TABLE I. Effect of ACTH on Excretion of Trypsin Inhibitor in 8 Normal Subjects.

Age, yr	T.I. units × 10^{-3} excreted: No treatment Day 1	No treatment Day 2	No treatment Day 3	ACTH, 25 i.u. i.m. Day 4	ACTH, 25 i.u. i.m. Day 5	Avg T.I. excretion/day: Before ACTH treatment	Avg T.I. excretion/day: During ACTH treatment	Increase during ACTH treatment, %
30	.0	.0	.36	3.15	7.46	.12	5.31	4325
30	1.35	.90	.0	1.52	3.96	.75	2.79	272
30	.68	1.10	1.40	2.03	2.40	1.06	2.22	109
22	2.02	1.20	.90	4.14	4.71	1.37	4.43	223
40	3.10	2.88	1.51	5.11	11.79	2.50	8.45	238
29	4.73	4.04	7.96	13.73	16.77	5.58	15.25	174
24	7.80	5.07	5.70	16.17	29.04	6.19	22.61	265
40	10.54	5.98	7.35	15.39	20.68	7.96	18.04	127

17-ketosteroids and 17-ketogenic steroids in urine suggests a close connection between function of pituitary-adrenal system and excretion of trypsin inhibitor. The increase in T.I. could be caused either by increased production of inhibitor or by increased renal excretion. Though it is too early to consider any connections between the observations here presented and pathological states in the organism, it is interesting to note that some investigators have reported proteolytic activity in tissues and blood in conditions where ACTH and corticosteroids have a therapeutic effect, especially in anaphylactic reactions. The results support our hypothesis that the increase of trypsin inhibitor in urine in various physiological and pathological conditions is caused by a stress reaction.

Summary. 1. Administration of ACTH, cortisone or hydrocortisone to human beings produces an increase in excretion of trypsin inhibitor in urine. 2. Excretion of trypsin inhibitor during the day is nearly parallel to excretion of 17-ketosteroids and 17-ketogenic steroids. 3. The pituitary-adrenal system plays a role in regulation of excretion of trypsin inhibitor.

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Nutritional Studies of Hydroxyzine and Rauwolfia in Cattle and Lambs. (23950)

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Although tranquilizing drugs have been studied with monogastric animals, the levels of the drugs fed were within the sedating range. No reports of investigations of nutritional effects of tranquilizing drugs upon ruminants have been found. The present report compares effects upon growth, feed efficiency and carcass quality of tranquilizing drugs fed to beef steers and wether lambs in a range generally below the level at which sedation would be expected. The tranquilizers tested were crystalline pharmaceutical grade hy-

TABLE I. Experimental Rations.

	Cattle		Lambs*
Ration No.	1	2	3
Corn + cob meal	Self-fed	Self-fed	
Alfalfa hay/day, lb	—	4	
Supplement/day, "	2	2	Self-fed
Mineralized salt	Self-fed	Self-fed	"
Composition of supplement		%	
Yellow corn meal			25.0
Soybean oil "	58.9	82.8	
Dehydrated alfalfa meal	20.0	20.0	
Sun cured alfalfa			64.9
Dried molasses	10.0	10.0	
Liquid "			10.0
Urea	5.0	3.0	
Dicalcium phosphate	2.0	4.0	
Ground limestone	1.75		
Trace mineralized salt	2.25		
Stabilized vit. A†	.1	.2	.1
Total	100.0	100.0	100.0

* The lamb ration was made into ⅜ inch pellets and self-fed.

† Gelatin stabilized vit. A mix containing 5,000 U.S.P. units of vit. A palmitate/g.

droxyzine, 1-(p-chlorobenzhydryl - 4 - (2-hydroxethoxy-ethyl)-diethylenediamine dihydrochloride, and ground *Rauwolfia vomitoria* root containing 0.24% reserpine, trimethoxybenzoylmethyl reserpate.

