STUDIES ON BLOOD HISTAMINE IN PATIENTS WITH ALLERGY. II. ALTERATIONS IN THE BLOOD HISTAMINE IN PATIENTS WITH ALLERGIC DISEASE[1]

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It has long been thought that anaphylactic shock, as produced in the experimental animal, and the allergic reaction, as it occurs in man, may be dependent on the same basic mechanism for their production (1). Both anaphylaxis and allergy come under the heading of "hypersensitiveness," which is an all-inclusive term and under which the phenomena of each may be conveniently grouped. In the search for an etiological factor, histamine has figured prominently ever since the studies of Dale and Laidlaw (2) who observed that the symptoms of histamine shock and anaphylaxis were strikingly similar. In 1929 Dale (3) postulated that histamine was released in anaphylactic shock as a result of cell injury, due to the interaction of the antibody with the antigen. This was subsequently shown to be true by Dragstedt and Gebauer-Fuelnegg (4) for the dog, and by Bartosch, Feldberg and Nagel (5) for the guinea-pig. Thus, until recently it was believed that anaphylaxis was always associated with an increase of the blood histamine, which in turn was responsible for the production of symptoms. In 1939, however, Code and Hester (6) noted that anaphylactic shock in the horse and calf was associated with a decrease in the histamine content of the blood. Rose and Weil (7) observed a similar change in the rabbit, and it was further noted that a decrease also occurred in the histamine content of some of the tissues of this species during anaphylactic shock (8). From these findings it appears that acute anaphylactic shock may be associated with a rapid increase in the blood histamine in certain species, and a marked decrease in others.

Investigations have also been carried out on the possible relation of histamine to allergic disease in man. For the most part, the results have been neither as clear nor as consistent as those obtained in experimental anaphylaxis, and the greater part of the evidence has been of an indirect nature. Thus Lewis (9) postulated that symptoms of allergic disease might be explained by the liberation of an "H" or histamine-like substance, because of the similarity between histamine wheals and

TABLE I

Blood histamine in cases of asthma

Case	Sex	Age	Diagnosis	Date	Blood histamine	Symptoms
					γ per 100 cc.	
2	F	30	Chronic asthma		1.0	++
46	F	29	Chronic asthma		4.0	0
52	F	48	Chronic asthma		2.0	++++
					4.0	0
64	M	54	Asthma, bronchitis, hay fever		8.0	0
68	F	24	Asthma, bronchitis		4.0	++
71	F	27	Asthma		6.0	0
76	F	9	Asthma		3.0	++
					3.0	++++
81	M	31	Asthma		3.0	0
82	F	49	Severe asthma and bronchitis	November 11, 1939	1.0	++++
					1.0	++
				December 5, 1939	5.0	++++
				December 6, 1939	1.0	+++
				December 13, 1939	4.0	+
				January 11, 1940	4.0	0
				January 12, 1940	2.0	0
83	F	10	Asthma		5.0	0
84	M	8	Asthma		6.0	0
85	F	8	Asthma and bronchitis		8.0	0
					9.0	++++
94	M	16	Asthma		3.0	0
104	F	25	Asthma		3.5	0
105	F	11	Asthma		9.0	Day after severe attack, still wheezing
106	F	43	Asthma and bronchitis		5.0	++
107	F	11	Asthma		12.0	24 hours after severe attack
108	F	14	Asthma and bronchitis		13.0	++++
124	M	16 mos.	Asthma		9.5	0
144	M	8	Asthma and bronchitis		1.5	+
145	F	38	Asthma		4.0	0
147	F	40	Asthma		3.5	0
165	F	45	Asthma and bronchitis	March 20, 1939	5.5	++++
				March 28, 1939	2.0	+
				April 1, 1939	4.3	0
				April 4, 1939	3.0	0
187	F	48	Asthma	May 3, 1939	3.2	0 8:30 p.m.
					3.8	0 11:30 p.m.
				May 4, 1939	3.0	0
239	M	19	Asthma		9.0	++++
140	F	22	Asthma		4.0	0
251	F	12	Asthma		19.0	++
74	M	53	Asthma and urticaria		4.0	++
					4.0	++
275	M	34	Asthma		4.0	+++

