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STUDIES ON HISTAMINE

VII

SOME ASPECTS OF BLOOD HISTAMINE IN
NORMAL, ALLERGIC AND TUBERCULOUS
CHILDREN¹

By

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INTRODUCTION

Many conflicting opinions have been published regarding the question as to whether there is an increased blood histamine in allergies. It is certain however that the histamine metabolism, and also the reactions to histamine are changed in allergic patients. Regarding reactions to histamine *Curry* (1946) compared the vital capacity of normal and allergic people after intravenous injections of small doses of histamine. In asthmatic patients a decrease was seen, in normal people no such change was observed. *Rose* (1947) found that after intravenous injections of histamine a peripheral vasodilatation occurs, but also that asthma, urticaria or headache are to be seen in patients who have an allergic predisposition and that it is exactly the symptom to which the patient is predisposed, which makes itself manifest.

That histamine metabolism is disturbed in allergic patients is made obvious by the increased histamine in urine (*Rose*

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et al. 1951), in faeces (*Myrrmann* and *Tomenius* 1939) and in lung tissue (*Rose* 1952). The increased excretion of histamine is interesting in connection with the investigation by *Katz* et al. (1941), who found that the exposure of sensitised blood cells to a specific antigen, results in the liberation of histamine into the plasma.

We have investigated whether the disturbed histamine metabolism could be made apparent by determining the trend of the histamine level (see this series No. I).

Besides the allergic children we extended our investigations to a group of tuberculous children. We did this as this group is homogenous as far as it is influenced by the same antigen. A third control group consisted of normal children.

METHODS AND MATERIAL

We investigated 39 normal boys and 20 normal girls, the group of tuberculous children consisted of 30 boys and 8 girls, the group of allergic children 10 boys and 11 girls. In total 924 histamine estimations were made. The research was carried out on patients whilst lying on a couch. A needle was inserted in the vena cubiti and the blood collected in a calibrated 2 ml syringe, after which it was introduced into 3 ml 10 % trichloroacetic acid. Twenty seconds later, using a second syringe, another sample was withdrawn. This was repeated several times at intervals of twenty seconds. The blood flowing from the needle between collections was not used for determination.

The length of the series varied from 3-12 samples with an average of 7.2 samples from each child.

The histamine was determined using the micro modification of *Code's* method (see this series no. II).

RESULTS AND DISCUSSION

The results of the determinations are given in Tables I, II and III. For a preliminary review of the material averages and dispersions were computed from each series. In Fig. 1 these two values were set against each other, for each group separately. The resulting figures suggest that in normal children a correlation exists between the dispersion and the

TABLE I
Progress of the histamine content in the blood of normal children (blood samples collected at 20 secs. intervals).

Sex	Age	Month of collection	Histamine value in γ /100 ml.										Average
♀	7	Feb.	5.0	3.0	4.8	5.0	2.0	2.0	3.0				3.4 ± 1.5
♀	8	April	4.3	4.4	4.4	5.8	7.4	7.3	8.3	7.3	7.4		6.4 ± 1.6
♀	9	April	2.6	5.6	4.0	3.6	3.0						3.7 ± 1.1
♀	6	April	4.6	6.9	6.0	6.0	6.0						5.9 ± 0.8
♀	5	April	6.5	5.5	4.5	5.1	3.7	2.7	4.1	3.6	3.4	4.0	4.3 ± 1.4
♀	10	July	3.4	2.5	3.4	2.9	3.5	3.0	3.1	2.9	3.6	1.6	3.0 ± 0.6
♀	10	July	3.0	2.8	3.0	3.0	3.0	3.3	3.6	3.3	3.3	3.5	3.2 ± 0.9
♀	11	Aug.	3.0	2.8	2.5	2.8	3.0	3.0	3.0	3.1	2.5		2.8 ± 0.2
♀	9	Aug.	7.1	7.4	4.9	5.8							6.3 ± 1.1
♀	5	Dec.	8.1	8.1	16.0	9.0	16.0	9.1	10.0	11.6	9.2		10.8 ± 3.05
♀	10	Dec.	5.0	5.0	12.1	9.2	5.0	5.5	5.0	4.0	4.0	5.9	6.1 ± 2.4
♀	3	Dec.	4.3	5.9	5.0	4.1	7.2	9.8	7.6	6.3	8.9		6.6 ± 2
♀	7	Jan.	7.4	4.7	4.7	5.5	6.6	5.1					5.7 ± 1.1
♀	10	Jan.	7.5	8.0	7.5	9.6	7.4	5.0	5.0	8.8	8.4	4.5	7 ± 1.3
♀	11	Jan.	3.0	5.5	3.0	3.5							3.7 ± 1.2
♀	8	Feb.	5.0	6.3	8.6	7.0	7.3	6.1					6.05 ± 1.4
♀	7	Feb.	3.2	1.8	2.0	2.0	2.7	2.3	1.5				2.2 ± 0.6
♀	9	Feb.	0.0	1.6	7.1	0.0	2.5	3.0	5.4	4.5	5.0	5.1	3.6 ± 2.3
♀	8	April	3.5	3.5	3.3	3.8	3.3	3.8	3.0	3.6	2.8	2.5	3.3 ± 0.4
♀	7	April	1.6	1.6	1.6	1.6	3.1	4.8	2.5	2.3	2.8		2.6 ± 1.2
♂	10	Feb.	3.8	2.8	2.3	2.3	3.3	3.0					3.0 ± 0.6
♂	4 mth	May	2.4	2.6	5.3								3.4 ± 1.6
♂	8	May	3.0	4.8	4.6	4.1	10.3	10.9	12.0	4.2	4.2		6.5 ± 3.5

