case, as judged by previous experiments and by results reported by other laboratories. Para-aminobenzoic acid is not known to be needed by chicks, but was fed as a precautionary measure. The calculated essential amino-acid content[3] of the diet satisfied the requirements of the chick for growth as described by Almquist and coworkers.[4] The chicks had an average weight of 1206 g at 10 weeks, and the group consisted of 2 males and 5 females. The chicks appeared normal in size, conformation and plumage. One of the males was observed to attempt copulation at 110 days of age. After the 155th day, 3 females and one male were kept in one group, and 2 females and one male in the other group. The males were rotated every 3rd day. Three of the females matured between the 151st and the 161st days of age, and the eggs were collected and incubated. On the 172nd day, an additional 1% of $CaCO_3$ was added to the diet to promote egg-shell formation. At 181 days of age the females averaged 2.26 kg in weight and the males 3.07 kg. The following record was obtained with the eggs:

Hen No.	1	2	3
No. of days	14	16	5
No. of eggs laid	8	9	4
No. of eggs incubated	6	4	3
Infertile	1	1	0
Dead embryo, estimated 1 to 7 days development	1	1	2
Dead embryo, estimated 17 to 21 days development	2	1	1
Live chicks hatched	2	1	0

The chicks appeared normal although they were small. They were placed on the same diet as their parents, without additional $CaCO_3$. They weighed an average of 28 g at hatching, and their average gain during the first month was 189 g.

Summary. Reproduction was obtained in chickens which were raised from hatching on a purified diet. The hatchability of the eggs was poor, but some apparently normal chicks were obtained.

[3] Block, R. J., and Bolling, D., *The Amino Acid Composition of Proteins and Foods*, Springfield, Illinois, C. C. Thomas, 1945.

[4] Almquist, H. J., *Fed. Proc.*, 1942, **1**, 269; Almquist, H. J., and Grau, C. R., *J. Nutrition*, 1944, **28**, 325; Grau, C. R., and Almquist, H. J., *Poultry Sci.*, 1944, **23**, 486.

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Antihistamine and Antianaphylactic Effect of Hetramine, a New Synthetic Pyrimidine Compound.

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There has been increasing evidence in recent years which indicates that some of the symptoms of anaphylactic shock and other hypersensitivities are due to the liberation of histamine during an antigen antibody reaction.[1-3] For this reason much investigation has been directed toward the discovery of a substance that can counteract the effects of histamine *in vivo*.[4-8] There has been additional evidence recently that substances having antihistamine properties can do much to

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[2] Dragstedt, C. A., *Physiol. Rev.*, 1941, **21**, 563.

[3] Code, C. F., *Ann. Allergy*, 1944, **2**, 457.

[4] Bovet, D., and Staub, A. M., *C. R. Soc. de Biol.*, 1937, **124**, 547.

[5] Staub, A. M., and Bovet, D., *ibid.*, 1937, **125**, 818.

[6] Staub, A. M., *Ann. Inst. Pasteur*, 1939, **63**, 400 and 485.

[7] Loew, E. R., Kaiser, M. E., and Moore, V., *J. Pharm. Exp. Therap.*, 1945, **83**, 120.

[8] Mayer, R. L., Huttrer, C. P., and Scholz, C. R., *Science*, 1945, **102**, 93.

TABLE I.
Acute Toxicity of Hetramine for Mice.

Dose mg/kg	Route of administration	No. of mice	No. dead	% dead
25.0	S.Q.	10	0	0
31.25	S.Q.	18	0	0
50.0	S.Q.	10	1	10.0
62.5	S.Q.	18	4	22.2
75.0	S.Q.	10	6	60.0
100.0	S.Q.	10	10	100.0
125.0	S.Q.	18	18	100.0
200	P.O.	15	0	0
250	P.O.	23	0	0
300	P.O.	20	4	20.0
400	P.O.	20	14	70.1
500	P.O.	13	10	77.0
600	P.O.	28	22	78.6

S.Q. = subcutaneously.
P.O. = orally.

Hetramine was studied for its antihistamine and antianaphylactic properties in experimental animals. It was found to have an unusually high degree of activity in preventing histamine-induced contractions of isolated intestinal strips. Similarly, it was found to be highly effective in blocking histamine-induced shock in the guinea pig and in preventing fatal anaphylactic shock in hypersensitive animals.

