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EFFECT OF ANTIHISTAMINES AND HISTAMINE DESENSITIZATION ON HEMATOLOGIC CHANGES INDUCED IN GUINEA PIGS BY HISTAMINE

By

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INTRODUCTION

Antihistamines antagonize almost all effects induced by histamine except a) increased gastric acid secretion and gastric lesions (1, 2); b) hematologic effects in dogs (2); and c) lethal effects of high doses in mice (3). In mice, a synergism between histamine and antihistamines was evidenced (4, 5).

However, Ambrus, *et al.* (6, 10) found that the gastric acid secretory and gastrointestinal ulcer-producing effects of histamine were antagonized by histamine desensitization in guinea pigs. These same investigators found that the antagonism between histamine and antihistamines in mice with regard to the toxic and hypothermic effects depended in part on the dose and route of administration (7). Histamine desensitization was ineffective against lethal doses of histamine in mice (8) and rats (9).

This present study was undertaken to investigate the effect of antihistamines and histamine desensitization on histamine-induced blood picture changes in the guinea pigs.

MATERIALS AND METHODS

Animals: English, smooth-hair guinea pigs of either sex, weighing 250 to 300 grams, were used. Animals in the desensitization study, which extended over 12 weeks, increased in

weight during the course of the experiment to 400 to 550 grams. The guinea pigs were kept in air conditioned quarters at 21 C and 40 % relative humidity, and maintained on Rockland guinea pig pellets, additional fresh greens twice a week, and water ad libitum.

Drugs: Histamine diphosphate, U.S.P., prepared in physiological saline, was administered in a dose of 0.5 mgm/kgm. The antihistamines included: B-dimethylaminoethyl benzhydryl ether hydrochloride (diphenhydramine hydrochloride, Benadryl); N,N-dimethyl-N'-2-pyridyl-N'-p-methoxybenzyl-ethylenediamine maleate (mepyramine maleate, Neointergan); 10-(2-dimethylamino-1-propyl) phenothiazine (RP 3277, Phenergan). The antihistamines were administered 15 minutes prior to the histamine injection in the dose of 10 mgm/kgm. All doses were calculated to the base, and all injections were given subcutaneously.

Desensitization: Desensitization was accomplished in the manner outlined by Ambrus, Ambrus, and Harrison (6). Before the schedule was started, the histamine sensitivity of each guinea pig was determined by the aerosol method described by Harrison, et al. (11). This consisted of exposing the guinea pig in a specially constructed chamber to 0.2 % aerosolized histamine and recording the reaction time on the basis of the time in seconds required to produce arbitrarily established responses—(a) hyperpnea, (b) forced cough, (c) dyspnea, (d) reeling, (e) collapse. The aerosol reaction time reported in the data represents the mathematical mean of the reaction times of (b) and (c). One to two hours after the aerosol reaction time was evaluated, the hematologic response to 0.5 mgm/kgm histamine subcutaneously was determined. Daily subcutaneous injections of histamine were then given for a period of eight weeks; 0.5 mgm/kgm during the first week with weekly increments of 0.5 mgm/kgm. Aerosol reaction times were determined weekly, always before the injection of histamine for that day. The animals were regarded as desensitized when their aerosol reaction time had increased to eight minutes or greater. Their hematologic response to

0.5 mgm/kgm histamine was again determined one to two hours after the animals were found to be desensitized. The animals were then permitted a rest period of three to four weeks, at the end of which time their aerosol reaction time had returned to its original level indicating return of histamine sensitivity. At this time, the animals were again challenged with a subcutaneous injection of 0.5 mgm/kgm histamine, and the blood picture response determined.

The animals in this phase of the work all served as their own controls, whereas in all other phases, animals in the experimental group were compared with an appropriate control group, treated as indicated.

