1944

Effects of fever on the body

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THE EFFECTS OF FEVER ON THE BODY

by
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SENIOR THESIS
PRESENTED TO THE
COLLEGE OF MEDICINE
UNIVERSITY OF NEBRASKA

OMAHA

1944

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INTRODUCTION

It has appeared to me that the student has a less clear idea of fever than of any disease which he meets within the wards of the hospital. The difficulty he experiences may arise partly from the want of correspondence of the particular case before him, with the description of some form of fever from which he has obtained his ideal, and partly, from his not possessing a knowledge of this condition and the laws which are common to all its variations.

It is not too much to say that the most dramatic and perhaps the most important of all clinical phenomena are those connected with fever. Clinicians as a rule accept fever as a diagnostic sign, an index of the prognosis or progress of disease, and as a factor which may be of benefit to the patient but more often proves itself a serious and troublesome manifestation of the morbid process. In my experience relatively few clinicians go back of this and consider the effects which fever has on the many functions and on the many organs which compose the human body. It is precisely this last statement which has stimulated my interest so as to guide me in my choice to select the title I have for this thesis. It is not my intention to enumerate or discuss each and

every effect which fever may produce on the body, but
to mention the more important effects which result
from fever. To be sure, each and every function of
the body may be disordered by fever.

It is paramount that it be mentioned that much of
the data to be presented has been obtained by the various
authors by experimental studies performed with laboratory
animals such as the rabbit and the cat. It is, of course,
self evident why all information cannot be obtained from
the human organism. In all cases it will be mentioned
as to the method of reaching the evidence presented. Of
course, there immediately arises the question as to whether
fevers which are induced physically will produce the same
effect on the body as a fever which has its source within
the body. This question cannot be answered with any
certainty; however in all probability the changes are
not exact in the two cases, but most authors agree that
after their studies they are inclined to believe that
the changes are quite similar. For the solution of many
problems it is evidently irrelevant whether the source
of heat be within or without the body.

To those of you whose ambition is to trend the path
of original investigation, medicine offers a rich and
tempting field of labor. The subject of fever, for example,
is one which has as yet been but imperfectly cultivated.

An immense mass of facts and observations has been accumulated, and a great advance has been made towards the elucidation of its natural history, pathology, and classification, but much remains for future labourers to do, and many minds will be employed in the development of its latent processes, and in determining their numerous and complex relations to healthy and to otherwise diseased functions.

CARDIOVASCULAR SYSTEM

Inasmuch as disturbances of the heart and the circulation in general are among the most important symptons of fever it is natural that much attention has been given to the study of the effects of heat upon the organs of circulation.

The cardiovascular phenomena which results from elevation of body temperature have been observed and studied, but one cannot predict with any degree of certainty the actual changes that may occur in the circulation in the terms of degree of fever.

The conclusion seems to be that as the temperature increases, the heart accelerates, the skin vessels dilate, the arterial pressures tend to decline, the pulse becomes larger and often dicrotic, while the minute volume of the circulation alters very little if at all. When the elevation of temperature has reached what may be termed the upper endurance level, death as a rule occurs from respiratory paralysis before significant changes in the heart or circulation have time to develop. Occasionally, when the heart is less resistant than normally, or the respiration more so, a circulatory crisis precedes the respiratory failure: the heart becomes extremely fast or irregular, its beat is feeble or alternating, and the

blood pressures fall to very low levels.

Knowlton and Starling (30) have studied the heart
and agree that the heart rate becomes progressively
faster until an optimum temperature, variously placed
between 40° C. and 43° C. is reached. At higher
temperatures, the rate declines rapidly until the heart
stops entirely or the rhythm becomes irregular and
terminates in ventricular fibrillation. These invest-
igators also agree that the amplitude of contractions
diminish with an increase in temperature, at even the
lower ranges, but a normal minute output is maintained
through the increased rate. As the temperatures exceed
an optimum, the contractions diminish still further so
that the minute output is no longer maintained. The
alterations in the contraction process responsible for
this cardiac depression are not yet fully understood.
A considerable divergence of opinion also exists as to
whether the circulatory effects of high temperatures are
chiefly or solely due to a direct action on heart and
blood vessels or whether they are partly induced by
effects on the controlling medullary centers. Evidence
on this question has been sought by heating the blood
as it flows through the carotid arteries.

It is apparent that certain essential information
is still lacking for a satisfactory interpretation of
the cardiovascular effects produced in hyperpyrexia.

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This is partly due to the fact that most of the invest-
igators concern themselves with special phases of the
circulatory problem; and partly to the fact that the
circulatory reactions in the intact animal are not
necessarily a consequence of a high temperature alone.

Cheer (7) used dogs which he placed in a specially
designed heating cabinet, and changes which take place
in the heart and circulation when temperature is raised
to a lethal point were studied. The heart rate increased
progressively; systolic and diastolic pressures fall
slightly. The S-A node remained the pacemaker even when
the rate reached 180 or more beats perminute. The P-R
interval of the electrocardiogram is slightly abbreviated,
the QRS complex is smaller and often bifurcated, and the
T wave changes to a positive form. The arterial pressure
curves indicate that systole and the velocity of eject-
ion are reduced. As temperatures rise, alveolar and
blood carbon dioxide are decreased, and a condition of
mild alkalosis exists. The S-A node still controls the
rhythm and A-V conduction time is further shortened. The
heart accelerates extremely; systolic and diastolic
pressures decline progressively. The arterial pressure
curves develop a peak contour and fall rapidly during
the latter portion of systole, suggesting a low peripheral
resistance. Durations of systole and systolic ejection

are reduced more than can be accounted for by the rapid rate. As the temperature was increased further, marked irregularity of the heart occurs before respiration ceases. Electro cardiographic studies show a variety of rhythms which lead to the conclusion that the S-A node is very resistant to effects of high temperature and remains the pacemaker until very near the end and also that ultimately A-V block and various types of ventricular rhythm develop. Systolic and diastolic pressures fall rapidly and the pulse pressure is small. The duration of systole and its phase suddenly increases in length as the heart finally fails. The cessation of the circulation is precipitated by the direct changes in the heart.

Knies (29) reported a series of twenty patients on whom fifty-two electrocardiograms had been taken during induced fever. He found that "the electrocardiographic changes were minor", and indicated "that fever has only a slight direct influence on the electrical activity of the heart", and that those minor and insignificant changes in electrical activity of the heart occurring with fever disappeared completely when the fever subsided, and that there were no permanent electrocardiographic changes noted. He further states: "In no instance were changes characteristic of coronary insufficiency

observed, and there was no evidence of cardiac damage insofar as electrocardiographic observations were concerned".

