THE EFFECT OF HISTAMINE ON BODY TEMPERATURE IN NORMAL AND HISTAMINE PRE-TREATED GUINEA PIGS, AND THE MECHANISM OF THE CHANGES.

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With 7 Figures and 2 Tables in the text.

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The first but incomplete record of the effect of a single injection of histamine (H) on the temperature of the normal guinea pig originates from PFEIFFER (1911), who states that very small doses cause a rise, small doses a small decrease, larger doses a larger decrease in body temperature. Most unfortunately the report contains only the bare conclusions, details of the number of animals used, the site of the injection and accuracy of dose are all lacking. KARÁDY and BENTSÁTH (1936) relate that when guinea pigs are "desensitized" with H after an anaphylactic antigen injection and given i. p. the provoking antigen re-injections, only a small drop in the rectal temperature is shown, whereas the normal controls suffered a drop of 2.5° C.

(In a lecture it was also stated by JANCSÓ (1945) that histamine desensitization decreases the fall in temperature observed after H injection.)

We reported in previous papers (BEZNÁK, GÁSPÁR-RÁDY, and KOVÁCH, 1947 and KOVÁCH, BEZNÁK, GÁSPÁR-RÁDY, 1947) that very small doses (5—75 μg/100 g. bw.) of H given sc, for 21 to 90 days alter the characteristic curve for histamine, causing it to show a marked positive skewness. That means that part of the animals do not succumb to the 100% H dose but only to a dose which is 5—6 times as great as

the standard deviation of the average (50%) lethal dose. We have also shown that in these animals which became resistant during the H shock the gaseous exchange in the lungs is considerably better than in the non-resistant ones. In such animals the O_2 content of the arterial blood is 70% of the normal value. Contrary to this, when an untreated animal dies in H shock the O_2 practically disappears from its arterial blood.

The physiological mechanism of the temperature response of the guinea pig to H may consist either in the central disturbance of the temperature-regulating centre, or it may be of peripheric origin.

The earlier observers were in favour of the central origin: FRIEDBERGER and MITA (1911) (who first reported that in anaphylactic shock small doses of the specific antigen cause an increase, large doses a fall in the body temperature.) CITRON and LESCHKE (1913) CHAHOVITCH (1929). These, however, were mere suggestions without experimental proof.

Experimental evidence supporting the possibility of the central origin was first brought forward by HASHIMOTO (1915). This author has shown that the anaphylactic fever does not develop if the function of the thermo-regulating centre is impaired by operation. Injections of very small doses of the specific antigen (and only of that) into the region of the thermo-regulating centre caused fever, larger ones a drop in the body temperature. This accords well with the observations of FRIEDBERGER and MITA (see above). It is possible that the H liberated locally in the brain disturbs the function of the temperature-regulating centre and provokes the body temperature changes.

INAMI (1941), after intra-carotidal injection of H solutions, found severe changes in the cortex and brain stem. These are probably caused by the vasoconstriction which develops on H injection.

Such alterations, being of more lasting nature, may be regarded as causes of the changes seen in the temperature response to H of the HT guinea pigs.

As regards the peripheral mechanism, the first experiments came from LOENING (1911) who showed the O_2 uptake, the ventilation of the lungs, to be increased in small anaphylactic shock, and considerably decreased in strong. DOMAGK (1925) suggested that the cause of the decrease in the body temperature during anaphylactic shock is a diminution of the oxidation processes consequential to histological changes in the walls of the alveoli hindering the O_2 diffusion.

In our previous paper we showed that the O_2 content of the arterial blood during a shock caused by a normally lethal dose of H is much greater in the HT animals than in the non-treated ones. It was therefore thought that the drop in body temperature might be due to the diminished O_2 content of the blood, and since in the HT animal this is less than in the normal ones, the temperature loss is smaller.

SENATOR (1868) was apparently the first to show that small reduction of the respiratory movement by compression of the thorax,

or trachea, injection of oil into it, etc., increases the body temperature, while large reduction decreases it. The decrease in body temperature was attributed to the diminution of the oxidative processes.