5	May	5.2	4.2	4.5	4.2	3.9	6.6	6.1	6.4	7.4	4.8	4.1	5.2 ± 1.2
2	June	6.5	7.9	7.5	7.1								7.2 ± 0.6
6	June	7.6	7.3	6.6	6.7	7.0	7.1	7.2	6.9	6.6	8.1	7.5	7.2 ± 0.4
6	June	4.0	5.0	4.1	3.0	3.8							3.9 ± 0.7
8	June	4.0	4.0	3.8	3.0	3.1	3.5						9.5 ± 0.4
8	June	1.5	4.4	3.0									2.9 ± 1.5
6	June	2.6	5.3	5.7	6.5	5.2	6.0						5.2 ± 1.5
8	July	2.8	3.3	3.0	2.5	3.5	3.5						3.1 ± 0.4
7	July	3.8	3.0	3.0	3.1	3.6	3.5	3.5	3.0				3.3 ± 0.3
7	Feb.	3.4	2.8	2.5	1.3	2.8	2.8						2.8 ± 0.03
7	Aug.	4.8	4.5	5.0	4.6								4.7 ± 0.2
11	Nov.	7.5	6.3	5.0									6.3 ± 1.24
6	Nov.	5.2	5.5	5.0	5.3	5.3							5.3 ± 0.17
5	Dec.	5.1	5.5	3.0	6.3	5.0	7.8	5.0					5.4 ± 1.45
8	Dec.	7.0	7.6	7.0	7.1	7.5	7.1						7.2 ± 0.1
5	Jan.	6.5	7.5	8.2	8.5	6.0	13.6	6.6	7.5				8.0 ± 2.4
2	Jan.	4.0	6.7	3.1	10.2	7.5	3.1	5.0	6.4	6.3			5.8 ± 2.3
6	Jan.	3.0	3.1	3.3	3.0	4.0	3.0	4.2	4.1	4.0	5.0	3.0	4.0 ± 0.8
5	Jan.	4.0	5.0	6.0	5.1	5.2	3.0	6.6	3.9				4.8 ± 1.2
10	Feb.	5.6	5.6	5.1	4.4	3.0	5.5	3.0					4.1 ± 1.3
8	Feb.	3.4	3.3	2.5	3.1	5.7	3.0	3.2	3.7				3.4 ± 0.9
6	Feb.	2.9	3.1	4.5	4.3	3.8	4.2	4.5	4.7	4.3			4.0 ± 0.6
6	March	4.6	4.0	3.8	3.5								4.0 ± 0.5
5	March	4.3	3.7	3.3									3.8 ± 0.5
3	March	3.4	2.8	3.5	2.6	2.9							3.1 ± 0.4
7	March	3.6	3.8	3.8	3.5	3.8	3.0	2.8	2.5	2.8	2.5		3.2 ± 0.5
11	April	5.0	3.9	5.4	4.9	4.6	4.7	3.9	4.3	3.8	3.8		4.4 ± 0.6
5	May	4.7	4.2	3.6	10.0	9.2	7.7	3.7					6.2 ± 3.3

TABLE II
Progress of the histamine content in the blood of tuberculous children (blood samples collected at 20 secs. intervals).

