DISCUSSION

Though Martin, Riehl and Unna (1960) studied the adrenergic blocking property of chlorpromazine in the rabbit aortic strip and characterized the drug as a slowly reversible adrenergic blocking agent, neither the antagonistic potency nor the precise nature of this antagonism was investigated in detail.

In the present study, the antagonism by chlorpromazine of the responses of the rabbit aortic strip to adrenaline and noradrenaline was investigated in detail by determining dose response curves of the amines alone and in the presence of a wide range of chlorpromazine concentrations. The antagonistic effect of chlorpromazine was expressed in terms of the dose ratio and the data were subjected to quantitative analysis as described by Arunlakshana and Schild (1959).

At all the concentrations studied, chlorpromazine caused a parallel shift of the dose-response curves to the right indicating that the antagonism of the response with adrenaline and noradrenaline by chlorpromazine is competitive.

The pAx described by Schild (1947) is a precise and generally accepted measure of the potency of an antagonist. It is customary to express the potency of antagonist in terms of pA_2 values. The pA_2 values for chlorpromazine in antagonizing adrenaline was 13.94

while in antagonizing noradrenaline it was 14.1. This result indicates that chlorpromazine is a potent adrenergic blocking agent.

The pAx values determined in the present study can also be used to determine the nature of antagonism. Thus in competitive antagonism the theoretical value of $pA_2 - pA_{10}$ is 0.95. In the present investigations the $pA_2 - pA_{10}$ was 0.82 for antagonism of adrenaline responses by chlorpromazine; for antagonism of noreadrenaline responses the $pA_2 - pA_{10}$ value was 1.2. These values for $pA_2 - pA_{10}$ are in good agreement with the theoretical value of 0.95 for competitive antagonism. This agreement demonstrates that the antagonism of adrenaline and noradrenaline by chlorpromazine is competitive. Moreover, in competitive antagonism $\log K_2 = pA_2$. In the present experiments the mean $\log K_2$ value for adrenaline antagonism was 13.99 which is almost the same as the calculated pA_2 value (13.94).

In order to confirm and extend these observations and conclusions, the antagonism of adrenaline and noradrenaline responses by chlorpromazine was studied using the rat seminal vesicles. The plan of the study and the analysis of data were the same as described for rabbit aortic strip. In the rat seminal vesicles the pA_2 and $pA_2 - pA_{10}$ values for chlorpromazine in antagonizing adrenaline and noradrenaline were 14.15 and 1.05 and, 14.06 and 1.06 respectively. The close similarity of these values with those obtained with the rabbit aortic

strip confirm the competitive nature of the antagonism of adrenaline and noradrenaline by chlorpromazine and also indicates that α-adrenergic receptors present in the rat seminal vesicle are similar to those contained in rabbit aortic strips. In rat seminal vesicles the mean log K_2 value was 14.09 which is also closely similar to the calculated pA_2 value of 14.15

Although chlorpromazine has been repeatedly described as an adrenergic blocking agent (Courvoisier et al.,1953; Huidobro,1954; Martin et al., 1960), the antagonism by chlorpromazine of the peripheral effects of adrenaline and noradrenaline is somewhat different from that described for other more established adrenergic blocking drugs like phentolamine, dibenzyline, tolazoline etc. For example chlorpromazine while consistently blocking and many times reversing the pressor response to adrenaline leaves the pressor effect of noradrenaline mostly unaltered. Thus the characterization of chlorpromazine as an adrenergic blocking agent rests primarily on its ability to diminish or reverse the pressor effect of adrenaline. No adequate explanation of this paradoxical property of chlorpromazine in selectively blocking the pressor effects of adrenaline has so far been advanced.

Tissue uptake and subsequent binding in an inactive form constitutes a major event in the termination of the pharmacological effects of noradrenaline (Axelrod,Weil-Malherbe and Tomchick,1959; Whitby,Axelrod and Weil-Malherbe, 1961). Chlorpromazine has been shown to inhibit the uptake of noradrenaline by these binding sites (Hertting et al., 1961; Axelrod,Hertting and Potter 1962; and Hertting et al., 1962).It was therefore,thought

likely that the inability of chlorpromazine to block the pressor effect of noradrenaline could have been due to the overshadowing of the blocking effect of chlorpromazine by potentiation caused by inhibition of uptake. However, the results of the experiments in animals in whom the tissue uptake of amines was previously blocked either by treatment with cocaine or hexamethonium demonstrated that this supposition is not tenable.

Ahlquist (1948) has postulated two different types of adrenergic receptors, the alpha and the beta. In relation to the blood vessels, excitation of alpha receptors causes vasoconstriction while beta receptors activation produces vasodilation. Noradrenaline acts predominantly on the alpha receptors, isoprenaline on the beta receptors while adrenaline excites both the alpha and beta receptors. Thus the rise of blood pressure after noradrenaline can be attributed almost exclusively to alpha receptors excitation whereas the pressor effect of adrenaline is the resultant of the algebric sum of its constrictor and dilator effects. In the present study it was observed that chlorpromazine potentiates the depressor effect of isoprenaline and the positive inotropic effect of adrenaline on the rabbit auricles. Martin et al., (1960) also observed an enhancement of the positive chronotropic effect of adrenaline and noradrenaline following chlorpromazine administration. Thus chlorpromazine in small doses appears to potentiate catecholamine responses mediated through an activation of the beta adrenergic receptors.

It was, thefefore, quite likely that the diminition of the pressor effect of adrenaline by chlorpromazine might be due to the potentiation of the vasodilator action of adrenaline. Indeed in animals pretreated with dichlorpisoprenaline this was found to be so. In such animals chlorpromazine (1 to 8 mg/kg) did not reduce the pressor effect of adrenaline and noradrenaline; on the other hand, a slight potentiation was observed. Furthermore dichloroisoprenaline could unblock the blocking action of chlorpromazine against adrenaline pressor effect but did not affect the pressor response to noradrenaline. These results thus demonstrate that in small doses chlorpromazine has no true adrenergic blocking action and that the reduction of adrenaline pressor effect is due to an enhancement of its vasodilator action by chlorpromazine. This contention is substentiated by the finding that in dichloroisoprenaline treated cats higher doses (32 mg/kg) of chlorpromazine produced an equal inhibition of the pressor responses to adrenaline and noradrenaline.

Further support for this idea could also be afforded by the observations on the effect of chlorpromazine on the pressor responses to adrenaline and noradrenaline in the rabbits. In this species adrenaline has no vasodilator action and acts as a pressor agent in all circumstances. In the rabbit chlorpromazine depressed the pressor effects of adrenaline and noradrenaline to the same extent. Incidentally it may be

observed that rabbit appears to be much more sensitive to the adrenergic blocking action of chlorpromazine than cat. since even 0.2 mg/kg of chlorpromazine produced good block of the pressor responses to both catecholamines while 40 times higher doses of chlorpromazine were necessary to elicit some block of noradrenaline pressor response in cats.

In chloralosed cats high doses (8 to 32 mg/kg) of chlorpromazine caused a parallel shift of the dose response lines of the pressor effect of noradrenaline to the right. When $\frac{1}{V}$ value before and after different doses of chlorpromazine were plotted against the corresponding $\frac{1}{S}$ values, lines of different slopes with a common intercept were obtained. This according to Chen and Russell (1950) constitutes proof of competitive antagonism.

Thus it can be concluded that chlorpromazine exerts an equipotent blocking effect both against adrenaline and noradrenaline pressor effects and that this antagonism is competitive.