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The Netherlands

STUDIES ON HISTAMINE
VI

A STUDY OF HISTAMINE-METABOLISM IN
SCHIZOPHRENIC PATIENTS¹

By

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INTRODUCTION

In 1930 Buscaino suggested that histamine might play a part in the pathogenesis of schizophrenia. This opinion was founded on the fact that in the brains of schizophrenics changes were found which resemble the changes in the brains of rabbits after a histamine intoxication. In a following article (1939) he conceived schizophrenia as an amine-intoxication (*tossicosi aminiche*) i.e.: besides a hyperhistaminemia, a higher content of other amines in blood might be found.

Jahn and Greving (1936) attribute several symptoms of schizophrenia (asthenia and the changing from yellow-into red bonemarrow, symptoms often to be found in this psychosis), to a histamine intoxication. Strengers and Gooszen (1946) found an increased histamine content in a number of schizophrenic patients, an observation confirmed later by Gooszen (1951).

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METHODS AND MATERIAL

I. *Static estimations of histamine*¹.

In this series, estimations of histamine in blood were made using Code's method, without modifications (1937). Three groups were investigated:

1. One group consisting of 51 women and 50 men, in which the diagnosis "Schizophrenia" was made after a long psychiatric observation.
2. One group consisting of 16 women and 26 men in which another psychiatric diagnosis was made, also after a long period of observation.
3. A control-group consisting of 38 "normal" women and 16 "normal" men.

II. *Dynamic estimations of histamine.*

In these observations the micro-modification of Code's method was used. (See this series II.)

Code's unmodified method was used in the histamine-estimation in a group consisting of 32 schizophrenic men and 22 schizophrenic women in which bloodsamples were withdrawn on different days at different intervals.

In 10 schizophrenic men, 8 men suffering from another psychosis and in 9 normal men bloodsamples were withdrawn daily (i.e. "day-observations"); in 6 schizophrenic men, 3 schizophrenic women, 7 men suffering from another psychosis and 12 normal men bloodsamples were withdrawn at one minute intervals (i.e. "minute-observations"). In 10 schizophrenic men and 1 schizophrenic woman bloodsamples were withdrawn continually during a certain period, with barely an interval between (i.e. "second-observations").

¹ For the meaning of the terms static and dynamic estimations see no. I of this series.

RESULTS

I. *Static estimations.*

The results of these observations are given in tables I, II and III. When investigating men suffering from a psychosis other than schizophrenia, it appeared that some of them when suffering from post-encephalitic disturbances had a high histamine content of the blood. The results of these determinations will be found in table IV. The blood histamine was estimated several times in this group.

TABLE I

Schizophrenic men		Schizophrenic women	
Number	Histamine in γ /100 ml.	Number	Histamine in γ /100 ml.
64	8.0	135	5.8
91	9.2	177	9.7
147	10.2	179	5.2
36	3.1	194	9.2
259	1.1	228	2.6
31	11.6	244	1.2
44	9.4	253	6.6
55	7.4	265	6.6
41	19.5	157	7.2
58	7.4	238	4.6
85	9.2	248	9.6
114	8.8	256	4.2
680	1.0	237	5.3
45	9.4	279	4.5
102	12.8	231	7.8
61	9.1	247	4.5
87	1.0	278	5.8
104	7.6	195	7.5
88	4.6	243	8.8
84	7.9	249	6.1
89	4.8	258	4.7
191	5.2	309	1
39	7.8	126	7.8
51	11.6	230	4.5
34	12.8	260	5.2
72	8	129	8.7
100	15.3	233	6.9
48	10.5	245	9.4

TABLE I (cont.)

Schizophrenic men		Schizophrenic women	
Number	Histamine in γ /100 ml.	Number	Histamine in γ /100 ml.
60	9.5	266	5.2
63	8.8	277	4.9
103	4.9	291	14.9
65	8.2	229	6.2
259	9.3	239	5.3
53	8.9	331	5.6
49	10.2	727	4.3
62	7.0	125	4.1
66	7.6	128	19.8
645	5	242	6.0
33	11.2	155	8.3
73	7.2	138	9.8
164	11.0	139	13.5
35	11.7	251	13.4
46	12.5	254	5.6
32	12	329	6.2
52	9.2	236	3.2
83	5.5	250	6.3
345	6.2	133	5.0
67	4.0	176	11.6
50	6.6	252	10.5
261	5	240	4.2
		679	12.7
Average:		Average:	
9.43 $\pm$ 4.26		7.22 $\pm$ 3.48	

TABLE II

Number	Histamine in γ /100 ml.	Diagnosis
<i>Women</i>		
183	7.9	Oligophrenia
122	10.7	Epilepsy
136	4.1	Involutional Psychosis
119	5.1	Epilepsy
154	5.6	Oligophrenia
181	7.1	Hysteria + oligophrenia
123	8	Cretinism with schizophrenic symptoms

TABLE II (cont.)