Blood Sampling and Counting: Guinea pigs were placed in a small restraining box just large enough to immobilize them, the ears gently rubbed with xylol, and the marginal veins nicked with the tip of a sharp scalpel blade. The first freely flowing drops of blood were discarded (12), and the subsequent drops taken up into a standard white blood cell pipette and diluted 1:20 with a modified Randolph stain (13). It was found from preliminary experiments that the various white cells stained best when the blood was diluted with a freshly prepared 1:1 ratio of 0.1 % methylene blue and 0.1 % eosin in 50 % propylene glycol. Total white cell counts, percent differential, and absolute eosinophile counts were made on the same blood sample dilution. Both sides of a Neubauer chamber were filled from each pipette, the cells permitted to settle, and the total white cell count established by counting the number of cells present in four large squares of each chamber. The differential count was undertaken by counting 100 cells under high power microscopy, and the eosinophile count by totaling all the eosinophiles present within the entire ruled areas on both sides of the chamber.

Statistical Analysis: The increase in the white cell count that followed administration of histamine was expressed in absolute figures rather than percent increase. This procedure was followed when analysis of covariance of the data of the desensitization experiment revealed that the rise in the total

white cells was independent of the initial base level (Table VI a). Simple analysis of variance was made for the determination of significance, with $P = 0.05$ taken as the criterion for significance.

RESULTS

Effect of Histamine on the Blood Picture: In a preliminary experiment, 0.5 mgm/kgm histamine was injected subcutaneously into a group of 24 guinea pigs. Total white cell

TABLE I
Effect of Histamine on the Total White Blood Cell Count in Guinea Pigs.

G. P. #	Control wbc count/cmm	Maximal wbc count/cmm	Time at maximal count (hr)	Absolute increase in wbc count/cmm
1	5,750	20,000	3	14,250
2	7,500	36,200	3	28,700
3	7,400	26,300	3	18,900
4	7,160	27,700	6	20,540
5	3,800	6,600	3	2,800
6	5,200	6,250	3	1,050
7	5,450	10,650	6	5,200
8	4,550	7,450	3	2,900
9	3,300	7,650	3	4,350
10	5,750	16,000	3	10,250
11	5,150	10,200	3	5,050
12	5,250	7,150	3	1,900
13	2,500	7,200	3	4,700
14	3,800	4,800	3	1,000
15	6,500	12,000	3	5,500
16	6,330	12,900	3	6,570
17	8,925	19,250	3	10,320
18	3,750	11,400	3	7,650
19	5,150	14,000	3	8,850
20	6,660	20,500	3	13,840
21	8,930	17,600	3	8,670
22	9,100	17,650	3	8,550
23	7,580	16,400	3	8,820
24	4,250	11,100	3	6,850
Avg.	5,820	14,460	3.2	8,640

TABLE II
*Comparative Effect of Histamine and Saline on the Total White Blood Cell
 Count in Guinea Pigs.*

G. P. #	Histamine				Saline			
	Control wbc count/cmm	Maximal wbc count/cmm	Time at maximal count (hr)	Absolute in- crease in wbc count/cmm	Control wbc count/cmm	Maximal wbc count/cmm	Time at maximal count (hr)	Absolute in- crease in wbc count/cmm
1	6,550	16,400	3	9,850	12,800	25,550	3	12,750
2	10,500	17,150	3	6,650	19,300	17,400	3	-1,900
3	5,550	17,700	3	12,150	9,500	13,050	12	3,550
4	5,350	15,900	3	10,550	12,800	20,800	3	8,000
5	2,600	7,800	3	5,200	10,000	10,000	3	0
6	7,400	23,500	3	16,100	7,400	15,900	3	8,500
7	15,000	20,000	3	5,000	5,850	10,900	3	5,050
8	4,100	9,750	3	5,650	9,600	12,300	3	2,700
9	9,750	22,750	3	13,000	9,995	12,700	3	2,705
10	9,250	23,250	6	14,000	13,400	13,150	3	-250
AVE.	7,605	17,420	3.3	9,815	11,065	15,175	3.9	4,110

•

counts were made before, and 1, 3, 6, and 12 hours after injection. The results (Table I) show that an average increase of 8,640/cmm occurred in the white cell count at a mean maximum time of 3.2 hours. A similar study was then made using 10 additional histamine-treated animals and 10 saline control animals. Differential and absolute eosinophile counts were made together with the total white cell counts. The increase in the white cell count in the histamine group averaged 9,815/cmm at a mean maximum time of 3.3 hours (Table II). This compared with the 4,110/cmm increase observed in the saline control group, with a P value of less than 0.01 (Table III). The leukocytosis always involved a marked granulo-

