Physiological reactions observed during fever therapy

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PHYSIOLOGICAL REACTIONS OBSERVED DURING FEVER THERAPY

BY

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INTRODUCTION

Fever therapy has been used to great extent in recent years, especially following the great work of Wagner Von Jauregg in 1918. As in many other treatments used in medicine, the curative value is well known but the exact nature of the physiological processes involved is still not entirely clear. In the very near past, the older physicians regarded fever as one of the more serious manifestations of disease and their efforts were, in many instances, directed almost entirely to the process of lowering the fever of a sick patient. In recent years, this view has been changed to one of just the opposite contention by a great many medical men. Actually, it is impossible to say at the present time whether the fever accompanying the common febrile diseases is harmful or beneficial or merely incidental. At any rate, the alarm with which a fever has been viewed in the past, largely has disappeared.

It is not the purpose of this paper to point out the various diseases which are cured by fever therapy but merely to attempt, in collecting information concerning the physiological reactions observed, to gain some knowledge of the real nature of the curative value of this treatment. I believe that only by obtaining this specific knowledge can fever therapy be properly evaluated in the role of present-day treatment. All major advances in the science
of medicine have been made thru the field of physiology. This applies especially in this respect, as is borne out by the vast amounts of experimental work done on the physiologic reactions seen in fever therapy.

Therapeutic fever has soared to dizzy heights in recent years and has been tried for practically every disease known to man. At present, it is gradually assuming its proper place in the therapeutic branch of medicine. I believe that it has a real and undisputed place in the treatment of the venereal diseases, Syphilis and gonorrhea and their various manifestations. Beyond this, it remains to be seen as a result of further study, just what other diseases are definitely benefitted by fever.

Fever therapy is a heroic treatment and in observing a patient under treatment, one is impressed with the seriousness of the therapy and the necessity for a well-trained staff of workers to carry out the procedures.
"Those diseases which medicines do not cure, iron (the knife) cures; those which iron cannot cure, fire cures; and those which fire cannot cure are to be reckoned wholly incurable." -- Hippocrates.

HISTORY

Heat as a therapeutic agent has been used in various forms since the time of the Greeks and quite possibly even before this. They were the first to convert their natural thermal springs into capacious baths. Many of these were administered by the priest-physicians and were renowned for their curative values. The ancient Egyptians, Chinese and Jews advocated hot baths. The American Indians had a vague idea that increased temperature had some curative value. They employed a "sweat box" which consisted of a dug-out in which several sick people were placed. The heat of the bodies soon raised the temperature of the compartment. After a thorough sweating they would run from this "sweat box" and jump into the icy waters of the nearest creek. Of course, the curative value of this procedure is extremely doubtful. The American Indians also used prolonged baths in hot springs for the treatment of syphilis. Simpson (58).

The Romans built luxurious baths with elaborate heating plants, occupying many acres of territory. These became the meeting places and social centers of Rome. Sy-
philis, probably imported from America by the members of Columbus' party, made these baths unhygienic and dangerous. The communal baths of medieval Europe were not only places of social but venereal pleasures and as a consequence, venereal infections. The spread of Syphilis caused these places to fall into disrepute. Neyman and Osborne (44).

The Japanese were the first modern people to use intensely hot baths solely for therapeutic purposes. This was, no doubt, because of the prevalence of hot springs in conjunction with volcanoes. At certain places, the temperature of these natural springs is between 100 and 160 degrees F. The baths are given in large communal tanks about 4 feet deep. As the water flows into these reservoirs, it is too hot for bathing. To cool it, the bathers stir it with large wooden paddles. They then immerse themselves to the neck and pour the water over their heads with dippers. After about 6 minutes of this treatment, they jump out with a body temperature ranging from 103 to 105 degrees F. The temperature continues for some time after the baths. Also, the people take about 5 of these baths a day so it can be seen that there is more or less of a persistence of the hyperthermia during a day.

These baths are quite famous for their therapeutic values. They are known for their beneficial effects on all forms of Syphilis, Arthritis, Rheumatism, Acute Urino-
genital infections and many other forms of disease.

In 1883, Phillips demonstrated that the temperature of the body could be raised to 103 degrees F. by immersing himself in hot water. He also noted an increase in the pulse and respiratory rate. Wagner Von Jauregg (63) in 1918 in his praiseworthy work with the treatment of dementia paralytica by malaria really set the modern wheels of progress in motion. Schamberg and Rule in 1926 (53) and Mehr tens and Pouppirt (41) in 1929 reintroduced the prolonged hot bath. Neyman and Osborne in 1929 introduced the use of the high frequency current and began a series of intensive studies on the therapeutic value of hyperpyrexia itself. (43)

Since 1931, the fever cabinet has been developed by Kettering and has risen to a very prominent place in the treatment of disease by hyperpyrexia.
BACTERIOLOGICAL ASPECTS

There have been a great many laudible experiments carried out in relation to the lethal temperatures of various organisms, both in vitro and in vivo. In relation to the thermal death point of the gonococcus, probably the most notable work has been done by Carpenter, Boak, Muca and Warren (11). The thermal death time of 15 strains of N. gonorrhea was determined in vitro at fever temperatures of 36, 40, 41, 41.5 and 42 degrees C. Seven of these strains had been under cultivation for 12 years and one strain for 10 years while the remaining seven strains were isolated 1 to 4 months prior to the beginning of the experiment. The resistance to the heat varied in the various strains. The cultures which were 10 to 12 years old had a longer thermal death time than the recently isolated ones. This further strengthens the popular idea that many diseases are much more amenable to treatment in the first stages than in the later stages.