We sought to provide experimental evidence to solve the question of peripheral or central origin of the effect of H on body temperature and the changes caused in it by the HT by recording the changes in body temperature in suffocation caused by strangulation when the trachea was tied, and while the O_2 content of the air breathed artificially was varied.

The paper of Miss HELGE COLLDAHL (1943) — from which we were cut off owing to the war — came to our notice only when we had finished our experiments. She has shown in very thorough experiments that in histamine asthma when the O_2 consumption drops, in spite of the increase in the frequency of the respiratory movements, rectal and skin temperature sink. In slight asthma caused by diluted homoserum of a sensitized guinea pig. when both frequency of respiration and O_2 consumption increase (the latter to a small degree) rectal and skin temperature increase greatly.

METHODS.

The animals described in our previous papers were used. 94 normal males (Groups I. and II.) for sc and 95 for ip injections (G. III.) and 38 normal sc-injected females (G. V.) served as controls. These, together 77 males (Gs. VI. VII. VIII.) and 40 females (G. IX.), received HT. The total number of temperature measurements of HT males was 284 and of the females 120. The H pre-treatment consisted in twice daily s. c. injections of H, starting with 5 μg/100 g. b. w. and rising by 10 μg/day until the 5th day, from then on, till the 21st day inclusive a daily dose of 55 μg/100 g. b. w. was maintained. These experiments were made in XII 1941 and VIII 1943. The group numbers given later in this paper refer to the groups of guinea pigs in our former paper (BEZNÁK, GÁSPÁR—RÁDY, KOVÁCH, l. c.) Details of the care of the animals, as well as other ways of HT, were given in the earlier paper. Besides these animals 18 more male guinea pigs were used between January 5th and February 2nd, 1947, for the suffocation and reduced O_2 experiments.

The changes in the rectal temperature after the test H injection given subcutaneously, or intraperitoneally, were observed both in untreated normal and in HT animals. It was measured by a mercury thermometer with 0.1° C divisions. The thermometer was inserted into the emptied rectum deep enough for the entire mercury container to be inside the bowel. The reading was taken 1 minute after the mercury column had stabilized. Readings were taken immediately before and 4, 16, 20, 40, 64 and 88 minutes after the test injection of H.

The rectal temperatures thus obtained were plotted against time in each individual dose and case on millimeter paper.

In the series of experiments on the mechanism of the effect of HT on the H reaction, the temperatures of the arterial and venous blood, of the rectum, of the skin, of the abdomen, and of the chest were measured with thermo-needles. The arterial blood temperature was measured in the left ventricle, into which the needle was lead through the left carotid, the venous blood in the right half of the heart through the external jugular vein. A thermo--needle was inserted about 2 cms into the emptied rectum. The skin needles were tied into a fold of dipilated skin. The reference needle stood in a large vessel containing boiling ether. The current was lead into a torsion galvanometer. 1.0° C change was projected from 50 cm distance to give a deviation of 25 mms. The thermocouple was made of copperconstantan wire of 0.2 mm ϕ.

EXPERIMENTAL RESULTS.

a. *Changes in the rectal temperature in normal and HT guinea pigs.*

1. Male animals.

a. Subcutaneous injections.

Comparison of the rectal temperature curves revealed that every feature of this curve varies greatly from animal to animal. The maximum value of the fall, its time, the time elapsing before recovery begins, as well as the time necessary for the complete recovery of the normal temperature vary greatly and irregularly. Following H injection three types of temperature changes were observed: 1.) a monophasic gradual fall. 2.) a biphasic response; a small elevation during the first 20 minutes, followed by a fall to below the normal level. 3.) inverted biphasic response; a fall at the beginning, followed by an increase above the normal temperature. Table I shows the distribution of the three types. The arithmetical mean of all the initial rises, irrespective of the dose, is 0.31°C, the standard deviation of the individual case is 0.16°. The maximum value of the initial elevation is variable, as is also its time: the maximum being measured at any time between the 4th and 20th minute; nevertheless small doses below 0.088 mg/100 g bw tend to cause greater and slower rises.