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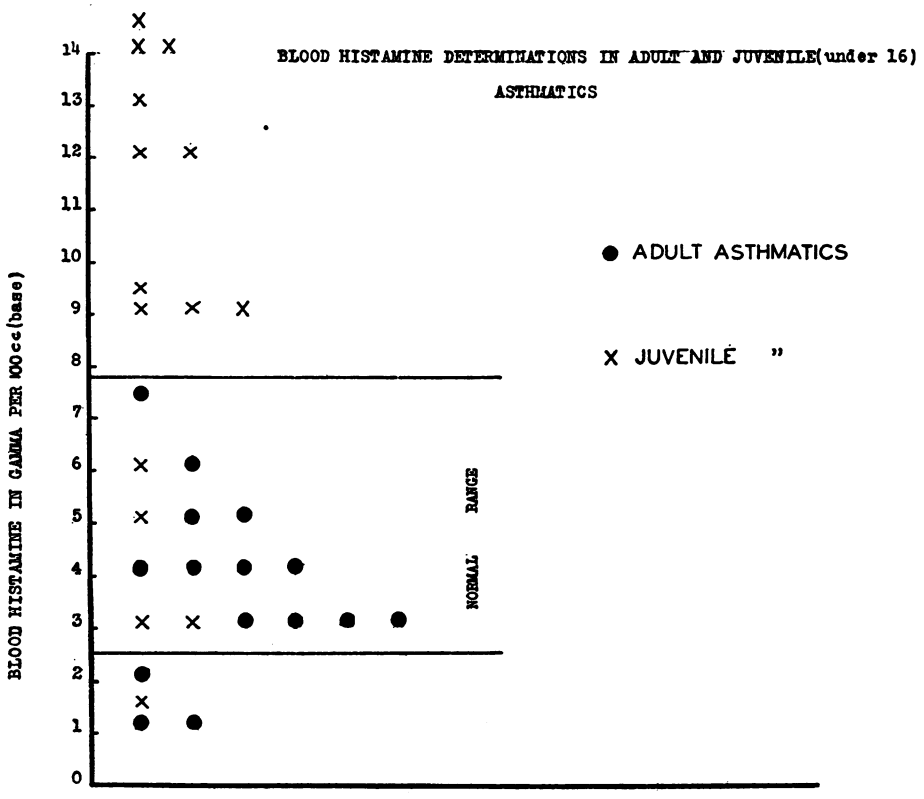

FIG. 1. THE HISTAMINE CONTENT OF THE BLOOD OF PATIENTS WITH ASTHMA CHARTED ACCORDING TO AGE GROUPS

Whereas the majority of adult asthmatics have a blood histamine level which is within normal limits (2.0 to 7.5 *y* per 100 cc.), that of many of the patients under the age of sixteen is elevated above this level.

those produced by stroking the skin of patients with dermatographia. Similarly, the liberation of free hydrochloric acid into the stomach following the production of wheals in a case of dermatographia (10) or by the immersion into ice water of the arm of a patient sensitive to cold (11) is another indirect method of demonstrating the liberation of histamine during the production of allergic phenomena.

In 1935 Barsoum and Gaddum (12) described a method for the determination of histamine in blood. Using this method or slight modifications thereof, a number of investigators have studied the blood histamine levels in patients with allergic disease. In six patients with urticaria, Cerqua (13) noted an increase of the blood histamine level during acute attacks, with a return to normal after six hours. His figures ranged from 13.0 to 30.0 *y* per 100 cc.

Observations on the histamine level of the blood in patients with asthma have been conflicting. Cerqua (13) noted a definite increase in eight cases of asthma during attacks, 18.0 to 30.0 *y* per 100 cc. During quiescent periods the blood histamine was normal, 7.0 to 10.0 *y* per 100 cc. Similar findings in a small group of cases were reported by Jacquelin (14) and Parrot (15). On the other hand, Haworth and MacDonald (16) did not find any significant alteration in the blood histamine level of sixty asthmatics. Riesser (17) was also unable to demonstrate a significant change.