At 39 degrees C. there was little, if any, effect on the growth of the organisms. At 40 degrees C. about 99.7% of the organisms were killed by 10 hours exposure, while death of all cells was not obtained at 30 hours in eight of the strains. At 41 degrees C. 99% of all organisms were destroyed in 4 to 5 hours exposure, while death of all of the gonococci required from 11 to 23 hours. At
41.5 degrees C. and 42 degrees C. 99% of the organisms were rendered non-viable at 41.5 degrees C. in from 7 to 20 hours, while at 42 degrees the thermal death time ranged from 5 to 15 hours. In all cases, the recently isolated cultures showed the least resistance. Kobak (35) and Carpenter, Boak, et al (11).

The normal temperature of the human body in degrees Centigrade is 36.87 according to Wiggers (64). The body temperature of man may safely be raised to 41 to 41.5 degrees for periods varying around 6 hours. This means that the gonococcus is actually killed by superheating in the human body. Add to this, the fact that there is, no doubt, an active phagocytosis occurring at the time of the fever. There are also immune forces at work. These facts are certainly in support of the high percentage of cures obtained in only one heating.

Syphilis is the other disease in which spectacular results have been obtained. The Treponema pallidum has been consistently destroyed in vitro with temperatures between 39 and 41.5 degrees C. when heated from 5 minutes to 1 hour; Kobak (36) however, the exact mechanism in the case of Syphilis is not as clear-cut as in that of the gonococcus. Certainly there are many other factors that enter the picture. The general consensus of opinion seems to be that the body's natural defenses are stimulated by
artificial fever and that probably this factor takes precedence over the actual hyperpyrexia in spirochetocidal action. This opinion is especially upheld by the malarial therapy advocates. Dr. G. A. Young (65). These authorities maintain that there is definitely a higher immune reaction in malarial fever. It seems to me that this is very likely the case in view of the excellent results obtained in neurosyphilis where there is considerable destruction of nervous tissue.

Halphen and Auclair (24) report an augmentation of the flocculent power in the human as well as in experimental animals. This is constant and extremely well marked. Also, the variations in the amount of flocculation follow almost exactly those of the temperature and are most apparent when the latter is highest. It also follows in temperatures below normal. This result is not reported by other authorities. Hadjopoulos and Bierman (23) found that the production of hyperpyrexia by physical means causes a temporary diminution of the complement fixing antibody titer of rabbits immunized against staphylococcus, streptococcus, Microcci catarrhalis and the diphtheria bacilli. Rolly and Meltzer (51) found that heated animals were more resistant to infection than unheated ones but could not identify any specific bacteriocidal substance in the blood. Phagocytosis was increased from 37 degrees C. to 40 degrees C.
while higher temperatures interfered with this phenomenon. They also demonstrated an increase in agglutinins and hemolytic amboceptor by heating animals. Besides the venereal diseases, the meningococcus has been observed in connection with fever. Bennett (3) found that most strains were killed on the water bath at 106.8 degrees F. within 8 hours. In using artificial fever therapy in connection with meningococcic meningitis, it was found that sustained fever at 107 degrees was effective against certain strains of meningococci. Finally, it may be said that recently, evidence is being shown that there are different reactions to the various forms of fever therapy. Jung (33) concluded that whatever beneficial effects hyperpyrexia had on asthma, paresis or inflammatory arthritis, is on a basis other than immunity and phagocytosis. He used diathermy and found no phagocytic response to this type of technic. Further evidence is certainly necessary in substantiation of this contention since it conflicts rather strongly with many other experimenters.
INDICATIONS FOR FEVER THERAPY

The indications for artificial fever therapy are by no means all known at the present time. Experimental work is going forward constantly and more uses for this form of treatment are being found daily. Some of the uses and indications for heat therapy have been known for many years. I refer specifically to local applications of heat in inflammatory processes. This continues to be the only accepted treatment of the acute lymphangitis following infection and in other forms of acute tissue inflammation. Also, it has been used both by the profession and by the laity for the relief of certain types of pain.

The present concept of fever therapy seems to be almost specifically in relation to the heating of the whole body. Although there are slight differences in the results obtained by the various methods of fever production, the results are essentially the same. Wagner Von Jauregg (63) in 1918 made the first real step in the use of hyperpyrexia in his case of the cure of a dementia paralytica. Since then, it has been used with a high degree of success in all forms of Syphilis. Bennett (3) reported on the spectacular results obtained in the intractible pains of tabetic crises. Certainly then, artificial fever therapy is indicated in cerebrospinal syphilis and also in earlier forms—specifically, during the chancre stage.
The gonococcus is the other organism which has been definitely conquered by fever therapy. For the initial infection, namely urethritis, one treatment is in many cases adequate for a complete cure. The use of hyperpyrexia has completely changed the prognosis in relation to gonorrheal arthritis. Uniformly good results and cures are reported in this connection. Simmons (55).

Bennett (3) obtained very satisfying results in certain strains of meningococcic meningitis. Also, (4) he found this form of therapy to be valuable in the treatment of neuritic pain. All types of neuritic pain were relieved but pain recurred in some cases, especially in the secondary neuritides from compressive lesions. Worthy of note are the following results: Sciatic neuritis was relieved in 80% of cases by combined fever and epidural injections. Relief of brachial neuritis was obtained in 50% of cases. The pain of herpes zoster was relieved in 100% of cases.

