that they are responsible for virulence.

The 18Z-C mutant actually appears to be a double mutant since it lost ability to produce fibrinolysin in addition to losing ability to produce soluble coagulase. Since this mutant is fully virulent it would appear that fibrinolysin is also not essential for virulence.

Isolation of the avirulent 18Z-D mutant likewise offered the possibility of identifying a factor which if lost results in loss of virulence. However, this mutant is identical with the parent strain in all aspects thus far studied with the exception of virulence. Further studies comparing these 2 strains are in progress.

Summary. Three mutants were isolated from a single strain of *Staphylococcus aureus* of known virulence for rabbits. Two mutants, one lacking the soluble type of coagulase and the other lacking the bound type of coagulase, were still virulent for rabbits. The third mutant which produced both kinds of coagulase had lost its virulence for rabbits.

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Correlation of Tryptamine-Induced Convulsions in Rats with Brain Tryptamine Concentration. (25762)

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Tedeschi *et al.*(1) recently reported appearance of clonic convulsions of forepaws of rats following i.v. injection of tryptamine (TA). A good dose response relationship was obtained between quantity of TA injected and relative frequency and intensity of resulting convulsions. This correlation suggested that the observed pharmacologic responses were associated with increased levels of TA in the brain. On the assumption that amine in rat brain was metabolized chiefly by monoamine oxidase (MAO), Tedeschi *et al.* postulated that inhibition of enzyme activity should prolong the elevated brain TA levels and, therefore, potentiate convulsant properties of the amine. Although pharmacologic expectations were fulfilled and procedure shown to be suitable for screening and pharmacologic evaluation of MAO inhibitors, the question of relationship with brain biochemistry remained unanswered. The purpose of our study was to determine whether the TA-induced clonic convulsions in rats pretreated with a MAO inhibitor were correlated with concentration of amine in the brain.

Procedure and methods. Male albino rats, Wistar strain, weighing between 175 and 225 g were used. Tryptamine hydrochloride in physiologic saline was injected into tail vein in dose of 5 mg/kg, calculated as free base. Trans 2-phenylcyclopropylamine hydrochloride (tranylcypromine)(2) and 1-isonicotinyl-2-isopropyl hydrazine phosphate (iproniazid) were dissolved in H_2O and administered orally. Doses of drugs used refer to free base content. Following injection of TA the animals were observed for 60-75 seconds for signs of convulsive activity, then sacrificed by decapitation. Brains were immediately removed, rinsed free of adsorbed blood, blotted lightly, quickly weighed and placed in chilled glass tissue grinder of Potter-Elvehjem type fitted with teflon pestle. For determination of TA the brains were homogenized and analyzed according to method of Hess and Udenfriend(3). Separate brains were homogenized

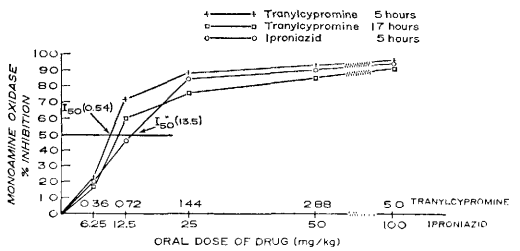

FIG. 1. Effect of drug on rat brain monoamine oxidase activity *in vivo*. Arrows indicate dose (in parentheses) of drug that produced 50% inhibition (I_{50}).

and assayed for MAO activity according to procedure of Bogdanski *et al.*(4).

Results. TA concentration of 14 individual rat brains was 0.032 ± 0.002 μg/g (mean ± S.E.M.). Oral administration of 0.72 mg/kg of tranylcypromine or of 25 mg/kg of iproniazid had no apparent effect upon normal brain TA concentration after 5 or 17 hours.* Sixty seconds after i.v. injection of 5 mg/kg of TA, brain concentration was increased to 0.173 ± 0.019 μg/g (mean of 10 brains ± S.E.M.). Injection of this dose of TA alone did not elicit observable clonic convulsions, although all animals appeared momentarily stunned shortly after injection.

In all rats pretreated with either tranylcypromine or iproniazid clonic convulsive activity was observed 30-40 seconds after injection of TA. With 0.72 mg/kg of tranylcypromine or 25 mg/kg of iproniazid, convulsions persisted for more than 3 seconds and were quite strong. In all animals brain TA concentration was markedly elevated. With 0.36 mg/kg of tranylcypromine the occurrence, duration and relative intensity of clonic convulsive activity appeared dependent upon relative brain TA concentration of the individual animal.

The results (Fig. 1) describe the effect of increasing doses of tranylcypromine and of iproniazid upon rat brain monoamine oxidase activity. Each point is an average of 3 to 6 individual brain values. In addition to showing that tranylcypromine was about 25 times more potent an inhibitor than iproniazid, the curves indicate that 20% inhibition was produced by 0.36 mg/kg of tranylcypromine, while 60-70% inhibition was obtained with administration of 0.72 mg/kg. These results together with data of Table I suggest that occurrence, duration and intensity of TA-induced convulsions were also related to degree of inhibition of monoamine oxidase activity of the rat brain.