Though it is frequently said that the physiological changes which occur during "natural fever" are similar to those which occur during fever induced by mechanical means, it is still rather difficult to evaluate the findings which are obtained by using animals and trying to transfer them to the human body.

Kopp (32) has found that the changes are similar, but more marked in cases of artificially induced hyperthermia. He reports increase in pulse rate with occasional arrythmias due to premature beats and auricular fibrillation; also that the velocity of blood flow is increased as body temperature rises. Increase may be as much as three-hundred percent. The circulation time fluctuates considerably. Reduction in blood plasma volume occurs in all occasions according to Kopp. The reduction is of considerable importance since shock symptoms have occurred with a concentration of twenty percent or more at body temperatures of 106° F. or above.

With reference to blood volume changes, Kopp working in association with Gibson (33) found that during artificial fever there was a gross loss of water

from the blood stream via both skin and lungs. Since
this loss may be more rapid than the rate of absorption
from the intestinal tract or the tissue spaces, there
is a reduction in plasma volume and consequently,
total volume.

Kovacs (34) goes so far as to state that the pulse
rate increases in proportion to from five to nine beats
per minute, to each degree Fahrenheit; also that the
blood pressure usually at first undergoes a slight
elevation of systolic pressure then declines. The
diastolic pressure falls, as a rule, as soon as the
temperature begins to rise and its usual range is from
fifty to sixty mm. in contrast to one-hundred twenty
to eighty mm. for the systolic. Kovacs (34) also states
that the loss of fluids through the skin, the lungs and
the urine promotes changes in acid-base balance of the
blood. This as well as the decrease of its carbon
dioxide content brings about a pronounced alkalosis.
The degree of alkalosis is dependent primarily upon
the severity of dehydration and secondarily, upon the
extent of the ventilation. Another important con-
sideration is the maintenance of the chloride balance.
It was shown that the development of alkalosis after
prolonged fever was accompanied by a low blood serum
chloride. It is suggested therefore, that there be

maintained a proper fluid intake, and that sodium
chloride by mouth be taken at intervals if sweating
is excessive.

Koehler (31) has concluded that the effect of
fever was, among others, a decrease in the hydrogen
ion concentration of the blood plasma with resultant
alkalosis.

Some of the pioneer work on the blood vascular
system and its relationship to hyperpyrexia was done by
Stewart (54). This work is of significance because the
studies were made during spontaneous fever. His studies
were all concerned with the human body. He noted that
the vasoconstriction mechanism of the peripheral parts
was abnormally excited, resulting in a diminished blood
flow through the extremities, and more particularly the
feet. This vasoconstriction was considered to be of a
compensatory mechanism, securing for the organs suffering
from the infections an increased blood flow. On this
basis the only rational treatment was to reduce the
body heat by a process which in itself would not diminish
and thereby remove the benefit of the vasoconstriction.
It was through this reasoning that efficacy of the now
commonly used cold baths and sponging was advocated.
Antipyretic drugs, by causing dilatation of the blood
vessels, reduce the temperature, but defeated the

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purpose of the valuable vasoconstriction.

In an attempt to explain the mechanism of hemor-
rhage in artificially induced fever, studies of capil-
lary resistance by means of the suction test were made
by Rossman (47). Artificial fever, induced by means of
the Kettering hypertherm, produced an immediate decrease
in capillary resistance as determined by the suction
test method. The exact cause of this decreased capil-
lary resistance is as yet unknown; however vasodilation
and increased intracapillary pressure are probably the
underlying factors. The focal hemorrhages seen at
autopsy following artificially induced fever in exper-
imental and clinical subjects may be due to this de-
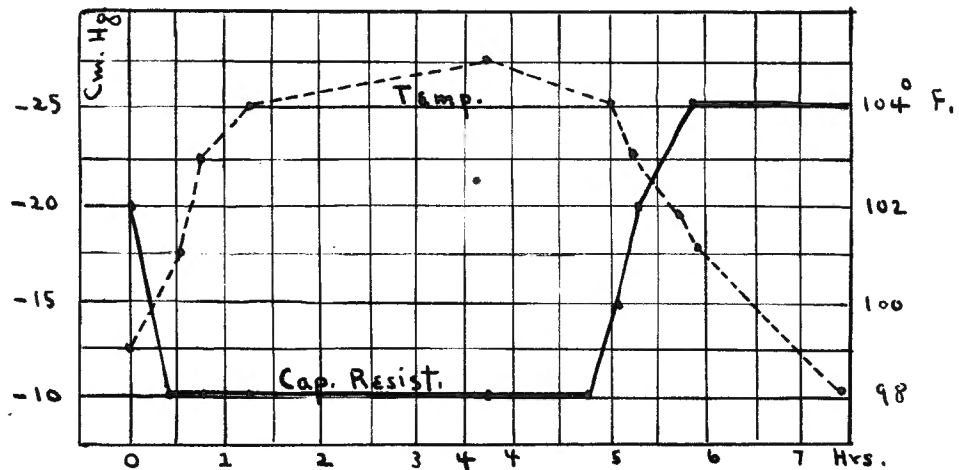creased capillary resistance.

Fig. 1.--Rectal temperature and capillary resis-
tance during an artificially induced fever treatment.

Landis (35) concluded from his studies that "heat
produces peripheral vasodilatation, raises capillary

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blood pressure conspicuously and, through relaxation
of capillaries, increases the area of capillary wall
available for filtration." It may also be mentioned
here that dilated capillaries are probably more easily
ruptured than those of normal caliber.

Wilson and Doan (61) exploring further into the
underlying mechanism of the hemorrhagic tendency
accompanying fever used normal patients except for
some type of gonorrheal infection. Fever was induced
by the Kettering hypertherm. A marked decrease in pro-
thrombin and fibrinogen occurred secondary to liver
damage. Sternal puncture revealed definite cytoplasmic
and nuclear damage of the megakaryocytic cells. Sub-
sequently there was a progressive thrombocytopenia.
The degree of thrombocytopenia depended upon the extent
of the megakaryocytic damage.

The pathogenesis of hemorrhage may be followed in
orderly sequence: the elevation of body temperature
results in anoxia and a depletion of liver glycogen;
these factors may result in hepatic and megakaryocytic
damage following which there is a decrease in pro-
thrombin and circulation of platelets. Fibrinogen
may also be decreased. Therefore, any such decrease in
these factors which are important in the coagulation of
blood contributes to potential or actual hemorrhage.

Artificially Induced Fever

Anoxia--Decreased O_2 Saturation of Arterial Blood
and Low O_2 Content of Venous Blood.

Depletion of Liver Glycogen

Increased Endothelial
Permeability
(?)