TABLE III
*Analysis of Variance of Absolute White Blood Cell Increase between
Histamine and Saline Group.*

Source of Variation	Degrees of Free- dom	Sum of Squares	Mean Squares	F Ratio
Between Treatment	1	161	161	8.90
Within Treatment	18	325	18.1	
Total	19	486		

$P < 0.01$

cytosis with a simultaneous lesser lymphocytopenia (Table XIV). This also occurred in the saline control group, but to a lesser extent. Histamine administration caused an average increase in the absolute number of circulating eosinophiles far exceeding that increase observed in the saline control group (Table IV).

Effect of Histamine on the Blood Picture of Desensitized Guinea Pigs: Injection of 0.5 mgm/kgm histamine subcutaneously into 15 guinea pigs one to two hours after their histamine sensitivity had been determined as normal by the aerosol method resulted in a mean increase of 9,820/cmm in the leukocyte count at a mean maximum time of 2.7 hours. At the end of eight weeks, during which time the guinea pigs

TABLE IV

Effect of Histamine and Saline on the Absolute Number of Circulating Eosinophiles in the Blood of Guinea Pigs.

G. P. #	Histamine				Saline			
	Control count/cmm	Maximal count/cmm	Time at maximal count (hr)	Increase in count/cmm	Control count/cmm	Maximal count/cmm	Time at maximal count (hr)	Increase in count/cmm
1	11	111	1	100	33	22	3	-11
2	56	500	6	444	11	22	1	11
3	177	266	1	89	11	11	1	0
4	56	100	1	44	143	165	1	22
5	11	44	3	33	55	78	3	23
6	188	455	1	267	44	78	1	34
7	56	222	1	166	11	111	6	100
8	33	111	3	78	0	111	6	111
9	22	377	3	355	22	78	3	56
10	133	532	6	399	314	188	12	-126
Avg.	75	272	2.6	197	64	86	1.6	22

developed tolerance to histamine, 0.5 mgm/kgm histamine subcutaneously caused a mean leukocyte increase of 6,270/cmm at a mean maximum time of 3.6 hours (Table V), $P > 0.05$. The leukocytosis occurring both before and during desensitization was due mainly to an increase in granulocytes. Injection of the same dose of histamine into the guinea pigs after their histamine sensitivity had returned to normal (as indicated by a normalized aerosol reaction time) resulted in a mean increase of 14,030/cmm in the white cell count. A P value of > 0.05 was calculated when this rise was compared to the rise observed in the group before desensitization, and $P < 0.01$ when compared to the increase at the peak of histamine tolerance. Tukey's gap and straggler test (26) confirmed the observation that histamine caused the lowest degree of leukocytosis in the histamine tolerant group ($P < 0.02$), and the highest degree of leukocytosis in the group in which normal histamine sensitivity had returned ($P < 0.02$) (Table VI b).

TABLE V
*Effect of Histamine on the Total White Blood Cell Count of Guinea Pigs before and during Desensitization,
 and after Return to Normal Histamine Sensitivity.*