In previous studies, Rose and Browne (18) observed that the blood histamine content of fifty normal persons averaged 4.0 *y* per 100 cc., with variations of from 2.0 to 7.5 *y* per 100 cc. It was also noted that the blood histamine level in any one person remained remarkably constant with little

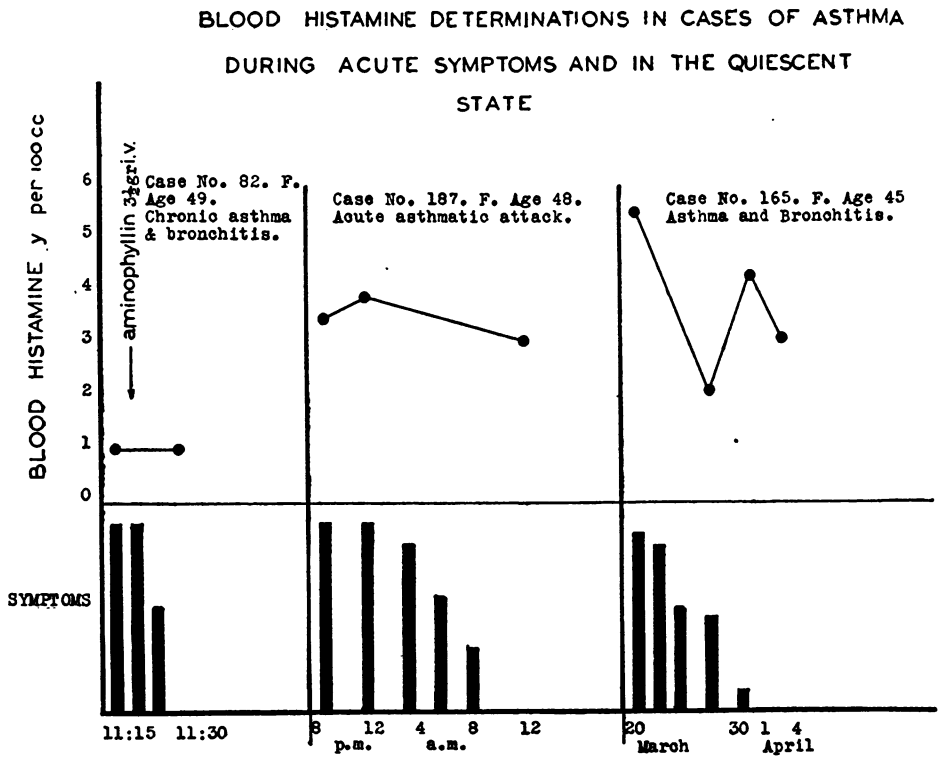

FIG. 2. THE HISTAMINE CONTENT OF THE BLOOD OF THREE ASTHMATIC PATIENTS BOTH DURING ATTACKS AND QUIESCENT PERIODS

It will be seen that, although there are variations in the blood histamine level, these are not necessarily correlated with symptoms.

or no alteration, even though examinations were made weeks or months apart. These findings agree in general with those of Code and MacDonald (19) and most other observers.

Further studies on the histamine content of the blood have been carried out in 116 patients with allergy. The results of some of these—cases of physical allergy and dermatographia—have already been reported (20). The results about to be described were obtained from observations on eighty patients with other forms of allergic disease.

METHODS

The blood histamine was determined by the Code (21) modification of the Barsoum and Gaddum (12) method. All assays were carried out on the guinea-pig ileum suspended in Tyrode solution at 38° C. to which atropine was added in a concentration of 1:10,000,000. This method is reasonably accurate in that small amounts of histamine may be detected to within 95 to 98 per cent when added to whole blood.

All results are expressed as gamma (gamma or γ = 0,001 mgm. or microgram) of histamine base per 100 cc. whole blood.

RESULTS

(a) *Cases of asthma*

Thirty cases of asthma, most of which were free of other allergic complications, were studied. The results are given in Table I. It will be observed that some of these patients have a blood histamine level which is below the normal (Cases 2, 82, 144), whereas others (Cases 64, 85, 105, 107, 108, 124, 239, 251 60) have a blood histamine level which is greater than normal. When these are charted according to age groups, it appears that patients of less than sixteen years of age tend to have high blood histamine levels as compared to adult asthmatics (Figure 1).