The acute toxicity of hetramine for mice was determined following subcutaneous and oral administration of the compound to respective groups of animals. The LD_{50} following subcutaneous administration is between 62.5 and 75 mg/kg of mouse weight. Following oral administration, the LD_{50} was determined to be approximately 300 to 400 mg/kg. The data showing these results may be seen in Table I.

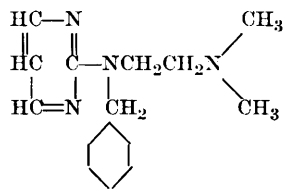
TABLE II.
Influence of Hetramine Upon Toxic Doses of Histamine.

No. guinea pigs	Hetramine pretreatment 30 min, mg/kg	Histamine mg/kg, intracardially	No. dead	% survival
6	1.0—I.P.	0.85	5	16.7
3	3.0—I.P.	0.85	3	0
6	4.0—I.P.	0.85	2	66.7
6	5.0—I.P.	0.85	1	83.3
7	6.0—I.P.	0.85	1	85.7
4	10.0—P.O.	0.85	3	25.0
5	20.0—P.O.	0.85	3	40.0
5	30.0—P.O.	0.85	3	40.0
5	40.0—P.O.	0.85	1	80.0
5	50.0—P.O.	0.85	0	100.0
8	Controls	0.85	8	0

I.P.—intraperitoneally
P.O.—per orally.

alleviate some of the symptoms associated with various types of allergies and other instances of hypersensitivity.

Hetramine which is N,N-dimethyl-N^{1}benzyl-N^1(a-pyrimidyl) ethylene-diamine,*



is a pyrimidine isostere of a pyridine compound which was found to have antihistamine activity.[8]

A preliminary experiment on the chronic toxicity of hetramine was carried out by testing the effect of continuous small daily doses in growing rats over a 35-day period. One group of 12 rat weanlings were put on a stock laboratory diet in which was incorporated a quantity of hetramine so that the rats consumed 50 mg/kg of rat weight per day. The concentration of hetramine in the food was adjusted daily to compensate for the growth of the rats and greater food consumption as the days passed, thus keeping the daily dosage to almost exactly 50 mg/kg per day. A second group of 12 weanlings were given a

* Synthesized by H. L. Friedman and A. T. Tolstoouhov of the chemical laboratories of the Pyridium Corporation.

TABLE III.
Efficacy of Hetramine in Preventing Fatal Experimental Asthma in Guinea Pigs Exposed to Atomized Histamine.

Hetramine mg/kg, I.P.	No. guinea pigs	No. dead	% survived
0 controls	23	22	4.3
0.156	3	3	0
0.312	3	2	33.3
0.625	7	3	57.1
1.25	4	1	75.0
1.55	6	2	66.7
2.0	6	0	100.0
2.5	4	0	100.0

I.P.—intraperitoneally.

stock diet and the drug was administered subcutaneously, twice daily, 10 mg/kg at each dose. The doses were adjusted daily to the weight of each rat. Injections were given at 9:00 a.m. and 4:30 p.m. A third group of 12 weanling rats, serving as controls, were maintained on the stock diet and given no drug.

The animals were weighed every 2nd or 3rd day and hemoglobin determinations were carried out at intervals during the 35 days of the test. These doses of hetramine were tolerated without any effect upon the growth of the young rats and without any effect on the hemoglobin, the initial average weight being 25 g in all groups and the final weight averaged 127 g in the control and 125 and 123 g in the treated groups.

The antihistamine effect of hetramine on smooth muscle strips was demonstrated in an isolated muscle bath apparatus using strips of guinea pig ileum. Kymograph tracings of the muscular contraction were made on the addition of hetramine in amounts to bring its concentration in the bath to 1 γ per cc. Histamine solution was superimposed on the hetramine to bring its concentration to 1 γ per cc. The resulting contraction if any, was recorded on the kymograph and the muscle was then washed with fresh Ringer's solution and retested with 1 γ per cc of histamine. The absence of a contraction following the addition of histamine in the presence of hetramine indicated the antihistamine effect of the latter compound. The proof of histamine activity in the concentration used was shown by the immediate contraction of the muscle on the addition of histamine after having washed out the hetramine.