G. P. #	Before Desensitization					During Desensitization					Return to Normal Sensitivity				
	Control wbc count/cmm	Max. wbc count/cmm	Time at max. count (hr)	Absolute in- crease in wbc count/cmm	Aerosol reac. time (sec)	Control wbc count/cmm	Max. wbc count/cmm	Time at max. count (hr)	Absolute in- crease in wbc count/cmm	Aerosol reac. time (sec)	Control wbc count/cmm	Max. wbc count/cmm	Time at max. count (hr)	Absolute in- crease in wbc count/cmm	Aerosol reac. time (sec)
1	5,080	23,400	1	18,320	60	12,900	18,800	3	5,900	600	10,000	24,750	3	14,750	72
2	8,600	10,000	1	1,400	60	10,150	11,300	6	1,150	600	16,000	29,950	3	13,950	55
3	13,900	21,200	3	7,300	50	14,300	23,300	3	9,000	690	19,350	38,150	3	18,800	100
4	9,500	15,000	3	5,500	65	16,900	24,250	3	7,350	540	17,650	35,500	3	17,850	75
5	9,600	13,100	1	3,500	52	7,050	9,750	3	2,700	510	16,800	23,800	3	7,000	70
6	7,900	11,600	3	3,700	64	5,450	11,500	3	6,050	468	13,500	32,700	3	19,200	90
7	7,910	31,800	3	23,890	75	11,300	14,000	3	2,700	580	7,700	17,000	3	9,300	80
8	5,250	16,600	3	11,350	48	10,300	12,750	3	2,450	620	*				
9	6,840	13,300	3	6,460	58	14,900	18,400	3	3,500	585	14,950	22,650	3	7,700	165
10	6,660	15,300	3	8,640	50	11,000	22,200	3	11,200	580	18,800	36,100	3	17,300	30
11	9,250	26,000	3	16,750	88	18,450	32,500	6	14,050	420	14,750	32,850	3	18,100	90
12	5,340	19,700	3	14,360	85	9,050	15,200	3	6,150	480	*				
13	5,500	6,760	3	1,260	70	12,500	23,100	3	10,600	720	*				
14	6,000	21,300	3	15,300	85	11,000	15,750	6	4,750	660	16,000	26,300	3	10,300	110
15	6,660	16,300	3	9,640	44	11,250	17,800	3	6,550	600	*				
Avg.	7,600	17,420	2.7	9,820	64	11,770	18,040	3.6	6,270	570	15,045	29,070	3	14,030	85

* Animals died.

TABLE VI a
Analysis of Covariance.

Source of Variation	Degrees of Freedom	(x)	(xy)	(y)	Degrees of Freedom	Sum of Squares	Mean Squares	F Ratio
Pigs	10	163.03	44.37	382.91				
Treatments ...	2	256.74	125.84	336.18	2	248.30	142.15	5.32
Residual	20	172.53	31.41	513.67	19	507.95	26.73	
Total	32	592.30	201.62	1232.76				
Treatments + Residual	22	429.27	157.25	849.85	21	792.25		

$$y = (\text{treatment-initial level})/1000$$

$$x = \text{initial level}/1000$$

Test for Significance.

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Squares	F Ratio
Reduction due to covariance	1	5.72	5.72	—
Residual	19	507.95	26.73	
Total	20	513.67		

$$P > 0.05$$

TABLE VI b
Tukey's Gap and Straggler Method for Comparing Individual Means.

$$\bar{m} = 333.8/33 = 10.1$$

$$m = 6.2 \text{ or } 14.0$$

$$S_m = s/r = 25.68/11 = 2.33 = 1.5$$

$$K = \frac{m - \bar{m}/S_m - 1/2}{3(1/4 + 1/D.F.)} = \frac{3.9/1.5 - 1/2}{3(1/4 + 1/20)} = 2.1/.9 = 2.33^{(*)}$$

The histamine-induced eosinophilic response observed in the histamine tolerant animals was slightly higher than that seen in the group before desensitization. After return to

TABLE VI c
Analysis of Variance without Covariance.

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Squares	F Ratio
Pigs	10	382.91		
Treatments	2	336.18	168.09	6.55
Residual	20	513.67	25.68	
Total	32	1232.76		

Mean leukocytosis before desensitization $\bar{B} = 6.2$

Mean leukocytosis during desensitization $\bar{D} = 6.2$

Mean leukocytosis after desensitization $\bar{A} = 14.0$

$\bar{A}-\bar{B} = 3.9$ ($P > 0.05$)

$\bar{A}-\bar{D} = 7.8$ ($P < 0.01$)

$\bar{B}-\bar{D} = 3.9$ ($P > 0.05$)

normal histamine sensitivity, the response was somewhat decreased (Table VII).

Effect of Histamine on the Blood Picture of Guinea Pigs Pretreated with Antihistamines: The mean leukocytosis induced by 0.5 mgm/kgm histamine injected into animals pretreated with antihistamines was less than the 9,815/cmm observed in the control group; for Benadryl the mean leukocytes rise was 5,110/cmm; for Neoantergan, 6,710/cmm; for Phenergan, 6,360/cmm (Table VIII). All of them had a P value of greater than 0.05 when compared to the control group (Table IX). The antihistamines were administered subcutaneously, 10 mgm/kgm, 15 minutes before the histamine injection. The eosinophile count increased in almost all the animals (Table X).