Number	Histamine in γ /100 ml.	Diagnosis
182	2.5	Dementia senilis
175	7.2	Dementia senilis
82	4.4	Cerebral tumour
124	4	Psychopathy
134	3.4	Hysteria
184	9.4	Dementia senilis
78	7.8	Mania
137	6.3	Idiocy
132	6.1	Oligophrenia
Average:		
5.89 $\pm$ 2.53		
<i>Men</i>		
296	7.1	Oligophrenia
42	6.6	Oligophrenia
76	6.1	Manic depressive psychosis
160	10	Manic depressive psychosis
101	7	Arteriosclerosis cerebri
150	11	Epilepsy
75	5.2	Dementia arteriosclerotica
109	2.6	Debilitas + psychopathy
107	2.7	Epilepsy
163	8.4	Psychopathy
188	5.1	Depression
575	1.5	Depression
873	3.2	Dementia arteriosclerotica
151	9	Epilepsy
169	2.2	Idiocy
339	8.1	General Paralysis
621	4.8	Hypochondria
185	3	Depression
110	8.2	Manic depressive psychosis
171	5.6	Encephalomyelitis
152	6.2	Epilepsy
57	4	Psychopathy
38	8.5	Manic depressive psychosis
74	6.1	Pick's disease
108	6	Compulsive neurosis
159	6.1	Affective psychosis
Average:		
5.69 $\pm$ 2.62		

TABLE III

Normal men		Normal women	
Number	Histamine in γ /100 ml.	Number	Histamine in γ /100 ml.
<i>Normals.</i>			
615	6.2	78	4.2
198	7.4	115	4
167	6.4	92	2.8
70	3.4	57	2.8
143	6.8	348	5
424	7.5	467	6.2
400	2.9	75	5.2
659	4.1	96	5.9
347	6.5	617	5.1
116	5.2	716	5.3
140	2.6	93	7.8
350	7.2	315	7.8
678	3.5	80	11.4
308	10.6	141	6.1
423	4.9	683	8.3
56	4.8	68	7.8
Average:		113	8.2
5.62 $\pm$ 2.10		144	7.3
		192	4
		572	3.5
		82	9.8
		349	6.4
		166	8.8
		69	3.8
		219	3.6
		485	7
		97	4.4
		94	5.3
		399	4.8
		79	2.2
		95	6.1
		111	9.2
		117	4.5
		71	6.3
		165	3.5
		112	8.4
		616	5.3
		202	8
		Average:	
		5.84 $\pm$ 2.17	

TABLE IV
Post-encephalitic disturbances.

Number	Histamine in γ /100 ml.				
184	9.3	9.5	12.2		
149	8.1	10			
54	13.5	5.4	7.9	10.2	
168	9.2	6.6	13.9	6.2	14.3
196	12.8	5.1			
153	11.8				
Average:					
9.5 $\pm$ 3.17 γ /100 ml.					

The averages and standard-deviations computed from the above observations will be found in table V.

TABLE V

	Men	Women
Normal subjects	5.62 $\pm$ 2.10 γ /100 ml	5.84 $\pm$ 2.17 γ /100 ml
Other psychosis	5.69 $\pm$ 2.62 γ /100 ml	5.89 $\pm$ 2.53 γ /100 ml
Post encephalitic disturbances	9.5 $\pm$ 3.17 γ /100 ml	
Schizophrenics	9.43 $\pm$ 4.26 γ /100 ml	7.22 $\pm$ 3.48 γ /100 ml

The blood histamine of these groups was compared statistically by means of Wilcoxon's "Two sample Test" (Wilcoxon 1945; Mann and Whitney 1947; Hemelrijk 1952), the results of which will be found in table A, Col. I.

