

From the Medical Clinic, State University, Utrecht, and from the Laboratory of the Willem Arntsz Hoeve in Den Dolder, The Netherlands

STUDIES ON HISTAMINE

V

INFLUENCE OF PHYSICAL EXERTION
ON BLOOD HISTAMINE¹

By

J. C. M. VERSCHURE, J. A. H. GOOSZEN, P. SJOUKES,
JOHANNA W. MAAS & TH. STRENGERS

INTRODUCTION

In the following experiments the blood histamine in normal subjects was investigated before, during and after physical exercise. Anrep & Barsoum (1935) discovered that during contractions of striated skeletal muscles histamine was set free in the venous blood—an observation re-affirmed by Anrep (1944) after Kwiatkowski (1941) had rejected the fact. Gabraoni (1950) also verified that after using the hand-muscles histamine was set free in the V. cubiti, detected only if the bloodsamples were taken immediately. Anrep, Barsoum, Talaat & Wieninger (1939) demonstrated that this histamine originates from a muscle depot. Anrep, Barsoum & Talaat (1936) demonstrated that extensive amounts of histamine also originate from heart muscle. Code, Evans & Gregory (1938) doubted if histamine was formed by the heart, but Marcou (1939) confirmed the observation by Anrep *et al.* Ambache & Barsoum (1939) demonstrated, that histamine is also set free during contraction of smooth muscle.

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METHODS AND RESULTS

The histamine determinations were carried out according to Code's method (1937) or according to the micromodification of Gooszen, Donker & Strengers. (This series no. II).

In a series of experiments we investigated whether a rise in blood histamine occurred after physical exertion. In a first series blood samples were withdrawn from the V. cubiti from 10 normal males, after which they raced up and down 34 stairs twice. Further samples were then withdrawn at once. The histamine values of both samples are given in Table I.

TABLE I

Normal males	Histamine content before physical exertion in $\gamma/100$ ml	Histamine content after physical exertion in $\gamma/100$ ml
1	6.4	8.0
2	4.0	11.8
3	3.8	9.8
4	9.0	9.8
5	6.1	8.1
6	8.8	9.8
7	5.7	12.3
8	5.0	3.4
9	7.7	4.0
10	2.8	2.1

Out of the 10 males, 7 were found to have an increased level of blood histamine. In three cases the rise was quite considerable, being greater than the experimental errors. In three cases a slight fall was observed.

A second series of experiments was carried out on 15 men and 7 women. They were asked to rest on a couch, during which time three blood samples were withdrawn. They were then asked to raise and lower their legs a number of times keeping them straight, during which time more samples were taken. Finally, during the following rest period, blood samples were again withdrawn. All blood samples were withdrawn from the

TABLE II
Results of blood histamine determinations in males, before, during, and after physical exertion.
(All samples taken at thirty second intervals).

Subject no.	Histamine 2HCl in $\gamma/100$ ml before physical exertion			Histamine 2HCl in $\gamma/100$ ml during physical exertion							Histamine 2HCl in $\gamma/100$ ml after physical exertion					
1	4.0	3.0		3.0	3.0	3.5	3.5	3.9	4.0	5.0	6.3	6.0	5.0	4.5		
5	6.1	6.4		5.1	7.7	6.7	12.7	7.7					6.5	7.0	6.4	7.5
6	3.6	3.8	3.8	4.5	4.8	5.0	5.6						4.8	4.3	5.0	
8	4.0	5.2		4.5	3.5	3.0	7.7	4.0	4.1	3.8			5.0	5.6		
10	3.0	4.0	4.0	5.4	3.6	4.8	4.0						3.6	3.0	3.0	
11	3.0	2.5	2.5	2.5	3.0	4.0	4.1						5.1	4.6	5.0	
12	5.2	3.6	3.6	5.0	6.4	3.0	4.0						3.0	5.1	4.6	5.0
13	5.5	5.5	4.0	6.2	6.6	6.4	3.2						3.4	3.0	3.5	
14	6.8	8.7	7.8	7.1	7.8	8.8	8.2						7.8	7.0	6.8	
15	6.0	7.8	8.0	8.3	9.9	10.2	11.6						10.0	10.3	9.4	
21	3.3	4.1	5.8	5.3	5.5								4.8	3.0		
22	4.3	4.5		3.9	4.1	4.5	4.2	4.1					3.6			
23	6.7	8.7	7.6	8.0	7.1	7.8	8.8	8.2					7.8	7.0	6.8	
24	5.0	5.0		3.0	4.1	5.1							4.3			
25	3.8	4.0	4.0	4.5	3.8	4.3	4.5						4.0	4.0	1.0	

TABLE III
Results of blood histamine determinations in females, before, during, and after physical exertion.
(All samples taken at thirty second intervals).