Administration of 10 mgm/kgm antihistamine alone did not cause any significant increase in the white cell levels; for Benadryl, 2,210/cmm; Neoantergan, 4,100/cmm; Phenergan, 3,380/cmm (Table XI).

The observations of all the experiments are summarized (Tables XII, XIII, XIV), and typical results following the

TABLE VII
Effect of Histamine on the Number of Circulating Eosinophiles of Guinea Pigs before and during Desensitization and after Return to Normal Histamine Sensitivity.

G. P. #	Before Desensitization				During Desensitization				Return to Normal Sensitivity			
	Control Count/cmm	Maximal Count/cmm	Time at maxi- mal count/cmm	Increase in Count/cmm	Control Count/cmm	Maximal Count/cmm	Time at maxi- mal count/cmm	Increase in Count/cmm	Control Count/cmm	Maximal Count/cmm	Time at maxi- mal count/cmm	Increase in Count/cmm
1	22	122	1	100	67	177	1	110	77	477	1	400
2	233	1531	6	1248	155	377	1	222	133	177	1	44
3	67	67	1	0	67	300	1	233	233	543	3	310
4	67	277	3	210	166	640	1	474	466	766	1	300
5	0	22	3	22	11	89	1	78	133	366	3	233
6	22	89	3	67	321	1032	6	711	44	44	1	0
7	44	199	1	155	133	3063	12	2930	56	288	1	232
8	78	599	3	521	11	56	1	45	0	266	1	266
9	89	134	1	45	0	33	1	33	0	388	3	-67
10	*				122	177	6	55	455	177	1	44
11	*				144	266	1	122	133			
12	*				0	144	1	144				
13	*				44	177	1	133				
14	*				67	133	1	66	935	866	1	-69
15	*				188	277	1	89				
Avg.	69	338	2.3	268	100	463	2.4	363	230	388	1.5	158

* Cells stained poorly, could not be counted.

TABLE VIII
Effect of Histamine on the Total White Blood Cell Count of Guinea Pigs Pretreated with Antihistamines.

G. P. #	Benadryl				Neoantergan				Phenergan			
	Control wbc count cmm	Maximal wbc count cmm	Time at maximal count (hrs)	Absolute increase in wbc count cmm	Control wbc count cmm	Maximal wbc count cmm	Time at maximal count cmm	Absolute increase in wbc count cmm	Control wbc count cmm	Maximal wbc count cmm	Time at maximal count (hrs)	Absolute increase in wbc count cmm
1	12,250	15,500	1	3,250	12,500	20,000	3	7,500	7,000	12,400	3	5,400
2	3,050	6,350	1	3,300	7,100	13,150	3	6,050	7,800	9,300	3	1,500
3	4,600	6,000	3	1,400	9,800	16,000	3	6,200	8,000	15,700	3	7,700
4	5,050	7,950	3	2,900	16,500	22,100	3	5,600	9,850	20,700	3	10,850
5	4,150	5,900	3	1,750	8,400	16,575	3	8,175	12,350	18,700	3	6,350
6	7,700	10,150	3	2,450								
7	7,900	11,000	3	3,100								
8	7,750	10,350	6	2,600								
9	9,400	30,000	3	20,600								
10	9,550	19,250	3	9,700								
Avg.	7,140	12,245	3.1	5,110	10,860	17,570	3	6,710	9,000	15,360	3	6,360

TABLE IX

Analysis of Variance of White Blood Cell Increase between Histamine Control and Antihistamine Pretreated Groups.

Benadryl

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Squares	F Ratio
Between treatment	1	109.23	109.23	4.28
Within „	18	459.00	25.50	
Total	19	568.23		

$P > 0.05$

Neoantergan

Between treatment	1	41.05	41.05	3.22
Within „	13	165.80	12.75	
Total	14	206.85		

$P > 0.05$

Phenergan

Between treatment	1	40.13	40.13	2.77
Within „	13	188.24	14.48	
Total	14	228.37		

$P > 0.05$

administration of histamine and saline are graphed (Figs. 1, 2).