From Column I of this table we can assume that in men suffering from schizophrenia and from post-encephalitic disturbances, factors are present which are causing an increase of the blood histamine. It is curious that in female schizophrenics similar factors were not observed to be present. It occurred to us that a form of schizophrenia might exist, which tends specifically to increase the histamine and that most of the men under investigation were suffering from this special form, whereas the females under investigation were suffering from some other form of schizophrenia.

TABLE A
Results of Wilcoxon's Two Sample Test on the bloodhistamine of normal and mentally disturbed people¹.

	Tailprobabilities			
	I. Single observations		II. Day observations	III. Minute observations
	Men	Women	Men	Men
Normal subjects—				
other psychosis	0.79 —	0.71 —	0.003 —	0.30 +
Normal subjects—				
schizophrenics	0.0001 —	0.11 —	0.004 —	0.11 —
Schizophrenics—				
other psychosis	0.0001 +	0.42 —	0.45 +	0.014 +
Normal subjects—				
post-encephalit. disturbances	0.02 —			

¹ A Tailprobability with a + sign indicates that the histamine content of the first mentioned group has a higher level than that of the second group. A negative sign indicates the opposite.

In order to study this hypothesis further, in table VI the schizophrenics were divided into the usual psychiatric subgroups and in each subgroup the number of patients with a histamine content of more than 9 γ /100 ml. has been mentioned.

TABLE VI

		Men		Women	
		Number	Increased	Number	Increased
Schizophrenics	Paranoids ...	17	13	6	3
	Hebephrenics	16	6		
	Katatronics ...	17	7	45	10
Total		50	26	51	13

The results in this table were analysed statistically by means of Pearsons χ^2 -test. This analysis indicates that there might be some factors tending to increase the histamine level in men

suffering from dementia paranoides ($K = 0.043$), whereas in the small number of female subjects suffering from dementia paranoides, such indications were not to be found ($K = 0.15$).

Because the majority of the schizophrenic men under investigation were belonging to the paranoid group and only a few of the females, it is possible that the difference in the blood histamine is due to this fact.

II. *Dynamic histamine estimations.*

The results of these observations are to be found in tables VII, VIII, IX and X.

TABLE VII
Schizophrenic men.

Number	Histamine in $\gamma/100$ ml.						
91	9.2	11.4	5.4				
147	10.2	11.2	6.8				
36	31	12.5	15.5	30	17.2	6.5	16.2
295	11	19	5.6	9.5			
31	11.6	9.1					
41	19.5	21.8	8.3	11.2	25.5		
58	7.4	6					
85	9.2	10.9					
680	10	2.8					
45	9.4	7					
61	9.1	10					
87	10	4.7					
89	4.8	5.1					
39	7.8	4.9	6				
51	11.6	12.4	7.3	4.4	3.3		
34	12.8	7.1	9				
60	9.5	5.5	7.4				
63	8.8	7					
103	4.9	3.7					
259	9.3	8.5	10	6.8			
53	8.9	5.2	6				
49	10.2	10.6					
33	11.2	4					

TABLE VII (cont.)

Number	Histamine in γ /100 ml.						
35	11.7	17.4	8.1	6.6	3.7		
46	12.5	7.7	14	15	8.7		
32	12	7.8	5.5				
52	9.2	3.1	9	8.3	10	12	
83	5.5	4.3					
345	6.2	6.1					
67	4	3.9	4	5.8			
50	6.6	7.9	2.5	1.3	3		
261	5	5.3					
<i>Schizophrenic women.</i>							
177	9.7	3.4	5.8	7.2	4.7	4.3	6.0
179	5.2	3.0	6.0				
194	9.2	2.9	15.1				
244	12	9.5	13				
265	6.6	3.9					
157	7.2	4.8					
248	9.6	5.9					
237	5.3	3.7					
247	4.5	1.4	6	5.4			
278	5.8	7.8					
249	6.1	7.8					
126	7.8	8.0	5.2				
233	6.9	4.6					
245	9.4	2.8					
242	6.0	2.3					
155	8.3	7.9					
251	13.4	9.0					
254	5.6	4.7	7.3				
250	6.3	6.7	8.3	5.7			
176	11.6	7.9					
252	10.5	3.2	9				
679	12.7	7.3					

A. Investigations on the level of the blood histamine.

Before attempting to form a conclusion about the movements of histamine in the blood, we compared the level of the different groups by means of Wilcoxon's Two Sample Test.

