tolerance which rapidly develops to several barbiturates. A second type of tolerance, however, that caused by adaptation by cells of the central nervous system to the continuous presence of a drug, develops when certain barbiturates are given chronically at a sufficiently high dose level. Both mechanisms may contribute to the tolerance which is observed during chronic barbiturate administration. The present study was undertaken to provide information on the mechanisms underlying the changes in hexobarbitone response in barbitone-dependent and withdrawn rats.

Female Wistar rats, weighing approximately 50 g at the beginning of the experiment, were made dependent on barbitone sodium by the administration of up to 400 mg/kg per day in the drinking water for 32 days. At the end of this period, withdrawal—effected by replacing barbitone solution by tap-water—produced a withdrawal syndrome. At intervals during barbitone treatment and after withdrawal, the duration of anaesthesia following hexobarbitone sodium (150 mg/kg I.P.) was determined. At the same times the ability of liver microsomal preparations from treated and control animals to metabolize hexobarbitone *in vitro* was measured.

On each occasion, the hexobarbitone response appeared to correlate well with the hepatic drug-metabolizing enzyme activity. During the period of barbitone administration the animals were tolerant to hexobarbitone and the ability of liver preparations to oxidize hexobarbitone was increased. In addition, throughout this period there was no appreciable change in the extent of tolerance or degree of enzyme stimulation produced. Three weeks after withdrawal a hypersensitivity to hexobarbitone, associated with a decreased ability of liver preparations to oxidize hexobarbitone was found; both changes were still evident some 4 months later.

The results indicate that the altered hexobarbitone response occurring during barbitone administration and withdrawal may be explained in terms of altered liver drug-metabolizing enzyme activity. The possibility of drug treatment and/or withdrawal producing changes in the sensitivity of the central nervous system, however, must also be considered. The brain concentration of hexobarbitone at which animals awoke following injection of labelled hexobarbitone was therefore determined. During barbitone treatment, tolerant animals awake at lower brain concentrations of hexobarbitone. Further experiments to determine the significance of brain barbitone in these animals are at present under way.

Changes of the rat superior cervical ganglion induced by guanethidine (histology and cholinesterase histochemistry)

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Guanethidine is a sympathetic postganglionic neurone blocking agent, causing some depletion of noradrenaline. Prolonged treatment in rats causes a pronounced loss of specific and non-specific cholinesterase activity in sympathetic ganglia (Jensen-Holm & Zaimis, 1967; Jensen-Holm, 1967). In addition a considerable increase of proteins is found. The present investigation deals with the histochemical localization of cholinesterases and general histology of the rat superior cervical ganglion following treatment with guanethidine.

In some experiments unilateral preganglionic nerve division was undertaken in order to exclude centrally conditioned mechanisms. In other experiments unilateral post-

ganglionic axotomy was performed to compare the results with those obtained after guanethidine.

Guanethidine monosulphate (20 mg/kg intraperitoneally) was administered daily from 3 to 14 days. Normal saline were used in controls. 1–30 days after discontinuation of the treatment the animals were killed and the superior cervical ganglia removed for titrimetric determination of cholinesterases (Jensen-Holm, 1965) or histochemical cholinesterase demonstration by means of the lead-ferrocyanide method modified from the technique described by Eränkö, Koelle & Räisänen (1967).

Fresh-frozen ganglia were sectioned at 5 and 10 μ in a cryostat and incubated for one hour at 22° C in a substrate mixture containing acetylthiocholine (2.5×10^{-3}M) for demonstration of both specific and non-specific cholinesterase activity, acetylthiocholine+mipafox (10^{-6}M) for demonstration of specific cholinesterase activity, and butyrylthiocholine (2.5×10^{-3}M) for demonstration of non-specific cholinesterase activity.

Biochemical analysis following guanethidine administration for 14 days shows an increase in protein content (approximately 50%) and a decrease per ganglion in specific cholinesterase activity (approximately 65%) and non-specific cholinesterase activity (approximately 50%), the changes being still more pronounced after preganglionic nerve division.

Histochemical localization shows that preganglionic nerve division leads to a decrease in cholinesterase activity of preganglionic fibres while the cholinesterase activity of the ganglion cells remains unchanged. Postganglionic axotomy leads to a decrease in the cholinesterase activity of the ganglion cells while the preganglionic fibres appear normal.

Following guanethidine, the decrease of the activity of both cholinesterases occurs in the ganglion cells as well as in the preganglionic nerve fibres. These changes were observed already after a few days of treatment with guanethidine and were still demonstrable 30 days after discontinuation of the drug.

After guanethidine and preganglionic nerve division, only traces of cholinesterases could be found. Furthermore, a pronounced increase of satellite cells was found, with increased distance between the nerve cells.

On the basis of these findings it is concluded that guanethidine has at least two probably independent actions: the depletion of catecholamines and of ganglionic cholinesterases, accompanied by increase of protein and by a satellite cell infiltration.

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The effect of drugs on the intracranial pressure of baboons

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Much of the carotid blood supply to the cat brain passes through the rete mirabilis from the external carotid artery. The internal carotid artery is rudimentary. In primates