only inhibited aggregation. Some compounds potentiated at low concentrations but inhibited at higher concentrations; these compounds included (—)-isoprenaline, octopamine, (—)-metaraminol and mephentermine. The potentiating action of tyramine, synephrine, naphazoline and clonidine also disappeared with increasing concentrations but did not inhibit at the concentrations used.

The substances which potentiated ADP most were (—)-adrenaline (10^{-8} M), (—)-noradrenaline and α-methylnoradrenaline (2×10^{-8} M), clonidine (2×10^{-7} M), phenylephrine (10^{-6} M), dopamine, ethylnoradrenaline and naphazoline (2×10^{-6} M), (+)-amphetamine (5×10^{-6} M), tyramine (10^{-5} M), (—)-metaraminol, (±)-amphetamine and phenylethylamine (2×10^{-5} M). The potentiating effect of most of the compounds rapidly reached a plateau after which no additional increase occurred. The initial rate of aggregation and the maximal extent of aggregation induced by ADP were increased by over 100% by (—)-adrenaline, (—)-noradrenaline, α-methylnoradrenaline, dopamine, (±)-amphetamine, ethylnoradrenaline, (+)-amphetamine and phenylethylamine. Phenylephrine, tyramine and (—)-metaraminol increased aggregation by more than 50%. Although clonidine was effective at low concentration it never enhanced ADP aggregation by more than 40%. Tetrahydrozoline and xylometazoline were inactive.

Our experiments support the conclusion that the catecholamine receptors on blood platelets are α-type. The most active drugs had the catecholamine structure with *para* and *meta* hydroxyl groups, but the hydroxyl group at the *meta* position seems to be the more important for the enhancement of platelet aggregation. The shape change and potentiation of ADP aggregation caused by indirectly acting sympathomimetics could result from the release of platelet constituents.

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Possible allosteric interaction between pharmacological receptors in guinea-pig vas deferens

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Stripped vas deferens preparations were mounted in Krebs solution at 34° C and isotonic contractions obtained under 0·5 g tension. Only supramaximal concentrations of all agonists were used. Differences reported are significant at the 5% level by paired-data *t*-test. Responses to supramaximal doses of noradrenaline ($1–2\times10^{-4}$ M) were completely blocked by exposing the tissue to phenoxybenzamine (10^{-8} to 10^{-7} M) for 5 min, a treatment which reduced but did not block the responses to methacholine ($0·5–3\times10^{-4}$ M). Subsequently, noradrenaline added in the presence of methacholine caused a further contraction. If the agonists were added in the reverse order, the final equilibrium was the same although the response to noradrenaline was absent and the response to methacholine was typical of those due to noradrenaline (Fig. 1). This phenomenon still occurs in the presence of hexamethonium, after pretreatment of the animals with reserpine (after which the tissues did not respond to tyramine), or after cold storage of the tissue for several days. The revived response to nor-

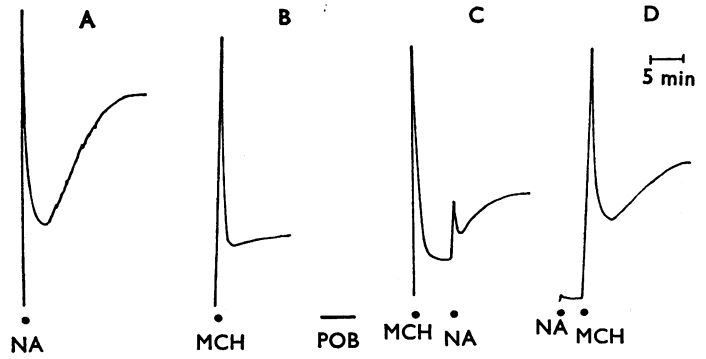

FIG. 1. Reversal of α-adrenoceptor blockade by methacholine (MCh). Doses of agonists are added at the dots. Between B and C the tissue was exposed to sufficient phenoxybenzanine (POB) to block noradrenaline (NA) (compare A and D). In C and D the agonists are added cumulatively.

adrenaline could be reversed by the addition of atropine, phentolamine or tolazoline during the response. Further treatment with POB only reduced the response to noradrenaline in proportion to the reduction in response to methacholine. We suggest that activation of muscarinic receptors uncovers new α-adrenoceptors (not susceptible to phenoxybenzamine) or reverses the effect of phenoxybenzamine temporarily without causing dissociation of phenoxybenzamine. The latter hypothesis would explain previous studies of the ability of cocaine to potentiate effects of maximal doses of noradrenaline in phenoxybenzamine-treated tissues (Nakatsu & Reiffenstein, 1968). However, the vas deferens does not normally respond to 5-hydroxytryptamine ($1–2 \times 10^{-4}$ M) but does so in the presence of methacholine, suggesting new 5-hydroxytryptamine sensitive receptors have been uncovered, or activated.

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Active factors in the venom duct of *Conus californicus*

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Marine snails of the genus *Conus* have an elaborate venom apparatus (Halstead, 1965) and produce a potent venom which can be lethal to humans. *C. californicus* feeds on other molluscs and worms (Saunders & Wolfson, 1961) but the venom from the species is also lethal to mice and rabbits. The toxic components of the venom are produced in a convoluted venom duct (Whysner & Saunders, 1963).

Because certain molluscs are the natural prey of *C. californicus* we decided to test the activity of venom duct extracts on some molluscan preparations in an initial attempt to determine the natural mechanism of action of the components of the venom.

Extracts prepared in artificial sea water produced an initial relaxation of the *Mytilus* anterior byssus retractor muscle similar to that caused by high concentrations of 5-hydroxytryptamine, and then a blockade of neurally induced contractions.

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