TABLE VIII
Bloodsamples drawn with 1 day-intervals.
 Normal men.

Subject	1	2	3	4	5	6	7	8	Average
N 1	5.1	4	4	4	5	3.6	5		4.4 ± 0.57
N 2	4.5	4.5	6.5	4.5	6.4				5.3 ± 0.96
N 3	3	3.3	4	5.2	5.2	4.5	3		4.0 ± 0.89
N 4	6.4	4.3	4.5	3	6.1				4.9 ± 1.23
N 5	2.8	2.8	2.1	5.3	3.1	3	6		2.6 ± 1.36
N 6	3	3.1	4.6	3					3.4 ± 0.68
N 7	4.1	4	4.8	3.2	5				4.2 ± 0.64
N 8	3.3	6.3			3	3.6			4.1 ± 1.32
N 9		4.3		3.2	5	4.2	5		4.3 ± 0.67

Men suffering from other psychosis.

AP 1	4.5	6.9	5.6	6.8	5.5	5.1	3.6	5	5.4 ± 1.03
AP 2	6.9	5.6	6.8	5.8	6.1	6.8	12.8	5.4	7.0 ± 2.25
AP 3	6.9	6.9	6.9	6.3	5	5	3.8	4	5.6 ± 1.12
AP 4	3.3	3.3	3.3	4.4	5		5	4.7	4.1 ± 0.73
AP 5	5	5.1	4.8	4.6	4.5	5.1	5		4.9 ± 0.22
AP 6	7.7	5	4.3	7.6	6.3	5.1	7.8		6.3 ± 1.37
AP 7	5	7.7	4.3	7.5	6.4	6	9.5		6.8 ± 1.64
AP 8	5.3	6.8	7.5	6.2	7.5	5.7	7.6		6.7 ± 0.87

Schizophrenic men.

52	7.5	10	7.5	6.3	7	7.7	6.5	7.6	7.5 ± 1.08
50	3.3	9	3.3	3.6	5.2	5.2	3.2	3	4.5 ± 1.88
46	3.3	3.6	6.3	6.9	8.7	7.3	7.5	7.1	6.35 ± 1.37
41	5.8	9.6	6.8	7.8	9.9	11	10	6.8	8.7 ± 1.79
36	17.5	15.9	11.3	17.3	21.4	21.2	18.2	27	18.7 ± 4.31
100	7.4	6.6	4.5	4.9	4.8	7.6	5.3		5.9 ± 1.20
31	6.3	6.3	6	4.5	9	5	8		6.4 ± 1.47
35	7.7	6.4	5.3	7.7	6.4	5.7			6.5 ± 0.97
32	4.5	7.1	4	4.3	5.5	5.7	5.4		5.2 ± 0.98
114	7.4	6.4	6.3	5.6	6.6	7.7	7.5		6.8 ± 0.71

TABLE IX
Sampling at 1-minute intervals.
 Schizophrenic men.

Number	Histamine in $\gamma/100$ ml.										Average	Dispersion in % of average
36	19.4	17.5	17.5	19.1	17.5	18.6	19.5	22.4	18.2	18.0	18.8 $\pm$ 2.3	12
41	5.6	3.3	5.5	6.0	6.0	5.6	5.8				5.4 $\pm$ 0.30	5
100	5.6	5.5	5.5	6.0	6.6	6.5	7.0	5.6	5.5	5.3	5.9 $\pm$ 0.6	15
31	5.8	6.8	6.0	4.8	6.6	5.3	5.9	5.9			5.9 $\pm$ 0.64	11
35	7.8	4.8	5.0	5.9	6.5	7.9	5.3	6.1	5.9		6.1 $\pm$ 1.1	18
83	5.3	4.0	4.6	4.9	4.8	5.5	5.5	5.6	5.5		5.1 $\pm$ 0.54	11

Schizophrenic women.

177	14.9	17.1	22.1	8.0	9.3	8.6	7.6				12.5 $\pm$ 5.7	45
250	5.5	5.0	5.5								5.3 $\pm$ 0.3	6
251	4.9	5.1	5.8	3.0	3.0	4.0	2.5	2.8			3.9 $\pm$ 1.2	30

Norman men.