Artificial fever therapy has been used in almost every disease known. In many cases, there have been good results but the cases so far, have been insufficient in number to draw definite conclusions. Other diseases in which hopeful results have been obtained are: Intractible bronchial asthma, selected cases of chronic infectious Arthritis (Simmons 55) Chorea, Undulant Fever and many other diseases.
Krusen lists 36 diseases which have been treated in this manner. (40)

In summarizing the indications for fever therapy, it may be said that this treatment seems logical for cases in which there is no known successful treatment and in which there are no contra-indications. Besides these cases, there are the definitely known cures in the venereal diseases. Hench (27) and others.

Other than these instances, we cannot as yet, say definitely just what pathological conditions are cured or alleviated by hyperpyrexia.
DANGERS AND CONTRA-INDICATIONS

The council on physical therapy has set forth certain precautions and contra-indications in the use of fever therapy. The contra-indications are listed as follows:

1. Advanced Age (beyond 60 years (7))
2. Cardiac or Renal insufficiency
3. Rheumatic Endocarditis
4. Aortic Aneurism
5. Advanced Arteriosclerosis
6. Pulmonary Tuberculosis
7. Diabetes
8. Late neglected Neurosyphilis that has progressed to complete dementia

It will be readily understood that careful selection and good judgment would automatically eliminate these people as candidates for fever therapy. Binet (9), in experimenting with dogs, found that death was a result of respiratory failure. He also states that invariably the heart action continued good for a considerable time after respiration had ceased. As a result of this observation, he concluded that respiratory stimulants should be used. Following this same line of reasoning, one may readily see why hyperpyrexia does just the thing that should be avoided in tuberculosis, namely raising the metabolism in the body. Lastly, in relation to tuberculosis, it is well known that the tubercle bacillus is not readily killed
by ordinary temperatures. I believe that the other contra-
indications mentioned are self-explanatory.

I believe that in this connection some of the accidents
and unfavorable reactions should be mentioned in order to
take precautions against them. The following have been
found:

13 physicians reported burns.

6 " " bad results because of poor technic.

1 physician reported 4 deaths as a result of humidity.

1 physician reported 2 deaths as a result of indirect factors.

Several physicians reported heat stroke, circulatory
collapse, herpes of the cornea, cerebral hemorrhage, al-
buminuria, tetany and convulsions. Herpes labialis was
reported in almost 100% of cases. Brodriff (10) also men-
tioned delirium, vomiting, nausea and headache. Neyman
and Osborne (44) say that skin burns are quite common
unless the bony prominences are protected.
LOCAL HEAT THERAPY

The use of local heat for the relief of pain has been used by the profession as well as the laity for many years. I believe this fact is significant because it has been so universally accepted. Also, it makes the treatment of neuritic pain by generalized hyperpyrexia seem logical. Many physicians believe that there is a definite relief of internal pain by the application of heat on the external surface of the body.

Probably of more actual therapeutic value is the use of local heat in localized inflammatory processes. This is especially true in the acute lymphangitis (Grodinsky 22), the furuncle and similar local inflammations. The general consensus of opinion among the staff members of the University of Nebraska Hospital, is that in most of the local warm saline administrations, the healing value is in the heat rather than in any other factor. This has been set forth by the gynecologists in the use of the hot douche, by the surgeons, in the use of hot magnesium sulphate dressings and by the nose and throat department in regard to any therapeutic value which a gargle may possess.

Considerable experimental work has been done in the treatment of local pelvic inflammations by the use of local heat. Bierman et al (8) found that the vaginal mucosa was coagulated at a temperature of 113 degrees F.
for 15 minutes. These experimenters believe that in local pelvic heat therapy, the local hyperpyrexia is relieved by a general body distribution, so that any local effects are doubtful.

Horowitz, Gottesman, Derow and Schwarzschild (30) conducted an experiment on local pelvic hyperthermia which has a decided effect on the question of local or general heat. They conducted their experiments by the use of short or ultra-short wave. Without going into lengthy, detailed discussion of the technic used, it will suffice to say that one electrode was placed in the vagina or rectum and the other over the nearest point on the external body surface. The mouth temperature and pulse rate were recorded immediately before and after 88 pelvic treatments. There was an elevation of mouth temperature in 1/2 of the cases of .5 degree F. in the first 10 minutes. There was an elevation of .8 degree after 60 minutes in every case. This shows rather conclusively that there is a generalized dissemination of heat during local application. Besides this general temperature elevation there was a definite change in the pulse. After 10 or 15 minutes, 2/3 of the patients had an elevation of the pulse rate averaging 6 beats per minute. After 25 minutes or longer there was always an elevation of the pulse of 10 beats per minute average. This small pulse elevation probably is not of any significance since prac-
tically every patient would normally show this much pulse rate increase under this set of conditions purely as a result of psychic influence. The following is a table of their results, recorded during pelvic short wave treatments with anterior and posterior condenser plates. Recorded in degrees F.

TABLE I

<table>
<thead>
<tr>
<th>Time (Min)</th>
<th>Bladder</th>
<th>Cervix</th>
<th>Vagina</th>
<th>Rectum</th>
<th>Mouth</th>
<th>Pulse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>100.0</td>
<td>99.8</td>
<td>99.2</td>
<td>99.5</td>
<td>98.0</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>100.0</td>
<td>100.0</td>
<td>99.5</td>
<td>98.8</td>
<td>98.0</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>100.2</td>
<td>100.0</td>
<td>99.6</td>
<td>100.0</td>
<td>98.6</td>
<td>80</td>
</tr>
<tr>
<td>15</td>
<td>100.2</td>
<td>100.0</td>
<td>99.6</td>
<td>100.0</td>
<td>98.6</td>
<td>80</td>
</tr>
<tr>
<td>20</td>
<td>100.2</td>
<td>100.0</td>
<td>99.5</td>
<td>100.0</td>
<td>98.6</td>
<td>80</td>
</tr>
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TABLE II
Average temperatures produced by 15-minute vaginal short wave treatments.