Subject no.	Histamine 2HCl in $\gamma/100$ ml before physical exertion		Histamine 2HCl in $\gamma/100$ ml during physical exertion				Histamine 2HCl in $\gamma/100$ ml after physical exertion			
2	4.8	5.0	4.6	4.5	4.4	6.0	4.2	4.8	5.2	4.6
3	5.1	4.0		4.0	5.0	4.7	5.1	4.6	4.5	4.1
4	7.5	7.5	8.8	5.1	7.7	7.8	8.2	6.5	4.7	12.5
7	15.3	11.3	12.5	10.2	8.8	8.9	9.7	10.6	5.0	7.5
9	15.0	15.0	20.4	10.5	12.5	15.0	12.5	10.2	10.6	8.8
16	6.4	5.0	10.3	5.0	3.1	4.1	3.0	3.0	6.3	5.3
17	7.2	5.0	7.8	5.1	20.4	12.6	5.2	5.2	4.1	6.0
										3.1
										3.0
										15.8
										10.2
										10.5

V. cubiti and all at intervals of 30 sec. The results of the histamine determinations on the males are given in Table II. The results on the females in Table III. From Table III it is apparent that 3 of the females showed results quite different from the others i.e. a high blood histamine before the exercise and a lower level during it. Statistical analysis therefore was only carried out on the results obtained from the males.

The histamine levels found before, during and after the exercise were studied in order to see if they remained constant or if they showed any systematic increase or decrease. A trend test (Kendall, 1948; Kaarsemaker en van Wijngaarden, 1952; Sillitto, 1947), based on rankcorrelations, was therefore applied to:

- A. Observations before physical exertion.
- B. The last observation before, together with the observations during physical exertion.
- C. The last observation before, together with the observations during the second restperiod.

The results are summarized in Table IV. (See for the indices used in the statistical analysis the schema.)

From the table it appears that the blood histamine rises during physical exertion and falls after it. There is also an indication that it rises just before the physical exertion started. The levels before, during and after the exercise were next-

Scheme of
the indices used in the statistical analysis

	Before physical exertion	During physical exertion	After physical exertion
Periods			
Indices			
Rank Nos	$x_1; x_2; \dots; x_{n-1}; x_n$	$y_1; y_2; \dots; y_{n-1}; y_n$	$z_1; z_2; \dots; z_n$
Differences	$x_2 - x_1$	$x_n - x_{n-1}$	$y_n - y_{n-1}$
Indices	a	b	c

TABLE IV

Trend test on the blood histamine values before (A), during (B), and after (C) physical exertion.

	$S_{\text{tot.}}$	σ	$\frac{S_{\text{tot.}}}{\sigma}$	Tail probability
A	+ 16	8.19	+ 1.95	0.05 +
B	+ 74	20.52	+ 3.61	< 0.001 +
C	— 24	11.28	— 2.13	0.03 —

TABLE V

Comparison of the blood histamine values before (A), during (B) and after (C) physical exertion, using Wilcoxon's Two Samples Test.

	$U - \mu$	σ	$\frac{U - \mu}{\sigma}$	Tail probability
B-A	— 25.5	11.96	— 2.13	0.03 +
C-B	20	11.73	1.73	0.08 —
C-A	1	8.81	0.11	0.91

compared by means of Wilcoxon's Two Sampe Test. The results of which are given in Table V.

This table shows that the blood histamine is higher during physical exertion than before it, that a slight difference exists between the levels during and after physical exertion and that there is no difference between the levels before and after the physical exertion.

