TABLE I.

	No. of sera tested	Avg optical densities at 530 mu, 1 cm light path	Stand. error of mean
Humans	27	.695	.026
Sheep	31	.265	.016
Cattle	15	.210	.010
Dogs	11	.131	.008
Guinea pigs	10	.112	.006

The tested sera from dogs and guinea pigs are significantly lower in oxidase activity than sera from cattle and sheep.

If Beer's law is valid for the coloured substance, or approximately so, these results mean that the tested unfractionated human sera exhibit approximately 2.6 times more oxidase activity than sera from sheep. This ratio is still higher when human sera are compared with sera from the other tested animals.

In connection with the observed difference in oxidase activity between various animal species, it is interesting to recall that a certain relation is believed to exist between ceruloplasmin (oxidase) content of human serum and the functioning of the brain. No effort has been made to identify the oxidase from the animal sera as ceruloplasmin.

A comparison of the copper content in sera from the tested species, or various fractions of these, has not yet been done.

Summary. Comparative determinations of oxidase activity of blood sera from humans and a few animal species were carried out. The substrate used was p-phenylenediamine. Human sera were found to contain significantly more oxidase activity than sera from sheep and cattle. Sera from sheep and cattle were found to be significantly higher in oxidase activity than sera from dogs and guinea pigs.

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Influence of Chlorpromazine and Cortisone on Protein Metabolism of Rats. (23257)

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Chlorpromazine increases survival time, survival rate, and tolerance to hypotension, of dogs in hemorrhagic shock(1). The protection afforded the stressed intact animal, as well as the beneficial effects obtained in a wide variety of clinical conditions (asthma, arthritis) which are also improved by ACTH or by adrenal steroids, suggest the possibility that chlorpromazine might alter the hypothalamic-pituitary response to stressful situations. However, enhanced survival by treatment with chlorpromazine of adrenalectomized animals exposed to bacterial endotoxin has also been reported(2). An inhibition of secretion of ACTH in response to various noxious stimuli in chlorpromazine-treated animals has been reported by Aron *et al.*(3, 4), but this observation could not be confirmed by other investigators(5). Rather, this drug has increased adrenal production of steroids in the intact, but not in the hypophysectomized animal(6). Chlorpromazine does not alter adrenal responsiveness to ACTH as measured by changes in ascorbic acid levels of the adrenal glands of hypophysectomized rats(7).

In view of the observations that chlorpromazine does not alter hypothalamic-pituitary response to noxious stimuli, nor response of the adrenal to ACTH, it was thought possible that this drug could alter peripherally, the response of the body to the adrenal cortical steroids. It was therefore decided to investigate whether the protein catabolic effect of

TABLE I. Urinary Nitrogen Excretion and Weight Changes of Rats Treated with Cortisone and Chlorpromazine.

	Mean N. excretion, mg/24 hr			"p"	Wt change, g/8 days		
	Control	Exp.	Diff., mg	of diff.	Control	Exp.	Diff.
	A. Cortisone acetate, 2.5 mg twice daily						
Mean (6)	196 ± 4.95*	268 ± 15.93	+ 72 ± 16.15	<.001	+ 7.5 ± 2.10	−10.8 ± 4.98	−18.3 ± 6.5
	B. Chlorpromazine, 1.7 mg; cortisone acetate, 2.5 mg, as b.i.d.						
Mean (6)	190 ± 4.94	291 ± 10.53	+101 ± 16.2	<.001	+11.2 ± 7.48	−14.6 ± 6.05	−25.8 ±10.4
B vs A			+ 29	<.02			
	C. Chlorpromazine, 1.7 mg b.i.d.						
Mean (6)	199 ± 8.77	223 ± 5.65	+ 24 ± 17	<.02	+ 13 ± 4.84	+ 4.8 ± 5.15	− 8.2 ± 8.5

* Stand. dev.

cortisone might be altered by administration of chlorpromazine. The results of these experiments form the basis of this report.

Methods. Male rats, descendants of the Wistar strain weighing between 200 and 250 g were used. The animals were kept in wire screened, individual metabolism cages in a constant temperature room. The animals were gradually adapted to tube feeding, after which they were fed twice daily a constant amount of the mixed diet described by Ingle *et al.*(8). The food intake was sufficient to permit weight gain during the control period, and this amount was fed during the experimental period. Urine specimens were collected in periods of 24 hours, and were analyzed by a micro-Kjeldahl method. The weight and the urinary nitrogen excretion of each animal were determined daily for a 7-day control period, followed by an 8-day experimental period. During the experimental period, 6 animals received 2.5 mg of cortisone acetate twice daily, 6 animals received 1.7 mg of chlorpromazine twice daily, and 6 animals received 2.5 mg of cortisone acetate and 1.7 mg of chlorpromazine, twice daily. All injections were given by subcutaneous route at the same time each day.