Liver Damage

Megakaryocytic
Damage (Bone Marrow)

Prothrombin   Fibrinogen
Decrease   Decrease

Platelet Decrease
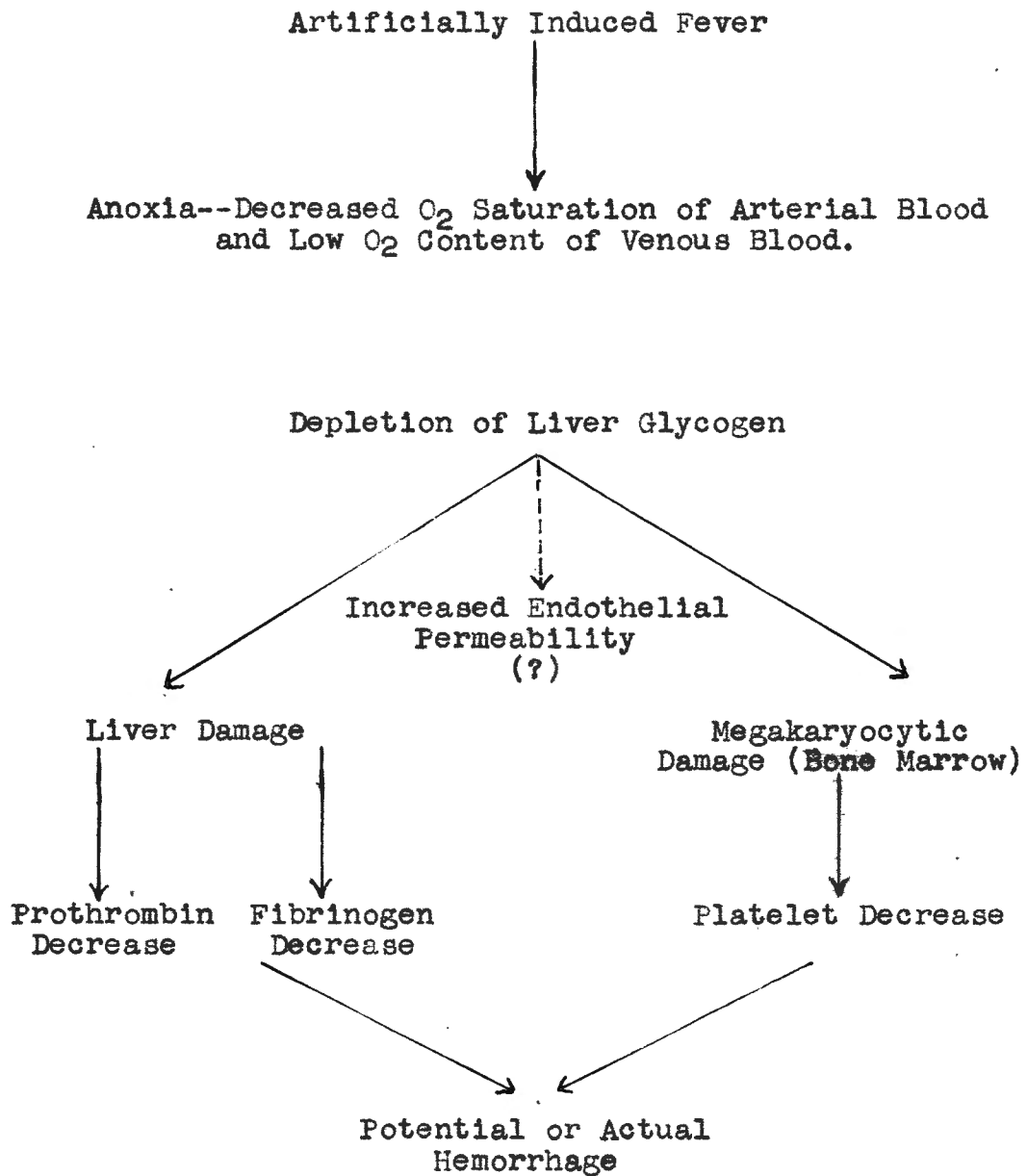
Potential or Actual
Hemorrhage

Fig. 2.--Etiology of hemorrhage in artificially
induced fever. (from Wilson and Doan)

The importance of the cellular elements of the blood and connective tissues to the maintenance of health and the control of disease has been apparent since the early studies of Metchnikoff. It is now recognized that every circumstance which affects the complex mammalian body affects the blood as well as the hemopoetic mechanism.

Hargraves and Doan (20) studied peripheral blood cell changes following varying degrees of fever in a series of rabbits, and found that a leucopemia persisted throughout the duration of the fever induction regardless of the method employed, and only during fever defervescence was leukocytosis of varying degree observed. Furthermore, the leucopemic phase was purticipated in by all of the white cell elements, the lymphocytes reflecting earlier and perhaps more profoundly, and certainly more persistently the inhibitory and destructive effects of the fever temperatures. Qualitatively the circulating lymphocytes became increasingly more pyknotic, less bosophilic, older appearing cells as the duration of fever was prolonged. Postmortem studies were made of all lymph nodes and of the spleen, and it was found that practically every lymph follicle had disappeared, having been replaced by an infiltration of granulocytes and a great increase in highly phagocytic clasmatocytes

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with an excess of clear lymph. The sequence of events as reconstructed from a controlled series of animals was as follows: Lymphocytic nuclear Karyorrhexis, cytoplasmic vacuolization, focal cellular necrosis, hemorrhage occasionally, granulocytic infiltration, clasmoatocytic proliferation, and inhibition of lymphocytic regeneration with progressive hypoplasia so long as the temperature remained elevated.

Conversely, however, the circulating granulocytes during the leucopenic period showed a steadily progressive nuclear "shift to the left" suggesting of course a constantly maintained delivery of new cells in an effort by the bone marrow to compensate for the increased exodus of polymorphonuclear cells. When the rabbit marrows were studied, the chronology of events appeared to be as follows: occasional temporary myelocytic nuclear Karyorrhexis was observed during the first hour of fever with more marked megakaryocytic damage, followed promptly thereafter by increased mitotic nuclear figures and myelocytic hyperplasia without progressive necrosis.

Simon (48) contributes the following data. Fever was maintained at approximately 103° for nearly four hours. The white cell count showed an increase of sixty-eight percent, nine percent probably due to concentration of blood; therefore fifty-nine percent must be accounted

for either by stimulation of the white blood forming
organs or by a pouring out of these cells from storage
depots within the body. Young cells discovered in the
blood indicated considerable stimulation to formation.

The effect of hyperpyrexia on the blood count has
also been studied by Bierman (3) who also observed an
initial fall in white cells followed by an increase,
due in part at least to stimulation of the hemopoetic
system as evidenced by the appearance of immature cells.
The lymphocytic series, he reported, decrease with the
relative increase in granulocytes.