Our results do not confirm the conclusions of PFEIFFER (l. c.), that small doses cause a rise, medium and larger doses exclusively a fall. The occurrence of the biphasic reaction in the different doses is quite irregular and independent of the dose.

As regards the influence of the HT, in spite of the great variations one effect seems to be certain. The inverted reactions appear after HT far more frequently than in the normal animals. In 77 normal injected males only the monophasic and biphasic reactions were ob-

served but no inverted reaction. After these and the other animals had received HT, of the 284 cases 22% inverted reactions took place. The effect is exactly the same in the case of the females. In 38 females no inverted reaction was observed. In 96 HT female animals, however, 49% was observed.

TABLE I.

The frequency of different types of temperature reactions after sc histamine injections.

Doses of H mg/100g	Biphasic				Monophasic				Inverse			
	des. H. T.		norm.		des. H. T.		norm.		des. H. T.		norm.	
	No.	%		%	No.	%		%	No.	%		%
Males												
0.06	0/24	0			1/24	4			23/24	96		
0.08	0/24	0			23/24	96			1/24	4		
0.10	12/47	26			26/47	55			9/47	19		
0.20	0/39	0			35/39	90			4/39	10		
0.25	0/17	0			15/17	88			2/17	22		
0.30	7/13	54			2/13	15			4/13	85		
0.01			3/10	30			7/10	70			0/10	0
0.08			1/8	13			7/8	87			0/8	0
0.126			2/8	25			6/8	75			0/8	0
0.22			4/16	25			12/16	75			0/16	0
0.27			2/15	13			13/15	87			0/15	0
0.31			1/4	25			3/4	75			0/4	0
0.36			7/14	50			7/14	50			0/14	0
0.407			3/12	25			9/12	75			0/12	0
0.01	0/17	0			7/17	41			10/17	59		
0.04	3/16	19			10/16	63			3/16	18		
0.06	2/16	12			11/16	69			3/16	19		
0.143	0/16	0			14/16	88			2/16	12		
0.64	3/15	20			11/15	73			1/15	7		
0.32	0/16	0			15/16	94			1/16	6		
Females												
0.025	2/8	25			1/8	12			5/8	63		
0.045	0/10	0			6/10	60			4/10	40		
0.055	2/14	14			9/14	64			3/14	22		
0.055	0/8	0			5/8	63			3/8	37		
0.055	0/8	0			5/8	63			3/8	37		
0.055	0/7	0			3/7	43			4/7	57		
0.055	0/8	0			2/8	25			6/8	75		
0.055	0/8	0			0/8	0			8/8	100		
0.055	0/8	0			2/8	25			6/8	75		
0.105	6/10	60			4/10	40			0/10	0		
0.20	2/10	20			8/10	80			0/10	0		
0.265	0/11	0			11/11	100			0/11	0		
0.370	1/10	10			4/10	40			5/10	50		
0.005			4/8	50			4/8	50			0/8	0
0.025			4/10	40			6/10	60			0/10	0
0.115			0/10	0			10/10	100			0/10	0
0.20			2/10	20			8/10	80			0/10	0

The great individual variations made it impossible to arrive at a reliable conclusion from a single comparison of any one feature of the temperature curve (such as the maximum of the temperature fall, or duration of the period required for temperature recovery, etc.) in the normal and in the desensitized animals.

In order to obtain — in spite of this great irregularity — sets of numerical results suitable for statistical treatment, we proceeded as follows: In each graphic curve a vertical was erected at the point of the last maximum fall of temperature; then the surface of the figure thus obtained was determined with a planimeter. This surface therefore represents the maximum temperature loss during the time elapsing between the injection and the beginning of the recovery of the temperature. This method is disadvantageous in that the elevation of the rectal temperature seen in certain cases does not manifest itself, because it is generally over-compensated by the subsequent greater loss.