As little as 1/16 of 1 γ of hetramine counteracted the muscular contractions produced by 1 γ of histamine and partial inhibition was obtained in a ratio of one part of hetramine to 32 parts of histamine.

The *in vivo* antihistamine effect of hetramine was examined by pretreating guinea pigs with various doses of the compound to be followed in 30 minutes with toxic intracardial doses of histamine. 0.85 mg/kg of histamine intracardially was found to be uniformly fatal to guinea pigs. In Table II it is shown that pretreatment with 4.0, 5.0 or 6.0 mg/kg of hetramine is effective in preventing acute toxic death of the majority of animals tested. It is also demonstrated in Table II that oral dosage is similarly effective in this respect,

TABLE IV.
Antianaphylactic Effect of Hetramine in Guinea Pigs Sensitized to Horse Serum.

No. guinea pigs shocked with 1.0 cc horse serum I.C.	Pretreatment (20 min) hetramine mg/kg I.P.	Results Intensity of reaction following shocking dose No. pigs ++++	+++	++	+	0
11	0 controls	11	0	0	0	0
6	3.5	6	0	0	0	0
8	5.0	4	1	1	1	1
8	6.0	1	1	3	1	2

I.C.—intracardially.
I.P.—intraperitoneally.
++++—fatal shock.
+++—severe shock with recovery.
++—moderate reaction with recovery
+—slight reaction with recovery.
0—no symptoms

but must be increased about 10-fold.

Exposure to atomized histamine induces a severe and frequently fatal bronchoconstriction in the guinea pig. It was found that hetramine can prevent the fatal bronchoconstriction so produced by protecting the animals with varying doses prior to exposure to a histamine atmosphere. The chamber into which atomized histamine is introduced was constructed in accordance with the methods described by Loew, *et al.*[7] It was found that vapor from 5 cc of a 0.125% solution of histamine was almost uniformly fatal to unprotected animals. This mortality could be significantly and increasingly reduced with doses of 0.3 mg/kg to 2.5 mg/kg of hetramine administered intraperitoneally. The data on this experiment are shown in Table III.

The antianaphylactic effect of hetramine was determined by sensitizing guinea pigs through intraperitoneal injection of 0.25 cc normal horse serum 14 days prior to shocking doses of 1.0 cc horse serum administered intracardially. Control animals uniformly succumbed to the shocking dose with typical symptoms of fatal anaphylactic shock. Pretreatment with intraperitoneal doses of hetramine up to 3.5 mg/kg were ineffective under our conditions. When doses of 5 mg/kg were administered 20 minutes before the shocking dose of horse serum, 50% of the guinea pigs survived and 6.0 mg/kg reduced the severity of the reaction still further, 7 out of 8 animals surviving the shocking dose. The data are shown in Table IV.

The antihistamine effect of hetramine as demonstrated by the above laboratory experiments would indicate that this drug may have a beneficial effect on some of the varied symptoms associated with hypersensitivity and physical allergies. Clinical trials are in progress to determine the effect of this compound in a variety of conditions such as, vasomotor rhinitis, hay fever, urticaria, bronchial asthma, cold allergy and other physical allergies, serum reactions and contact dermatitis.

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On Breeding "Wild" House Mice in the Laboratory.

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The white laboratory mouse may well be regarded as a classical example of the domestication of an animal at the hand of man. The consequences of that domestication have provided laboratory experimenters with a small docile animal the usefulness of which has been demonstrated so often as to be an established tradition. However, another consequence of that domestication has been the emergence of many genotypes distinguishable one from another by a variety of characters. This multiplicity of genotypes is a forceful reminder of the variation inherent in the species, and when, for example, a given diet produces a certain result in a certain laboratory strain of mice, we next may be expected to inquire whether (a) other genotypes will react similarly, or (b) all genotypes will do so, or (c) whether the wild species will do so. In many ways an investigation of the wild type would seem to have the greatest interest and meaning. This necessitates a laboratory supply of the wild genotype obtained either by trapping the numbers required, or by breeding them in the laboratory. For many purposes the latter method is the more preferable.

Recent investigations in the nutritional aspects of experimental epidemiology[1] have raised this question of host genotypes among

* With the technical assistance of Mr. S. A. Greenhalgh.

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