M 203	4.1	4.6	4.1	5.7	5.2	4.1	4.6	5.0	3.6		4.6 $\pm$ 0.7	15
M 214	3.6	4.6	4.6	6.1	6.2	5.2	5.2				5.1 $\pm$ 0.9	18
M 221	6.8	5.6	5.5								6.0 $\pm$ 0.7	12

Patients with other psychosis.

M 224	5.7	5.6	6.2	5.8	5.8	5.6	5.4				5.7 ± 0.2	4
M 231	3.0	2.8	2.5	3.0	2.0	3.1	3.0		2.5		2.9 ± 0.4	14
M 241	4.0	3.5	3.0	3.5	3.1	3.5	3.0		3.1		3.3 ± 0.4	8
M 249	2.6	3.0	4.0	3.0	4.0	4.0	4.0		6.3	6.8	4.2 ± 1.4	30
M 259	7.3	5.0	6.8	6.5	6.8	6.8	6.8		6.5		6.5 ± 0.7	11
M 268			3.6	4.6	4.3	4.0	4.3				4.2 ± 0.8	19
M 291	6.1	6.1	6.2	6.1	6.2	5.4	4.8		4.6	5.1	5.5 ± 0.7	13
M 301	4.6	6.1	5.6	5.7	7.0	7.0	6.0		6.6	7.1	6.2 ± 0.8	13
M 211	5.6	6.1	5.6	6.0	6.0	5.6	5.0		5.0	5.5	5.6 ± 0.4	14

42	5.3	5.3	5.3	5.0	5.0	5.8	5.5	5.3			5.3 ± 0.3	6
352	2.8	2.8	3.8	1.4	1.4	1.3	1.5	2.6			2.2 ± 0.9	40
1081	3.8	4.6		3.5	3.2	3.0	3.0	3.5			3.5 ± 0.5	14
1073	5.8	5.8	5.8	5.6	5.3	4.3	2.8	3.5			4.9 ± 1.2	25
1088	5.1	3.4	3.1	3.3	2.5	2.5	2.8	2.6			3.2 ± 0.9	29
1097	2.5	2.8	3.5	3.5	3.9	4.6	3.8	3.8			3.5 ± 0.6	17
1105	3.7	3.8	3.8		3.3	3.5	3.3	3.3			3.5 ± 0.2	6

Histamine determinations in 18 samples from one quantity of blood. 4.3 5.0 3.8 4.3 4.0 4.3 5.0 3.0 4.3 3.5 3.5 4.7
 5.0 4.0 4.5 4.3 4.5 4.2; Average: 4.2 ± 0.6.

TABLE X
Bloodsampling without intervals.
 Schizophrenic men.

Number	Histamine in γ 100 ml.										Average	Dispersion in % of average
	1	2	3	4	5	6	7	8	9	10		
187	7.8	7.8	7.0	5.1	4.1	3.6	5.2	5.7	6.4		5.8 $\pm$ 1.5	26
36	30.2	20.3	15.2	21.0	10.5	20.9	20.0	20.0	21.0	20.3	19.9 $\pm$ 4.9	24
1184	5.0	5.4	7.7	6.3	6.3	6.2	5.4	5.3			6.0 $\pm$ 0.85	14
52	6.4	6.9	7.5	6.4	6.4	5.7	6.8	6.7	5.2	7.0	6.5 $\pm$ 0.65	10
50	3.0	2.5	2.2	1.6	2.0	1.5	0.5	1.0	1.5	1.5	1.7 $\pm$ 0.64	38
41	7.7	9.7	8.0	9.9	8.3	7.5	8.6	9.2	9.1	8.8	8.7 $\pm$ 0.92	13
114	6.5	5.3	5.4	5.7	5.9	7.2	5.3	5.2	6.0	6.9	5.9 $\pm$ 0.73	12
46	6.0	6.4	6.4	6.4	6.2	7.5	6.3	6.6	6.3	5.8	6.4 $\pm$ 0.5	8
259	12.5	6.4	6.8	7.2	5.1	4.8	8.8	7.0	7.0	6.6	7.2 $\pm$ 1.2	17
51	7.1	3.2	7.0	6.3	6.5	7.0					6.2 $\pm$ 1.5	24
Schizophrenic woman.												
329	9.5	10.0	18.2	10.0	10.3	9.9	12.9	10.0	8.7	8.7	10.8 $\pm$ 2.8	26

a. Day observations.

