THE TEMPERATURE OF ACUTELY INFLAMED PERIPHERAL TISSUE.

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INTRODUCTION.

The rise in the local temperature observed in peripheral areas of the body at the site of acute inflammation is generally attributed to the increased afflux of blood in these parts. This assertion is supported by the finding that in general the temperature of the inflamed peripheral tissue is not greater than the temperature of the internal parts and by the clinical observation that the temperature of the inflamed center is in proportion to the degree of the inflammatory hyperemia present. The fact is therefore excluded, and has recently been denied (1) that the inflamed center should have in reality a temperature higher than that of a corresponding area. The heat of the part has been attributed to the hyperemia.

The argument is of considerable theoretic importance and was discussed during the whole of the past century. The older treatises devoted many pages to the point, which appears now to have been solved as has already been stated. The subject has, however, scarcely received mention in the text-books, which as a rule paraphrase the statement of Cohnheim (2) made in his manual.

HISTORICAL.

The last known experiments on this point date from the year 1885. At that time Maximow demonstrated by a series of accurate determinations carried out with thermoelectric batteries that in no part of the inflammatory process is the temperature higher than that of the heart's blood or the blood of the larger vessels. Maximow thus confirmed what had been proved previously by Jacobson (3), Bernard (4), Schneider (5), and Huppert (6); namely, that if the inflamed center has a temperature higher than that of the corresponding area, it cannot be asserted that its temperature is above that of the central blood.

The older literature has a treatise by Weber which appealed to Liebermeister (7) who was conservative on this point, which Cohnheim (8) overlooked. Cohnheim merely stated that others more competent than himself had contradicted his statements.

Weber stated his experimental findings as follows: Measuring with thermoelectric batteries the temperature of the vein and that of the artery of the inflamed area, it is found that the venous blood is warmer than either the arterial blood from the same part or the venous blood from corresponding parts not inflamed.

The oblivion into which the controversy has fallen, particularly Weber's treatise, is demonstrated by the report of Galeotti (9), wherein Hunter, Weber, and Simon are mentioned as being of the same opinion, while in fact Hunter opposed the ideas of Weber and Simon.

The Problem.

I have failed to find that Weber's experiment was technically in error. It would seem to be a simple matter to establish whether the blood by its passage through an inflamed part gives off or absorbs heat. On the other hand, an impartial analysis of the problem leaves us uncertain as to the demonstrative value of the experiments mentioned in solving the point.

Considering the mass of tissue in the peripheral area in comparison with the volume of blood which circulates there, and bearing in mind also that the specific heat of blood is much like that of water, one is inclined to ask whether the blood is not a disturbing element, inasmuch as it conceals the real temperature of the inflamed center, giving to the part its own temperature in proportion to the blood volume which is renewed continually.

With regard to the liver, for instance, which has a much larger mass than a small inflamed area has, Claude Bernard proved that the circulating blood carries off heat from the parenchyma. Cavazzani measured an increase of over half a degree in the parenchyma when the hepatic artery and the portal vein were blocked. In cases of parotitis the classic experiments of Ludwig and Spiess (10) confirmed by Bayliss and Hell and Burton-Opitz (11) demonstrate an almost analogous fact: marked local heating and a temperature elevated above that of the arterial blood, with the venous blood warmer than the arterial blood.

It appears, therefore, that the experiment which I call Maximow's, although others have done it before him, cannot be considered exhaustive. On the other hand, our increased knowledge regarding the histology of the inflammatory process—and we know that there is an intense local metabolism—favors the idea that such metabolism may be accompanied by an increased release of heat, especially in view of the fact that most of the biologic reactions, as we know them, are strikingly disintegrating and isothermal in their effects. Virchow shared this view when he asserted the histogenetic origin and nature of the inflammatory process. Courmont (12) stated that to exclude all local production of heat contradicted accepted ideas.

Among the numerous authors who believe that the temperature of the inflamed area depends upon the increased afflux of blood, none has reflected on the physiological postulate that in general the tissues warm the blood and that it is not the blood which gives heat to the tissues. Claude Bernard (13) in discussing this point presented the problem as to whether the flow of blood to a part might not be considered the result of local calorification.

EXPERIMENTAL.

It seemed inadvisable to repeat Weber's experiment, because of the difficulties encountered in carrying it out accurately. It is necessary to be constantly near the animal under experimentation and also to make manipulations in the immediate vicinity of the thermoelectric batteries, which may readily lead to errors. Anyone who has had experience with this delicate instrument will acknowledge the difficulty of avoiding radiations of heat. Moreover, according to Weber's technique, it is necessary to introduce one electrode into the lumen of an artery and the other into that of an important vein. The possibility is always present that by this method the afflux and efflux of blood in the part may be altered in an indeterminable, irregular manner.