DISCUSSION

Leukocytosis occurring within a few hours after histamine administration has been reported by other authors (14, 15). In this study, the leukocytosis observed was significantly higher than that of the saline control group. The increase in the white cell count seen in the saline control group may be ascribed to the mild stress reaction induced by handling. Schweizer (23) reported a 30 % decrease in the number of mononuclear cells and no alteration in the polynuclear leuko-

TABLE X
Effect of Histamine on the Number of Circulating Eosinophiles of Guinea Pigs Pretreated with Antihistamines.

G.P. #	Benadryl				Neoantergan				Phenergan			
	Control count/cm	Maximal count/cm	Time at maxi- mal count (hrs)	Increase in count/cm	Control count/cm	Maximal count/cm	Time at maxi- mal count (hrs)	Increase in count/cm	Control count/cm	Maximal count/cm	Time at maxi- mal count (hrs)	Increase in count/cm
1	56	78	1	22	277	466	3	189	11	111	1	100
2	78	366	1	288	111	366	1	255	44	200	1	156
3	22	56	1	34	22	88	1	66	144	177	1	33
4	122	266	1	144	88	255	6	167	77	201	1	124
5	22	288	3	266	88	155	3	67	67	122	1	55
6	11	67	1	56								
7	44	589	12	545								
8	100	56	3	-44								
9	88	111	1	23								
10	67	579	12	512								
Avg.	61	246	3.6	185	117	266	2.8	149	69	162	1	93

TABLE XI
Effect of Benadryl, Neointergan, and Phenegan on the Total White Blood Cell Count of Guinea Pigs.

G.P. #	Benadryl				Neointergan				Phenegan			
	Control wbc count cmm	Maximal wbc count cmm	Time at maximal count (hrs)	Absolute increase in wbc count cmm	Control wbc count/cmm	Maximal wbc count cmm	Time at maximal count (hrs)	Absolute increase in wbc count/cmm	Control wbc count cmm	Maximal wbc count cmm	Time at maximal count (hrs)	Absolute increase in wbc count cmm
1	6,650	10,000	6	3,350	7,550	11,150	3	3,600	4,700	10,200	1	5,500
2	22,250	21,750	1	—,500	7,350	12,050	1	4,700	11,800	13,900	3	2,100
3	4,700	7,150	1	2,450	6,000	10,000	6	4,000	13,750	16,275	1	2,525
4	8,000	12,550	3	4,550								
5	5,900	8,150	12	2,250								
6	9,650	10,850	6	1,200								
Ave.	9,530	11,740	4.8	2,210	6,970	11,070	3.3	4,100	10,080	13,460	1.6	3,380

TABLE XII

Summary of the Effects of Treatments on the Total White Blood Cell Counts of Guinea Pigs.

Treatment	Number of Animals	Average Absolute increase wbc count/cmm
Histamine alone	34	9,280
Saline alone	10	4,110
Histamine before desensitization .	15	9,820
Histamine during desensitization .	15	6,270
Histamine after return to normal histamine sensitivity	11	14,030
Histamine after Benadryl	10	5,110
Histamine after Neoantergan	5	6,710
Histamine after Phenergan	5	6,360
Benadryl alone	6	2,210
Neoantergan alone	3	4,100
Phenergan alone	3	3,380

TABLE XIII

Summary of the Effects of Treatments on the Number of Circulating Eosinophiles in Guinea Pigs.

Treatment	Number of Animals	Average increase in count/cmm
Histamine alone	10	197
Saline alone	10	22
Histamine before desensitization ...	9	268
Histamine during desensitization ...	15	363
Histamine after return to normal histamine sensitivity	11	158
Histamine after Benadryl	10	185
Histamine after Neoantergan	5	149
Histamine after Phenergan	5	93
Benadryl alone	6	33
Neoantergan alone	3	49
Phenergan alone	3	40

cyte number induced by the stress condition of the blood sampling procedure in guinea pigs. He, however, worked with much larger and heavier animals and employed a dif-

TABLE XIV
Percentages of Animals Exhibiting Respective Lymphocyte and Polymorphonuclear Count Changes at Peak of Leukocytosis.