Sex	Age	Month of collection	Histamins value in $\gamma/100$ ml.										Average
♀	6	Dec.	7.2	8.6	5.7	7.7	5.1	8.8	9.0	8.8	9.5		7.8 $\pm$ 1.5
♀	6	Dec.	5.2	8.1	10.4	8.1	7.6	3.5	10.6				7.3 $\pm$ 2.6
♀	12	Feb.	4.0	3.0	4.5	4.0	5.0	3.5	3.5				3.9 $\pm$ 0.7
♀	15	Feb.	4.3	3.0	4.5	3.0	5.0	4.3	3.5				3.7 $\pm$ 0.8
♀	14	Feb.	5.0	3.7	4.0	5.1	5.3	4.5	5.0				4.6 $\pm$ 0.6
♀	10	Feb.	5.0	5.0	3.0	2.5	3.0	2.5	2.5				3.3 $\pm$ 1.1
♀	9	Feb.	3.0	4.1	3.6	0.0	3.6	3.5	3.1				3.0 $\pm$ 1.4
♀	11	Feb.	3.0	1.5	5.4	3.1	2.5	3.0					3.3 $\pm$ 1.3
♂	12	Nov.	7.6	7.0	8.1	7.8	10.0	10.0	8.2	10.0			8.6 $\pm$ 1.2
♂	6	Nov.	7.0	3.0	8.8	7.6	7.6	7.5	3.5				6.4 $\pm$ 2.3
♂	12	Jan.	7.0	4.5	5.1	5.1	10.4	8.5	5.7	4.6	6.6		6.4 $\pm$ 1.9
♂	11	Dec.	7.1	3.0	3.0	5.0	3.0	2.6	3.5	6.1			4.2 $\pm$ 1.7
♂	12	Dec.	5.5	7.5	8.9	7.6	7.3	5.1	3.0	3.1			6.0 $\pm$ 2.2
♂	8	Nov.	8.8	8.1	15.1	10.2	8.2	8.4	16.2	10.0	12.6	14.1	11.4 $\pm$ 2.9
♂	6	Jan.	10.0	5.0	7.7	7.5	7.3	8.4	5.2	4.1	7.7	5.3	7.1 $\pm$ 1.9
♂	3	Dec.	5.1	4.6	3.7	12.3							4.5 $\pm$ 0.3
♂	7	Dec.	8.0	14.4	4.0	4.4	8.7	5.4	3.0	6.2	6.5	4.5	6.0 $\pm$ 1.9
♂	7	Nov.	5.0	5.0	4.0	5.0	5.0	4.8	7.5	8.1	5.0	5.0	4.8 $\pm$ 0.4

♂	11	Nov.	3.2	7.7	4.6	3.5	3.0	4.0	3.1	2.5	3.4	3.6 ± 1.5
♂	3	Jan.	5.3	4.8	3.5							4.5 ± 0.9
♂	5	Jan.	7.6	3.0	3.8	5.5	5.1	4.5	3.1	3.5		4.5 ± 1.6
♂	6	Jan.	3.0	3.0	7.7	3.0	5.0	4.1	4.0			4.3 ± 1.3
♂	12	Feb.	3.5	3.5	6.6	4.0	4.5	5.3				4.6 ± 1.2
♂	14	Feb.	3.8	5.0	5.0	4.5	7.5	7.0				5.5 ± 1.8
♂	11	Feb.	7.0	6.5	5.0	5.5	4.0	7.6				5.9 ± 1.4
♂	15	Feb.	5.0	5.6	10.0	5.0	7.0	10.0				7.1 ± 2.4
♂	13	Feb.	7.5	7.6	6.1	7.7						6.9 ± 0.7
♂	15	Feb.	3.1	4.5	3.0	4.0						3.7 ± 0.8
♂	11	Feb.	2.6	3.9	2.5	3.0	2.5	1.5				2.7 ± 0.9
♂	16	Feb.	2.8	1.5	1.5	3.0	3.0					2.4 ± 0.7
♂	11	Feb.	10.0	5.0	4.1	5.0	4.8	4.2				5.5 ± 2.2
♂	9	Feb.	5.1	4.8	4.0	4.0	3.3	3.0				4.0 ± 0.8
♂	8	Feb.	4.0	3.0								3.5 ± 0.7
♂	9	Feb.	7.5	5.1	10.0	4.5	5.1	5.1	5.0			6.2 ± 2.2
♂	6	Feb.	4.7	5.0	5.0	4.5	3.0	4.8				4.5 ± 0.8
♂	7	Feb.	5.1	3.0	5.1	5.5	4.5	2.5				4.3 ± 1.3
♂	16	Feb.	4.3	3.5	3.0	3.5	3.5	3.0				3.5 ± 0.5
♂	14	Feb.	5.0	4.5	5.0	4.3	5.1	3.0				3.6 ± 0.8

TABLE III
Progress of the histamine content in the blood of allergic children (blood samples collected at 20 secs. intervals).

