CONCLUSIONS

The present work confirms the earlier observation (146,148) that chloroquine and amodiaquin potentiate the pressor responses to injected adrenaline and noradrenaline in intact animal preparations. The potentiation was characterized by the following features. (a) The potentiating effect of chloroquine and amodiaquin could be observed in different animal species and both in anaesthetised as well as in spinal vagotomised animals. (b) The potentiation developed maximally only after an interval of time. (c) When the pressor responses to injected catecholamines were maximally augmented the responses of the nictitating membrane or of spleen to the amines were not augmented; the potentiating effect of the 4-aminoquinolines thus appears to be restricted, at least initially, to the cardiovascular action of the injected catecholamines. (d) At the time of peak potentiation of the catecholamine effects the pressor action of tyramine was also potentiated. The cardiovascular effect of other agents was not augmented; the potentiating effect of the 4-aminoquinolines thus appears to be restricted to sympathomimetic amines.

Chloroquine and amodiaquin did not augment the action of catecholamines on isolated tissue preparations. On the other hand they inhibited the responses of these preparations to catecholamines, probably through a blocking effect on the adrenergic receptors.
The study of the potentiating effect of the 4-aminoquinolines in intact animal preparations pretreated with reserpine, cocaine, hexamethonium or nialamide indicated the possible nature of the mechanism involved in the potentiation. The compounds thus appear to potentiate the responses to the sympathomimetic amines by liberating catecholamines from the tissue stores; the increased concentration of the amines in vicinity of the receptor sites then probably adds to the effect of the injected amines. Such a mechanism has been proposed to explain the augmentation of the effects of sympathomimetic agents following acute intravenous administration of reserpine. Chloroquine, in addition, appears to exhibit a cocaine like action, that is, it potentiates the amine responses by inhibiting the uptake of the injected amines by the tissue amine stores.

In animals pretreated with methylamphetamine both chloroquine and amodiaquin induce brisk pressor responses which in all probability are due to liberation of catecholamines from tissue stores. This was evident from the observations that the pressor responses were adrenergic in nature and were dependant on the intact tissue catecholamine stores. The liberation of the amines evoked by chloroquine and amodiaquin appears to be in vicinity of receptor sites and not in general circulation; moreover, adrenal medulla did not participate to any major extent in the amine release process. Though this study in itself
does not prove that the 4-aminquinolines liberate the 
catecholamines in normal (untreated) animals as well, 
it does show that the compounds have a capacity to 
interact with the tissue amine stores. This appears to 
lend a strong support to the hypothesis proposed to 
explain the potentiation of the amine pressor responses 
by chloroquine and amodiaquin.

Chronic treatment of the animals by amodiaquin 
resulted in considerably greater supersensitivity to the 
Injected amines than that observed in acute experiments. 
This supersensitivity may have an entirely different basis. 
On the other hand chronic treatment of the animals with 
chloroquine led to marked subsensitivity to the injected 
amines. The present results do not support the concept 
that a vascular spasm underlies the ocular toxicity of 
chloroquine.