Treatment	# of Animals	Polymorphonuclears			Lymphocytes	
		% increase			% increase	
		0-50	51-100	over 100	0-50	51-100
Histamine alone	10	10	10	80	40	10
Saline alone	10	—	40	50	70	10
Histamine before desensitization	9	—	20	80	50	20
Histamine during desensitization	15	20	27	53	33	33
Histamine after return to normal histamine sensitivity	11	—	9	91	46	44
Histamine after Benadryl ...	10	—	—	100	10	80
Histamine after Neoantergan	5	—	20	80	20	80
Histamine after Phenergan ...	5	—	—	100	20	80

Percentage change in lymphocyte and polymorphonuclear counts expressed in absolute % change.

ferent restraining method. The animals in this study were deprived of food for the entire 12 hour period which may have contributed to the leukocytosis reaction.

Histamine desensitization was found to slightly reduce the leukocytosis-inducing effect of histamine. The increase in the base white cell level from 7,600/cmm to 11,770/cmm may be due partly to an increase in age and weight of the animals, the effect of constant histamine injection, and constant handling. The base level remained high even after histamine sensitivity had returned to its former level, and the degree of leukocytosis induced by histamine was also higher than that experienced by the group before and during desensitization.

The three antihistamines employed in this study prevented to a small extent the leukocytosis induced by histamine. The magnitude of the leukocytosis experienced in the animals pre-treated with antihistamines did not differ very much from that of the desensitized animals, but the significance was

EFFECT OF HISTAMINE (0.5 mgm./Kgm. SUBCUTANEOUSLY)
ON THE BLOOD PICTURE OF THE GUINEA PIG
GUINEA PIG No. 9

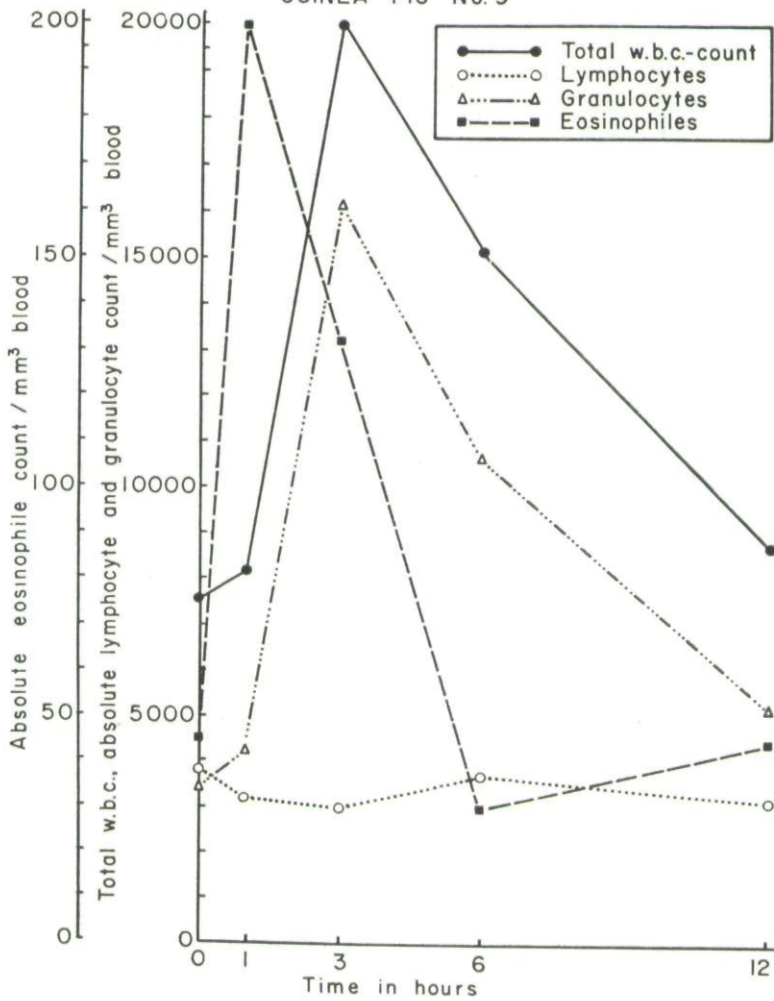


Fig. 1.

Injection at 0 time after taking of first blood sample.