It will further be noted that the histamine content of the blood of patients with asthma tends to fluctuate greatly as compared to that of normal

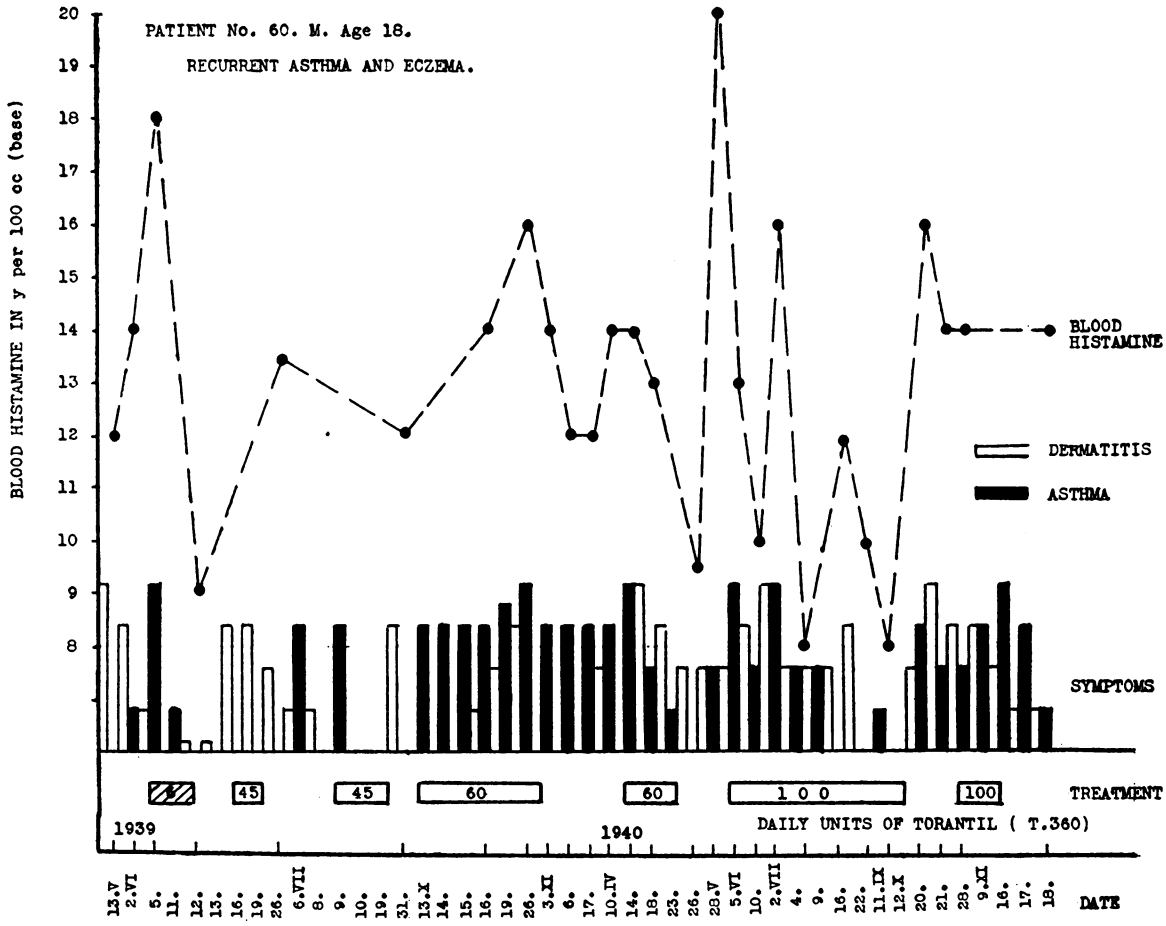

FIG. 3. THE HISTAMINE CONTENT OF THE BLOOD OF A PATIENT WITH CHRONIC ASTHMA AND ECZEMA TAKEN OVER A PERIOD OF ABOUT TWO YEARS

The determinations were made at random intervals both in and out of attack.

patients. However, there does not seem to be any consistent correlation of these changes with the onset or disappearance of symptoms. This is shown in Figure 2 where the symptoms and blood histamine levels of three patients with asthma are recorded both during severe attacks and during a symptom-free period.