Doan (10) using rabbits in the Kettering hypertherm
also observed a definite and usually worked leukopenia,
and believes that there is also a later increase in
marrow output, but that it has never been observed to
result in a leukocytosis because of the rapid exodus
of the cells from the blood stream into the tissues.
Doan also reports a "shift to the left" in the Erythroid
elements, with appearance of plasma cells and a marked
increase in highly phagocytic clasmatocytes. This data
was obtained by serial sternal bone marrow biopsies on
a patient subjected first to hypertherm and then to
malaria.

In conclusion, we may say that there is a rather
constant hemopaetic response to fever and that the

majority of the cells making up the post-febrile leukocytosis are polymorphonuclear neutrophils newly delivered by the bone marrow as shown by their youth.

Sheard (51) of Mayo Clinic has shown the fever which accompanies infection exerts an adverse influence on the growth of bacteria, favors phagocytosis, diminishes the potency of toxins and stimulates the development of immune bodies. He has shown that as the temperature of the body is elevated above normal, the physical properties of the leukocytes change from the gel toward the sol state, thereby becoming more permeable and able to ingest greater numbers of bacteria or other foreign bodies. It was also observed that leukocytes travel about four times faster at 35°C. than at 25°C.

Sheard (51) also reported certain chemical changes in the constitments of the blood. He observed that with increased respiratory metabolism, there was a decrease in content of carbon dioxide in the blood. He also reported an increase in creatinine, urea nitrogen, uric acid, and calcium in the blood due to a combination of blood concentration, and elevated metabolism. Blood chlorides behave somewhat differently, showing a decline of 40 milligrams percent at the end of the febrile period in eighty percent of the patients. The ingestion of sodium chloride eliminates any sense of fatigue and

exhaustion, which together with nausea, vomiting, abdominal cramps and muscular twitchings constitute the symptoms of impending heat prostration, and which are due to a reduction in blood chlorides.

Simon (48) reported slight decrease in blood chlorides, averaging two percent. This was obtained by maintaining fever at approximately 103° for nearly four hours. He also noted the hemoglobin increased nearly nine percent, which was assumed to be due to concentration and to oxygen demand. Creatinine increased fourteen percent and nonprotein nitrogen thirteen percent. He also reports a rise in blood sugar, the actual increase amounting to nearly twenty percent. Contrary to these findings, Hopkins (24) states that the augmented body metabolism of fever produces a fall in the blood sugar level as measured by the rise in the respiratory quotient; also that alkalosis may exert some influence on the reduction in the blood sugar level. Macleod (36) has shown that alkalosis from bicarbonate feeding will lower the blood sugar.

It has been known for many years that changes in the water content of the blood follow exposure to high temperatures. Concentration of the blood during protracted fever may be expected, but Hopkins (24) states that when dogs were subjected to hot baths at 40°C. the

blood was diluted to roughly ten percent. This he
believes is a protection of the body against overheat-
ing. By this means larger quantities of blood were
made available for filling the dilated peripheral
vascular bed, bringing more blood to the surface to be
cooled. However, of course, the initial dilution of
the blood gives way to concentration following the loss
of water from the body in the pulmonery air, sweat and
urine. This concentration of the blood he states amounts
to between ten and sixteen percent.

As regards the effects of hyperpyrexia upon the pH
figure of the blood and the carbon dioxide combining
power of the plasma, Ferguson and Buckholtz (15)
corroborated with observations of Hall and Wakefield (17).
They found an increase of lactic acid and a decrease of
carbon dioxide combining power. The average increase of
lactic acid was 96.2 percent; carbon dioxide combining
power decreased 35.3 and a decrease of serum pH of 0.19
percent. The data was obtained from seventy patients
who were subjected to heat of 106.5 F. for seven hours.
(See Fig. 3.)

Cullen (9) on the contrary states he noticed a
rise in pH of the blood in his fever patients. The
rise in pH he states is probably due to loss of carbon
dioxide through the hyperventilation accompanying the

fever.

Yammakita (64) found in experimental fever and
also in febrile diseases in man that the percentage
saturation of the blood with oxygen decreases in fever.
This decrease in oxygen which is known to cause mental
confusion, restlessness, and excitment was also observed
by Cullen (9) and it was on this basis he determined the
value of oxygen therapy during hyperpyrexia. Some fever
therapy deaths have been well established as the result
of anoxemia of the central nervous system.

Fever and a disturbance of the suspension stability
of the blood may occur independently but usually occur
together, and accompany most if not all infections
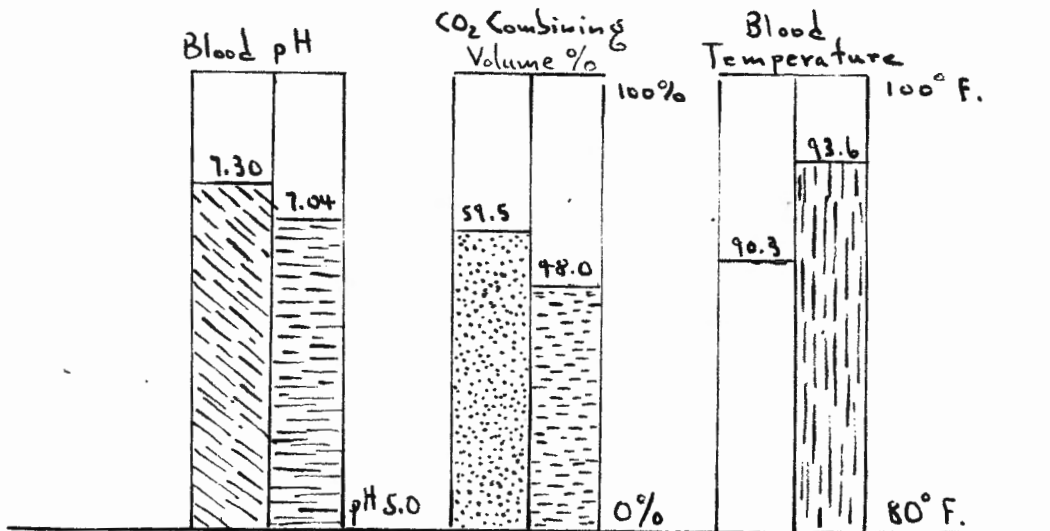diseases. The decrease of suspension stability was

Fig. 3.--Averages obtained from seventy patients
before and after hyperpyrexia of 106.5° F. for seven
hours. (from Hall and Wakefield)

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shown to be due to an increase of globulin and fibrinogen content of the blood which occurs in most febrile states. Whether fever alone is responsible for this or whether it is due to effects of the invading organisms has not been decided. It is probably a combination of factors causing a stimulation of globulin and fibrinogen presumably from the bone marrow or the endothelial system. With increase in the globulins, there occurs an increase in the viscosity of the plasma; then, as a result of an alteration of electrical charges the erythrocytes clump and settle rapidly. Both erythrocytes and bacteria are known to carry negative electrical charges so that if erythrocytes tend to clump when the electrical equilibrium is disturbed by a change of plasma proteins, bacteria should theoretically be similarly affected. If it can be shown that the changes in the plasma which accompany febrile infections diseases favor clumping of bacteria, another point will be added in favor of fever as a mechanism of defense against infection.