In a problem of this nature, with opinions so greatly at variance and so strongly impressed in the minds of pathologists, the services of expert technicians are required in order to eliminate criticism. In my experiments the difficulty has in the main been surmounted by regarding the blood not as the criterion, but rather as a disturbing element.

In the experiments presented here the attempt was made to compare the temperature of the inflamed tissue with that of the corresponding healthy area, at the moment when the circulation of blood was definitely arrested by the death of the animal or temporarily by ischemia. The temporary arrest of the circulation for thermostatic purposes is not a new device. Kussmaul and Tenner (14) tried it as far back as 1857 in the neuroparalytic hyperemia produced by incision of the sympathetic nerve in the area not inflamed. Cavazzani, as already stated, more recently used the same measure to establish the thermogenetic power of the liver.

The experience of other observers served as a guide in the choice of an indicator. Thermoelectric batteries, if connected to a sensitive measuring apparatus, are preferable to mercury thermometers which are slow, bulky, and require direct reading.[1]

Technique.

The electromotor force developed on the contact surface between two metals placed at different temperatures is indicated below. The electromotor force developed by the contact of two metals is equal to the difference between the values registered against them. For instance, the electromotor force developed between patent nickel and constantan is 8, between bismuth and antimony 100.

Electromotor Force Developed between Two Metals.

Bismuth	0
Constantan	30
Patent nickel	38
Nickel	51
Platinum rhodium	61
Platinum iridium	61
Platinum	66
Mercury	67
Gold, silver	74
Iron	83
Antimony	100

[1] I am indebted to Professor V. Grandis, Director of the Department of Physiology of the University of Genoa, for his courtesy in teaching me the technique and for his supervision of some of the experiments.

As in our experiments we were obliged to use thin wires, we could not employ bismuth-antimony electrodes, and on the other hand, not finding a sufficient quantity of constantan of the required diameter, Professor Grandis prepared from a disc of patent nickel (German nickeline) a long, thin wire which he soldered to a soft, iron wire as shown in the following diagram:

A and *B* were flattened and reduced to a lanceolated form. The highest possible potential was 45 microvolts for each degree of difference between 0 and 100. For measuring the developed potential we employed a Thompson galvanometer, to which the battery was attached directly after the internal resistance in respect to the inserted system had been regulated. After a number of attempts we succeeded in getting exact readings; *i.e.*, to 0.1 of a degree. This was done by adjusting the scale of the galvanometer. By means of this sensitive scale, the deviations did not require correction on direct reading, because the variations of temperature in the limits of observation were proportional to the angle of deviation of the galvanometer. This finding is corroborated by a number of observers.

To avoid abnormal radiations of heat which might lead to errors, the animal under experimentation was kept in a large, isolated room especially designed for calorimetric researches; here the temperature was practically constant. The readings of the valuations of potentiality were made in an adjoining room.

An inflammatory lesion was created by breaking, under ether anesthesia, the femur of a guinea pig without, however, injuring the skin. Inflamed areas appeared not earlier than 4 days later, or later than 12 days.

For the experiment one of the electrodes was introduced into the inflamed area of the guinea pig, while the other was inserted in a corresponding area on the other side. In general the introduction of the electrodes was not followed by considerable hemorrhage; when, however, hemorrhage did occur, the experiment was discontinued.

The system having been properly installed, the guinea pig was killed quickly by puncturing the medulla, or temporary ischemia of

the posterior part of the aorta was produced by compressing the thoracic portion. In the latter case, every precaution was taken to see that the heat from the compressing hand did not radiate to the electrodes. A bolometer was also adjusted to the animal, in order to record the reduction in temperature of the erythrocytes.

The protocols which follow do not give the absolute temperatures of the two parts, but rather the differences in temperature between the areas, as read directly from the galvanometer.

Experiment 1.—3 days after fracture of the left femur. At 2.40 p.m. one electrode was introduced into the inflamed area and the other into the corresponding area of the other limb.