One patient (Case 60) was followed at intervals in this manner for a period of two years. The results of the blood histamine determinations are shown along with symptoms in Figure 3. It will be noted that the histamine content of the blood fluctuated markedly without a consistent relationship to the symptoms of active asthma or dermatitis. Many of the attacks were associated with a high blood histamine level, such as that in June 1939 when the histamine content of the blood rose to 18.0 *y* per 100 cc. as an acute attack of asthma came on, and fell to a low level on June 12th when symptoms disappeared. In October 1939, there was persistent asthma and severe eczema. The histamine content of the blood rose and fell without much obvious change in the symptoms. Again, a marked increase of the blood histamine level (20 *y* per 100 cc.) was observed in May 1940; there was only a slight increase in symptoms of asthma. On June 5th he returned with severe asthma and the histamine content of the blood was only 10.0 *y* per 100 cc. At the last visit made on February 14th, 1941, this patient was completely free of asthma, and there was a moderate amount of eczema. The blood histamine content was 22.0 *y* per 100 cc., higher than at any previous time. It would seem that the symptoms

TABLE II

Blood histamine in cases of uncomplicated urticaria

Case	Sex	Age	Blood histamine	Symptoms
			y per 100 cc.	
15	F	24	1.7	0
28	F	14	4.0	0
			4.0	++
48	F	24	3.0	0
			2.0	++
59	F	25	4.0	0
			4.0	++
			3.0	++++
61	F	18	2.0	+++
			3.5	0
63	M	24	8.0	++
			7.0	++++
97	F	17	7.0	0
			6.0	++
189	M	10	4.0	++
			5.0	0
			4.0	+++
			4.0	0
178	F	40	3.0	++
			4.2	0
51	F	40	8.0	0
121	F	30	6.0	0
			6.0	++
			6.0	0
			11.0	++++
133	F	48	3.5	+++
			3.8	++
151	F	22	6.0	0
174	F	23	6.0	0
			3.0	0
			4.0	++
202	F	36	3.0	+++
214	F	60	1.5	++
217	F	23	5.5	+++
259	M	3	6.8	0
			6.6	++

of allergy are not associated with any consistent change in the histamine content of the blood in this patient.

(*b*) *Cases of uncomplicated urticaria*

Twenty-three patients with recurrent urticaria were available for study. For the most part, no difference in the histamine content of the blood was noted as compared to that of normal persons, as will be seen in Table II. In one case only (Case 121) a moderate increase was observed during an acute attack. In the remaining twenty-two patients, minor fluctuations of the blood histamine level occurred, and these were usually in the nature of a small decrease coincident with an attack of urticaria. These findings, therefore, are not in agreement with those of Cerqua (13) who noted an increase of the histamine content of the blood during attacks of urticaria.

TABLE III

Blood histamine in cases of angioneurotic oedema

Case	Sex	Age	Date	Blood histamine	Symptoms
				y per 100 cc.	
37	M	9		2.0	++
				0.5	++++
73	F	22		3.0	0
79	F	12		1.0	+++
87	M	21		0.5	After severe attack (24 hours symptoms receding
89	F	26		5.0	0
				0.5	++++
91	M	22		1.0	++
				1.0	36 hours after (subsiding)
21	F	24		0.8	Severe attack ++++
219	F	27	June 13, 1940	5.0	0
			July 22, 1940	0.5	++++
			September 9, 1940	1.5	++
			October 11, 1940	3.0	+
			November 21, 1940	0.7	No oedema, but complaining of blurred vision

(*c*) *Cases of angioneurotic oedema*

The patients susceptible to attacks of acute angioneurotic oedema, of whom there were eight, showed the most consistent alterations in the histamine content of the blood. The results are given in Table III. It will be noted that in each instance, with the exception of Case 37, a moderate-to-marked decrease in the blood histamine occurred when acute symptoms were present. This was observed in repeated attacks in two patients. For example, in Case 89, the blood histamine level was low when symptoms were marked, and returned to within normal levels as they decreased (Figure 4).

TABLE IV

Blood histamine in cases of eczema

Case	Sex	Age	Blood histamine	Symptoms
			y per 100 cc.	
43	F	38	4.0	++
72	F	34	4.0	+
90	F	6	9.0	++++
			8.0	+++
92	M	20	9.0	++
98	M	7	6.0	+++
101	F	40	10.0	+++
179	F	10	8.0	+
190	F	40	5.0	++
220	M	47	28.0	++++ (weekly intervals)
			12.0	++++
			13.0	++++
60	M	18	14.0	++