Sex	Age	Histamine value in γ /100 ml.					Average
♀	13		9.2	9.5	9.9		9.5 $\pm$ 0.36
♀	13		8.0	8.5	8.0		8.2 $\pm$ 0.13
♀	6		6.4	6.8	6.0	4.4	5.9 $\pm$ 1
♀	10		7.0	7.0	7.0	6.6	6.9 $\pm$ 0.2
♀	7		7.6	8.0	8.1	7.3	7.7 $\pm$ 0.3
♀	12		3.0	5.0	5.0	5.1	4.0 $\pm$ 1.1
♀	6		5.2	7.7	7.0	7.0	6.9 $\pm$ 0.27
♀	7		3.0	3.0	3.0	3.3	3.3 $\pm$ 0.1
♀	2		12.0	10.0	7.7	20.5	12.5 $\pm$ 5.5
♀	3		4.5	4.3	4.3	3.0	4.0 $\pm$ 0.6
♀	8		20.1	7.6	8.3	10.3	11.7 $\pm$ 4.6
♂	13 months		5.6	2.6	4.5		4.2 $\pm$ 0.12
♂	17 months		0.0	7.5	12.5	18.9	11 $\pm$ 3.4
♂	10		5.1	3.0	3.1	3.0	3.4 $\pm$ 0.9
♂	5		3.8	5.0	4.8	4.5	4.6 $\pm$ 0.5
♂	5		4.8	2.7	3.0	3.4	3.3 $\pm$ 0.8
♂	7		4.3	4.8	4.3	4.5	4.8 $\pm$ 0.7
						5.1	6.3

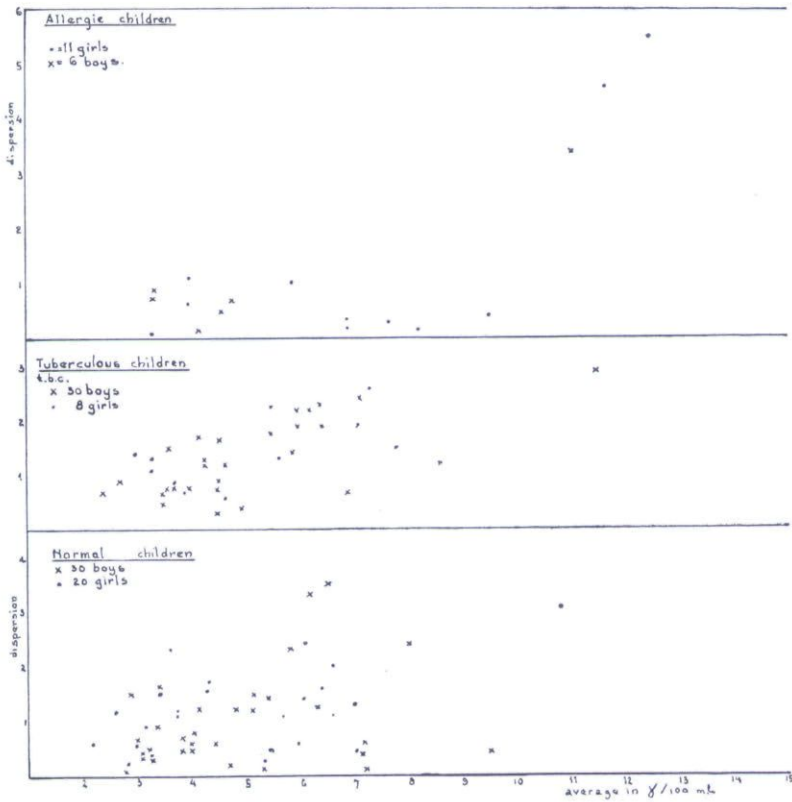


Fig. 1.

level of the blood histamine, showing that the dispersion increases with the histamine level. The same conclusion can be formed in the case of the tuberculous children. In relation to this we would like to point out that *Gooszen* found instances where a similar correlation existed, when investigating the histamine metabolism of schizophrenics (this series no. VI). The allergic children, however, show different results. Although this group is smaller than the other groups, the graph shows that there are more increased histamine levels than in the other two groups. A clear correlation between the histamine level and the dispersion does not exist here. The

dispersions in the different series are not greater however, than those of the other two groups. In the allergic child the changes in the histamine level that occurred during the test-period were not greater than those found in the normal and the tuberculous children.