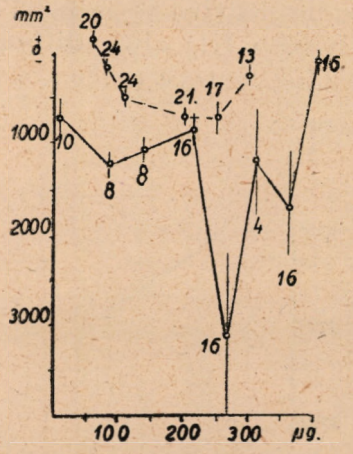

Figure 1. The maximum temperature loss in male guinea pigs, after sc injections of different doses of H. Normal o—o, HT o - - - o animals. X axis: µgH/100 g bw. Y axis: temperature loss in mm². The numbers at each point indicate the number of animals in this group. The small vertical lines at the points show the values of twice the standard deviation of the averages.

The arithmetical means of these surfaces and their standard deviations in each sub-division of the two groups were calculated. In Figure 1 these results are plotted against the doses of H.

It is clear from the curve of the total temperature loss that in the normal animal this is no simple function of the H dose. At the lowest ranges between 20—220 µg/100 g. b. w., although the dose increases as 1:22, the averages of the temperature losses remain the same. When,

however, the dose is increased from 220 μg to 270 μg, the fall increases from 1000 mm^2 to 3000 mm^2. Apparently the largest doses cause smaller temperature losses, but this is due to the circumstance that some of the animals died before the maximum of the temperature fall could have been reached.

Figure 1 also shows the rectal temperature changes in the HT animals recorded similarly to those of the normal ones. Only the results obtained with the animals of Group VII are shown.

A comparison of the two sets of results yields the conclusion that the averages of the maximum rectal temperature losses in the HT male animals on all the tested doses is smaller than those in the normal ones. The distance between the two means is greater than twice the values of their standard deviations.

β. Intraperitoneal injections.

Figure 2. shows the maximum losses of rectal temperature in normal male animals (Group III) after different doses of H given intraperitoneally. In striking contrast to the s. c. injections (after which

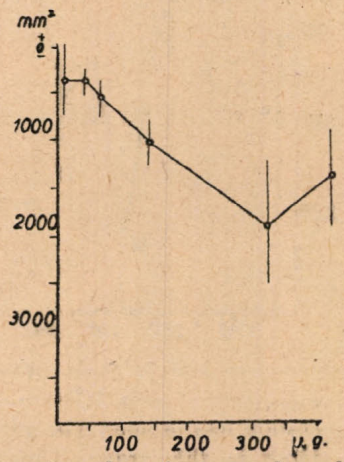

Figure 2. Maximum temperature loss in normal male guinea pigs after i. p. injections of different doses of H. Details as in Figure 1.

the temperature losses did not increase with the increase of the dose, after i. p. injections on the range of tested doses they were the positive function of the dose, and the standard deviation of the individual cases was considerably smaller.

The effect of the HT on the temperature response of i. p. injected H was studied in 24 male animals after the short but energetic HT

(Group VII). The animals which survived the HT received half the 100% i. p. lethal dose, and the rectal temperatures themselves were recorded. 12 normal male animals (Group IV) were similarly observed. In each group and each time the rectal temperatures themselves were averaged, their standard deviation calculated. Figure 3 shows the results thus obtained. Since the distance between the averages is greater than twice the value of their $\mu_{\bar{x}}$, it is clear that in the HT animals after the same dose of i. p. injection the maximum decrease of rectal temperature is smaller, and that the rate of decrease is also slower.

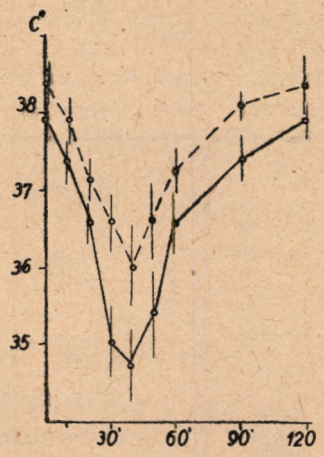

Figure 3. Variations in rectal temperature of male guinea pigs after i p injections of the 50% LD of H. Normal o—o, HT o - - - o animals.