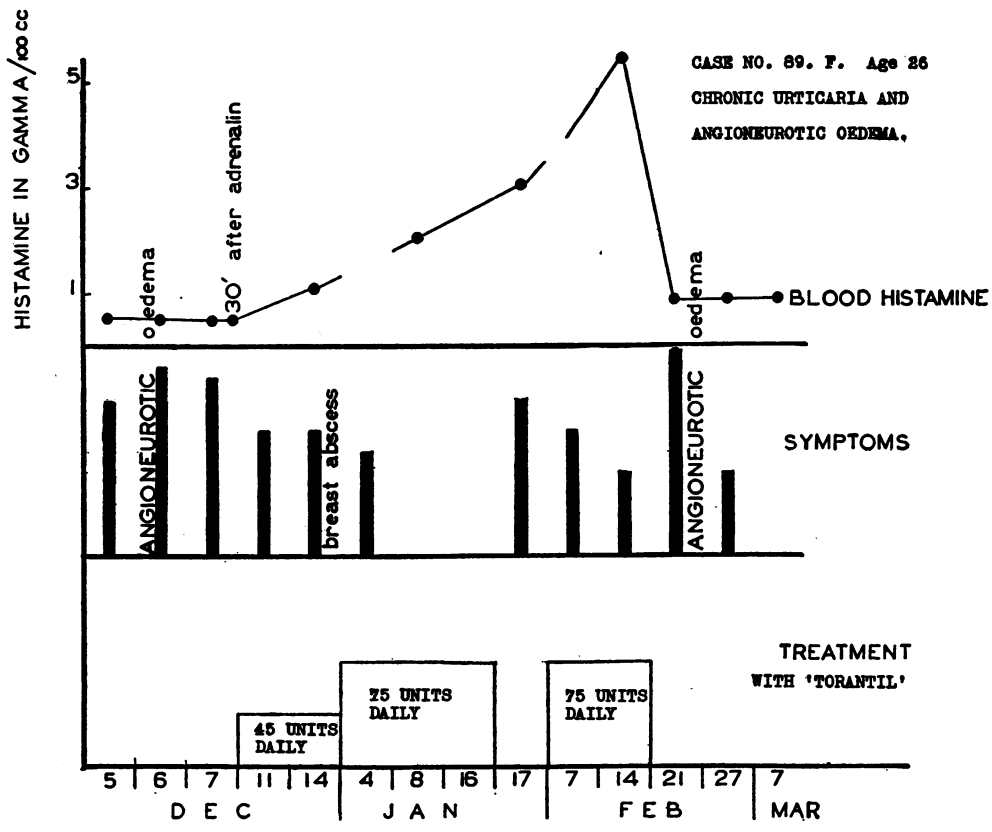

FIG. 4. THE HISTAMINE CONTENT OF THE BLOOD OF A PATIENT SUBJECT TO URTICARIAL ATTACKS AND ANGIONEUROTIC OEDEMA

It will be seen that coincident with an attack of angioneurotic oedema, a marked diminution of the histamine content of the blood occurs.

(*d*) *Cases of eczema*

The blood histamine level was determined in ten cases of eczema (Table IV). Unfortunately, single determinations only were made on most of these patients. It will be seen from the results that the blood histamine tends to be at levels higher than normal. Case 60, who was described previously with the group of asthmatic patients, is included. The histamine level of the blood was raised when eczema alone was present. In Figure 5, determinations of the blood histamine level in patients with eczema, urticaria and angioneurotic oedema are shown.

(*e*) *Vasomotor rhinitis and colitis*

There remains a small group of patients, six with vasomotor rhinitis, and two with colitis. The results of the blood histamine determinations are given in Table V. Here again, it will be noted, there is little difference in the blood histamine level of patients with vasomotor rhinitis as compared to normals. In one of the cases of colitis (Case 153) the histamine content of the blood is definitely increased and there are marked fluctuations which are not associated with increase or decrease of symptoms.

The results of treatment, indicated on some of the figures, will be discussed elsewhere.

DISCUSSION

In reviewing the above results, several points may be noted. It will be seen that, in contrast to the marked stability of the blood histamine level of non-allergic or normal patients, that of patients with allergic disease, with the exception of urticaria, may vary considerably in the same person.