From table VIII the averages of the observations on different days on each subject, were computed.

These averages were compared. The tailprobabilities are to be found in table A, Column II.

b. Minute observations.

From table IX we compared the data of the first columns.

The tailprobabilities are to be found in table A, column III. We did not compare the averages of a series of observations on one subject, as a difference between these averages could have been caused by different changes of the blood histamine in the several subgroups.

Concerning the histamine level in schizophrenics we may conclude from the day-observations that in these patients there are influences tending to increase the level, this is in agreement with the results of the single observations (see table A, Column I). The minute observations give only a slight indication in this direction.

The observations on the sufferers from other psychoses contradict each other in some instances.

In the day observations there is an indication that there are in those patients influences tending to increase the histamine-content of the blood (tailprobability 0.003 —).

In the single observations (table A) such influences could not be demonstrated in our material (tailprobability 0.79 —).

The minute observations even show a slight indication that the histamine level in sufferers from other psychoses is lower than in normal subjects (tailprobability 0.30 +).

One has to conclude therefore that the sufferers from other psychoses do not form a homogenous group and that only in some patients are there influences which tend to increase the blood histamine.

B. Investigations on the movement of the blood histamine.

In order to obtain some information about the changes of the blood histamine, we shall study the data in table VII.

A statistical analysis of the data is not possible owing to the unequal length of the series and the irregular time-intervals. But it will be seen from the table that hyperhistaminaemia in schizophrenics is not a permanent phenomenon at all.

For the subjects in the tables VIII, IX and X the averages and the dispersions have been calculated. These data are to be found in the last columns of the tables.

In fig. I the dispersions and the averages have been plotted against each other.

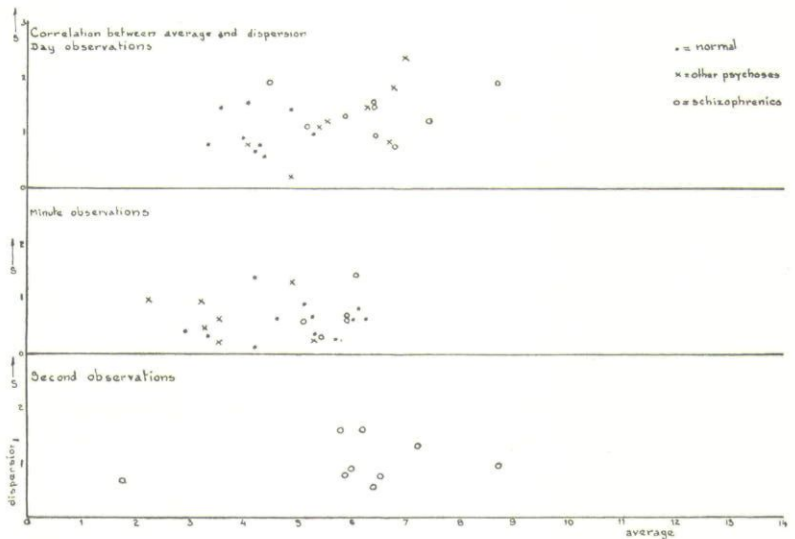


Fig. 1.

The graph shows that in the day observations the dispersions and averages increase somewhat proportionately, a relationship such as this could mean that the blood histamine level in patients having a raised blood histamine is liable to fluctuate more readily than in those patients having a low blood histamine.

The minute and "second" series do not show this relationship between the dispersions and averages. The disper-

sions are also on the whole lower than those of the day observations.

So we have no reason to presume that the blood histamine fluctuates in the minute and in the day observations.

A "classical" statistical analysis by means of e.g. the analysis of variance was not possible owing to the accuracy of the observations not being constant.

Though on studying the statistical analysis of the data obtained from schizophrenics no indications could be found which confirmed the hypothesis that the blood histamine is liable to sudden and rapid changes, we must point out that some of our patients did show such changes. (See table IX no. 177 and table X nos. 36, 259 and 329.)

Statistically these observations have no significance, but they might help us to understand some of the problems connected with the metabolism of histamine.

DISCUSSION

When considering what the increased blood histamine level indicates, we will make some hypotheses.