2. Female animals.

Figure 4. shows the maximum total loss of the rectal temperature in the normal female group (Group V) and HT animals (Group IX). The normal female animals in the dose range between 5—200 μg/100 g, compared with the males, do not show the same irregularity in the

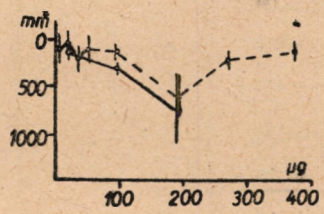

Figure 4. Maximum temperature loss in female guinea pigs after sc injections of different doses of H. Normal o—o, HT o - - - o animals. Other details as in Figure 1.

relationship between dose and temperature loss. It appears here that the temperature loss is a positive function of the dose. In HT animals as indicated by the curve of the averages there is a tendency to react with a smaller temperature loss, but the difference between the normal and HT animals is smaller than in the males. As the standard deviation of the means is greater in the females than in the males, the two curves of the averages fall within the value of one μ_x. In the females, therefore, the tendency to give a smaller reaction after HT is present but its statistical certainty is rather small.

TABLE II.

The rectal temperature response of ♂ guinea pigs (groups IX) After 55 μg/100 g. H. s. c., in the normal state (col. a) and after Ht (col. b.)

No of the animals	a 1st day	b on the 11th day of HT
29.	—320	+20
67.	+105	—50
35.	—520	—20
98.	— 20	+10
56.	—350	—100
99.	—135	+170
38.	—140	+35
21.	+ 35	— 5
97.	—440	—45
77.	—200	—40
33.	—420	—250
9.	— 65	—20
54.	—120	+55
10.	+115	+385
	—2730	—530
	+ 255	+675
	—2475	+145

a.	b.
A = —176.8	A = + 10.4
No = 14	No = 14
ϑ = 169.9	ϑ = 87.6
μ = 212.9	μ = 109.8
μx = 56.9	μx = 29.4

Sign. diff. $k = 3.0$

In Group IX the maximum total temperature loss after the s. c. injection of 55μg/100 g. H was determined in the intact animals and

again after 10 days of HT in the same animals. The results, shown in Table II indicate clearly that after 11 days of HT the maximum total temperature change had altered decisively. In the intact animal there was a loss averaging —176.8 mm², in the HT animals there was an increase in temperature averaging +10.4 mm². The standard deviation of the individual cases decreased from 213 to 110 and the factor K = 3. It is therefore certain that the difference is not due to sampling but is caused by the HT. In our 12 out of 14 animals the temperature loss became considerably smaller after the HT than it had been while the animal was intact.

The conclusion that HT decreases the maximum rectal temperature in the female guinea pig is therefore warranted.

The observations of KARÁDY and BENTSÁTH (l c.) are in conformity with this. They found that the fall of the rectal temperature during the anaphylactic shock is smaller in animals surviving a HT between the anaphylactic sensitizing and provoking injections.

b. *The body temperature changes in H shock and in suffocation.*

In these experiments we used 11 male, normal guinea pigs of 358 g bw. for the H shock. The animals, in a cotton-wool covering, were tied supine to a small operating table. In local novocaine anaesthesia the trachea was canulated. A thermo-needle was led through the left carotid into the left ventricle, another one into the right ventricle through the external jugular vein. Then the thermo-needles on the chest and abdominal skin were fixed, and finally a last one was introduced into the rectum. Then for 50 minutes the temperatures were recorded. The H (410 μg/100 g bw. H base) was injected s. c. in 0.1 ml/100 g bw. of saline. The recording of the temperature changes was continued until the death of the animal. In Figure 5 the normal values are the ones found just before the injection of the H. These are lower than the original normal values. During the 50 minutes the temperature values all sink slowly. The rate of this drop can be seen in Figure 6.

In the suffocation experiments 7 male animals were used, average b. w. 354 gs. All the procedures, with two exceptions, were identical with the H shock guinea pigs. Not thermoneedle was introduced into the right heart, and the chest temperature was not recorded.