Time.	Difference in temperature between inflamed and healthy areas.	Time.	Difference in temperature between inflamed and healthy areas.
p.m.	°C.	*p.m.*	°C.
2.48	0.8	4.45	3.0
2.49	0.9	4.55	3.0
2.55	0.8	5.10	2.6
3.05	0.7	6.15	1.9
3.18	0.9	6.30	1.7
(Killed by puncturing the medulla.)		6.40	1.7
3.21	1.3	6.50	1.6
3.24	0.9	7.05	1.4
3.30	1.0	7.15	1.4
3.37	1.9	7.30	1.3
3.45	2.3	9.35	0.9
3.53	2.7	10.05	0.6
4.00	3.0	10.35	0.5
4.10	3.1	10.55	0.5
4.18	3.2	11.00	0.5
4.40	3.1	After 10.00 a.m. the following day.	0.2

In the foregoing experiment the difference of the initial temperature of the inflamed area and the healthy area is seen to vacillate between 0.7° and 0.9°C. When the circulation of the blood is arrested because of the death of the guinea pig, the difference in temperature increases considerably. After 17 minutes it was 1.9°C. and after an hour 3.2°. This progressive derangement in the equilibrium of the post-mortem temperature of the two parts under the same conditions

may be considered as being due to slow cooling or to the persistence of a longer isothermal activity in the warmer area.

The hypothesis of retardation in cooling which first presents itself might be admitted as true if it were possible to demonstrate greater persistence of activity in the inflamed area, but this hypothesis cannot be readily advanced in this special case where the volumes and surfaces of the parts were small and equal in sensitivity. On the other hand, the hypothesis cannot be excluded, inasmuch as the surrounding temperature was low and the temperature of the body as a whole did not control the rate of cooling.

A reasonable hypothesis appears to be the assumption that the accentuation and maintenance of the differences of temperature stand in relation to differences of isothermal, biochemical activity of the two parts. In the inflamed area we have actively proliferating tissues. It is probable that the local life of the inflamed tissues continues for some time after circulatory and respiratory death has occurred, and that there is an emission of heat which differs according to the initial activities of the affected tissues. The difference in temperature remains high for 1½ hours and then diminishes gradually, but it was still 0.5°C. after 8 hours.

But the fact which is particularly interesting for this work is the variation of the initial temperature and the increase of the difference between corresponding areas which takes place in a few minutes. This increase tends to confirm the principle first laid down; *i.e.*, that as the circulation of a volume of liquid at uniform temperature ceases, the local temperature becomes apparent. This in the case under consideration would be different; *i.e.*, higher in the inflamed zone than in the corresponding healthy area.

The following experiments elucidate these points.

Experiment 2.—Fracture of the left femur, 4 days before. Surrounding temperature 39.5°C. At 10.25 a.m. one electrode was introduced into the inflamed area and the other into the corresponding area of the other side. A bolometer was applied to the thorax.

Time.	Difference in temperature between inflamed and healthy areas.	Temperature of guinea pig.	Time.	Difference in temperature between inflamed and healthy areas.	Temperature of guinea pig.
a.m.	°C.	°C.	*p. m.*	°C.	°C.
10.35	1.2	39.0	12.10	3.2	27.8
10.40	1.2	39.0	12.17	3.0	
10.45	1.2	39.0	12.30	3.0	
10.47	(Killed.)		12.35	2.7	
10.49	2.2		1.30	2.0	
10.50	2.6	39.0	1.55	1.9	
10.51	2.6		2.25	1.5	
10.53	2.8	38.6	2.55	1.4	
10.55	3.0	38.6	3.15	1.2	
10.57	3.0	38.0	3.40	1.0	
11.00	3.1		4.20	0.9	
11.13	3.4	37.0	5.07	0.9	
11.32	3.4	33.4	5.50	0.8	
11.44	3.2		11.35	0.3	15.5
11.51	3.2				13.2

The experiment was conducted under the same conditions as those of Experiment 1.

During life the difference in temperature between the inflamed and the healthy zones was 1.2°C.; immediately after the death of the animal at 10.47 a.m. the difference increased. At 10.50 a.m., *i.e.* approximately 2 minutes after death, when the temperature of the bolometer was not sensibly altered, the local difference rose to 2.6°; *i.e.*, 1.4° more than during life. At 10.55 a.m., 5 minutes later, when the temperature of the body had fallen 0.4°, the difference between the two areas was 3°.

In this case we must exclude, I think, the idea that the causative factor is slower cooling, because the phenomenon manifests itself with a rapidity incompatible with that hypothesis. The temperature of the inflamed area was considerably higher than was apparent. The fact is demonstrated immediately when the disturbing influence of the blood which tends to carry off heat is no longer present.

The course of Experiment 2 corresponds approximately to that of the preceding experiment. The highest degree of difference was attained in a shorter period (after an hour, 3.4°C.), and it is noteworthy that even after 13 hours the difference was 0.3°.