Since the respiratory system is so closely related to the circulatory system, it will be discussed here.

As body temperature rises, respirations become deeper but the rate may show little change and may even

be slowed. As body temperature continues to rise and is maintained, marked variations in depth and rate occur, especially if the patient is uncomfortable. Kopp (32) states that the respirations may become rhythmical resembling Cheyne-Stokes breathing with marked periods of apnea, as much as sixty seconds. This may be due to a great extent to the alkalosis which occasionally occurs and possibly to some edema of the brain. Kopp maintains that the use of morphine and barbituric acid derivatives during fever is dangerous. It is dangerous since the respiratory center is already depressed. Temperature control is more difficult and sudden and dangerous rises occasionally occur. Respirations often become rapid and shallow (59), this continues until the crisis is reached at temperatures varying from forty to forty-five degrees centigrade in different instances. At the crisis an abrupt diminution followed by total cessation of breathing takes place and death follows as a result of respiratory paralysis.

NERVOUS SYSTEM

Physiological and pathological changes must occur
in the nervous system, at least, some changes must occur
in order to explain changes which occur in patients
suffering from neurologic desease, and changes recorded
in non-neurologic patients. It may be a question of the
alteration of certain physical and biochemical states.
Collins (8) states that two of these specific states
are alkalosis and anoxia. Factors favoring anoxia are:
the early alkalosis, the increased blood temperature,
and the increased oxygen demand due to increased
metabolism. The cells of the nervous system, being
specialized cells, are more prone to react to alkalosis
and anoxia than other cells.

It is widely known that the nervous system of
children and of some adults is extremely susceptible to
febrile states in that convulsions occur quite frequently,
especially in the children.

The transitory alterations are difficult to explain.
There is still controversy over whether it is the heat
alone, or an additional biological factor which explains
the neurological changes. Jacobsen and Hosoi (26),
Solomon and Kopp (52), Wilber and Stevens (60) have all
presented evidence that fever produces congestion and

edema of the brain, varying degrees of meningeal as
well as focal parenchymatons hemorrhages, and pyknosis
and chromatolysis of ganglion cells. Hartman (21), in
a report of lesions of the brain of patients dying
following hyperthermia, stated that they usually
consisted of edema and congestion in the cerebrum and
cerebellum and degeneration of cerebral and cerebellar
cells, especially the pyramidal and Purkinje cells.
Hemorrhagic encephalitis has also been found quite
frequently in these patients.

Collins (8) reports cases on which he did neurological
examinations during hyperpyrexia. The most consistent
finding was loss of deep tendon reflexes in those
patients which exhibited some reflex action before treat-
ment, the loss being transitory during the fever. One
other patient with multiple sclerosis complained of
weakness and "numbness" during the treatment. Examina-
tion showed loss of deep tendon reflexes which were
hyperactive before treatment. Nystagmus is usually
intensified during the fever.

Wood and McGravey (63) have studied cerebral
hydrodynamics and report an increase in spinal fluid
volume and pressure due to increased meningeal permea-
bility which produces a compensatory elevation of the
systolic blood pressure and, in turn, pulse pressure.

Manometric determinations show a definite increase in
cerebrospinal pressure and volume during artifically
induced fever by use of electromagnetic induction. The
clinical status of such patients is usually that of
stupor and drowsiness probably due to cerebral anoxia,
the result of an increase in cerebrospinal fluid volume
and decrease in cerebral blood volume. In cases of
Wood's (63) when these signs and symptoms were present,
reduction in spinal fluid volume by lumbar puncture
and drainage of from twenty-four to forty-eight cubic
centimeters increased the blood volume circulating through
the brain and was followed by a prompt fall of the pulse
pressure to normal, the mental state also returning to
normal. The depth of stupor was proportional to the
height of pulse pressure; it was therefore determined
that this is the best clinical index as to the state
of cerebral circulation.

Mehrtens and Allred (39) produced hyperpyrexia
by baths and noticed definite increases in intracranial
pressure in epileptic patients, but questionable evidence
of increase in normal individuals.

Headache associated with fever is reported by
Sutherland and Wolff (55) who stated that decreasing the
cerebrospinal fluid pressure relieved headache; it is
likely therefore that the intracranial arteries are the

chief contributors to the pain. Vasodilation of the pial vessels was vizualized through a skull window of experimental animals whose fever was produced by foreign protein injection, extreme vasodilatation suggests that headache would probably follow such a state.

Stein (53) reported an unusual complication of hyperthermia in the appearance of frank signs of pyramidal tract involvement in an individual in whom no such findings were elicited prior to treatment in the heat cabinet in which his temperature was raised to 106°F., and maintained there for five hours.

These experimental and human postmortem data emphasize the fact that nervous tissue is susceptible to high temperatures. Probably neurological abnormalities would be found more commonly if hyperthermin patients were examined neurologically at the peak of temperature more commonly. One cannot be sure whether the neurological alterations are on the basis of transitory edema, hyperemia, anemia, anoxemia, alkalosis, increased or decreased blood flow, temporary thrombosis, or other physiological and biological factors.

METABOLISM

Since fever produces so many differences in the body, it is natural to expect to find differences in the body metabolism. DuBois (12) compared the level of basal metabolism in various fevers and found that it was rather closely proportional to the level of the body temperature. He suggested that this was an expression of Van't Hoff's law. For ordinary temperatures this law can be expressed as follows: "with a rise in temperature of 10° C. the velocity of chemical reactions increases between two and three times. In other words, the coefficient is between two and three." In other words,
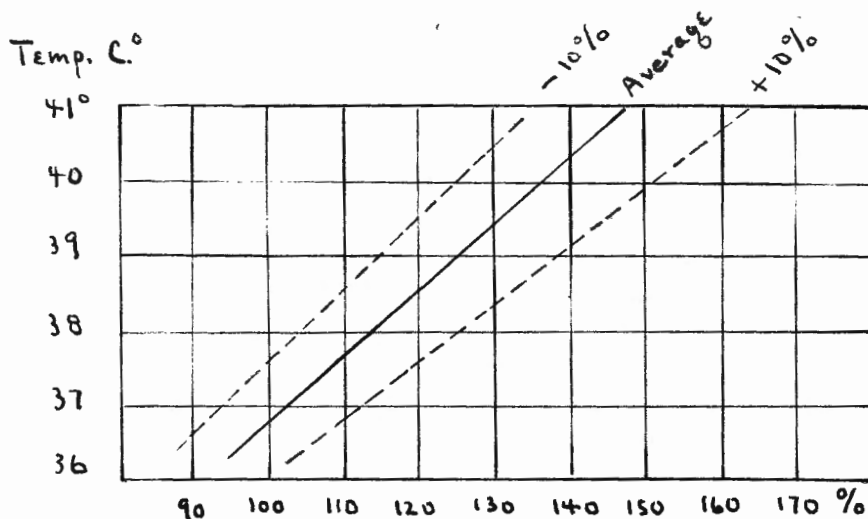
Temp. C.°

