Table 2. Effect of Chlorpromazine and Reserpine on Stimulated Mice treated with Cocaine*

Drug	Dose (mg/kg)	Experimental conditions	4-h mortality Dead/injected	%
Sodium chloride	90	Aggregated	13/20	65
Chlorpromazine	5	Aggregated	9/10	90
Chlorpromazine	20	Aggregated	0/10	0
Reserpine	5	Aggregated	1/10	10
Sodium chloride	90	Shocked	15/24	63
Chlorpromazine	5	Shocked	6/10	60
Chlorpromazine	20	Shocked	1/10	10
Reserpine	5	Shocked	4/10	40

* 100 mg of cocaine per kg of body-wt. was injected 1 h after chlorpromazine or 4 h after reserpine into all the mice.

Chlorpromazine also protected shocked mice. Effect of reserpine in shocked mice was inconclusive since in shocked mice reserpine exhibited some toxicity of its own.

Recently several investigations have demonstrated rapid and specific uptake of circulating norepinephrine by tissues[13,15,16], sympathetic nerve endings[17], and isolated granules from nerve endings[18]. In isolated perfused heart, more norepinephrine is lost by tissue uptake than by enzymatic metabolism[17]. Denervation[19], which depresses tissue uptake of norepinephrine, produces supersensitivity to injected norepinephrine.

On the basis of these observations it has been suggested that intensity or duration of biological action of circulating or locally released norepinephrine is limited to a large extent by 'recapturing mechanisms'. Interference with these mechanisms by drugs or other procedures may result in increased and prolonged pharmacological effects of exogenously or endogenously released norepinephrine. Present studies of effects of sensory stimuli in presence of cocaine or amphetamine provide *in vivo* evidence of an exaggerated sympathetic syndrome. Excessive sensory stimuli liberate norepinephrine through central and peripheral sympathetic discharge. Inactivation of liberated norepinephrine by 'recapturing mechanisms' is prevented by cocaine or amphetamine, resulting in prolonged and intense action of norepinephrine on tissue, causing tissue damage and death. Pretreatment with normal noradrenergic blocking agents may provide protection against the exaggerated sympathetic syndrome.

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Interference by the Carcinogenic 4-Nitroquinoline *N*-Oxide of Tryptophan and Indole Uptake in *Escherichia coli*

The potent water-soluble carcinogen 4-nitroquinoline *N*-oxide (NQO) is remarkably versatile and thus represents a good means of discerning pre-requisites for carcinogenesis. NQO condenses readily with sulphydryl groups; is mutagenic to bacteria, tobacco mosaic virus, and *Aspergillus niger*[1]; inhibits incorporation of phosphorus-32 into nucleic acids of Ehrlich ascites carcinoma cells[2]; induces nucleolar 'caps' in Chang liver cells[3]; and inhibits growth of the flagellates *Ochromonas danica*, *Euglena gracilis*, of *Corynebacterium bovis*, and of the photosynthetic purple bacterium *Rhodopseudomonas palustris*. These growth inhibitions are competitively annulled by L-tryptophan; D-tryptophan is also effective. The competitive annulment ratio is 0·2 mg/ml. tryptophan : NQO 2 μg/ml.

This growth competition suggests that NQO uptake is mediated by a tryptophan transport mechanism[4]. To investigate this possibility, two tryptophan-requiring mutant strains of *E. coli*, *T*3 and *T*24 (cultures obtained from Dr. C. Yanofsky), both utilizing tryptophan or indole were investigated. NQO was tested for interference with the inducible tryptophan permease of both strains by a modified Burrows and DeMoss[5] technique: 24 mg (dry weight) log-phase cells were collected on a 'Millipore' cellulose filter (0·05μ pore size) and washed for 80 sec with isotonic C- and N-free medium and the filtrate discarded. C- and N-free medium + tryptophan (or indole) at equimolar concentrations was then washed over the cells for 40 sec and this filtrate collected. Absorbancy of the medium + tryptophan or indole was measured before and after exposure to NQO by means of a Beckman *DU* spectrophotometer set at 280 mμ.

Table 1. Interference by 4-Nitroquinoline *N*-Oxide of L-Tryptophan and Indole Uptake in *E. coli*
(Readings as absorbance at 280 mμ)

Additions	Readings before exposure to cells	Control (after 40 sec washing)	Cells exposed to 4×10^{-4} M NQO for 5 min (readings taken after 40 sec washing with C- and N-free medium)
NQO 4×10^{-4} M	0·002	0·0019	0·003
L-Tryptophan $0·5 \times 10^{-4}$ M	0·43	0·30	0·42
Indole $0·5 \times 10^{-4}$ M	0·195	0·04	0·15

Introduction of NQO at 4×10^{-4} M (shown by viability investigations to be non-inhibitory in a culture of this density) into the growing culture completely inhibited uptake of L-tryptophan and inhibited indole uptake by 80 per cent within 5 min (Table 1). Both strains behaved alike.

These results are construed as supporting our earlier idea that ability to deceive tryptophan transport systems may underlie the carcinogenic specificity of polycyclic carcinogens.

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HAEMATOLOGY

Plasma Co-factors in Adenosine Diphosphate-induced Aggregation of Human Platelets

The aggregation of washed human platelets *in vitro* by adenosine diphosphate (ADP) requires calcium and is stimulated by the addition of platelet-free plasma[1]. The identity of the plasma activity has been the subject of recent conflicting reports. Hellem and Owren[2] have suggested that the plasma factor is that entity missing in von Willebrand's disease; but others[3,4] have found that ADP-induced platelet aggregation proceeds normally in plasma from patients with established von Willebrand's disease. McLean *et al.*[5] and Cross[4] have indicated that fibrinogen may be the plasma co-factor, and Caen[6] has