A further analysis was then carried out and the following "differences" were computed:

- The difference between the second and first observations during the period before physical exertion. This difference being a measure of the rise at the start of the experiment.
- The difference between the last observation during the period before physical exertion and the last observation but one during that period. This difference being a measure of the rise directly before physical exertion.

- c. The difference between the first observation after the start of the period of physical exertion and the last one before it. This difference being a measure of the rise at the start of the period of physical exertion.

The hypothesis that the differences c-a and c-b respectively have the same probability distribution, was investigated by means of the Test of Symmetry (Hemelrijk, 1950). The results are given in Table VI.

TABLE VI
Test of symmetry to compare rises before and at start of physical exertion.

	n	r	u	v	Tail probability
c-a	15	8	1	6	0.02 —
c-b	14	7	1	4	> 0.10 —

From these results we may conclude that the rise at the beginning of the experiment is greater than the rise at the start of the period of physical exertion and that there is no reason to accept a difference between the values just before and just after the start of the period of physical exertion.

To investigate whether a demonstrable increase occurs both at the beginning of the experiment and at the start of the period of physical exertion, the test of symmetry (T_2) was applied to the differences a and c separately. (See Table VII.)

No increase in blood histamine was indicated in either case. We must therefore conclude that the increases before and

TABLE VII
Test of symmetry T_2 to investigate increase of blood histamine at the beginning of the experiment and at the start of the period of physical exertion.

	n	r	u	v	Tail probability
a	13	7	2	1	> 0.10 +
c	13	6	2	3	> 0.10 —

during the period of physical exertion, shown in Table IV were secured gradually.

Starting physical exertion did not appear to have any effect on the blood histamine. This perhaps may be explained by the hypothesis that histamine is set free by the contracting muscle. This histamine will only appear after a lapse of time, depending on the rate of circulation.

The influence of cessation of physical exercise on the blood histamine was next investigated. Table IV shows a fall in the blood histamine after physical exertion. Table V shows no difference between the levels before and after physical exertion. In the subsequent analysis the following "differences" were computed:

- d. The difference between the last observation during the period of physical exertion and the last observation but one during that period. This difference being a measure of the rise at the end of the period of physical exertion.
- e. The difference between the last observation during the period of physical exertion and the first observation in the second restperiod. This difference being a measure of the decrease after the cessation of physical exertion.

These values were tested by applying the test of symmetry T_2 to the differences d-e, while the same test was also applied to the differences e themselves. The results will be found in Table VIII.

TABLE VIII

Test of symmetry T_2 to compare the rise at the end of the period of physical exertion with the decrease immediately after cessation of physical exertion.

	n	r	u	v	Tail probability
d-e	14	7	1	2	0.04 —
e	15	8	2	1	0.05 —

It appears that the rise just before the end of the physical exertion period is less than the fall just after it. There is also

an indication that a decrease does occur on cessation of physical exertion. The question arises whether from this decrease we are justified in assuming that physical exertion does indeed cause an increase of blood histamine. It is possible that the increased level found at the start of the experiment and which cannot be attributed to physical exertion, gradually fell to below normal, in an effort to recover the equilibrium, and that the moment of decrease coincided with the end of the period of physical exertion. We therefore investigated whether the blood histamine was still raised during the latter part of the period of physical exertion, by applying the test of symmetry T_2 to d . A tailprobability >0.10 was found. Towards the end of the period of exertion therefore no increase could be demonstrated.

The rise in histamine during the physical exertion period was analysed further by comparing the histamine values of those people, on whom observations were made over a long period (long series), with the histamine values of those, on whom observations were made over a short period (short series). The total number of observations was counted here as the number of observations from the start of the experiment upto and including the end of the period of exertion. In the one group only 7 observations or less had been made on each person, in the other group, more than 7. In each we investigated whether the difference d (the difference between the last observation and the last observation but one during the physical exertion period) was positive or nega-

TABLE IX

Distinction between short and long series of observations from the beginning of the experiment upto and including the end of physical exertion period.

d	+	-	Total
long	1	5	6
short	6	3	9
Total	7	8	15

tive. The results of these computations are summarized in Table IX.