The results (averages of H shock and of suffocating animals) are shown in Figure 5. It may be seen in this Figure that previous to the H injection the temperatures measured at the same time decrease

in the following order: right heart 38°C → rectum —0.1°C. → left heart —0.3°C. → chest skin —1.0°C → abdominal skin —1.2°C. Each difference measured from the temperature of the right heart. During H shock all the 4 values diminish, the asymptotic minima being reached at about the 20th minute. A very obvious change is seen in the rectal temperature, which drops far below that of the arterial blood. The order now is as follows: right heart 37.2°C (loss compared with normal —22%), → left heart —0.2°C (—19%), → rectum —3.5°C (—29%), → chest skin —1.0°C (—20%), → abdominal skin —1.5°C (—30%). Compared with the left (!) heart and with the normal value in all the peripheral surfaces the temperature decreases, consequently their arterial blood supply is diminished. (Atten-

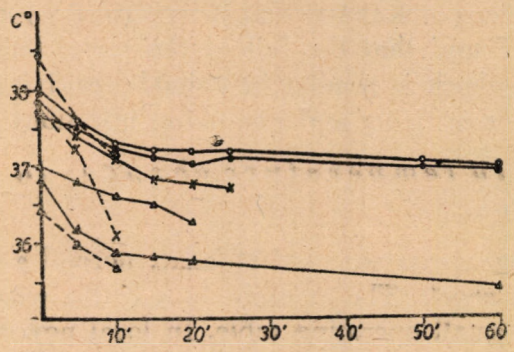

Figure 5. Temperature changes in the

	H. shock	Suffocated guinea pigs
right heart	○—○	·····
left „	●—●	····· ○---○
chest skin	▷—▷	·····
abdominal skin	▶—▶	····· ▶---▶
rectum	×—×	····· ×---×

tion should be drawn at this point to the circumstance that the temperature of the rectum, normally going parallel with the right heart, begins to run independently.) The greatest diminution as compared to the normal value is seen in the rectum and in the abdominal skin -30%. The arterial blood supply is therefore the worst in these regions. The great diminution of the temperature of the right heart proves that heat production cannot keep pace with heat loss, however diminished the latter is. Regarding the temperature of the right and

left hearts, it is to be noted that the difference between the two halves disappears during the later stages of the H asthma. This is obviously caused by the broncho-constriction, and possibly vaso-constriction, of the pulmonary blood vessels, thus abolishing the cooling effect of the respiration.

In the suffocating animal the same changes are seen as in H asthma. (See Figure 5). Normally the order of the temperature values are the same as in the other group: left heart 38.4°C, → rectum -0.5°C, → abdominal skin -1.9°C. During suffocation at the final, tenth minute: left heart 37.2°C (loss compared with normal -21%), → rectal temperature -2.3°C (-29%), → abdominal skin -1.5°C (-22%). When the O_2 supply is cut off by strangulating the trachea, exactly the same changes take place in the different body temperatures measured by us as was seen when the O_2 supply was cut off by asthma. Here again the arterial blood supply of the rectum decreases, so does that of the abdominal skin, and the heat production cannot make up the heat loss.

c. Body temperature changes on inspiration of air containing different proportions of O_2.

In another series of experiments we tried to show the dependence of the body temperature on the O_2 supply by allowing the guinea pigs to breathe an air mixture of varying O_2 content and registering the body temperature. The experimental procedures were identical with those described in Chapter 1b.

It will be seen in Figure 6. that the order of temperature differences and their magnitude is the same in this group as in the two previous ones. The left heart and abdominal skin temperatures decrease from the 20th minute, that of the rectum from the beginning. This general decrease goes on till the end of the experiment and it is this decrease which is enhanced or slowed down by alternately giving less or more O_2. In this general descent of the temperature it is interesting to note that after the first diminished O_2 supply the temperature of the rectum rapidly reaches the level of the skin and then sinks parallel with it. When, therefore, the blood supply of the rectum has once deteriorated owing to reduced O_2 content, it is not easily restored.