Fig. 4.--Relation of basal metabolism to temperature in six different fevers. The continuous line shows the average and the dotted lines are drawn to represent metabolism 10% above and 10% below the average. (from DuBois)

the reactions in a fever patient respond to a rise in
temperature in a manner which resembles closely the
chemical reactions in a test-tube suspended in a water-
bath; however, there is a tremendous difference between
the simple reactions in the test-tube and the complex
oxidations in the human body.

The graph is a plot of the temperature coefficients
of six various feverish states.

It has long been known that during the febrile
reactions, the katabolism of protein is intensified
resulting in an increased excretion of nitrogenous
substances in the urine. Best and Taylor state that
as much as 300 to 400 grams may be destroyed daily.

This loss of body protein, which apparently occurs
during all acute infections fevers, is due both to an
increased destruction and to a decrease in the regenera-
tive processes, both changes serving to intensify the
disproportion between the anabolism and katabolism of
protein. The subject becomes poorer in nitrogenons
substances. Shaffer and Coleman (50) have shown however,
that if the diet is reinforced with proteins and the so
called "protein sparers", carbohydrates and fats, the
nitrogen equilibrium can be established, therefore, the
old addage "feed a fever" holds true. Nevertheless,
even on an increased calorie diet composed of the

carbohydrates and fats, nitrogen excretion still remains well above that of a normal person.

Shaffer and Coleman (50) are inclined to believe that protein loss is not entirely due to the pyrexia, but also to the action of bacterial toxins on the body cells or fluids, for increasing the temperature of a normal person to 104° by immersion in a hot bath does not increase the nitrogen output as significantly as when the pyrexia is accompanied by an acute bacterial infection.

Creatinine, uric acid, purine bases and phosphates also appear in the urine in increased amounts, which is still further evidence of a destruction of body protein.

Simpson (49) among others has observed that moderate degrees of hyperglycemia exists in artificial fever, and also in infections fever. According to these observers, the hyperglycemia is due to a blood concentration. Kirstein and Bromberg (28) however, attribute the increase in blood sugar to disturbances in the carbohydrate metabolism. There concept is based on the exquisetly fine and responsive regulatory mechanism which maintains a constant blood sugar level. Kirstein and Bromberg had twenty-one patients which they reported. The Kettering Hypertherm was used to raise the temperature to 104 - 106° for three to six hours; all the patients

showed a rise in blood sugar averaging approximately nine milligrams percent.

The metabolism of body fat is not markedly affected. In patients upon a low food intake, body fat is utilized as a fuel, and acidosis may result from incomplete combustion of fat, and this results only if the available carbohydrate is inadequate in amount.

Another interesting metabolic change in fever concerns the salt balance. This is studied by observing the amount of sodium chloride excreted in the urine. During the course of fever the urine volume is markedly reduced, and also the urinary chlorides. The retention of chloride is a result of the deposition of the chlorides in the tissues. The salt retention is related to the concentration of the blood, a marked rise in which is usually accompanied by a rise in temperature and is an unfavorable prognostic sign. This retention of chloride results in a retention of water and a consequent gain in weight. After the crisis, however, chloride and water are lost and the body weight decreases.

Carpenter and Benedict (6) made preliminary observations on metabolism during fever in the early part of the twentieth century. They found that the pulse and respiration rates were raised, and that carbon dioxide production, which is an index of the total metabolism,

was increased along with the oxygen consumption.
There was a tendency for the respiratory quotient to
be elevated, although complications attending the
ingestion of food, variations in muscle metabolism,
and errors in oxygen determination rendered the results
unstable.

Brody (5) investigated the influence of fever
produced by diathermy on the metabolism of anesthetized
dogs. Body temperature was raised from 3.6 to 8.5
degrees F. above normal. Metabolic rates were raised
from 27 percent to 172 percent. The carbon dioxide
content of the blood stream was also reduced along with
the alkaline reserve.

PARENCHYMATOUS CHANGES

Haam and Frost (16) have investigated the effects of artificially induced fever on the parencheymatous organs of the body, using a healthy standard breed of adult rabbits for experimental study. Fever was induced by the diatherm or radiotherm method.

The principal changes in the parenchymatous organs have been grouped in Figure 5. The frequency of their occurrence in each experimental group is indicated by a plus sign: 1 plus indicates a frequency from 5 to 25%; 2 plus a frequency up to 50%, 3 plus to 75%, 4 plus to 100%.

The most important changes in the heart were scattered interstitial hemorrhages of the myocardium and severe degenerative processes of the muscle fibers. The cells lost distinctness of cross striations and intercalated dises, and with the Sudan stain a fine emulsion of fat droplets could be noted in many of the muscle fibers. Small focal areas of necrosis with hyalinization and fragmentation of muscle fibers could be observed in the animals exposed to prolonged lethel doses of fever.

The principal changes found in the lungs were acute venous hyperemia and intra-alveolar hemorrhage. The

		A Lethal Temp. 30-60'	B 109° 8-9 hr.	C 107° 40 hr.	D 106.5° 3 hr. 6 times	E Healthy Control
Heart:	Hemorrhages	X	XXX	X	X	O
	Fatty degen.	XXX	XXXX	XXX	XX	O
	Necrosis	X	XX	X	O·	O
Lung:	Hemorrhages	XXX	XXXX	XXX	X	O
	Atelectasis	O	X	X	O	O
	Pneumonia	O	X	O	O	O
Liver:	Hemorrhages	O	X	X	O	O
	Loss of glycogen	XXXX	XXXX	XXX	XX	O
	Fatty degen.	X ·	XXXX	XX	O	O
	Focal necrosis	O	X	X	O	O
Spleen:	Congestion	X	XX	XXX	XX	O
	Hemorrhages	X	XX	X	X	O
	Follicular necr.	X	XXX	XX	O	O
Kidney:	Hemorrhages	XX	X	X	O	O
	Tubular degen.	XX	XXXX	XX	X	O
	Glycogen infiltr.	X	XX	X	O	O
Adrenal:	Hemorrhages	X	XX	O	X	O
	Lipoid depletion	XX	XXXX	XX	X	O
	Cortical necrosis	O	XX	X	O	O
Testis:	Atrophy	X	XX	XX	X	X
	Necrosis	O	XXX	XX	O	O

Fig. 5.--Principal changes in the parenchymatous organs with stated duration of fever. (from Haam and Frost)

arterioles and small bronchi appeared constricted, the
small veins dilated. Varying degrees of atelectasis
was present, sometimes being severe, but not widespread
or complete. A small percentage of the animals showed
development of pneumonia.