- A. Blood histamine in some patients shows fluctuations which closely resemble those shown by allergic patients (Rose 1941). We could therefore assume that a similar mechanism occurs in both cases.

Certain symptoms found in allergics and attributed to histamine were not however found in our schizophrenic patients.

This observation agrees with the fact that in schizophrenic patients allergic reactions rarely occur (Coca, Waller and Thommen 1931; McInnis 1937; Blaisdell 1939; Levitt 1943). A possible explanation as to why such allergic reactions do not occur, is, that schizophrenia itself is a specific allergic reaction and thus inhibits the appearance of other allergic reactions.

- B. The same fact of schizophrenics rarely showing allergic reactions might give us another clue.

It is possible that schizophrenics are less sensitive to histamine, in the same way as they are less sensitive to certain other drugs. Hoskins (1946) mentions a defective reactivity to stimulating agents in schizophrenia.

This decreased sensitivity could be attributed to a disturbance of the mechanism whereby histamine is bound to the tissues. Such a disturbance might cause an increase of the blood histamine.

It might be possible also that some psychotic symptoms are the result of this disturbance.

We are tempted here to refer to the fact that after administering antihistaminics an increase of the histamine level sometimes occurs (Nelemans 1952) and also that a number of authors have pointed out that after the administration of these drugs psychotic symptoms have occurred, closely resembling schizophrenia (Sternberg 1947; Weil 1947; Huber 1948; Yapalater 1950).

- C. We must remember the theory that histamine might be an alarming agent (Fischer 1952). That histamine can stimulate the hypophysis-adrenal system is shown by many authors (Noble and Collip 1949; Sayers and Sayers 1949; Ellinger 1948; Gray and Munson 1951). But this only establishes the fact that histamine is able to act as a "stressor". It has as yet not been proved that histamine is a necessary link in the series of phenomena leading to secretion of ACTH (Selye 1950).

Harris et al. (1952) investigated the possibility of histamine being a link between hypothalamus and hypophysis, they found large amounts of histamine in the eminentia mediana and fluctuating amounts of histamine in the anterior and posterior lobes of the hypophysis. As a result of their findings they hypothesise:

"In the median eminence histamine may be related to nerve terminals from where histamine dependent on the state of activity is carried to the anterior lobe in quantities anywhere between minimal and maximal". The effect of histamine would be specific and comparable with the ef-

fect of histamine on the cells of the gastric mucosa. Histamine would be accepted in this sense as the "final mediator stimulating the adenohypophysis".

Considering the facts put forward f.i. by Gjessing (1938) and Ewald (1939) that functional changes in the brain-stem are found in schizophrenia, and by Morgan (1940) that morphological changes in the hypothalamic centres in early stages of the disease occur, then one can relate the hyperhistaminaemia with the above mentioned findings.

The hyperhistaminaemia which we observed in post-encephalitic disturbances also indicate a similar relationship, as the same sort of morphological changes were found in these disturbances. If we are going to accept hyperhistaminaemia as a symptom of a disturbance in the middle brain, we may only speculate on the type and the genesis of this disturbance.

It is possible that certain parts of the hypothalamus are overexcited secondarily as a result of the psychic disturbances or primarily as a result of functional disturbances.

Related to this I should like to remark on the curious fluctuating histamine curves, which were often observed in the "second observations". It is possible that histamine was liberated locally during this experiment, in which case the phenomenon would only have local importance, but it is also possible that an abnormal alarm reaction had occurred as a result of a functional disturbance in the hypothalamus.

- D. Finally we should like to refer to the observation of Fleetwood and Diethelm (1951) who found a cholinergic substance in the blood of persons in states of resentment. They could not define this substance, but according to their statement it was definitely not acetylcholine. We would like therefore to suggest that it might be histamine or a histamine-like substance.

SUMMARY

1. In schizophrenics influencing factors were demonstrated which tend to increase the blood histamine.
2. There was an indication that these influencing factors were especially present in some subgroups of schizophrenia.
3. Hyperhistaminemia in one patient was not a constant phenomenon.
4. There was a slight indication that patients having a raised histamine level, showed a tendency for the level to fluctuate during the day.
5. In patients with post-encephalitic disturbances influences tending to increase the level of the blood histamine were also demonstrated.
6. In some patients suffering from other psychoses such influences could be demonstrated as well.
7. The relationship between hyperhistaminemia and psychosis was discussed.

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