than effects resulting from paralysis of conduction along the peripheral nerves. The cats used were made spinal under ether anaesthesia by destruction of the brain rostral to the first cervical segment, and subsequently maintained on artificial ventilation. This avoided the complicating effects of long-acting anaesthetics and of respiratory arrest and hypotension that otherwise would have resulted from administration of the neurotoxins.

Saxitoxin or tetrodotoxin (1–3 μg/ml. in 0.9% NaCl) was given by slow intravenous infusion. When the dose reached 2.4–7.8 μg/kg the monosynaptic and polysynaptic spinal reflexes began to fall in amplitude. Simultaneous recording of the ingoing afferent volley in the dorsal root, central to the dorsal root ganglion, showed, however, that this was also being blocked. Superimposition of the partially blocked responses on a control of the input–output curve of the monosynaptic reflex showed no significant central depression of the reflex during the development of the block. The temporal patterns of facilitation, inhibition and post-tetanic potentiation of monosynaptic reflexes did not change during the administration of the neurotoxins, other than a decrease in absolute amplitude from control levels.

When a partial block of the afferent input, and consequent diminution of reflex amplitude had been produced no more toxin was given. The degree of block continued to increase slowly during the next few minutes. Between 1 and 3 hr later, the nerve responses began to recover and in some experiments this recovery was followed for 6 hr after stopping the administration of toxin. In some experiments there was never any evidence that the neurotoxins had a significant central effect, but in others the monosynaptic reflex remained small at a time when the afferent input at the dorsal root had largely recovered. Only in these experiments was there evidence that saxitoxin and tetrodotoxin had a central depressant action following intravenous administration, but this may not be significant in view of the length of time which elapsed before recovery commenced.

It is concluded that saxitoxin and tetrodotoxin cannot readily pass from the blood into the spinal cord during the time of a short experiment. The loss of reflexes reported here, and by other workers, can be accounted for by the well known ability of these neurotoxins to block conduction peripherally in the afferent limb of the reflex arc. Only after prolonged exposure to the toxins is there some evidence that they may have a central depressant action within the spinal cord.

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Centrally-active drugs and the discharge rate of spontaneously occurring action potentials in the superior cervical trunk of the cat

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Elliott (1967) described a reduction in the rate of discharge of action potentials occurring in the preganglionic sympathetic fibres of the superior cervical trunk of the cat, anaesthetized with ether, following the intravenous injection of chlorpromazine (0.5 mg/kg). Using the methods described in detail in that communication some other drugs have been studied.

Perphenazine, a congener of chlorpromazine, produced a reduction in the discharge rate (Fig. 1 C and D). When the rate of discharge 10 min after intra-

venous injection of perphenazine (1 mg/kg) was compared with the rate immediately before injection, the mean percentage reduction in the rate was 62% (range 35–87%, $n=7$). In four experiments there was full recovery within 55–120 min, but in the remaining experiments recovery was only partially complete within the 2 hr period after injection of the drug.

Pentobarbitone sodium (2 mg/kg) had little or no effect on the discharge rate; however, 10 mg/kg intravenously produced a mean percentage reduction of 66% (range 47–97%, $n=5$, Fig. 1 A and B). Typically there was an initial phase of fast recovery during the first 10–15 min after the injection followed by a slower phase of recovery sometimes interrupted by a second fall in the rate. In two experiments recovery was not complete within 2 hr of the injection.

With hydroxyzine results were more variable than with the other drugs; in three experiments with 2 mg/kg intravenously there was no action. In the other six experiments there was a reduction in rate which varied between 25 and 70% of the pre-injection control, recovery occurred within 20–130 min.

The reduction in discharge rate produced by chlorpromazine, perphenazine, pentobarbitone and hydroxyzine probably reflects a centrally mediated action provided that the possibility of a local anaesthetic action on the preganglionic nerve can be excluded.