<table>
<thead>
<tr>
<th>No. of Treatments</th>
<th>When Peak Was Reached</th>
<th>Peak °F.</th>
<th>Terminal Temp. °F.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>68</td>
<td>11</td>
<td>107.5</td>
</tr>
<tr>
<td>Rectal</td>
<td>58</td>
<td>12</td>
<td>106.2</td>
</tr>
<tr>
<td>Bladder</td>
<td>58</td>
<td>13</td>
<td>106.0</td>
</tr>
<tr>
<td>Cervical</td>
<td>28</td>
<td>11</td>
<td>106.8</td>
</tr>
</tbody>
</table>

Table I shows some rise in temperature (100.0 °F.)
in the pelvic organs. While this may attenuate some gonococci it is certainly not their lethal temperature and since these treatments were not carried out for an appreciable length of time, their effectiveness is questionable.

Table II shows a more favorable rise in temperature by using one electrode inside the vagina. Even for as short a period as 15 minutes, these temperatures probably have some value. It was found also that at a distance of 10 centimeters from the electrode there was no appreciable rise of temperature. In conclusion, these experimenters are doubtful of any real benefit in this form of treatment.
PULSE: The pulse invariably shows a marked increase in rate in proportion to the rise in temperature. The increase is very rapid at the beginning of each session of treatment. Desjardins and Stuhler (17). The pulse may go to 120 degrees F. to 150 degrees F. A pulse of 160 or over is taken as a potential danger and the patient is watched very closely for any signs of circulatory failure. Some patients have tolerated a heart rate of 190, but these cases are rare. In a later paper, Desjardins (16) sets forth the following rules as he follows them: If the pulse rate rises to 160 per minute, the treatment is discontinued. If it rises to 160 beats per minute on a second occasion, the treatment is given up. Bierman (7) in a study of 500 cases, noted an increased pulse rate of 8.5 beats per minute for each degree rise in temperature. He noted that this increase was similar to that observed during any other fever. This was also noted by Bazett (2) who found this rise to be independent of the vagus and of the splanchnic nerves. When commencing circulatory failure is induced by heat, the pulse rate may show a sudden acceleration.

VELOCITY: Kopp (37) found that there was an increase in the velocity of the blood flow from 40% to 54%. Certainly with the marked increase in heart rate, there should be
an associated increase in the velocity of the blood flow. This was measured in various ways; one of the most used methods was the injection of some substance into the brachial vein and measuring the time taken for it to reach the tongue. Kopp found that the time necessary for the decholin to reach the tongue was diminished both in a patient with a normal heart and in a patient with a luetic heart. Bazett (2) found that in experimental exposure to heat, the flow thru the superficial capillaries, venules and veins appeared to be rapid and the vessels appeared to be greatly dilated. According to well-known physical principles, this very dilatation allows for a higher rate of flow. It can be readily seen that it is necessary to maintain the fluid balance of the body so that the heart may continue to function at an efficient rate and manner. Dr. A. E. Bennett (4) suggests that this increased blood flow is a direct and potent factor in bringing about the beneficial effects of fever therapy.

**BLOOD PRESSURE:** The blood pressure in patients undergoing artificial fever therapy undergoes a slight change. In more recent work, the blood pressure has not undergone such marked changes as formerly. This is undoubtedly due in a large part, to the increasing improvement in technic, including the proper administration of fluids, etc. The systolic pressure as recorded uniformly by all experimenters,
first undergoes a sharp rise. Then it slowly begins to drop so that at the end of a session of fever, it has fallen below its normal mark. The diastolic pressure goes in the opposite direction. At first, it may be nearly zero. Then after an hour, it is higher so that finally, it reaches a point slightly above the original one. Bierman and Fishberg (7). Desjardins (16) found that the blood pressure rose more rapidly than the temperature. This is interpreted as a response of the heart in an effort to dissipate the heat. He found the systolic pressure to be increased 20-30 mm. of mercury. After the maximal temperature was reached, there was a gradual drop in the pressure. Unlike Bierman, he found the diastolic pressure to slowly fall thru out the entire period. In these experiments, the following rule was evolved: If the pulse pressure diminishes, it is a danger signal, but if it falls to 20 milimeters of mercury, the patient should be removed from the heating unit. It is a sign of cardiovascular insufficiency. Kobak (36) and Giles (20) also report a steady fall in diastolic pressure with the rise in temperature. Kobak explains this on the basis of capillary dilatation and a widening of the aortic ring.

VASOMOTOR RESPONSE: As regards the response of the vasomotor system to hyperthermia there yet remains much to be known. Pasteur Vallery and Radot (45) in an original
experiment, found that by using acetylcholine, adrenalin and histamine, the peripheral vasomotor reactions in artificial fever therapy were the same as those found in the normal human organism. In further experimentation, they found that there was a general increase in tone of the sympathetic nervous system as evidenced by the action of the vasoconstrictor nerves. Hench (27) noted an increase in number and size of the visible nail bed capillaries during artificial fever. Halphin and Auclair (24) compared the results obtained during artificial fever and those noted during spontaneous fever. They report that in spontaneous fever, in which the organism itself causes the rise in temperature, the vasodilatation affects principally the deep seated organs (visceral and muscular). It corresponds to a general increase in the metabolism.