Results. Results are summarized in Table I. Chlorpromazine at a daily dose level of 3.4 mg caused a mean increase of urinary nitrogen excretion of 24 mg day. The difference of the mean N-excretion in the control and experimental period was statistically significant at 5% level. This increase of urinary nitrogen was associated with a decrease in the rate of weight gain. The mean weight gain during the control period was 13 g, the mean weight gain during the experimental period was 4.8 g.

Cortisone acetate, in daily doses of 5 mg increased the mean daily urinary N-excretion of the treated rats by 72 mg and caused weight loss of 10.8 g/8 days. The increase in mean daily urinary nitrogen excretion of the animals treated with 5 mg of cortisone acetate and 3.4 mg of chlorpromazine was 101 mg and was associated with a weight loss of 14.6 g during the treatment period. The difference of the urinary nitrogen loss induced by treatment with cortisone acetate, and that induced by treatment with cortisone acetate plus chlorpromazine is statistically significant at the 5% level. The difference of weight loss of the 2 groups is significant at the 5% level.

Discussion. The weight loss of N-loss induced by 5 mg of cortisone acetate was not decreased by treatment with chlorpromazine, rather each was increased. The agent itself caused an increase in urinary nitrogen excretion of each animal treated, accompanied by a decrease in the rate of weight gain. The data would suggest that the effects of cortisone acetate and chlorpromazine are additive as measured by the changes in urinary nitrogen excretion and weight loss.

The mechanism through which chlorpromazine exerts the effects on N excretion and body weight, both alone and in combination with cortisone are unknown. These changes in protein metabolism could be the manifestation of a stimulating action of the drug directly on the adrenal cortex, or an increased secretion of adrenocortical steroids might be the result of a drug-induced increased release

of ACTH. The latter explanation is supported by the observation that this drug increases production of adrenal steroids in the intact animal both with normal, and with high levels of circulating adrenal steroids(6). The observations reported here might, on the other hand, be the result of an enhancement of the protein catabolic effects of the adrenal steroids by chlorpromazine. In support of a peripheral synergistic or additive action of chlorpromazine and cortisone, the findings of DeBias *et al.*, may be quoted; they found that doses of cortisone too small to protect completely a stressed, adrenalectomized rat, are much more effective when combined with subeffective doses of chlorpromazine(9).

Summary. Chlorpromazine at a dose level of 3.4 mg daily causes an increase of urinary nitrogen excretion and a decrease of weight gain in the intact tube fed rat. These changes are statistically significant. The protein catabolic effect of 5 mg of cortisone acetate administered daily is increased significantly by simultaneous treatment with chlorpromazine.

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Further Studies on Release of Serotonin and Histamine During Anaphylaxis in the Rabbit. (23258)

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During anaphylaxis in the rabbit, there is a transient increase in plasma concentrations of both serotonin (5-hydroxytryptamine) and histamine(1). The increase occurs immediately after intravenous injection of the antigen, and indicates release of these amines from a bound to a free form within the animal. When an antigen is added to the whole blood of a rabbit previously sensitized to this antigen, concentrations of serotonin and histamine also increase in the plasma(1). In rabbit blood both serotonin and histamine are found almost exclusively in the platelets (2). Therefore, the rise in plasma concentrations of these amines, during the *in vitro* antigen-antibody reaction, must be due to their release from platelets. However, serotonin and histamine are found in a variety of rabbit tissues in addition to the blood platelets. The major portion of the body serotonin is found in the gastrointestinal tract; a much smaller amount is found in the lung(3) and the brain(4). Consequently, during *in vivo* anaphylaxis, the increase of serotonin and histamine in the plasma could be due to their release either from the platelets or tissues, or from both sites. The *in vitro* study, with whole blood, suggests that at least some of the free serotonin and histamine is derived from platelets. *In vitro* studies have shown that histamine is released when organs of sensitized rabbits are perfused with a solution of the specific antigen(5). Thus, it appears that in the rabbit histamine may be released not only from platelets but also from tissues, during anaphylaxis. Similar *in vitro* studies