25-30 mg./kg. have to be administered in cats.

On the basis of these observations, we come to the conclusion that the centres of the reticular formation influencing the tone are considerably more susceptible to the paralysing action of interneuron blocking drugs such as Myanesin and Diparcol, than the reflex regulating centres. This observation corresponds well to the clinical experience, indicating that the increased muscle tone in disorders of the extrapyramidal motor system is particularly reduced by Diparcol.[7]

1. Bovet D. and Longo, V. G., *J. Pharmacol.*, 1951, **102**, 22. 2. Kaada, B. R., *J. Neurophysiol.*, 1950, **13**, 89. 3. Henneman, E., Kaplan, A. and Unna, K., *J. Pharmacol.*, 1949, **97**, 331. 4. Schweitzer, A. and Wright, S., *J. Physiol.*, 1936, **88**, 459. 5. Lindsley, D. E., Schreiner, L. H. and Magoun, H. W., *J. Neurophysiol.*, 1949, **12**, 197. 6. Berger, F. M., *Brit J. Pharmacol.*, 1947, **2**, 241. 7. Bovet, D. and Bovet-Nitti, F., *Medicaments du systeme nerveux vegetatif*, *Bale*, 1948, *cf.* p. 616.

ATOMIC FURNACE FOR DETECTION OF IMPURITIES

A NEW and highly accurate method of using atomic energy to detect and measure impurities in foods, pharmaceutical producs, metals and other materials has been developed at the Oak Ridge National Laboratory, Tennessee. The technique involves placing the test sample in a graphite reactor or 'atomic furnace', and exposing to neutron bombardment, so that traces of impurities will be rendered radio-active. Highly sensitive instruments and detectors are then used to measure the exact quantities of impurities present. This is possible because the elements to be tested, when irradiated, produce radio-active isotopes having characteristics never exactly duplicated by other radio-isotopes. This analysis technique, which should help to ensure purity of the manufactured product, is now being offered to industrial, scientific and medical organisations in other countries, by arrangement with the U.S. Atomic Energy Commission.