The peripheral circulation, on the other hand, in order to afford the maximum cooling, remains practically normal, at least during the rise of temperature. In artificial fever it is the peripheral circulation that bears the brunt, in order to assure the cooling of the organism struggling against an abnormal rise of temperature. It is manifested by a pronounced peripheral congestion. So far, there has not been adequate study as to the reaction of the deeper circulation. It is known, however, that there is normally a compensatory visceral vasoconstriction
when there is a peripheral vasodilation. This seems to be supported by the fact that there is an ischemia of the brain found at autopsy in patients dying during fever therapy. Hartman (25), Johnson and Osborne (31), experimenting on the pulse volume of the finger suggest that the vasodilation of foreign protein injection is probably of central origin while artificial fever produced by external means is peripheral in origin. During the rise of temperature in fever patients, there has been noted a pallor of the skin, a constriction of the veins and a failure of this area to increase in temperature in spite of the evidence of diminished peripheral resistance, showing rather definite proof of an actual vasoconstriction during this period. This is in accordance with the recent original work of Pasteur Vallery and Radot mentioned previously. Evidence has been advanced by Von Euler (62) that the blood of fever patients contains some substance capable of inducing constricting the superficial skin vessels. He further believes that this substance in many ways, resembles adrenalin. There is no reason to believe that this substance is not adrenalin since these patients undergo quite a period of excitement at the onset of fever therapy. Whether or not this is the actual cause of the probable increase in epinephrin is only speculative. Bazett (2) suggests that there is an increased metabolic rate in pyrexia
whether of infectious or artificial origin and that this
increased metabolism is likely to be associated with some
vasodilatation in the muscular areas. This probably bal-
ances the vasoconstriction in the skin. I believe that at
present, it is generally agreed that the reaction of the
peripheral vessels depends on the type of fever used.
Wiggers (64) states: "In artificial fevers, produced by
high frequency currents, the fundamental cause of the rise
in temperature is in effect opposite to that produced by
application of external heat."

**ELECTROCARDIOGRAM:** Many authors report no significant
changes in the electrocardiogram. Hench (28). This has
not, however, been the observation in all cases. Claude
Bernard found that there were some definite changes in the
cardiac muscle of dogs subjected to prolonged heat. Whether
or not these changes cause any alterations in the electro-
cardiographic tracing is not known. Hench and Slocumb
(28) in a resume' of the various effects of fever therapy,
report contractions of lowered voltage. Cheer (12), in a
very good piece of work in this connection, observed a
variety of rhythms and came to the conclusion that: (a)
The S-A node is very resistant to the effects of high
temperature and remains the pacemaker until very near the
end; (b) That ultimately A-V block and various types of
ventricular rhythm develop.
VISCOSITY: There is no change in the viscosity of the blood if the fluid intake is kept at a sufficient level to care for the fluid lost thru the increased perspiration and metabolism. Hench, Slocumb and Popp (28).

BLOOD VOLUME: Hench (28) and Bierman (7) found no change, or a very slight concentration of the blood.

GASTRIC SECRETION: Gastric secretion is generally diminished during a session of artificial hyperpyrexia. Kobak (36) and Giles (20). With this lowering of secretion, there is a marked lessening of the acidity, both free and total. This latter observation could very possibly be explained on the basis of the loss of blood chlorides thru other channels. Hench, Slocumb and Popp (28) found a definite increase in the lactic acid of the stomach.

WATER BALANCE: The maintenance of an adequate water balance is one of the major considerations which must be met in the administration of artificial fever. The importance of keeping up a large intake can be readily understood when one realizes that the heightened metabolism causes a great fluid loss from the blood, the intestines, the subcutaneous tissue and the muscles. Kobak (36). Obviously, it is necessary to replace this fluid in order to supply an adequate circulating blood stream for the heart to work upon. Patients may lose 5 pounds during
a single treatment. Kobak (36) advocates the replacement of this fluid by .6% sodium chloride water. Hench and Slocum (28) report a loss of 18 to 26 grams of sodium chloride in 3 to 4 liters of sweat during a single session of fever therapy.

The kidneys have suffered considerably during periods of hyperpyrexia in the past. Karr and Nasset (34) claim that oliguria and anuria are almost invariable sequellae to hyperthermia carried to 42 degrees C. or higher. They base this on the dehydration and subsequent renal damage. The urine has also been observed to become increasingly alkaline. Simon (56). I believe that the above observations may support the contention that the residual nephritis of scarlet fever and other infectious diseases is due to the high fever and the accompanying dehydration. This factor is probably not as great a danger at the present time due to the increasing efficiency in the handling of the patients during the period of exposure to heat.

**BASAL METABOLIC RATE:** Obviously any treatment such as the use of prolonged hyperpyrexia is going to elevate the metabolic rate. Kopp (39) states that the basal metabolic rate is increased up to 200%. He also found that the metabolic rates tend to parallel the amount of hyperpnea present. The rise in metabolic rate was so uniform that there was a definite increase in percentage for every degree rise
in temperature. It was found during these experiments that the metabolic rates were higher for the same temperature when the temperature was rising than when it was falling. Apparently repeated fever treatments had no residual effect on the basal metabolic rate. An interesting light was shed on this angle when it was observed that the metabolic rate returned to normal as soon as the patient was taken out of the blankets, even though the temperature remained high, suggesting a psychic element. Giles (20) suggests that there is some relation to the beneficial effects noted in bronchial asthma where the B.M.R. is low.