From the 40th minute till the 100th the animals breathed only 8% O_2. Heart and rectal temperature diminishes rapidly, skin temperature slowly. The rapid decrease in temperature of the arterial blood indicates

that the heat production is impaired, in spite of the fact that the heat loss through the skin is less than was seen in the H-poisoned animal, because here the diminution of the blood supply does not take place.

From the 100th minute on the animals received 40% O_2. The temperature loss of the heart blood becomes very slow indeed, but the loss in the rectal temperature continues at a rate only slightly diminished. The drop in the skin temperature goes on somewhat more quickly than during the 8% O_2 breathing period. Essentially the same results were obtained on repeating the 8% and 40% periods.

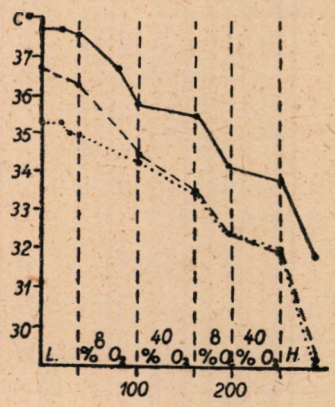

Figure 6. The effect of the O_2 content of the air breathed on the temperature of the left heart ○—○, rectum ●– –●, abdominal skin ●···●, in normal guinea pigs.

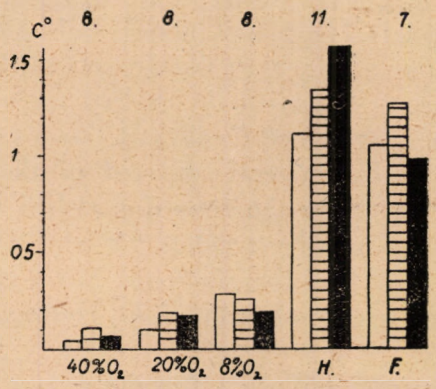

Figure 7. The gradients (°C/10 min.) of the temperature loss in normal guinea pigs while breathing air of varying O_2 content. Heart ▭, rectum ▤, abdominal skin ▬. Top figures are numbers of cases.

The animals were killed by H injection (410 μg/100 g) given at the 200th minute. During the lethal H asthma all the three temperatures decreased rapidly and parallelly. Comparing this curve with the one in Figure 5, it is seen that in the former case, when the normal animals are poisoned with H, the heart blood temperature sinks only from 38°C to about 37°C, whereas in the animals in which this temperature had already sunk in consequence of exposure and breathing air of low O_2 content, the drop is from 34°C to 32°C.

In Figure 7 the gradient of temperature losses (°C/10 min.) are shown. In H asthma and in suffocation the velocity of the temperature-loss is about the same. It is, however, less in the skin of the suffocating animal, indicating that besides the diminished O_2 content, histamine causes a specific vaso-constriction in the skin of the guinea pig. When the animal breathes O_2 of varying pressure, the rate of temperature loss becomes inversely proportional to the O_2 content.

From all this we feel the conclusion to be warranted that the diminution of rectal temperature in H poisoning is due to the diminished O_2 supply, which in its turn has a double effect: it depresses heat production and decreases the blood supply to the rectum and the skin. Since the rectal temperature varies directly with the O_2 content of the blood and since, as we have shown in our earlier paper (KOVÁCH, BEZNÁK, GÁSPÁR-RÁDY, l. c.) this — during H shock — is higher in the HT animals than in the normal ones, it seems justifiable to conclude that the smaller drop in rectal temperature in such animals on H injection is due, at least to a large degree, to the better oxygenation of the blood in the lungs.

DISCUSSION.

As to whether the changes in the body temperature of the normal guinea pig on H injection are caused by the disturbance of the thermo-regulatory centre or by events taking place peripherally in the body, our experiments definitely support the latter possibility. During H shock the O_2 content of the arterial blood diminishes practically to nothing. The normal decrease in body temperature of the motionless animal is slowed down on breathing air rich in O_2. When the air contains little O_2 this drop in temperature is enhanced. In suffocation the body temperature decreases both in extent and in rapidity almost identically as in H asthma. Finally, in the H shock of the HT animals, in which it has been proved that the O_2 content of the blood is higher than in the non-treated ones, the drop in temperature is smaller.

