at 10^{-4} M. Ethambutol (10^{-3} M) had no significant effect. The decrease in accumulation with chloroquine was greater than that with hydroxychloroquine at the same concentration. Both chlorpromazine and chloroquine at 10^{-3} M in the ganglion compartment caused a significant fall in protein synthesis.

The results indicate that, with the exception of ethambutol, the drugs have an inhibitory effect on the axonal transport of proteins *in vitro*. The extent to which this contributes to their retinotoxic action is unclear. Retinal RNA and protein biosynthesis are also affected by chloroquine *in vitro* at the same concentration (Giuffrida, Sjöstrand, Cambria, Serra, Vanella, Avitabile, Jarlstedt & Karlsson, 1975).

A study *in vivo* was also undertaken in which albino and pigmented rabbits were fed chloroquine diphosphate (100 mg/kg) three days per week for 6–8 months. Vagus nerves were then removed and the axonal transport of labelled proteins examined *in vitro* by the above method. No significant difference was found between control and drug-treated animals. These results with chloroquine are consistent with previous work which indicated a lack of effect of the drug on RNA and protein synthesis *in vivo* (Karlsson, Giuffrida, Jarlstedt, Serra & Sjöstrand, 1976).

Drugs were donated by: Bayer (chloroquine); Winthrop (hydroxychloroquine); Sandoz (thioridazine); Ciba-Geigy (clioquinol); Leo (chlorpromazine) and Lederle (ethambutol).

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An examination of the action of tetrabenazine on peripheral noradrenergic neurones

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Tetrabenazine has been used recently in the treatment of various forms of chorea (McLellan, Chalmers & Johnson, 1974). Its action resembles that of reserpine, but it is less potent and shorter-acting (Quinn, Shore & Brodie, 1959). The present study has examined these differences, comparing the actions of tetrabenazine and reserpine on peripheral noradrenergic neurones of rats (male Wistar; weight range 200–220 g).

Tetrabenazine (100 mg/kg i.p.) markedly decreased catecholamine induced histofluorescence in the iris, mesenteric arterioles and hepatic portal vein. Depletion was maximal 4 h after injection and fluorescence intensity returned to normal 24 h after injection. Reserpine (0.5 mg/kg i.p.) produced a similar loss of histofluorescence from the same tissues but this effect was not maximal until 18 h after injection and histofluorescence was still sub-normal 4 days after injection.

Amine-depleted irides, venae cavae and mesenteries removed from rats ($n=5$ for each drug) either 4 h after tetrabenazine treatment (100 mg/kg) or 18 h after reserpine treatment (0.5 mg/kg), were incubated with noradrenaline (5×10^{-6} M) in Krebs' solution at 37°C for 15 minutes. After washing in Krebs' solution to remove unbound noradrenaline they were incubated with 2% glyoxylic acid (buffered at pH 7) and prepared for fluorescence microscopy. Tissues from tetrabenazine-treated rats contained noradrenergic nerve terminals which had been markedly repleted by incubation with noradrenaline. Those from the reserpine-treated rats showed no restitution of fluorescence after noradrenaline-treatment. Fluorescence was restored to reserpine-treated tissues if tranylcypromine (3×10^{-5} M) was included with noradrenaline in the incubation.

Ultrastructural studies supported these findings. Noradrenaline restored electron density to synaptic vesicles in nerve terminals of the iris from

tetrabenazine-treated rats. Incubation with noradrenaline had no effect on the vesicles of terminals in reserpine-treated irides. Electron-density of vesicle cores in iris nerve terminals was also induced by incubation of tetrabenazine-treated tissues with 5-hydroxydopamine (1×10^{-4} M). This did not occur in reserpine-treated irides.

Hepatic portal veins were also removed from the treated rats and suspended between platinum-wire electrodes in Krebs' solution gassed with 95% O_2/5% CO_2 at 37°C. Log frequency/response curves to nerve stimulation (140 V, 200 μs, 10 s trains; 1–20 Hz) were recorded. The responses of veins, from tetrabenazine- or reserpine-treated rats to each frequency of stimulation were much lower than those obtained from veins of untreated animals. The veins were then incubated with noradrenaline (5×10^{-6} M) for 15 min and log frequency/response curves repeated. This treatment increased the slope of the curve for tetrabenazine-treated veins but had no effect on that obtained from reserpine-treated veins.

These findings are consistent with the suggestion that tetrabenazine causes a reversible impairment of vesicular uptake and storage of noradrenaline but that the effect of reserpine on a particular population of vesicles is irreversible.

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The influence of pre-synaptic α-adrenoceptors on the overflow of noradrenaline in the stimulated mouse vas deferens

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In sympathetically innervated tissues a negative feedback system regulates noradrenaline (NA) output via a pre-junctional α-adrenoceptor (Langer, 1974). This receptor was implicated in the control of the twitch response of the mouse vas deferens (Marshall, Nasmyth, Nicholl & Shepperson, 1977). The present experiments provide direct evidence for the existence of this α-adrenoceptor.

Eight vasa deferentia were tied together and stimulated at 256 mA, 1 ms for 120 pulses at 1, 10 or 16 Hz. Contractions were recorded isometrically. The bath was emptied 3.5 min (or 5 min when drugs were present) after stimulation and the Krebs solution was assayed for NA by the specific radio-enzymatic method of Henry, Starman, Johnson & Williams, 1975.

Although the tension developed by the vasa was greater with increasing stimulation frequency, NA overflow did not increase proportionately. Addition of cocaine (10 μM) and oestradiol (3.7 μM)to the Krebs significantly inhibited the twitch (52.7%) at 1 Hz ($P < 0.05$) but not at 10 Hz or 16 Hz. However, at all three rates of stimulation NA overflow was approximately doubled. When phentolamine (10 μM) was added to the Krebs containing cocaine and oestradiol, the inhibition seen at 1 Hz was reversed and NA overflow was now increased a further 5-fold, a 12-fold increase over controls.

These results show that inhibition of the twitch response by cocaine and oestradiol (Marshall, Nasmyth & Shepperson, 1977) at 1.0 Hz correlates with increased NA overflow. In other tissues regulation of NA output is mediated by pre-junctional α-adrenoceptors only at low rates of stimulation (Starke, Endo & Taube, 1975). In agreement with this, phentolamine produced a much greater increase in NA overflow at low rates of stimulation.

In other experiments vasa deferentia were pre-incubated for 45 min with 100 ng/ml of [7-^{3}H]-(−)-noradrenaline (specific activity 5.8 Ci/mmol). The [^{3}H]-catechol overflow from 4 vasa after 120 stimuli at 0.2, 1.0 or 10 Hz, 2 ms, 256 mA was absorbed onto alumina and counted.