In the liver evidence of hemorrhage or congestion
was only slight. The most significant change was the
complete depletion of the liver cells of glycogen in
the animals exposed to lethal doses of fever. The
protoplasm of the liver cells showed the typical course
granular appearance of parenchymatons degeneration with
numerous fat droplets present in the cytoplasm. Scattered
areas of patchy focal necrosis could be found in the
groups exposed to longer lasting lethal doses of temper-
ature. They were usually located in the mid-zone of
the liver lobules and consisted of acidophil hyalinized
cellular debris invaded by leukocytes and macrophages.

The most characteristic change in the spleen was
the necrosis of lymphocytes in the malpighian follicles
and in the splenic pulp. Marked congestion was present.
The hemosiderin pigment in the pulp was slightly increased
in the chronic fever animals.

In the kidney, congestion with hemorrhage was
present in all fever animals along with degenerative
processes of tubular epithelium. This consisted of

irregular enlargement of the tubular epithelium with
obstruction of the tube lumen, an increased desquama-
tion of epithelial cells, and the formation of cellular
casts. An interesting finding was the appearance of
glycogen in the tubular epithelium of the animals with
depleted liver glycogen -- a histological evidence of
fever glycosuria. The adrenals show a marked depletion
of lipoid and the presence of extensive cortical necrosis.
Small hemorrhages are reported in all fever experimental
animals.

Necrosis of germinal opithelium was edema and
hemorrhage in the interstitial tissues was reported in
the testicles. The nuclei of the germinal epithelium
showed changes varying from simple pyknosis to complete
lysis. Giant cells with dense peripheral nuclei and
a hyaline cytoplasm were also frequently present.
Acidophilic cell debris fills the lumina of the tubules.
The changes seemed to affect the spermatids first, the
spermatocytes second, and the spermatogonia last. The
interstitial cells showed only a slight swelling with
some vacuolar degeneration.

Haam (16) also reported that examination of the thymus,
lymph glands, striated muscle, and omentum showed small
petechial hemorrhages, and that examination of the
intestinal tract, pancreas, bladder, ureters and the

larger vessels showed no significant change. The
thyroids of all fever animals showed moderate to severe
depletion of colloid with corresponding hyperplasia
of the epithelium lining the acini.

Above all, it is urged with apparently convincing
arguments that the weakness of the heart which is
undoubtedly one of the gravest dangers of fever, is
the direct effect of prolonged high temperature and is
manifested anatomically by parenchymatons or fatty
degeneration of the cardiac muscles.

Welch, W.H. (57) states that mammalian animals
whose temperature is raised artificially, dies when its
internal temperature reaches 111.2° F. (44° C.) or 113° F.
(45° C.). Death is preceded by convulsions and immed-
iately or soon after death rigor mortis appears at the
moment of death the irritability of the heart and muscles
ceases. Death seems to be due to heart paralysis.
Welch believes this stated temperature is probably the
maximum for the human body.

Welch succeeded in keeping for three weeks a
large black rabbit with a rectal temperature of 107.3° F.
(41.8° C.). The rabbit was then killed and autopsied
and presented marked fatty degeneration of the heart,
liver and kidneys. The rabbit also lost weight. Further
experimentation showed that the liver was first affected,

and then the heart and kidneys; this fatty degeneration
was discovered to be present only after temperature had
been maintained for five or six days.

Hall and Wakefield (18) studied dogs placed entirely
within a heated and humidified chamber. Rectal temper-
atures of 106° F. to 113.4° F. were produced and main-
tained for periods of twenty to seventy-five minutes.
Necropsies revealed generalized venous congestion,
most marked in the mucous membranes, lungs and liver;
blanched and rigidly contracted intestines, dilated
stomach's; cloudy swelling of the kidneys; contracted
bladders, and petechial hemorrhages. Microscopically
there were consistently cellular degenerative changes
of varying degree, most prominent in lungs, kidneys,
liver, intestines, thyroid and brain, and acute
passive congestion in all tissues.

Jacobsen and Hosoi (26) elevated the temperature
of dogs by means of radiothermy. Maximum temperatures
of 107.5 to 112.4 F. were attained. These authors
summarize their detailed account of morphologic changes
as: "congestion of the organs, peripheral hyperaemia,
cloudy swelling, fatty degeneration, dehydration,
glycogen depletion, focal hemorrhages, especially in
the gastro-intestinal tract, epithelial hyperplasia in
the parenchymatous organs, stimulation of the bone

marrow, and, following prolonged periods of heating, degenerative lesions in the male germinal epithelium".

Hartman and Major (22) reported two clinical cases coming to necropsy after fever therapy in the Kettering hypertherm. The lungs were dark in color, especially the lower lobes. Congestion and edema were marked. Both lungs had gained in weight the right gaining more. Microscopically sections from the lungs showed the parenchyma of the lower lobes hemorrhagic. The bronchioles were well preserved but the alveoli were filled with erythrocytes. The liver appeared grossly normal but showed acute parenchymatons degeneration microscopically there was marked engorgement of the sinuses. Kidneys also showed parenchymal congestion and degeneration. The sections from the adrenals showed marked engorgement of the blood vessels and a marked granular and hyaline degeneration of the zona fasciculata. The brain showed some engorgement of meningeal vessels but convolutions were of usual width; on section the basal nuclei were markedly congested with minute hemorrhages here and there. No other abnormal findings were reported. It seems that most of the pathology is microscopic with little or no gross pathology, except probably for the dark congested areas.

In summarizing, it can therefore be stated that the

most frequent pathological changes observed in animals exposed to fever are vascular phenomena: congestion and hemorrhage. From Figure 5 it is revealed that a certain length of time must elapse before the cells of the various parenchymatous organs show evidence of damage, and that fever over a brief period is not very harmful. The regeneration of the damaged parenchymatous tissues apparently takes place quite promptly and completely. When fever is used within the usual limits of therapeutic application, the changes are all reversable.

