Based on the findings of this study, we concluded that, in the rat, the intermediate metabolism of [^{14}C]5-hydroxytryptamine is altered by the administration of chloral hydrate. This alteration appears to occur at the 5-hydroxyindoleacetaldehyde level and is similar to the changes seen after ethanol injection. In addition to the "ethanol-like" effect of blocking 5-hydroxyindoleacetaldehyde conversion to 5-hydroxyindoleacetic acid, chloral hydrate apparently acts on alcohol dehydrogenase to limit the formation of 5-hydroxytryptophol.

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The tricyclic antidepressants—Inhibition of norepinephrine uptake as related to potentiation of norepinephrine and clinical efficacy

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THE CLINICAL activity of the tricyclic antidepressants has been attributed to a sensitization of central adrenergic receptor sites,[1] since the antidepressant activity appeared to be correlated with the ability of these compounds to potentiate both the peripheral response to exogenously administered norepinephrine[2] (NE) and the response to sympathetic nerve stimulation.[3] Imipramine was also reported to block the uptake of infused ^{3}H-NE in the heart by causing a decreased permeability of the cell or

storage granule membrane.[4] Since the uptake and binding mechanisms have been suggested to be the major means of inactivating released NE,[5] a blockade of the uptake mechanism would reduce NE inactivation and result in a sensitization of the adrenergic receptor.

This study examines the effect of a number of tricyclic antidepressants and phenothiazine compounds on the uptake of ^{3}H-norepinephrine in the mouse heart; the results demonstrate a lack of correlation between blockade of uptake and other parameters such as clinical efficacy and potentiation of norepinephrine.

The procedure of Daly *et al.*,[6] with minor modifications, was used in this study. The drugs were administered to male Carworth Farm mice, 18–22 g, by the intraperitoneal (i.p.) route 1 hr prior to the intravenous (i.v.) administration of 3·0 μc ^{3}H-NE (specific activity, 5–10 c/m-mole). The animals were sacrificed by decapitation 3 hr after the administration of ^{3}H-NE. Hearts were removed and rinsed in cold saline, the atrium was removed and the organs were homogenized in 3·0 ml of 0·4 N perchloric acid. The homogenate was centrifuged at 10,000 *g* for 10 min and then a 1·5-ml aliquot of the supernatant was transferred to a scintillation vial containing 15 ml of a toluene:Triton X-100 (2:1) scintillation fluid.[7] Two hearts were used per determination and three determinations were made per drug treatment. In those cases where the ED_{50} values are given, at least three doses were used for the determination and the values were obtained from plots of per cent of control values versus dosage. Samples from vehicle-treated animals contained approximately 5000 counts/min per 1·5 ml of supernatant.

The data presented in Table 1 on the tricyclic antidepressants and in Table 2 on the phenothiazines demonstrate that the blockade of uptake of ^{3}H-NE by the mouse heart is not a property common to all members of these two classes of drugs. Those compounds, from either class, which are the most active blockers of uptake contain a propylamine side chain in which the terminal amine is methylated. Incorporation of the terminal amine and side chain into a pyrrolidine ring, i.e. methdilazine, results in a slightly less active compound. Incorporation of the terminal amine into a piperazine ring results in a dramatic loss of activity, as demonstrated by the tricyclic antidepressant, opipramol, and the phenothiazines, perphenazine and trifluoperazine. It is of further interest that thiothixene, a clinically active antipsychotic and antidepressant,[8] which is a thioxanthene derivative with its terminal amine incorporated into a piperazine ring, is not active in blocking ^{3}H-NE uptake. Although opipramol is the only tricyclic antidepressant tested with a piperazine side chain, its lack of effect on the uptake of ^{3}H-NE correlated very well with the structure–activity relationship of the phenothiazines on uptake, where species with the piperazine side chain are also inactive.

Iprindole does not fit the described structure–activity relationship, since it has no effect on uptake and yet it is a tricyclic structure containing a methylated propylamine side chain. The results obtained from iprindole suggest not only that a propylamine side chain is necessary for blockade of uptake but that the proper tricyclic structure is also needed.