**RESPIRATION:** The respiratory system undergoes very marked changes during a session of artificial hyperpyrexia. There is, of course, an increase in the respiration along with the other signs of increased metabolism. Bierman (7) noted that there are periods of apnea which appear with increasing frequency as the fever treatment progresses. Many authors agree that in the presence of apnea of pulmonary overventilation, overstability of the oxyhemoglobin creates a functional anoxemic condition. Hopkins (29). Early writers attributed the nervous symptoms of hyperpnea to oxygen want within the tissues. Binet (9) states that the animal subjected to hyperthermia needs more oxygen to live than the normal animal. In his original work, he found that in the overheated dog, respiration stops 2
minutes before the heart does. He is convinced, and other workers support this contention, that death by hyperthermia is, in many cases, due to failure of the respiratory center. He further suggests that in the use of artificial fever therapy in the human, this factor should be kept in mind and respiratory stimulants should be used. He recommends sodium bicarbonate as a means of bolstering the respiratory center.

SEDIMENTATION RATE: Bierman (7) noted a definite fall in the sedimentation rate of fever patients. Bennett, Person and Simmons (3), in treating meningococcal meningitis with the Kettering fever cabinet, found that the blood sedimentation rate was returned to normal in every case and that the blood was rendered sterile. Some authorities feel that due to the increased erythrocyte count and general concentration of the blood, the sedimentation rates taken during fever are inaccurate. Moen (42).
BLOOD FORMED ELEMENTS

RED BLOOD CELLS: There has been much controversy over the effects upon the red blood count by prolonged hyperpyrexial treatments. Some writers report little change and others report an increase. Hench, Slocumb and Popp (28) reviewing the physiological effects of fever therapy, found that in carefully controlled fever sessions, there was no appreciable change in the red count. Very likely, the increase reported by earlier writers was due to the general dehydration. This has, no doubt, been largely eliminated thru increasing efficiency in technic.

PLATELETS: Binet (9) in a set of original experiments on dogs, found an increase in the number of blood platelets.

WHITE BLOOD CELLS: In the study of the leukocytic response to fever therapy, will probably be found the real reason for the beneficial effects obtained by this method of treatment. Invariably, there has been observed a leukocytosis or an increase in the white cell count during artificial fever therapy. Binet (9), Bierman (7), Cohen (13) etc. (Graph I)

Bierman (5) found that there is an initial reduction in number of about 25 to 30% during the first 2 hours. (Graph I) Following this there is an increase, reaching a maximum of about 16,000 between 6 and 9 hours. Cohen and Warren (13) found that in 8 of their 10 patients, the maxi-
GRAPH SHOWING THE RELATIONSHIP BETWEEN THE TEMPERATURE AND THE LEUKOCYTE COUNT

GRAPH I

Intervals in Hours

Temp  W.B.C.  0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
107  17000
106  15000
105  15000
104  14000
103  13000
102  12000
101  11000
100  10000
99   9000
98   8000
97   7000
96   6000
95   5000

Temp F.
106
105
104
103
102
101
100
99
98

Bierman ( )
mum increase in the white blood cells was more than 100% of the original number. In 3 of their cases, the maximum rise occurred at the end of the fever. The time necessary for the temperature to return to normal varied from a minimum of 3 hours to 1 day. The white blood cells were found to increase out of proportion to the red cells and the hemoglobin, showing that the increase is not entirely due to dehydration.

There was a marked relative and absolute increase in the polymorphonuclear cells in all cases. They (13) suggested that the increase in pulse rate might lead one to believe that the cells were washed out of their storage places, but the fact that sometimes the peak of the leukocytosis was reached many times, after the pulse rate was nearly normal, would tend to, but not altogether disprove this theory. The observation that there is an increase mainly in the polymorphonuclears suggest a mobilization into the circulation of available and nearly mature cells of the myeloid and erythrocytic series as a result of the fever.

Bierman (5) found that the greatest percentage of increase occurred in the staff cell count. (Graph II). This increase averaged about 300% and was from 200 to 300% in most instances, on one occasion rising to 1420%. The peak of the staff cell count usually occurred at about the
ninth hour. In about 1/3 of the observations, the rising number of staff cells was preceded by a fall, usually occurring at the end of the first or second hour, and which, in the majority of cases, amounted to about 30%. The swing of the staff cell count coincided more or less with that of the total neutrophile count.

In about 1/2 of the cases, there was a diminution in the number of the monocytes, which averaged about 45%. The low point of the fall occurred at the end of the first, second or third hour; the high point, from the fifth to the fourteenth hour. The average percentage of increase was about 27%.

The average reduction in the number of lymphocytes amounted to about 40%. The smallest numbers were observed at the third or fourth hour. In about 1/2 of the instances, the lymphocyte count had not returned to its original figure when blood counts were made for a period of 6 to 8 hours. In the other 1/2, the rise was about 35%. When the counts were observed for 13 to 14 hours, it was noticed that the time of the height of the rise occurred from the sixth to the eleventh hour and the increase averaged about 90%.

In general, the white blood cells from the bone marrow first showed the stimulating influence of the hyperpyrexia—the segmented neutrophils and the staff neutrophils. The monocytes whose origin is believed to be in the reticulo—
Graph Showing the Differential Leukocytic Response—
Taken From Pierman

Total Neutrophile
Staff Neutrophile
Monocytes
Lymphocytes

GRAPH II

W.B.C. Intervals in Hours
20000 0, 2.5, 5, 7.5, 10, 12.5, 15
19000
18000
17500
17000
16000
15000
14000
13000
12500
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
endothelial system are the next to give evidence of an increase in number, and last, those from the lymphatic system, the lymphocytes. The leukocytic response diminished with each following treatment. In only 2 cases was there no increase in the total number of leukocytes. Hench and Slocumb (28) report an increase in phagocytosis. This would be expected in view of the above observations on the increased white cell count.