For the statistical analysis the results were arranged primarily according to the month in which the blood was collected. Then for each month the grand average of all the serial averages was computed, in each of the three groups separately. The results of these computations are given in Fig. 2, where it can be seen that the three curves nearly

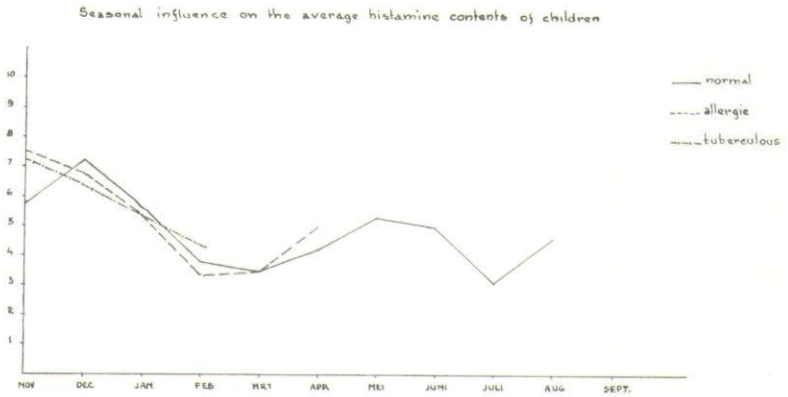


Fig. 2.

coincide. There is thus no indication that differences between these groups exist.

By means of *Kruskal's* test (*Kruskal* 1952) significant differences in the blood histamine level during different months of the year can be demonstrated in the normal and tuberculous groups (see Table IV).

In the allergic children this difference is not evident statistically. However, this material is small: in two of the months only one observation has been made. On the other hand we must be careful before coming to conclusions about these seasonal differences, for it is well known that the

TABLE IV

Investigations of the differences between blood histamine levels during different months of the year, by means of Kruskal's test.

	H	C-1	Tail probability
Normals	20.3	9	0.017
Allergics	7.8	5	0.17
Tuberculous	10.7	3	0.014

sensitivity of the guinea-pig gut varies in the different seasons of the year. It could be possible that interfering substances sometimes present in the extract also have a varying influence on the guinea-pig gut during the different months of the year (see this series no. III). The possibility that these two factors might coincide in some months of the year, thus giving a false result, cannot be excluded.

The average histamine values of the three groups were compared by means of *Wilcoxon's* two sample test (*Wilcoxon* 1945; *Mann and Whitney* 1947; *Hemelrijk* 1952). The averages for each month were first compared, and the results of the different months were combined afterwards (see Table V).

TABLE V

Comparison of the blood histamine levels of the three groups of children by means of Wilcoxon's test.

	$U - \frac{1}{2}$	σ	$\frac{U - \frac{1}{2}}{\sigma}$	Tail-probability
Normal-tuberculous	30	24.5	1.22	0.22 —
Normal-allergies	1	9.6	0.10	0.92 —
Tuberculous-allergies	— 8	11.4	— 0.70	0.48 +

The results confirm the already formed conclusion that no difference between the three groups exists.

Finally, the different blood histamine values of each child were analysed by investigating it in the series if an increasing or decreasing trend was found similar to that observed in

subjects preparing themselves for physical exertion (see this series no. V). As the series of each child were of unequal length, only the method of m-rankings (*Kendall* 1948) could be used in the first three observations. The tailprobabilities were of such magnitude that no justification existed for accepting an increase or a decrease of the histamine level during the test period. The test of symmetry was applied to the first and second observations and gave the same result.

Summarising we can say therefore that we have no reason to presume that a different histamine level between normal, tuberculous and allergic children exists.

The only indication of any difference in histamine metabolism between the groups was that in the allergic group of children a higher proportion showed a raised histamine level. Seeing that the averages of the three groups were more or less equal, we should therefore presume that the allergic children also had a higher proportion of lowered histamine values. As we found that the dispersion in the series of each allergic child is less than that found in the normal group, this possible disturbance of the histamine metabolism in allergics cannot be a result of the appearance of rapid changes in the histamine level, but of a relatively constant high or low level in certain patients.

SUMMARY

The blood histamine was investigated in normal, allergic and tuberculous children.

No reason was found to presume that a different average histamine level exists between normal, tuberculous and allergic children.

In the allergic group of children, however, a higher proportion shows a raised or a low histamine level.

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