Discussion. Hess *et al.*(5) recently suggested that marked central effects, including convulsions, in rabbits and dogs injected i.p. with massive dose (800 mg/kg) of tryptophane after pretreatment with iproniazid were related to measured increase in brain TA concentration. At the same time they considered the possibility that appreciable increases in brain serotonin occurred. More recently Hess *et al.*, in an abstract(6), reported that "characteristic excitement" produced in rats pretreated with monoamine oxidase inhibitor followed by tryptophane or 5-hydroxytryptophane was in no way directly related to brain levels of serotonin and tryptamine. Thus, it was concluded "that increase of brain indoleamines is not in itself sufficient to produce excitement." Our results, however, indicate existence of a good correlation between elevated brain levels of TA and clonic convulsive seizure activity, as described by Tedeschi *et al.* Furthermore, in view of demonstrated ability of systemically injected TA to penetrate the rat brain, it is reasonable to conclude that the elicited pharmacologic effects represented a central mechanism of action of the amine, potentiated by inhibition of brain MAO activity. The question may be raised, however, whether the interaction of the drugs in spinal cord itself may have contributed to production of clonic convulsive seizure activity.

Summary. Normal rat brain tryptamine concentration was 0.032 ± 0.002 μg/g (mean ± S.E.M.). Oral administration of 0.72 mg/kg of tranylcypromine (trans 2-phenylcyclopropylamine) or 25 mg/kg of iproniazid (1-isonicotinyl-2-isopropyl hydrazine) had no apparent effect upon normal rat brain tryptamine concentration. Sixty to 75 seconds after i.v. injection of non-convulsive dose of tryptamine (5 mg/kg) brain concentration of the amine was increased to 0.173 ± 0.019 μg/g. Occurrence, duration and relative intensity of clonic convulsions produced by injec-

* Hess *et al.*(5) reported similar results with guinea pigs pretreated with iproniazid.

TABLE I. Effect of Pretreatment with Tranylcypromine or Iproniazid and Subsequent Injection of Tryptamine upon Brain Tryptamine Levels and Convulsive Activity.

	Iproniazid		Tranylcypromine			
Dose (mg/kg)	25		0.36		0.72	
Pretreatment time (hr)	5	17	5	17	5	17
	Tryptamine conc., μg/g brain (clonic convulsions)*					
	1.080 (+3)	.902 (+3)	.218 (1)	.411 (+3)	1.30 (+3)	.504 (+3)
	.460 (+3)	.779 (+3)	.200 (0)	.175 (0)	.938 (+3)	.451 (+3)
	.648 (+3)	.888 (+3)	.145 (0)	.350 (1)	.699 (+3)	.348 (+3)
	.845 (+3)	.478 (+3)	.500 (+3)	.217 (0)	.856 (+3)	
	.669 (+3)	.605 (+3)	.164 (1)	.388 (+3)	.612 (+3)	
			.059 (0)	.278 (2)	.936 (+3)	
			.195 (1)		.768 (+3)	
					.369 (+3)	
					.252 (+3)	

Dose refers to oral administration of tranylcypromine and iproniazid at indicated time prior to intrav. inj. of tryptamine (5 mg/kg).

* No. in parentheses represents duration of clonic convulsions, in sec. In all cases of (+3), clonic convulsions were sustained beyond 3 sec. and, in most cases, were very marked. Convulsions were elicited 30-40 sec. after tryptamine inj. and animals were sacrificed 60-75 sec. after inj. Control values of tryptamine concentration (μg/g ± S.E.M.):

Normal, .032 ± .002 (N = 14); after either drug (N = 10), same as normal; after tryptamine, .173 ± .019 (N = 10).

tion of tryptamine into rats pretreated with either of above monoamine oxidase inhibitors were correlated with increased concentration of amine in the rat brain. In view of demonstrated ability of systemically injected tryptamine to penetrate rat brain, it is reasonable to conclude that the elicited pharmacologic effects reflected a central mechanism of action of the amine, potentiated by inhibition of brain monoamine oxidase activity.

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Properdin Titers of Dogs Surviving Hemorrhagic Hypotension.* (25763)

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Attention has been called to a relationship between serum properdin levels and hemorrhagic shock(1). It was demonstrated that properdin titers, measured by the zymosan assay, dropped progressively during oligemic and post-transfusion periods of shock. More recently, by phage neutralization assay, titers decreased after hypotensive period had been terminated(2). In these studies, duration of hemorrhage was quite prolonged, and all animals died. To explore further the relationship between properdin and hemorrhagic shock, duration and intensity of hemorrhage was utilized so that approximately 50% of dogs survived. A second group of dogs was subjected to more severe conditions of hypotension so that irreversibility might be expected in virtually all cases. These animals,

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