In the preceding experiment we introduced a new element, the determination of the body temperature. It was shown that after a few minutes the general temperature had decreased 0.4°, while the difference between the local centers had increased 3°. This led me to consider it advisable to reduce the eventual causes of error consequent to external radiation. Experiment 3 was carried out in a room having a high and constant temperature (36° C.).

Experiment 3.—The guinea pig was placed in the calorimetric room which was kept at a temperature of 36°C. by means of electric lamps. A pair of batteries was connected with the fractured area and another pair with the corresponding healthy femur. The animal was provided with a bolometer.

Time.	Difference in temperature between inflamed and healthy areas.	Temperature of guinea pig.	Room temperature.
p.m.	°C.	°C.	°C.
2.20	3.1	39.4	36.0
2.25	3.1		36.0
2.27	3.1	39.4	36.0
	(Killed by puncturing the medulla.)		
2.31	4.6	39.1	36.0
2.40	4.6	39.0	36.0
2.47	3.6	39.0	36.0
2.50	3.0		
2.55	2.6		
3.03	2.1	39.0	35.8

In this manner, as the difference in the temperature of the guinea pig and that of the room was at a minimum, the curve of postmortem cooling should have had a slow course. From 2.28 p.m., when the animal was killed, until 2.30 p.m. the general temperature diminished 0.3°, and the difference between the local temperature of the inflamed area and the healthy zone increased 1.5°. A new fact is here brought out; *i.e.*, the markedly lessened permanence of the postmortem increase of thermal inequality between the two parts, the inflamed and the healthy areas.

This experiment does not give sufficient data to explain the fact,

but it should be noted that the initial difference in temperature of the inflamed center and the corresponding area was high, even before the guinea pig was killed, being about double the average. It is probable that the high room temperature which diminished the possibility of external radiation and kept the part warm, prevented the cooling effect of the blood. On the other hand, it is not excluded that the surrounding temperature itself may have caused some modification of the biochemical activity of the center by intensifying its activity.

To confirm and control the results that have been cited, other experiments were carried out. These consisted of experiments in which the circulation was interrupted permanently by the death of the animal and temporarily by local ischemia produced by compressing the abdominal aorta. In the latter case, it is possible to repeat the experiment a number of times and to modify it in details, thus by degrees neutralizing the errors of observation.

Experiment 4.—Fracture of the femur. The animal was placed in position at 1.30 p.m. Compression of the abdominal aorta at 3.10 p.m. and 3.21 p.m.

Time.	Difference in temperature between inflamed and healthy areas.	Time.	Difference in temperature between inflamed and healthy areas.
p.m.	°C.	*p.m.*	°C.
1.30	1.5	3.12	3.0
2.10	1.4	3.20	1.5
2.40	1.7		(Ischemia for 2 min.)
3.00	2.0	3.23	4.0
3.10	2.0	3.40	1.7
	(Ischemia for 2 min.)	3.50	1.5

The experiment could not be more convincing. Immediately following the ischemia the difference in temperature of the two parts became accentuated, but it returned to the initial value or somewhat below it as soon as the normal circulation of blood was restored. The experiment cannot, however, be considered perfect, because the determination of the differences was not made during the ischemia, but immediately afterwards.

Experiment 5.—Fracture of the femur 5 days before. Conditions the same as in other experiments.

Time.	Difference in temperature between inflamed and healthy areas.	Time.	Difference in temperature between inflamed and healthy areas.
a. m.	°C.	*p. m.*	°C.
10.10	1.8	2.20	1.2
10.30	1.7		(Beginning of ischemia.)
10.50	1.8	2.21	1.5
	(Beginning of ischemia.)	2.22	2.1
11.08	2.9	2.23	2.5
11.10	3.1	2.25	3.5
11.12	3.4		(Cessation of ischemia.)
	(Cessation of ischemia.)	2.27	1.2
11.14	1.9	2.45	1.2
11.20	1.8		

This experiment is a repetition of the preceding one, but marks an improvement in that readings were made during the ischemia; in addition, the second trial did not immediately follow the first, but was separated from it by an interval of 3 hours. An interesting point for further study is the fact that the initial difference in temperature of the inflamed and healthy areas amounts to 1.8°, while after 4 hours it is 1.2°. During the whole period when the thermoelectric battery remained in place, it probably initiated local injuries, and it is possible that these might have been the cause of an increased production of local heat.