Miss COLLDAHL came by experiments similar to ours, independently and before us, to this same conclusion. This author also dealt with the temperature rise seen in light anaphylactic shock: she found that in slight asthma, caused either by anaphylactic shock or by very small doses of H both respiratory movements and O_2 uptake increase. We have found that respiration of air containing 40% O_2 increases the body temperature relatively. These results are capable of explaining the temperature rises in the biphasic and inverse reactions.

We reported that in the HT animals inverse reaction of the rectal temperature on H injection is very frequent. We have also shown that the broncho-constriction is less after HT. It is therefore possible, indeed likely, that the inverse reaction is due to the initial broncho-constriction, not strong enough, being over-compensated by an increased lung ventilation. The O_2 content of the blood is thus raised, leading to an elevation in body temperature.

Though Miss COLLDAHL's and our experiments offer good evidence in support of the mechanism of the peripheric origin of the changes in body temperature seen in H shock, it remains interesting why the heat-regulatory centre is not able to adjust the heat loss to the diminished heat production. There are several possibilities to explain this. The simplest is that the loss in heat production is too great to be made good by such an adjustment. Another possibility is that the heat loss cannot be prevented because the blood vessels of the skin have lost their responsivity, due either to direct poisoning by the H or by the diminution of the O_2. It is also possible that the heat loss can not be prevented because the function of the centre is impaired, either by the direct effect of H or by the lack of O_2. All these possibilities are highly unlikely, however, because, as we have shown, the heat loss both in H shock and in suffocation is smaller through the skin, since the circulation in it is much reduced. The only justifiable conclusion is that the changes in body temperature are due to the diminution of heat production consequential to drop in the O_2 content of the blood.

The possibility of a combination of central and peripheric mechanism still exists. May it not be that, owing to being paralysed, the heat centre cannot increase the heat production by other means than oxidation?

Miss COLLDAHL has produced evidence that lack of O_2 and excess of CO_2 cause damage to the cozymase systems. This is especially marked in the liver, but absent in the kidney.

It follows that until further evidence to the contrary is brought forward, we must accept the hypothesis of the peripheral origin of the temperature changes in normal, and their alterations in HT. animals as the only one capable of explaining the phenomena observed.

The flat contradiction between this conclusion and HASHIMOTO's (l. c.) needs some new experiments for elucidation.

SUMMARY.

1.) Recording of the rectal temperature in normal guinea pigs after s. c. and i. p. H injections showed that two kinds of reactions exist: a monophasic gradual fall, and a biphasic reaction, i. e., an initial rise followed by a fall.

2.) In animals treated with increasing small doses of H for some weeks a third type of reaction, the inverse, is very frequently observed. In HT animals the total maximum temperature loss is smaller than in the non-treated ones.

3.) Recording of the temperature in the right and left half of the heart, in the rectum, on the skin of the chest and of the abdomen during H shock showed that there is a decrease in the heat production, besides this a great slowing of the blood-flow through the rectum and a smaller one through the skin. The same results are obtained if the animal is strangulated, except that the fall in the skin temperature is somewhat less.

4.) The temperature of the heart, rectum and skin slowly decreases in the guinea pig tied supine in a cotton-wool covering. This slow drop is enhanced if the air breathed contains less O_2, decreases if it contains more.

5.) It is suggested, in agreement with Miss COLLDAHL, that the temperature changes in H shock are to a large extent due to changes in the O_2 supply to the blood in the lungs. Small broncho-constriction, with consequential compensatory increase of the ventilation, increases O_2 supply and body temperature; a large one, through diminution of the O_2 supply, decreases body temperature. The possibility of the involvement of the heat-regulating centre can almost certainly be excluded.

6.) Since it was shown in our previous paper that in HT animals under the influence of the same H dose better oxygenation takes place than in the normal, it is suggested that this in its turn is the cause of the smaller diminution of the rectal temperature. The inverse

reaction seen in these animals is suggested to be due to this decreased broncho-constriction combined with a secondary compensatory hyperventilation.

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