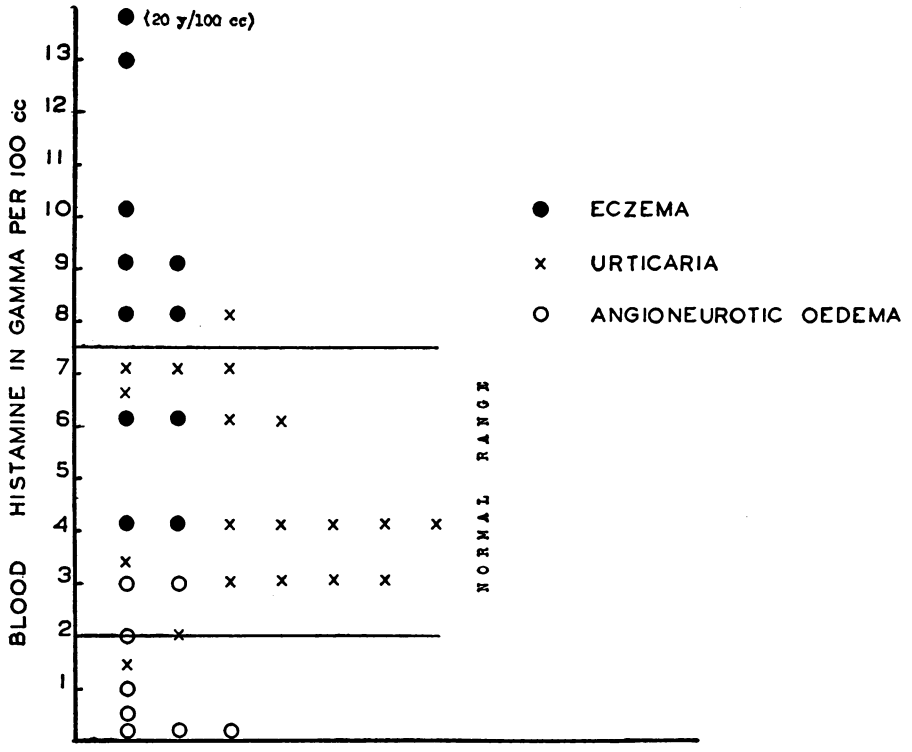

FIG. 5. THE HISTAMINE CONTENT OF THE BLOOD OF PATIENTS WITH ECZEMA, URTICARIA AND ANGIONEUROTIC OEDEMA

It will be observed that the histamine content of the blood of many of the patients with eczema tends to be at levels higher than normal, whereas that of patients with angioneurotic oedema is at a level below that of normal. Patients with urticaria, on the other hand, have a histamine content of the blood within normal limits.

Furthermore, the histamine content of the blood of allergic patients may increase considerably above the normal, as in young asthmatics or in cases of eczema, or may almost entirely disappear, as in cases of angioneurotic oedema. In this connection, it is interesting to note that Cerqua (13) also observed that the blood histamine level decreased in patients with serum sickness during attacks, and that it later returned to normal. Such a decrease has also been observed in cases of asthma where the attack was induced by the subcutaneous injection of histamine (22) and in cases of physical allergy following the production of wheals by the proper stimulus (20).

It is important, however, to distinguish between the fluctuations in the blood histamine level in patients with angioneurotic oedema, and those which occur in other types of allergic disease, for it is only in the former that the change in the histamine content of the blood is definitely correlated with the onset of symptoms, while in the latter group of cases, such as eczema or asthma, fluctuations in the histamine content of the blood may or may not occur at the time of onset of symptoms. Furthermore, the blood histamine level always decreases in cases of angioneurotic oedema with the onset of symptoms, whereas in the other types of allergy, either an increase or a decrease may be observed.

The observations of Myhrman and Tomenius (23) are interesting in connection with the relation of histamine to asthma. They found that, whereas the stools of most patients contained relatively small amounts of histamine, averaging 1.3 γ per cc., those of asthmatic patients contained large amounts. In one patient, for example, the histamine content of the stool was found to be 256 γ per cc. and 100 γ per cc. was found in the

TABLE V

Blood histamine in cases of vasomotor rhinitis and colitis

Case	Sex	Age	Diagnosis	Date	Blood histamine	Symptoms
					y per 100 cc.	
102	F	25	Vasomotor rhinitis		8.0	++
77	F	39	Vasomotor rhinitis		6.0	++
					7.0	++++
					12.0	++++
69	F	33	Vasomotor rhinitis		4.0	0
78	F	14	Vasomotor rhinitis	April 27, 1940	3.5	++
				May 13, 1940	2.5	++
				May 23, 1940	10.0	++++
				June 5, 1940	3.0	++
				June 8, 1940	5.0	++++
				June 13, 1940	3.0	+++
				July 11, 1940	3.0	++++
207	F	29	Vasomotor rhinitis		8.0	+++
225	M	25	Colitis		8.0	+++
153	M	20	Colitis	April 13, 1940	8.0	++
				May 23, 1940	14.0	+
				May 31, 1940	10.5	+
				June 15, 1940	14.0	++++
				June 20, 1940	9.0	++++
				June 21, 1940	6.5	++++
				June 28, 1940	8.0	++++
				July 8, 1940	7.0	++++

stool of another. On the other hand, no increase was noted in cases of urticaria. Histamine-like substances have also been found in the sputa of asthmatic patients (17, 24).