Procedure. Forty-one yearling Hereford steers and 108 whiteface cross-bred Texas wether lambs were employed as test animals. The basal rations for the animals in the different experiments are given in Table I. Feed consumption records were kept for each group of animals and individual body weights were taken for the steers and lambs every 28 and 14 days, respectively. In Trial 1, which lasted 84 days, *Rauwolfia vomitoria* was fed to groups of 4 steers each at levels of 5, 25 and 125 mg per head per day. An additional group of 4 animals which received the basal ration served as controls. In Trial 2, which lasted 111 days, hydroxyzine was given to groups of 4 steers each at levels of 1.25, 2.5, 10, 50 and 500 mg per head per day. A group of 5 comparable animals served as controls. All steers in Trial 2, including controls, were initially implanted with 36 mg diethylstilbestrol. In Trial 3, which lasted 69 days, 2 replicate groups of 12 lambs served as negative controls. Two additional replicate groups of 12 each were implanted with 50 and 3 mg, respectively, of oxytetracycline* and stilbestrol and served as controls for the tranquilizer treatments. Groups of 12 lambs each received the oxytetracycline-stilbestrol implants and were fed rations containing hydroxyzine at levels of 0.24, 1.2, 6.0 and 30 g per ton, respectively. An additional group of 12 lambs were fed on diets containing 3 g per ton of *Rauwolfia vomitoria*. These animals were also implanted with oxytetracycline-stilbestrol.

Results. The feed efficiency, dressing per cent, carcass grade and average daily weight gains of steers fed rations containing *Rauwolfia vomitoria* or hydroxyzine are given in Table II. In Trial 1 all levels of *Rauwolfia vomitoria* improved the daily weight gains. The best growth effect was found in the group receiving the 25 mg level. It showed a gain of 16% over the controls. The feed efficiency with all 3 levels of Rauwolfia was slightly improved over that of the controls. No effect upon the dressing per cent or carcass grade was apparent in these animals. In Trial 2, hydroxyzine improved both the rate of gain and feed efficiency of steers over the entire range of feeding levels. However, no consistent dose-response relationship was apparent with either of these phenomena. Although the carcass grade of the 2.5 mg level suggested a possible improvement, it remained practically unchanged with virtually all the other levels. Because of the limited number of steers in the various groups in Trials 1 and 2 differences in the average daily gains were not statistically significant at the 5% level but approached significance at the 10% level and when all levels of hydroxyzine were compared with the control the difference was significant at the 10% level. The dressing percentages of the groups which received 1.25 and 2.5 mg hydroxyzine in Trial 2 were significantly better than the control at the 10% level.

The results of Trial 3 in which tranquilizing drugs were fed to lambs are given in Table III. The lambs with stilbestrol-oxytetracycline implants made significantly greater weight gains than the negative controls and feed efficiency was improved. Neither the dressing percentage nor the carcass grade was significantly altered. With the exception of the lowest levels, all hydroxyzine

* Terramycin, Chas. Pfizer & Co., Inc.

TABLE II. Response of Beef Cattle (Steers) to Oral Hydroxyzine and *Rauwolfia vomitoria.*

Supplement	No. of animals	Avg daily gain, lb	Lb feed per lb gain	Dressing, %	Carcass grade*
Trial 1, 84-day results					
Control	4	2.77	8.38	62.0	10.00
+ *Rauwolfia vomitoria,* 5 mg†	4	2.95	8.18	62.0	9.50
+ " " 25	4	3.21	8.12	62.0	10.25
+ " " 125	4	2.81	8.30	61.0	9.50
Avg, all Rauwolfia levels		2.99	8.20	61.7	9.75
Least significant difference (P <.10)					
Each treatment		.46			.79
All Rauwolfia treatments combined		.37			.65
Trial 2, 111-day results					
Stilbestrol implant, 36 mg	5	2.25	10.41	59.4	10.40
+ Hydroxyzine, 1.25	4	2.83	9.12	61.2‡	10.25
+ " 2.5	4	2.68	9.16	61.1‡	11.25
+ " 10	4	2.82	9.16	60.1	10.25
+ " 50	4	2.74	8.68	59.8	10.50
+ " 500	4	2.61	9.16	59.2	10.33
Avg, all hydroxyzine levels		2.74‡	9.06	60.2	10.52
Least significant difference (P <.10)					
Each treatment		.60		1.35	1.80
All hydroxyzine treatments combined		.44		1.26	1.40

* Carcass grade numerical rating: 11 avg choice; 8 avg good.
† Reserpine levels supplied by 5, 25 and 125 mg of *Rauwolfia vomitoria* were respectively 12, 60 and 300 μg.
‡ Difference from control statistically significant at P <.10.