Doan and Hargraves (18) working with typhoid and malarial fevers, report more of a shift to the left with typhoid than with the fever cabinet. During malaria there was found to be a marked leukopenia during the incubation period. Here also there was a marked shift to the left. The leukocytosis following a chill was found to be small, rarely exceeding 15,000, in a patient who had, in the hypertherm, a leukocytosis of 40,000 to 60,000. Monocytes are the most strikingly altered in their qualitative characteristics. They return to the circulation to make 30 to 40% of the total count and are extremely young and markedly stimulated. Extremely young lymphocytes dominate in the secondary leukocytosis which follows each fever period. One wonders if, in this particular experiment, the lowered response to fever of malarial origin was not the natural decrease in response following prolonged fever treatments, since the malaria was given to patients who had already taken artificial fever.
These experimenters also found that vacuolization was not of the rosette formation but was a diffuse scattering of enlarging vacuoles throughout the increased quantity of the cytoplasm. There is a marked diminution of lymphocytes and monocytes during the chill and resultant leukopenia. During the period of monocytosis there appears in the peripheral blood, an abnormal number of actively phagocytic clasmatocytes, as high as 7 to 8%. This response was observed in no febrile hemogram observed by agents other than malaria. Results of a bone marrow biopsy taken in one patient:

Biopsy taken before treatment— Normal
  "  " after cabinet treatment — Normal
  "  "  " malaria — Shift to
    the left in myeloid elements
    and also in erythroid elements
BIOCHEMICAL PHENOMENA

**BLOOD UREA:** Binet (9) experimenting on dogs found the blood urea to be markedly elevated. Coincident with this there was an increase in the ratio of the urea nitrogen to the total nitrogen, thus showing that the urea nitrogen was increased more than the other forms of nitrogen. It was also found that the blood urea remained elevated even after the temperature had returned to normal. Giles (20) found an increase in the blood urea nitrogen from 13 to 19 mg. per 100 cubic centimeters. Krusen (40) had similar results, ranging from 12.3 mg. per 100 cubic centimeters to 17.2 mg. per cent. Others report only a small increase, probably due to concentration phenomenon. Sheard (54).

Karr and Nasset (34) also working with dogs, found that in hyperthermia induced by high frequency current, the urea, amino acid, creatinine and uric acid nitrogen fractions of the blood N.P.N. maintain essentially the same relative concentrations up to a rectal temperature of 42 to 44 degrees C.

**URIC ACID:** The results regarding uric acid concentrations during artificial fever have been uniform. Sheard (54), Hench, Slocumb and Popp (28) and Giles (20) all report no change in uric acid content.

**NON PROTEIN NITROGEN:** This factor shows an elevation of approximately 11% during the first prolonged fever treat-
ment. Giles (20). Simon (56) found an N.P.N. of 27.4 mg. per cent before treatment and 30.8 mg. per cent after treatment. This is rather a slight rise and could very well have been on a basis of general blood concentration due to dehydration.

**CREATININE:** Simon (56) reports an increase in creatinine from 1.23 mg. per cent to 1.4 mg. per cent. No increase was found by Sheard (54), Hench, Slocumb and Popp (28) and Giles (20). Grant (21) in working with a series of 15 patients with various febrile diseases (Chart I) found that creatinine clearances varied from 60% to 600%. The group in this series whose behavior was most difficult to explain was that in which blood pressure and temperature were both elevated while the creatinine clearance was lowered. Two known factors may be responsible for this behavior:

(a) There may be a decrease in the flood flow to the kidney in spite of the elevation of temperature and blood pressure, and

(b) There may be a direct effect of infection on the kidney, temporarily resulting in a closing off of some of the glomeruli or in an altering of their permeability.

**BLOOD PROTEIN:** There has been a slight increase of blood proteins observed in dogs as a result of artificial fever. Binet (9). The increase ranged from 56.6 grams per 100 cc. of blood to 61.3 grams per 100 cubic centimeters. The serum globulin increased from 23.95 to 25.50 grams per 100.
The serum albumin increased from 32.65 to 35.80 grams per 100 cc. of blood. Hench, Slocumb and Popp (28) believe that there is no change.

**BLOOD SUGAR:** Binet (9) in his original work on dogs found that there was an increase in plasma lipids following almost exactly the fever curve. He also noted a disappearance of the liver glycogen. Giles (20) reports an increase in blood sugar of 20%. Krusen (40) found an increase from 86 mg. per 100 cc. to 103 mg. per 100 cc. and Simon (56) obtained similar results with a rise from 99.9 mg. per cent to 121.3 mg. per cent. This may lend support to the contention of Binet (9) that there is a hyperfunction of the adrenal glands. It is interesting to note in connection with the blood sugar that there is no glycosuria during hyperpyrexial treatments even after the concentration reaches or passes the threshold value. Simon (56).

**BLOOD LIPIDS:** There seems to be considerable disagreement as to the effect on the blood fats. Stoesser and McQuarrie (59) claim that the lipid values vary inversely with the white blood count. This would indicate that there was a lowering of the fats. They further state that they found no relationship between the height of the fever and the hypocholesteremias and hypolecithinemia. Binet (9) found that there was a gradual increase in lipid content of the blood. Hench, Slocumb and Popp (28) maintain there is no
change.

**BLOOD CALCIUM:** Here also there is considerable debate. Hopkins (29) reports a fall in the blood calcium. Sheard (54) and Hench, Slocumb and Popp (28) found a slight increase which they assigned to concentration.

**BLOOD PHOSPHORUS:** Hopkins (29) reports a rise in the phosphorus content. He also noted a changing of the inorganic to the organic phosphorus. Hench, Slocumb and Popp (28) found little or no change here.