By means of a 2×2 table we checked the hypothesis that discernment between long and short observational series is not dependant on discernment between increase or decrease at the end of the exertion period. The theory was also checked against an alternative hypothesis that the probability of a decrease at the end of the exertion period is greater in long series than in short series. The one sided tailprobability turned out to be $= 0.08$. We thus found a slight indication that continuous physical exertion over a long period, results in a decrease of histamine before the exertion ceases.

In order to investigate the behaviour of the histamine independantly from physical exertion, a distinction was again made between the short and long series and also between the positive and negative differences between the 7th and 8th observations. (In the long series, this differences fell during the exertion period, in the short series it fell between the last observation during, and the first observation after the physical exertion period. In cases with less than 7 observations, this latter difference was also used.) Results will be found in Table X.

TABLE X

Distinction between short and long observational series and positive and negative differences between the 7th and 8th observations.

	+	-	Total
long	5	1	6
short	2	7	9

Again we find a one sided tailprobability of 0.035. In this case it indicates that when physical exertion was continued beyond the 7th observation, the blood histamine was more often increased than in those cases who stopped after or before 7th observation. Analysing further, but counting the length of the series from the beginning of the exertion period

instead of the beginning of the experiment and then again distinguishing between long and short series, the application of the 2×2 table resulted in one sided tailprobabilities of 0.02 and 0.76. The first result supports our previous conclusions that in long series the decrease occurs already before the end of the exertion period. The large tailprobability in the second result, might be due to the fact that by shifting the boundary between the long and short series, it has approximated the end of the physical exertion period so closely that in most cases a decrease had already occurred.

Finally in order to investigate the trend of the decrease after the period of physical exertion, the trend test was applied to the above observations but this time omitting the last observation during the exertion period. The results will be found in Table XI.

TABLE XI
*Trend test to investigate the decrease of histamine after physical exertion
omitting the last observation during the exertion period.*

$S_{\text{tot.}}$	σ	$\frac{S_{\text{tot.}}}{\sigma}$	Tail probability
— 3	7.60	0.39	0.70 —

The tailprobability was found to increase from 0.03 to 0.70 when omitting the last observation during the period of exertion (cf. Table IV). This indicates that the fall in histamine after physical exertion occurs for the greater part directly after the exertion has ceased.

As the increase in the tailprobability is partly caused by the decrease of the numbers of observations, the test of symmetry was also applied to the differences between the first and last observation after physical exertion. A tailprobability of > 0.10 (—) was found. No decrease was found therefore, to support our previous conclusion.

DISCUSSION

On reviewing the results of the statistical analysis, we find that the conclusions formed by different tests are all compatible. Whilst some tests, however, give a clear answer to a certain question, others give only an indication.

It appears, that the blood histamine rises before and during physical exertion. After the exertion has ceased, the histamine decreases, but in some cases this decrease occurs even earlier, probably in those cases with a long period of physical exertion. The decrease after the exertion period is probably a quick one. These last conclusions are in accordance with the opinion that the normal organism compensates increases of histamine rapidly (see no. I of this series).

The fall in histamine during a long period of exertion could be explained perhaps by presuming that histamine is set free from muscle, bound histamine changing into free, but that during longer periods of muscular exertion some depletion of the bound histamine occurs. Here we refer to the investigations of Strengers and Maas (this series no. IV) who found that in muscle of the guinea-pig the bound histamine is probably completely changed into free histamine during contractions in the agonal phase. Referring to the increased histamine during physical exertion we were unable to ascertain whether this gradual increase results from physical exertion, or is a continuation of the increase already observed before the exertion period. But referring to the investigations mentioned in the introduction (this series no. I) our opinion is, that physical exertion does have a direct influence on the histamine level. Most striking is the established increase during the period before physical exertion. We are bound to conclude that a psychic factor is the cause here of the "auslösend Moment" of histamine mobilisation. Relating to this we would like to draw attention to the irregular behaviour of the histamine level before physical exertion in three of the seven women under investigation. We refer also to Gooszen (this series no. VI) who ascertained that in a number of schizophrenic patients rapid changes in the histamine level occurred.

SUMMARY

The effect of physical exertion on blood histamine was investigated.

The blood histamine rises just before (due to a psychic factor) and during physical exertion. The blood histamine decreases after the exertion has ceased, and in some cases the decrease occurs even earlier. The decrease after the exertion period is probably a quick one.

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