While it is as yet not possible to account for the fluctuations in the blood histamine level or to explain its relationship to allergic disease, a consideration of the state of the blood histamine and its behaviour following the injection of histamine may somewhat clarify these findings. It is agreed by the majority of observers that most of the blood histamine is held within the cellular elements—the white blood cells (19) or the platelets (25, 26). Thus an increase of such histamine-rich cells would account for an increase in the total blood histamine. Code and MacDonald (19) reported five patients with an eosinophilia of over 9 per cent, in four of whom the histamine content of the blood was raised above normal. The results of the present investigation support this finding in general, for the majority of patients in whom the blood histamine was found to be increased also had an eosinophilia of from 10 to 20 per cent. This parallelism, however, was not invariable. For example, one patient (Case 273), a case of Loeffler's syndrome, had an eosinophilia of 60 per cent on one occasion, and of 55 per cent on another. The blood histamine level on both, respectively, was 2.0 *y* per 100 cc. Similarly, Case 43, Table IV, had an eosinophilia of 15 per cent. The histamine content of the blood was 4.0 *y* per 100 cc.

It should, however, be noted that marked increases in the histamine content of the whole blood may exist without any symptoms being manifest. Thus, in cases of myelogenous leukemia, as much as 1500 *y* per 100 cc. have been reported. Such histamine is probably bound to the cells (19, 27). On the other hand, a sudden liberation of histamine into the blood may produce a rapid and severe fall of the blood pressure and tachycardia. Even as small an amount as 7.0 gamma, when rapidly injected intravenously, will produce such changes (28).

It is probable that, in certain cases of physical allergy, histamine may be released free into the plasma and there may produce a decrease in the blood pressure and tachycardia along with a release of free hydrochloric acid into the stomach (11). Actual increases in the blood histamine have been observed in one such case by Capps and Young (29) and in eight cases by Rose (20). Such increases are transient and are frequently followed by a decrease in the blood histamine level within twenty to thirty minutes. It is probable that this histamine is in the plasma rather than in the cells and, as such, would rapidly be withdrawn from the circulation (30). This is further supported by the observation that, following the subcutaneous injection of histamine in allergic patients, the histamine level of the blood may remain at a stationary level, or may decrease even at the height of the symptoms of histamine intoxication, such as tachycardia, headache or allergic manifestations (22). Thus, even when histamine is liberated, it is possible that the tissue affected may absorb the free histamine and withdraw it from the circulating blood. This may possibly account for the lack of correlation between the blood histamine levels and symptoms in other forms of allergic disease, as noted above. It would also ac-

count in part for the decrease in the blood histamine level in cases of angioneurotic oedema. If it is believed that histamine is carried by the eosinophiles, the finding that there is a gradual increase of these cells in wheals (31) would also account for the decrease in the blood histamine.

Finally, it is possible that human allergy may resemble both types of animal anaphylaxis, with a liberation of histamine in certain types and a decrease of the histamine content of the blood in others.

CONCLUSIONS

1. The histamine content of the blood of a group of eighty patients with allergic disease including asthma, urticaria, angioneurotic oedema, eczema, vasomotor rhinitis and colitis has been studied.

2. With the exception of cases of urticaria, there is much more fluctuation of the histamine content of the blood of patients with allergic disease, as compared to the marked stability of that of normal persons.

3. In cases of asthma, eczema or vasomotor rhinitis, these fluctuations are not necessarily correlated with the onset of symptoms.

4. With the development of angioneurotic oedema, a marked diminution of the histamine content of the blood occurs. The blood histamine level returns to normal when the symptoms subside.

5. Although it is possible that histamine may be released in the types of allergic disease studied in the present communication, the results of the above observations do not warrant such a conclusion.

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