EFFECT OF SALINE (0.5 ml. SUBCUTANEOUSLY) ON
THE BLOOD PICTURE OF THE GUINEA PIG
GUINEA PIG No. 5

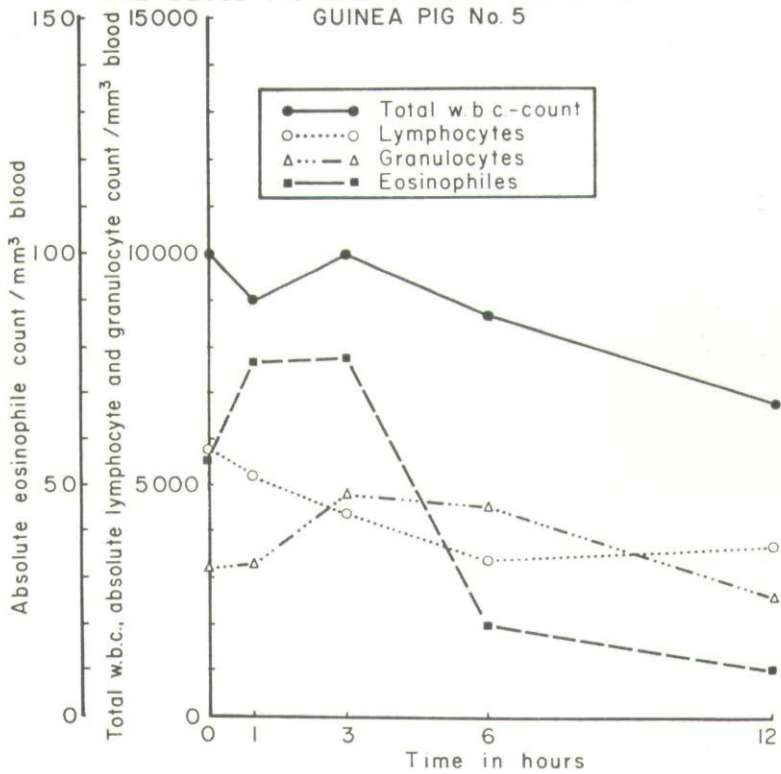


Fig. 2.

Injection at 0 time after taking of first blood sample.

found to be somewhat less. That antihistamines alone have little effect on the blood picture has been observed in this study as well as in other investigations (27, 28).

The normal eosinophile levels reported here agree more with the low levels observed by Vaughn (16) and Samter (17) than with the high level of 500/cmm quoted by Scarborough (18). Although the histamine-induced eosinophilia we observed confirms the work of other investigators (19-21), the results should be regarded critically in view of the small number of cells counted. Possible alterations in the count due to diurnal effect, fasting, and stress may be regarded as minimal, for the eosinophilia occurred before the diurnal effect was able to express itself (22), and fasting and stress tend to lower rather than raise the eosinophile count (23, 24). The direct chamber cell count increased the accuracy, but the greatest source of error still was present in the number of cells counted. In counting single blood samples, the error depends upon the number of cells counted. According to Uhrbrand (25), in a statistical analysis of the chamber method for counting eosinophiles, it is necessary to count at least 500 cells in order to reduce the error to 10 %. Despite this, many investigators have reported on blood eosinophile levels similar to those described in this report.

CONCLUSIONS

1. The characteristic hematologic changes induced in guinea pigs by histamine administered subcutaneously included leukocytosis and an increase in the blood eosinophile level. Both of these changes occurred within three hours after injection. The leukocytosis always involved a large granulocytosis with a small degree of lymphocytopenia.

2. Histamine desensitization slightly decreased the degree of leukocytosis induced by histamine, but did not alter the eosinophilic response. After the return of normal histamine sensitivity, histamine caused a greater leukocytosis than was originally observed.

3. Antihistamines given 15 minutes prior to the histamine injection lessened the leukocytosis to the same extent as in the histamine desensitized animals, but they did not appreciably alter the eosinophilia.

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ACKNOWLEDGEMENT

We wish to acknowledge the assistance rendered in various phases of this work by Dr. C. A. Leonard and the aid of Mr. J. L. Ciminera in the statistical analysis of the data.

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