The experiments reported above are supported and controlled by other analogous trials which are not given here because of the limitation of space. The experiments establish the fact that the difference in temperature of the inflamed and the corresponding healthy area increases rapidly and in a notable degree when the afflux of blood ceases because of a temporary stopping of the circulation or by a definite anemia. In view of these experiments made in an environment with a high temperature and taking into account for comparison the temperature of the body in relation to the time, we have excluded the possibility that the phenomenon depends upon retarded radiation of heat.

Because of the rapidity with which the phenomenon manifests itself, it does not seem probable that it could be related to a sudden

and more intense biochemical function of the inflamed cells stimulated to activity by an asphyxial condition.

It is consequently not the blood which heats the inflamed area, but, on the other hand, this area is kept by the active local hyperemia at a lower temperature than it would otherwise have. The finding which is apparently paradoxical is in fact true physiologically. In addition to the results cited by Cavazzani in his experiments on the liver, in muscle during contraction the venous blood is warmer than the arterial blood. The same is true of the parotid gland. Burton-Opitz (11) and Lefèvre speak of an equalizing temperature action of the circulation. In inflammation as well as in muscular contraction we have a notable local chemical activity. The circulation of the blood in both cases exercises its normal function, with the tendency of equalizing the temperature of the various areas.

The problem might be considered complete at this stage, but at the suggestion of Professor Grandis a more detailed study of the process was made, in order to establish if possible under what special conditions calorification develops and is influenced.

In the experiments made at a high room temperature it had been shown that the disturbance in thermal equilibrium of the corresponding areas was less permanent than at a low room temperature. Hence it seemed worth while to try the partial saturation of the organism with carbon dioxide to diminish the intake of oxygen into the tissues, or poisoning by cyanide of potassium or chloral to inhibit the local processes of oxidation. This series of studies, however, did not always lead to concrete results on account of the difficulty of attaining the required degree of saturation of the organism with the substances employed before death occurred. The experiments made with illuminating gas and cyanide of potassium failed to give convincing results, because death occurred at an early stage, when it was not probable that the toxic substances had been uniformly diffused in the organism so as to give the necessary degree of saturation. The experiments are therefore omitted. The results were better with chloral.

Experiment 6.—

Time.	Difference in temperature between inflamed and healthy areas.	Remarks.
a.m.—p.m.	°C.	
10.50	2.0	
11.20	1.8	
11.50	1.8	
12.30	1.8	
2.00	1.2	
	(Beginning of ischemia.)	
2.10	3.1	
2.15	1.4	
	(Cessation of ischemia.)	
2.20	1.5	
	(Chloral administered.)	
2.40	1.1	Animal alive.
2.45	1.2	" "
3.00	1.2	" "
3.20	1.0	Heart beating.
3.35	0.8	Seems dead.
3.40	0.8	Animal "
4.00	0.7	

This experiment confirms in the first place a diminution of difference in temperature of an inflamed and a sound limb after some hours of irritation of the healthy part. It also confirms the fact initially demonstrated, that the temporary ischemia always augments considerably and with great rapidity the disproportion of temperature of the parts. In addition, it establishes the fact that by administering a strong dose of chloral such as kills a guinea pig in a period varying from an hour to less than 80 minutes, there is an absence of the phenomenon normally observed when the guinea pig is killed by puncture of the medulla.

During the entire period in which the chloral manifested its toxic action and particularly in the interval between 3.20 p.m., when the guinea pig was certainly alive, and 3.40 p.m., when the animal was undoubtedly dead, the difference in temperature of the healthy and the inflamed areas did not increase; on the contrary, it showed a tendency to diminish. It is well known that chloral exercises an inhibiting effect on organic cellular oxidations (15). Even if my statements were not confirmed by the extensive literature on the subject,

which shows that there is a diminution of the carbon dioxide emitted and a lessened consumption of oxygen by the respiratory change, the suggestive experiments on the emission of heat before death, which diminishes with increased doses of chloral,[2] would be convincing.

These experiments, therefore, seem to indicate that the increase in the temperature of the inflamed area is due to a local cellular hyperfunction, for when this cellular activity is paralyzed the increase does not occur.

SUMMARY.

The experiments set forth here establish the fact that the heat of the inflamed part has its origin primarily in the local biochemical activity of the cellular elements which participate in the inflammatory process. The inflammatory hyperemia, instead of being the necessary and constant source of the inflammation must be considered a natural physiological compensation for the abnormal local calorification.

The rapid circulation of the blood in the inflamed part tends to moderate the increase in local temperature and to equalize the temperature with that of other parts of the body.

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