MISCELLANEOUS CHANGES

Some of the earliest experimental work done with
fever concerning its relation to the physiological
processes of the body is shown by the work of Beaumont (2),
who in the year 1833 recorded the following: "In febrile
diathesis or predisposition from whatever cause... The
villous coat becomes red, dry, at other times pale and
moist and loses its smooth and healthy appearance; the
secretions become greatly vitiated, greatly diminished,
or entirely suppressed, and the mucous coat scarcely
perceptible, the follicles flat and flaccid, with
secretions insufficient to protect the nervous papillae...
When there are corresponding symptoms of disease, as
dryness of the mouth, thirst, accelerated pulse, etc.,
no gastric juice can be extracted, not even on application
of alimentary stimulus. Drinks received are immediately
absorbed or otherwise disposed of, none remaining in
the stomach ten minutes after being swallowed. Food
taken in this condition of the stomach remains undigested
for twenty-four to forty-eight hours or more, increasing
the derangement of the whole alimentary canal and
aggrevating the general symptoms of disease."

Clinical and experimental evidence confirms these
early observations of Beaumont. Meyer, Cohen and

Carlson (40) experimented with dogs, and raised their
temperature by external heat. They concluded that
during fever there are definite changes in the gastric
secretion which are chiefly a diminution of volume,
diminished free and total hydrochloric acid, a per-
centage increase in pepsin, and a nearly constant
percentage of chlorides; also the secretion is mucous
and ropy in character. It was suggested that during
fever, toxins are elaborated having a direct depressor
action on the cells of the stomach so that they fail
to react to the secretory nerve impulses and to the
secretogognes. The gastric secretions again return
to normal within twenty-four hours.

Osborne and Greenguard (44) raised the body
temperature of dogs by means of shortwave diathermy.
Raising the body temperature resulted in an increased
flow of pancreatic juice up to seven times the original
rate, and lowering of the temperature caused complete
cessation of secretion. These findings are probably
accounted for on the basis of alterations in circulation
through the pancreas.

It is known clinically that heat applied to various
parts of the body causes muscular relaxation. There
are no records, however, to prove that heat actually
relaxes intestinal sphincters, so Doubilet and Bierman (11)

recorded kymographically the effect of hyperpyrexia
on the common bile duct sphincter on the cardiac
sphincter. Changes in tonus of the sphincter were
measured by means of a Levine tube to the end of which
a balloon was attached. Kymographic tracings indicate
clearly that hyperpyrexia causes relaxation of the
common bile duct sphincter and of the cardiac sphincter
in the human.

Vitamin C nutrition in fever received the attention
of Zook and Sharpless (66) who studied the excretion
of this substance before and after the induction of
fever. It was found that fever increases the requirement
of Vitamin C in man. It was discovered that there is
no significant change on the concentration of ascorbic
acid in the blood.

Optimal thiamine requirements for rats was found
to be twice as high at 91° F. as at 65° F. environmental
temperature by Mills (41). These findings may be of
some bearing on human existence at elevated temperature.

Boyd, Orr and Reed (4) investigated the relation-
ship of plasma lipids and body temperature in rabbits,
and found that plasma concentration of phospholipid and
free cholesterol had no relation to body temperatures
between 100 and 103° F.

McGuigan (38) studied the effects of temperatures

on the action of digitalis. At higher temperatures
this drug is somewhat more toxic. The increased
irritability of the heart during fever interferes with
the slowing action of digitalis. It was concluded that
the height of the fever determined the benefits to be
derived from the drug, and that in high feverish states
it may be useless, due to the greatly exaggerated
irritability of the heart.

Wien (58) showed in experiments on cats that "fever
may abolish the action of insulin not only by increasing
the forces which raise blood sugar but by inhibiting the
action of insulin in lowering the blood sugar". This
resistance he believes could partly be explained from
stimulation by pituitary, adrenal and thyroid glands,
which in turn upset metabolism of carbohydrates in the
muscles.

The effects of cervical lymph flow as a result of
hyperthermia were investigated by McCarrell (37) who
used anesthetized and curarized dogs and cats as
experimental animals. He subjected them to high
environmental temperatures (40 to 45° C.) and noted
that cervical lymph flow increased and protein percent-
age decreased. An increased rate of capillary filtration
caused by peripheral hyperemia may be the explanation.
If temperature was raised to the point of circulatory

collapse still further increase was noted, caused by
a tremendous increase in capillary filtration resulting
from a high venous pressure and from capillary stasis
and anoxemia leading to injury to capillary endothelium.

The effect of fever upon transplanted neoplasms
was investigated in a number of mice and rats by
Woglom (62) who after raising the body temperature
several degrees even for a total period of three hundred
and forty-eight hours states that there was no adverse
effect upon the growth of the transplantable tumors
employed.

Abels (1) reports a bit of interesting work. He
found that during the presence of fever and immediately
afterward, many more teeth erupted than during later
periods. He believes that teething does not cause fevers
and digestive disturbance, but that, on the other hand,
dentition becomes more rapid after fevers. His obser-
vations were made on nineteen cases of measles in young
children from eleven to twenty-seven months of age.

Ernsting (14) has studied the effects of electro-
pyrexia on the intraocular tension. In the majority of
nineteen cases studied that were examined thirty minutes
after fever treatment, the intraocular tension was lowered.
No definite conclusions can be drawn, but it is readily
seen that it is important, as fever therapy may be

contraindicated in those diseases of the eye where
herniation may be a factor.

CONCLUSION

In drawing a conclusion to the subject discussed in this thesis, one must consider the two effects which fever is known to produce in the body. These effects are of a beneficial or non-beneficial nature. A conclusion cannot be made which will favor either of these entirely, because both effects do occur. The severity and duration of fever are the factors which govern the results of its presence. That these changes do occur and are present, has been proven by experimental work.

Fever effects almost every physiologic process of the body. If the fever does not exceed the critical point, it is, in a great majority of cases of definite value to the organism. This is particularly of importance in the infectious fevers where it has been shown that fever aids the body in its return to normal function. Pathological changes are produced when fever goes beyond the critical level, and is of sufficient duration.

It is important and desirable that the clinician understand the fundamentals of fever and its effects. It is only through such and understanding that he may hope to establish a criterion for either treating or not treating the feverish process.

In conclusion, it may be stated that most fevers, excluding those of central origin, are of value to

the diseased body, providing that the critical level is not exceeded. If the critical level is exceeded the fever is definitely a pathologic rather than a therapeutic process.

In closing, I believe the words of Sheard are very apropos, "In the light of present conceptions regarding fever we should consider fever as a natural, active factor produced within the body to aid in the destruction of an infectious agent, and to repair tissue injury from any cause."

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