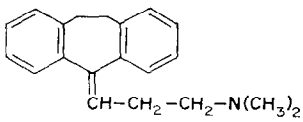
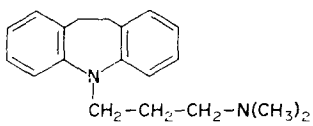
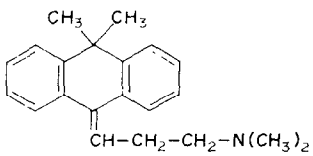
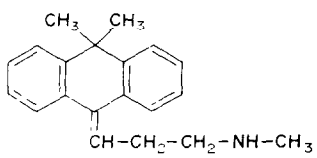
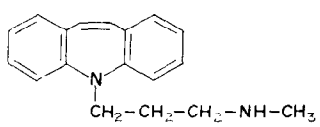
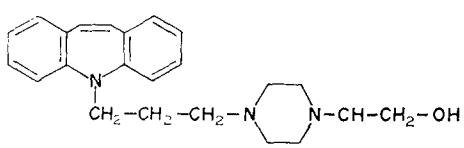
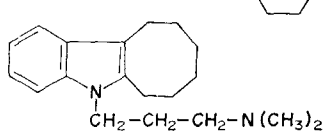
A particularly noteworthy discrepancy is found between the effects of the tricyclic antidepressants on the uptake of ^{3}H-NE and their potentiation of the pressor response to NE.[9,10] Opipramol and iprindole potentiate the effect of NE on blood pressure but do not block the uptake of ^{3}H-NE. There also seems to be a poor correlation between the effect on uptake and clinical efficacy. It has been reported in a review[11] of a number of clinical studies that there is little difference in efficacy among the various tricyclic antidepressants in treating depression. These clinical data would suggest a common mode of action for these drugs and, as demonstrated here, the effect on uptake is not common to all of these compounds, i.e. opipramol and iprindole.

All of the tricyclic antidepressants potentiate the pressor effect of NE;[9,10] therefore, there does seem to be a correlation between the potentiating effect and clinical efficacy. However, not all the tricyclic antidepressants block ^{3}H-NE uptake and this finding relegates the postulated significance of a blockade of ^{3}H-NE uptake, as related to NE potentiation, to an obscure role. The lack of correlation between blockade of NE uptake and NE potentiation raises two questions: first, what is the mechanism by which the tricyclic antidepressants potentiate the action of NE; and second, is there a physiological response associated with a blockade of NE uptake?

Support for the above findings was recently reported in a study using cocaine, from which it was concluded that the potentiation of and inhibition of uptake of the sympathomimetic amines reflect two independent actions.[12] Similar findings have recently been described in brain studies[13] in which it was demonstrated that relatively few of the tricyclic antidepressants block the central norepinephrine-depleting actions of 4-α-methyl-*meta*-tyramine. The authors concluded that the correlation between blockade of amine uptake by central norepinephrine neurons and general clinical efficacy seems to be poor.

In conclusion, it has been shown that incorporation of the terminal amine of protriptyline, the most effective tricyclic antidepressant in blocking ^{3}H-NE uptake, into a piperazine ring results in a compound which has no effect on uptake, i.e. opipramol. This structure–activity relationship was further exemplified by comparing the phenothiazines, chlorpromazine and perphenazine, and triflupromazine

TABLE 1. EFFECT OF VARIOUS TRICYCLIC ANTIDEPRESSANTS ON THE UPTAKE OF ^{3}H-NOREPINEPHRINE BY THE MOUSE HEART*

Drug name	Structure	ED_{50} (mg/kg)
Amitriptyline		6·0
Imipramine		5·0
Melitracen		16·0
Desmethylmelitracen		6·0
Protryptyline		1·0
Opipramol		Inactive at 30 mg/kg
Iprindole		Inactive at 200 mg/kg

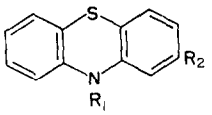
* Drugs were administered i.p. 1 hr prior to i.v. administration of ^{3}H-NE. Mice were sacrificed 3 hr after injection of the labelled drug. Two hearts were used per determination and 3 determinations were made per dosage. Three doses were used to obtain the dose producing a 50 per cent inhibition of uptake.

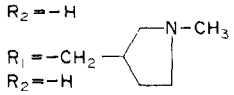
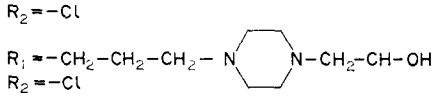
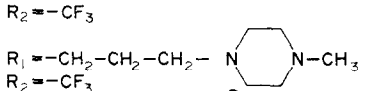
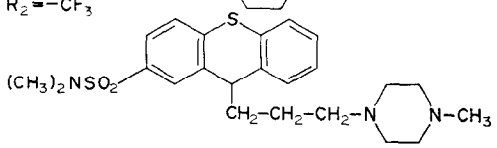
and trifluoperazine, where the methylated amines were effective in blocking the uptake and those containing the piperazine moiety were inactive. Iprindole did not fit this structure–activity relationship.