**BLOOD CHLORIDES:** In earlier work with fever therapy there was considerable anxiety in the minds of experimenters as to the marked loss of blood chlorides during a session of fever therapy. This has, with increasing skill in technic, been largely eliminated. Krusen (40) in 1934 found a slight increase in the chloride content of the blood following artificial fever (7 mg. per 100 cc.). Simon (56) on the other hand, found a slight decrease (9 mg. per cent). Giles (20) found that there was a decrease only if the chloride intake was not maintained at an adequate level.

Danielson and Stecher (15) conducted 4 experiments on the same patient as follows: In 2 of the experiments, the patient was allowed to drink water and in the other 2 he was allowed to drink a .6% solution of sodium chloride. The body temperature was maintained at an average of 40 degrees C. The serum acid base changes observed when
water was given were: An elevation of the pH, a fall in the carbon dioxide tension and a fall in the bicarbonate, chloride and total base concentrations. The total determined acid decreased more than the total base so that there was an increase in the undetermined acid. These same changes were observed whether the hyperthermia was carried on for 2 or 4 hours. A recovery specimen taken 2 hours after the short term experiment showed a fall in the pH below the control level, a further fall in the chloride and total base concentrations, a partial recovery of the carbon dioxide tension and bicarbonate concentration and a complete return of the undetermined acid to its control level.

Similar changes were observed when the .6% salt solution was given. However, the chloride and total base concentrations increased slightly. A control specimen taken 2 hours after the short term experiment showed about the same tendency except that the total base and chloride levels tended to return toward the control level. As a result of these observations, these experimenters concluded that the drinking of a solution of salt water seemed to prevent a loss of base and chlorides from the serum and to better enable the individual to undergo fever therapy.

**ACID BASE BALANCE:** There seems to be a general agreement among various workers in therapeutic fever that there is a loss of carbon dioxide from the blood stream and con-
sequently a loss in the carbonic acid content during artificial hyperpyrexia. It seems at first thought that this fall in carbonic acid content is due to overventilation, but it is not so simple. If one lowers the temperature to 36.3 degrees C. and then raises it to 39.2 degrees C. (normal) the respiratory rate remains unchanged but the carbon dioxide tension falls from 1 to 5 volumes. Binet (9). Even after apomorphine to ward off any increase in respiration, there is a fall in the carbon dioxide. This fall continues long after the fever is stopped and the respiratory rate has returned to normal.

The compensatory mechanism consists in a shifting of the alkali. Hopkins (29). This shift is chiefly bicarbonate ions out of the blood in order to reduce its alkalinity. Two avenues of escape are thought to exist: One into the tissues and the other into the urine via the kidneys. Proof of this escape is found in the measurable reduction of the alkaline reserve of the plasma. Finally, the net result in all these cases is a tendency toward alkalosis.
PATHOLOGICAL CHANGES

Hartman (26) has probably done the most work in connection with the pathological changes resulting from fever therapy. The pathological changes found in all of his cases were: Engorgement of the blood vessels, especially the capillaries, hemorrhage and degeneration. The most vital changes seen were those in the brain amounting to hemorrhagic encephalitis in some instances, those in the lung constituting hemorrhagic pneumonia and those in the adrenal characterized by degeneration in the cortex with hemorrhage. Death occurring during or immediately after treatment was due to vascular collapse. Although the changes described have been noted in animals receiving morphine alone as a sedative, both the human patients and most of the animals received sodium amytal, a drug which in large amounts is known to produce congestion and even capillary damage, especially in the brain. Since both the fever therapy and the sodium amytal tend to produce marked dilatation and engorgement of blood vessels, it is suggested that the combination not be used in patients.

Hartman (25) also found a constant and severe anemia as shown by the decreased oxygen saturation of the blood and the low oxygen content of venous blood in animals after fever therapy. Factors producing anoxia during fever therapy are alkalosis, accelerated blood flow, increased
temperature of the blood and increased demand for oxygen in the tissues. The last factor named results from the increased metabolism and the depressed utilization of oxygen by the tissues, especially the brain, due to the histotoxic effects of the sedatives used. These pathologic changes resulting from anoxia are typical of anoxia produced in other ways, such as prolonged asphyxia, carbon monoxide poisoning and acute alcoholism. This anoxia may be prevented by the administration of oxygen throughout fever therapy, provided respiration and blood pressure are maintained at reasonable levels. Combinations of oxygen and carbon dioxide may be used to counteract the apnea and the alkalosis. Hartman (25) further suggests that this oxygen may be given easiest by means of the nasal catheter.
SUMMARY AND CONCLUSION

I Fever, instead of being regarded as a dangerously serious symptom, is now regarded as a beneficial phenomenon in most diseases even to the point of being used as a therapeutic agent.

II There is invariably a leukocytosis accompanying artificial fever therapy.

III Leukocytosis is suggested as being the main factor responsible for the beneficial results obtained from fever.

IV The gonococcus organism is killed at temperatures which are withstood by the human body, making artificial fever therapy a specific cure for gonorrhea.

V The leukocytes are a natural, strong defense against the gonococcus organism, thus the leukocytosis accompanying fever and the increased phagocytosis is an additional benefit derived from this form of treatment.

VI General body heating seems to be generally regarded as more satisfactory than local heat, especially in pelvic inflammatory disease. This is attributed to the rapid dissipation of local heat throughout the body.

VII The increased metabolism and enhanced blood flow is also suggested as a beneficial factor.

VIII Ischemia of the brain and respiratory center with resulting failure is the usual pathology found at
autopsy on patients dying as a result of fever.

Biochemical values are minimal or unchanged if proper technic is employed.
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