fed lambs showed an increase in weight gain over the estrogen and antibiotic implanted controls. The best weight gain and feed efficiency were seen in lambs fed the ration containing 1.2 g of hydroxyzine per ton. The 15% increased gains with this level were statistically significant at (P<.05). Best feed efficiency of the experiment also occurred in the group receiving 1.2 g per ton hydroxyzine. Dressing percentage did not appear to be affected by hydroxyzine except at the 30.0 g per ton level where it was slightly lower. There was evidence of improvement in grade with 1.2, 6.0 and 30.0 g per ton hydroxyzine. Significant growth responses were obtained with Rauwolfia but feed efficiency was not equal to that with 1.2 g per ton hydroxyzine. There was also indication of lower dressing percentage and slight downgrading in the Rauwolfia fed group.

Discussion. No evidence is immediately available to explain the mechanism by which

TABLE III. Response of Lambs (Wethers) to Oral Hydroxyzine and *Rauwolfia vomitoria* (Trial 3-69 Days).

Supplement	No. of animals	Avg daily gain, lb	Lb feed per lb gain	Dressing, %	Carcass grade*
Control	24	.370	9.48	47.3	7.9
Stilbestrol impl., 3 mg + oxytet. impl., 50 mg	24	.477‡	7.35	46.0	8.0
+ Hydroxyzine, .24 g/ton	12	.473	7.54	45.7	7.5
+ " 1.2	12	.547‡	6.98	45.6	8.2
+ " 6.0	12	.498	7.17	45.7	8.2
+ " 30.0	12	.485	7.31	44.8	8.3
+ *Rauwolfia vom.,* 3.0†	12	.551‡	7.16	44.8	7.8
Least significant difference (P <.05)		.070		3.7	.7

* Carcass grade numerical rating: 11 avg choice; 8 avg good.
† The 3 g of *Rauwolfia vomitoria* contained 7.6 mg of reserpine.
‡ Difference from appropriate control statistically significant at P <.05.

these tranquilizing drugs at low levels produce growth and feed efficiency responses. The obvious reasoning that the drugs decreased physical activity and consequently lowered energy expenditure without decreasing feed intake is not sustained. Frequent observations made on the degree of activity of these animals and ease of handling failed to produce evidence that any of the levels of hydroxyzine or *Rauwolfia vomitoria* fed to steers and lambs had produced any gross evidence of sedation. The doses which produced the best growth and feed efficiency responses in these experiments were at least 25 to 50 times below those recommended for therapy as tranquilizers. It is possible that minute doses of tranquilizing drugs exert a protective effect against environmental stress which does not present itself in the animals' gross behavior or otherwise. Reserpine, an active constituent of *Rauwolfia vomitoria* is known to counteract stress-induced depression of operant behavior using feed as a reinforcement(1). In contrast to this, the food intake in untrained rats was either unchanged(2) or depressed(3) following higher doses. This phenomenon, therefore, appears to be dependent on dose and possibly species.

The direct effects of these drugs on metabolic process as well as its influence on central mechanism controlling growth have also to be considered. The present interpretation of the mode of action of tranquilizing drugs in general points toward a specific effect of these compounds on the central nervous system(4), especially the brain stem. Brodie and Shore(5) postulated either release or blockade of specific neurohumoral agents to be an essential part of tranquilization, thus shifting the equilibrium of the autonomic balance from the ergotropic (sympathetic) towards the trophotropic (parasympathetic) component (6). Such a mechanism of action might serve as a working hypothesis for the growth effects observed.

The importance and practical value of the observations reported here are obvious. The improvement in feed efficiency associated with growth promotion as a result of feeding tranquilizing drugs could have considerable economic importance. Extensive field tests, however, are essential before a final appraisal can be made.

Summary. 1. *Rauwolfia vomitoria* root fed to cattle at levels of 5, 25 and 125 mg per head per day improved growth rate and feed efficiency. Best results were obtained with the 25 mg level. Hydroxyzine fed to cattle at levels of 1.25, 2.5, 10, 50 and 500 mg per head per day improved growth with best results at 1.25 and 10 mg per head per day.

2. Wether lambs fed rations containing hydroxyzine at levels of 0.24, 1.2, 6.0 and 30.0 g per ton, or Rauwolfia, 3.0 g per ton, responded to all supplements. Optimum growth was obtained with a level of as low as 1.2 g per ton of hydroxyzine and 3.0 g per ton of Rauwolfia.

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