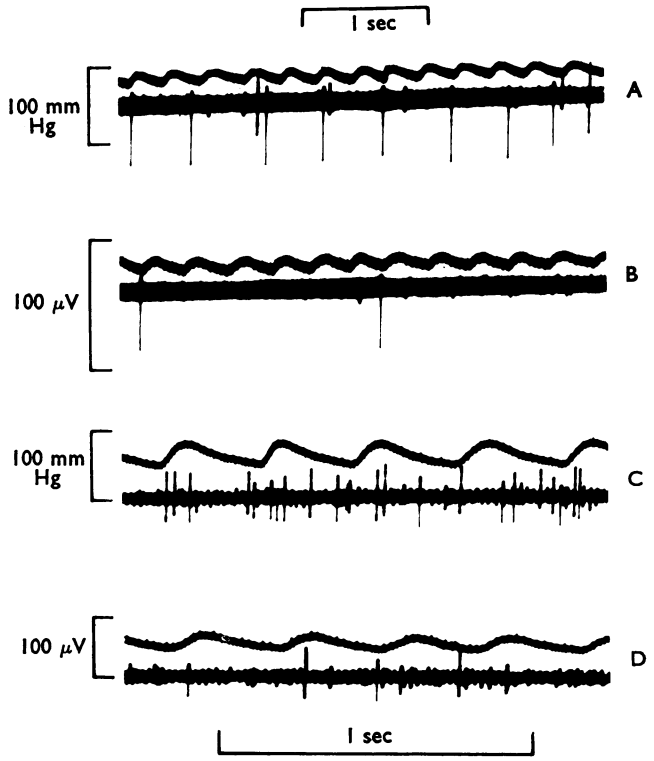

FIG. 1. Effects of drugs on the spontaneous discharge of action potentials in the superior cervical trunk. The upper trace in each record is the blood pressure, the lower trace is the discharge of action potentials in a small bundle of fibres dissected from the superior cervical trunk of the cat. (A) Before and (B) 17 min after pentobarbitone sodium (10 mg/kg, intravenously); (C) before and (D) 18 min after perphenazine (1 mg/kg intravenously).

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Pentobarbitone distribution in various regions of the rat brain in relation to the kinetics of its effect

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The radioactivity of rat brain was measured at various intervals (5, 10, 15, 20, 30, 40, and 70 min) after intraperitoneal administration of ^{14}C-labelled pentobarbitone (20 μc/kg) together with unlabelled pentobarbitone (62 mg/kg). The brain was carefully dissected, and pieces of nervous tissue were sampled. The regions studied were as follows: frontal, parietal and occipital cortex, fornix and nucleus caudatus, anterior and posterior thalamus, rostral and caudal hypothalamus, ventral mesencephalus, anterior and posterior colliculi, pons, cerebellar hemispheres and vermis, medulla oblongata and cervical spinal cord.

Close agreement was observed between the overall time-course of the distributions and that of its concentration on the receptor biophase, as determined from the times of the disappearance and reappearance of the righting reflex (Palumbi, Rossini & Segre, 1966; Giorgi, Palumbi, Rossini & Segre, 1966). The highest activity was reached after 20 min in the inferior posterior nucleus of the hypothalamus. This area does not appear to have an especially high blood flow, as evaluated with ^{131}I-labelled serum albumin (150 μc/kg, i.v.). The inferior posterior basal ganglia showed a much higher concentration than the other regions when incubated for 20 minutes at 37° C in oxygenated Krebs-phosphate medium containing non-labelled pentobarbitone at 62 mg/l. and labelled pentobarbitone with an activity of 20 μc/l.

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A metabolic explanation for differences between species of the anticonvulsant activity of diazepam

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A selective activity against metrazol-induced convulsions is a characteristic property of benzodiazepines, although species differences have been observed. The anticonvulsant activity of diazepam (5 mg/kg intravenously) in respect to metrazol (100 mg/kg, intraperitoneally) disappears in rats after 6 hr while it is present in mice for about 24 hr. Furthermore diazepam (5 mg/kg) antagonizes a higher dose of metrazol in mice (300 mg/kg) than in rats (150 mg/kg).