Evidence has also been presented which indicates that a blockade of uptake of ^{3}H-NE by the mouse heart does not correlate well with either the norepinephrine potentiating effect or the clinical efficacy of the tricyclic antidepressants. The poor correlation led to a conclusion, supported by others,[12,13] that the inhibition of NE uptake and the norepinephrine potentiating activity reflect two independent actions.

In light of the data presented here and elsewhere,[12,13] it would appear that further studies are

TABLE 2. EFFECT OF PHENOTHIAZINES AND RELATED DRUGS ON THE UPTAKE OF ^{3}H-NOREPINEPHRINE BY THE MOUSE HEART*



Drug name	Structure	ED_{50}
Promazine	$R_1 = -CH_2-CH_2-CH_2-N(CH_3)_2$ $R_2 = -H$	8·0
Desmethylpromazine	$R_1 = -CH_2-CH_2-CH_2-NH-CH_3$ $R_2 = -H$	5·0
Methdilazine	 $R_2 = -H$	11·0
Chlorpromazine	$R_1 = -CH_2-CH_2-CH_2-N(CH_3)_2$ $R_2 = -Cl$	3·0
Perphenazine	 $R_2 = -Cl$	Inactive at 60 mg/kg
Trifluprornazine	$R_1 = -CH_2-CH_2-CH_2-N(CH_3)_2$ $R_2 = -CF_3$	6·0
Trifluoperazine	 $R_2 = -CF_3$	Inactive at 25 mg/kg
Thiothixene		Inactive at 200 mk/kg

* Drugs were administered i.p. 1 hr prior to the i.v. administration of ^{3}H-NE. Mice were sacrificed 3 hr after injection of the labelled drug. Two hearts were used per determination and 3 determinations were made per dosage. Three doses were used to obtain the dose producing 50 per cent inhibition of uptake.

needed to evaluate the action of the tricyclic antidepressants, as related to a blockade of NE uptake and the potentiation of certain physiological responses to norepinephrine. The best evidence for such an evaluation should be obtained from studies in the brain and in peripheral sympathetic nerve endings and should be concerned with several structurally different tricyclic antidepressants.

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Aminoquinoline antimalarials—Paradoxical regulation of hepatic tryptophan oxygenase and tyrosine aminotransferase by primaquine*

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THE 4-AMINOQUINOLINE antimalarials (of which chloroquine is a prototype) differ from the 8-aminoquinolines (of which primaquine is a prototype) in that the 4-aminoquinolines (4-AQ's) in general affect primarily the asexual erythrocytic forms of *Plasmodia*, whereas the 8-aminoquinolines (8-AQ's) generally affect the primary and secondary tissue (exoerythrocytic) stages of the parasite.[1] The mechanism of schizontocidal action of the 4-AQ's has been widely attributed to result from their binding to plasmodial DNA, and its consequent inhibition of DNA synthesis and function in replicative processes.[2–4] While the 8-AQ's have recently been demonstrated to interact with DNA *in vitro*,[5] it had been proposed earlier that antimalarial agents of this class are schizontocidal due to inhibition of electron transport systems in the parasites.[6] However, it was shown that both chloroquine and primaquine completely inhibited ^{32}P (orthophosphate) incorporation into DNA and RNA of *Plasmodia* at relatively high (10^{-4} M) concentrations *in vitro*.[7] It has also been found recently that both primaquine and chloroquine appreciably inhibited uridine-^{3}H incorporation *in vivo* into mouse liver RNA.[8] These findings would support a common mechanism of antimalarial action of both the 4-AQ's and the 8-AQ's, namely, inhibition of gene synthesis or function, or of both.

Chemical agents (physiologic substrates or drugs) which interact with DNA generally produce, if anything, either inhibition of DNA function and replication, e.g. actinomycin-D,[9] mitomycin C,[10] or opposite "anabolic" effects, e.g. steroids in certain tissues[11–14] or carcinogens such as benzpyrene.[15,16] Drugs of the actinomycin-D type inhibit induced enzyme synthesis by a mechanism generally believed to result from their interaction with DNA, and subsequent inhibition of genome-directed RNA synthesis.[9] Since chloroquine and primaquine both possess some actinomycin-D-like properties (see above), it was postulated that either or both of these drugs should inhibit genomic function *in vivo*. As a measure of genomic function *in vivo*, the hydrocortisone inducibility of two hepatic enzymes,

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